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Neglected Mendelian causes of stroke in adult Chinese patients who had an ischaemic stroke or transient ischaemic attack

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ABSTRACT

Background and purpose Multiple factors play important roles in the occurrence and prognosis of stroke. However, the roles of monogenic variants in all-cause ischaemic stroke have not been systematically investigated. We aim to identify underdiagnosed monogenic stroke in an adult ischaemic stroke/transient ischaemic attack (TIA) cohort (the Third China National Stroke Registry, CNSR-III).

Methods Targeted next-generation sequencing for 181 genes associated with stroke was conducted on DNA samples from 10 428 patients recruited through CNSR-III. The genetic and clinical data from electronic health records (EHRs) were reviewed for completion of the diagnostic process. We assessed the percentages of individuals with pathogenic or likely pathogenic (P/LP) variants, and the diagnostic yield of pathogenic variants in known monogenic disease genes with associated phenotypes.

Results In total, 1953 individuals harboured at least one P/LP variant out of 10 428 patients. Then, 792 (7.6%) individuals (comprising 759 individuals harbouring one P/LP variant in one gene, 29 individuals harbouring two or more P/LP variants in different genes and 4 individuals with two P/LP variants in *ABCC6*) were predicted to be at risk for one or more monogenic diseases based on the inheritance pattern. Finally, 230 of 792 individuals manifested a clinical phenotype in the EHR data to support the diagnosis of stroke with a monogenic cause. The most diagnosed Mendelian cause of stroke in the cohort was cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. There were no relationships between age or family history and the incidence of first symptomatic monogenic stroke in patients.

Conclusion The rate of monogenic cause of stroke was 2.2% after reviewing the clinical phenotype. Possible reasons that Mendelian causes of stroke may be missed in adult patients who had an ischaemic stroke/TIA include a late onset of stroke symptoms, combination with common vascular risks and the absence of a prominent family history.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Strokes caused by single-gene mutations are an important type of stroke aetiology. However, the prevalence of strokes with Mendelian causes in all-cause ischaemic stroke is unknown.

WHAT THIS STUDY ADDS

⇒ We identified that 7.6% individuals harboured at least one pathogenic or likely pathogenic variant associated with one or multiple monogenic diseases in a Chinese all-cause ischaemic stroke cohort of 10 428 individuals.

⇒ After reviewing electronic health record data, the rate of a monogenic cause of stroke was 2.2%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Care should be taken to diagnose monogenic causes in all-cause ischaemic strokes, and an effective Mendelian stroke gene panel should be used to aid diagnosis.

INTRODUCTION

Deleterious mutations in a single gene can cause a Mendelian form of ischaemic stroke (IS), either as a primary or a secondary manifestation.[1] Despite numerous genetic studies of IS,[2–4] very few monogenic causes of strokes have been identified to date, and these have been found only in patients with a very early age of onset or with some types of small-vessel disease (SVD).[5 6] Few studies have attempted to systemically quantify the prevalence of monogenic stroke or to identify corresponding pathogenic variants in patients who had a stroke in the general population, especially in older individuals. The recent progress in genomic technology and the reduction of sequencing costs now make such an investigation feasible.[7] Understanding the rare genetic variants associated with stroke is an essential step to identify the causes of stroke, decipher the underlying mechanisms, facilitate the identification of novel therapeutic targets and optimise prevention strategies.[6] The current

Table 1 Characteristics of the included patients in CNSR-III

	NGS analysis cohort (n=10 428)	CNSR-III cohort (n=15 166)	Remaining cohort (n=4738)
Age at time of study entry，mean±SD	62.25±11.32	62.23±11.30	62.19±11.26
≤45 years	735 (7.05)	1074 (7.08)	339 (7.15)
>45 years	9693 (92.95)	14 092 (92.92)	4399 (92.85)
Male, n (%)	7137 (68.44)	10 364 (68.34)	3277 (68.11)
Ethnicity, Han, n (%)	10 118 (97.03)	14 726 (97.10)	4608 (97.26)
Current smoker, n (%)	3320 (31.84)	4752 (31.33)	1432 (30.22)
Heavy drinker, n (%)	1482 (14.21)	2126 (14.02)	644 (13.59)
BMI (≥25 kg/m²)	4464 (42.81)	6468 (42.65)	2004 (42.30)
Medical history, n (%)			
Ischaemic stroke	2349 (22.53)	3355 (22.12)	1006 (21.23)
Coronary heart diseases	1152 (11.05)	1608 (10.60)	456 (9.62)
Atrial fibrillation	737 (7.07)	1019 (6.72)	282 (5.95)
Hypertension	6540 (62.72)	9494 (62.60)	2954 (62.35)
Diabetes mellitus	2490 (23.88)	3510 (23.14)	1020 (21.53)
Dyslipidaemia	882 (8.46)	1191 (7.85)	309 (6.52)
Stroke type			
IS	9728(93.3)	14 146 (93.27)	4418 (93.25)
TIA	700 (6.7)	1020 (6.73)	320 (6.75)
Family history of Stroke	1395 (13.38)	2013 (13.27)	618 (13.04)
CCS			
Large artery atherosclerosis	2999 (28.76)	4364 (28.77)	1365 (28.81)
Cardioaortic embolism	718 (6.89)	971 (6.40)	253 (5.34)
Small arterial occlusion	2614 (25.07)	3747 (24.71)	1133 (23.91)
Other aetiologies	86 (0.82)	152 (1.00)	66 (1.39)
Undetermined aetiology	4011 (38.46)	5932 (39.11)	1921 (40.54)

Note: Heavy drinker: alcohol ≥20 g/day.
BMI, body mass index; CCS, Causative Classification System for Ischaemic Stroke; CNSR-III, the Third China National Stroke Registry; IS, ischaemic stroke; NGS, next-generation sequencing; TIA, transient ischaemic attack.

study was based on a cohort from the Third China National Stroke Registry (CNSR-III), which enrolled more than 10 000 consecutive patients who had an IS or transient ischaemic attack (TIA). We sought to determine the prevalence of pathogenic variants associated with Mendelian causes of stroke and to estimate the extent of potentially missed genetic diagnoses in adult patients who had an IS.

METHODS

Study population and classification of Mendelian causes of stroke

The CNSR-III is a nationwide prospective registry for hospitalised patients who had IS/TIA between August 2015 and March 2018 in China. A total of 15 166 stroke patients were enrolled. The detailed CNSR-III protocol has been published.[8] Most CNSR-III participants were also included in a genetic sub-study (n=12 603), for which targeted next-generation sequencing (NGS) was successfully conducted for 10 613 patients (online supplemental eFigure 1).

Monogenic disorders with a stroke phenotype were classified into the following subgroups: large-artery disease, SVD, embolic stroke, a prothrombotic state and other diseases (including neurofibromatosis 1, polycystic kidney disease, Fabry disease and cerebral cavernous malformations), based on the references[2 9] (online supplemental eTable1).

Clinical classification of IS was performed according to the Causative Classification System for Ischaemic Stroke (5-item CCS).[10]

NGS and data analysis

Briefly, DNA was isolated from peripheral leukocytes using a DNA Isolation Kit (Bioteke, AU1802, Beijing, China). DNA libraries were prepared using a KAPA Library Preparation Kit (Kapa Biosystems, KR0453, Wilmington, Massachusetts, USA) following the manufacturer's instructions. Genomic DNA capture, library construction and targeted NGS using a panel for Mendelian strokes were conducted as previously described.[11] Paired-end sequencing (150 bp) was performed on HiSeq X Ten or NovaSeq (Illumina, San Diego, California, USA). The

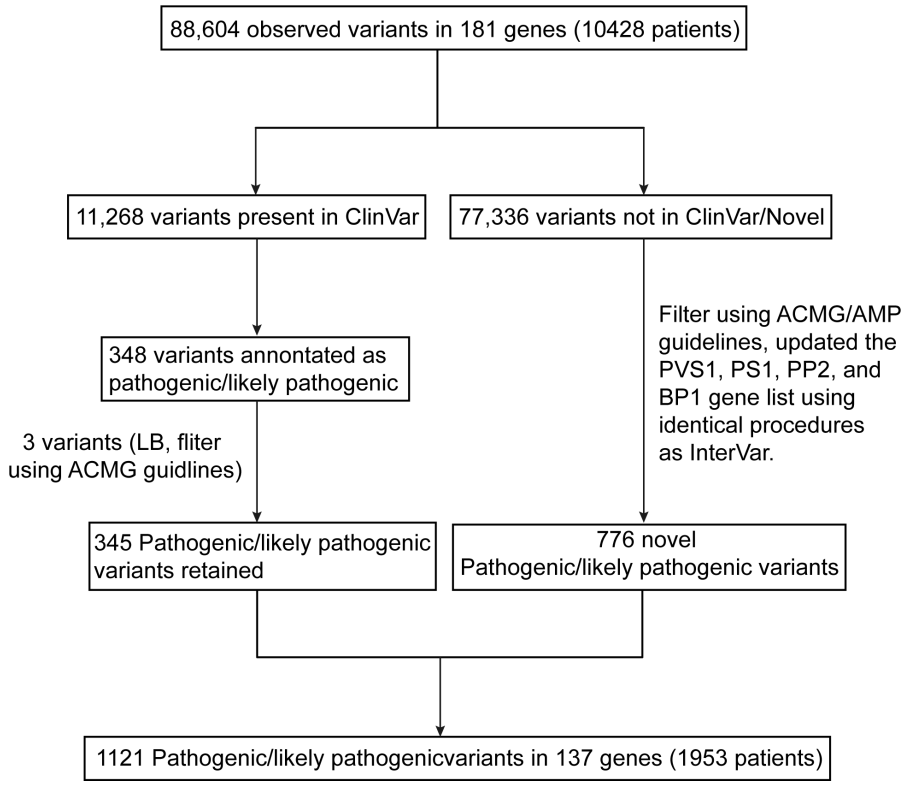


Figure 1 Identification and selection of pathogenic/likely pathogenic variants in the CNSR-III cohort. In total, 88 604 observed variants in 181 genes were enrolled in this study. We used 345 pathogenic/likely pathogenic variants after filtering using the ClinVar database (left), and 776 novel pathogenic/likely pathogenic variants after annotation using the ACMG/AMP guidelines (right). ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; CNSR-III, the Third China National Stroke Registry; LB, likely benign.

sensitivity and specificity of the targeted sequencing were evaluated by comparing the results with the results of Sanger sequencing from a previous study by our group.[11] Variant calling and quality control are described in online supplemental file 1. For the current analysis, we focused only on 181 candidate genes associated with Mendelian stroke or stroke-related risk factors (online supplemental eTable 2). The pathogenicity was evaluated using InterVar software and customised scripts (V.2.0.1) according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).[12] The ClinVar database (ClinVar 20200622 version) was used to aid the evaluation.

Evaluation of the concordance between clinical phenotypes and the genetic classification of monogenic stroke

Through electronic health record (EHR) review and based on the availability of diagnostic criteria and the manifestation of relevant disease phenotypes, we classified the extent of the confidence of a diagnosis of monogenic stroke into several categories: undetermined (ie, without phenotypic expression of the relevant monogenic disease), possible (ie, with some features of the monogenic disease), definite (ie, met diagnostic criteria for the monogenic disease) or insufficient information. Based on the literature, some but not all monogenic diseases have well-established diagnostic criteria. For those without existing diagnostic criteria, we used the disease-related phenotypes listed on OMIM and published data to classify the diagnosis. Full details of the classification scheme for each phenotype can be found in the Phenotyping section of online supplemental file 1.

Statistical analysis

We used R software (V.3.6.1) to perform analysis. Multivariable logistic regression analysis was used to predict the relationships between age or family history and the incidence of monogenic stroke in patients without a history of stroke, controlling for hypertension, hyperlipidaemia, diabetes, coronary heart disease, atrial fibrillation, smoking history, drinking history and body mass index (BMI) ≥25 kg/m².

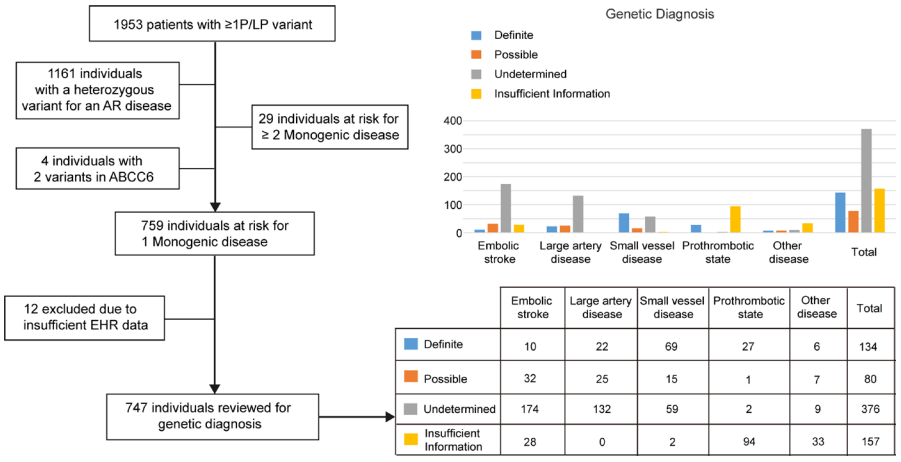
Data availability

The data that support the findings of this study are available from the corresponding authors on reasonable request.

RESULTS

Description of NGS analysis cohort

After filtering out 147 contaminated samples and 38 duplicated samples from 10 613 individuals, 10 428 patients remained for NGS data analysis (online supplemental eFigure 1). The final set of 10 428 samples had



	Embolic stroke	Large artery disease	Small vessel disease	Prothrombotic state	Other disease	Total
Definite	10	22	69	27	6	134
Possible	32	25	15	1	7	80
Undetermined	174	132	59	2	9	376
Insufficient Information	28	0	2	94	33	157

Figure 2 Individuals diagnosed and potentially missed diagnoses. Flow chart (left) illustrating the number of individuals harbouring one or more P/LP variant, and the number of individuals predicted to develop one or more monogenic disease. Bar plot (right) illustrating the proportions of the groups at risk for one monogenic disease, showing their likelihood of a missed diagnosis. EHR, electronic health record; P/LP, pathogenic or likely pathogenic.

an average mean depth of coverage of 192, and 96.2% of targeted bases had a coverage depth of at least 20.

In this study cohort, patients who had an IS accounted for 93.3% (9728/10 428) and patients who had a TIA accounted for 6.7% (700/10 428). The ages ranged from 19 to 95 with a mean (SD) of 62.3 (11.3) years old. Of the patients, 93.0% were 45 years old or older, 7137 (68.4%) were men, 2349 (22.53%) had a history of IS and 1395 (13.38%) had a family history of stroke (table 1).

Pathogenic/likely pathogenic (P/LP) variants

In total, 88 604 variants were found in the 181 candidate genes among the 10 428 individuals. We implemented two pipelines to annotate the variants: one for variants annotated by ClinVar (11 268 variants) and the other for 77 336 variants that were not present in the ClinVar database. The first pipeline focused on P/LP variants classified in ClinVar (348 variants in 1031 individuals) followed by verification through manual review according to the ACMG/AMP guidelines, which filtered out three variants re-annotated as likely benign. The second pipeline used our own customised scripts based on ACMG/AMP principles to classify the remaining 77 336 not present in the ClinVar database. The second pipeline included updating the PVS1, PS1, PP2 and BP1 gene lists based on identical procedures used in InterVar. This identified a total of 1121 variants, in 137 genes, presented in 1953 individuals, that were classified as P/LP and were further analysed for evaluation of their inheritance patterns and genotype–phenotype concordance (figure 1).

We further considered the inheritance pattern of the disease, excluding individuals with a heterozygous variant of an autosomal recessive disease. A total of 759 (online supplemental eTable 3) individuals harboured one P/LP variant in 80 genes and were predicted to be at risk for one monogenic disease (figure 2), while 29 individuals harboured more than two P/LP variants and were predicted to be at risk for multiple monogenic diseases (online supplemental eTable 4). In addition, four individuals harboured two P/LP variants (without confirmation of paternity and maternity) in *ABCC6* (online supplemental eTable 5). The Mendelian causes of stroke identified in our cohort included 245 embolic stroke cases (32.3%), 184 large-artery disease cases (24.2%), 148 SVD cases (19.4%), 124 cases of a prothrombotic state (16.3%) and 58 other disease cases (7.6%) (total, 759 individuals; online supplemental eTable 6). Detailed aetiological classifications are shown in online supplemental eTable 3.

Diagnostic rate of individuals predicted to develop one monogenic disease

EHR data registered in the CNSR-III cohort were available for 747 of these 759 individuals with one P/LP variant at risk for one monogenic disease, to verify the genetic diagnosis (figure 2). Classification of the monogenic stroke and the corresponding genes involved are shown in figure 3. Among the 747 individuals, 157 individuals were classified as having insufficient information, as although EHR data were present in the registry, we anticipated that the phenotypes of their monogenic diseases would not be evaluated through EHR review. After reviewing clinical information for the remaining 590 individuals, we classified them into three groups according to the level of support from clinical evidence: definite genetic diagnosis (134 individuals), possible genetic diagnosis (80 individuals) and inconclusive/undetermined genetic diagnosis because of the absence of clinical phenotypes (376 individuals, figure 2). The positive diagnosis rates (definite+possible diagnosis) were 19.4% (42/216) for embolic stroke, 26.3% (47/179) for large-artery disease, 58.7% (84/143) for SVD, 93.3% (28/30) for a prothrombotic state and 59.1% (13/22) for other diseases. Overall, the positive diagnosis yield among patients with genetically diagnosed monogenic stroke showed the highest yield for monogenic prothrombotic state.

We also found four individuals with two P/LP variants in the *ABCC6* gene (online supplemental eTable

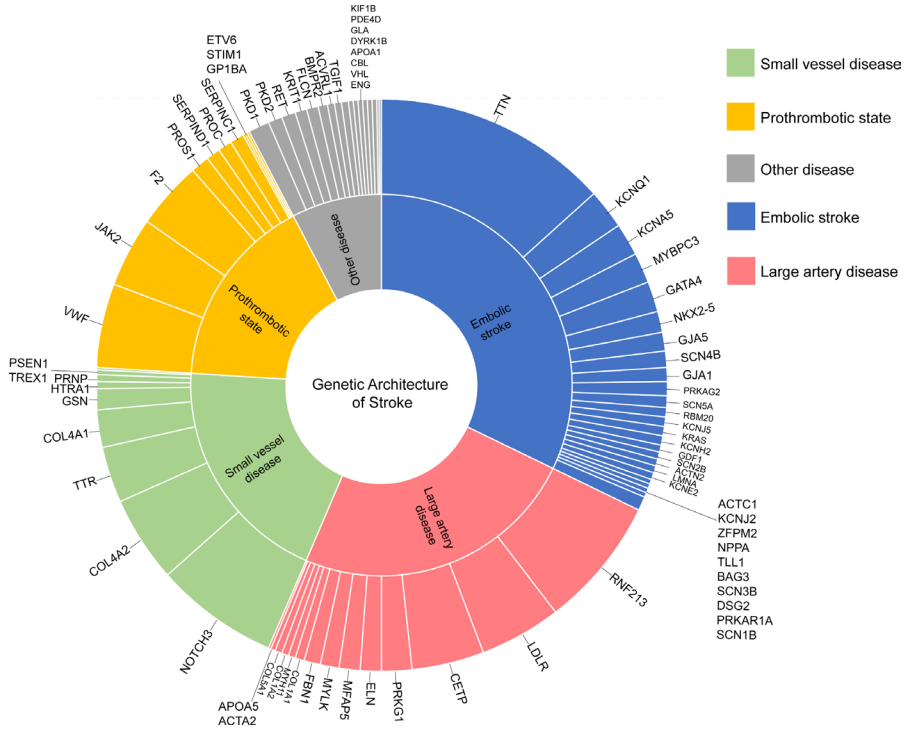


Figure 3 Genetic architecture of stroke. Each gene related to monogenic stroke identified in 759 individuals was classified into five subgroups: large-artery disease, small-vessel disease, embolic stroke, a prothrombotic state and other diseases (shown in the middle text circle). The proportions of affected genes are shown in the outermost circle.

5), predicted to have pseudoxanthoma elasticum in an autosomal recessive inheritance pattern. We reviewed the EHR data from these four patients and found no evidence to support a clinical diagnosis of pseudoxanthoma elasticum.[13]

Diagnostic rate of individuals predicted to develop two or more monogenic diseases

Surprisingly, we identified 29 individuals who harboured two P/LP variants in multiple genes and were predicted to develop two or more relevant monogenic diseases based on the inheritance pattern (online supplemental eTable 4). Two of them (patients #CNSR302050 and #CNSR303839) harboured three variants, and one (patient #CNSR306857) harboured four variants. Of these 29 individuals, three showed definite or possible clinical evidence to support the presence of two monogenic diseases. Thirteen of them had definite or possible clinical evidence to support the presence of only one monogenic disease. The remaining 12 patients did not have sufficient clinical phenotypes to support a genetic diagnosis. This group showed a clinical concordance rate (55.2%, 16/29) (online supplemental eTable 4).

Summary of the diagnostic rate of all individuals with one or more P/LP variant

In total, 792 of 10 428 individuals (7.6% of all patients) were identified as carrying at least one P/LP variant for monogenic disease, according to the ACMG/AMP guidelines or the ClinVar database. EHR data were available for 780 individuals, and 624 individuals had relevant phenotypic information for evaluation in the EHR data that corresponded to their genetic diagnoses of a monogenic disease. A total of 230 individuals (36.9%, 230/624) exhibited definite or possible clinical evidence to support their genetic diagnoses, including 227 individuals with one monogenic disease and three individuals with two monogenic diseases. In other words, 2.2% (230/10 428) of individuals from our cohort not only carried at least one P/LP variant related to monogenic stroke but also demonstrated definite or possible clinical phenotypic evidence to support a genetic diagnosis.

At the gene level, individuals with *NOTCH3* P/LP variants had the highest rate of positive genetic diagnosis (89.3%, 50/56). Mutations in exon 11 of *NOTCH3* accounted for 44.0% (22/50), with R544C and R587C as the most common (28.0% and 14.0%, respectively). Variants in exon 6–24 accounted for 88.0% (44/50). Surprisingly, we identified a *JAK2* variant (p.V617F) in 33 individuals, 29 of whom had corresponding phenotypes (ie, thrombocythemia or erythrocytosis). The third and fourth monogenic diseases with relatively high genetic diagnosis were familial hypercholesterolemia caused by heterozygous *LDLR* mutations (60%, 24/40) and *COL4A2* microangiopathy caused by heterozygous *COL4A2* mutations (52.5%, 21/40).

The characteristics of 230 individuals with Mendelian causes of stroke

Patients in our cohort with Mendelian causes of stroke had a mean age of 61.8 years old, and 65.4% were men.

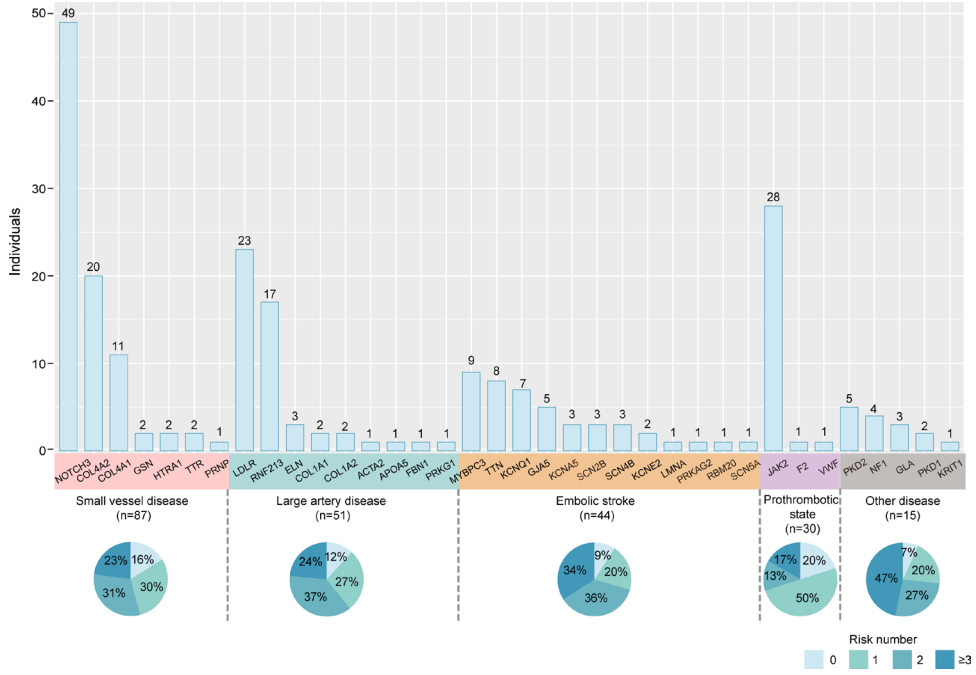


Figure 4 Characteristics of 227 individuals diagnosed with Mendelian causes of stroke. The bars represent the number of individuals diagnosed with Mendelian causes of stroke identified for each gene, which are coloured according to the classification of stroke aetiology. Three individuals with two monogenic diseases were ruled out. The percentages in the boxes indicate the distribution of risk factors, including hypertension, hyperlipidaemia, diabetes, coronary heart disease, atrial fibrillation, smoking history, drinking history and body mass index ≥25.

Only 17 individuals of the 230 (7.4%, 17/230) had been diagnosed with an identified aetiology in EHR prior to genetic testing (online supplemental eTable 7), including eight cases of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with *NOTCH3* mutation, six cases of idiopathic thrombocytopenia with V617F mutation in the *JAK2* gene and three cases of Moyamoya disease with a *RNF213* R4810K mutation. The common risk factors for IS, such as hypertension, hyperlipidaemia, diabetes, coronary heart disease, atrial fibrillation, smoking history, drinking history and BMI ≥25 kg/m², were carried out by 86.5% (199/230) of individuals. Of them, 30% (69/230) of all patients with monogenic causes carried one risk factor, 30.4% (70/230) carried two risk factors and 26.1% (60/230) carried three or more risk factors (figure 4). Only 10.87% of individuals among these patients with Mendelian causes of stroke had a family history of stroke. According to the multivariable logistic regression model, after eliminating the confounding effect of common risk factors, there were no relationships between age (OR=0.99, 95% CI: 0.98 to 1.01, p=0.23) or family history (OR=0.66, 95% CI: 0.36 to 1.11, p=0.14) and the incidence of first symptomatic monogenic stroke in patients.

DISCUSSION

In this study, at least 2.2% of our cohort had definite or possible clinical evidence to support genetically diagnosed Mendelian causes of stroke/TIA, which is similar to other studies on complex diseases. For example, it was found that the diagnosis rate of monogenic disease was 1.7% in a cardiovascular disease cohort.[14]

Several features among the individuals identified as having a Mendelian cause of stroke in our cohort presented complexity and obstacles for a correct diagnosis of monogenic stroke, including late-onset symptoms of stroke, coexisting common risk factors and a low prevalence of a positive family history. Most of the monogenic stroke individuals with a first symptomatic stroke in our cohort were relatively old with a mean age of 61, and most of the patients carried common risk factors similar to other stroke patients with non-Mendelian causes in our adult IS cohort. However, similar exceptions were already known for some monogenic diseases. For example, patients with CADASIL can have stroke events that occur after the age of 60 and can carry common cerebrovascular risk factors.[15–18] Hypertension is present in 20% of patients with CADASIL, and hyperlipemia and smoking are present in 50% of patients with CADASIL.[19] More than 90% of the patients with *COL4A1/COL4A2* mutations in our cohort did not present with haemorrhage, either now or previously, or had only microbleeds with other characteristics of cerebral SVD, a result that somewhat contradicts prior literature indicating that *COL4A1/COL4A2* mutations are a cause of haemorrhagic stroke.[11 20] Similarly, among 16 cases of Moyamoya disease caused by *RNF213* mutation, only three cases were clinically diagnosed as Moyamoya disease in EHR before genetic testing while the remaining cases were diagnosed as vascular stenosis,

either owing to coexisting common risk factors or only unilateral internal carotid artery involvement. However, a similar complex presentation has been reported in *COL4A1/COL4A2* microangiopathy,[21–24] Moyamoya disease[25] and CADASIL,[17 26–28] whose patients can present with mild signs or symptoms, or even have a negative history of stroke and family history.

The *NOTCH3* gene contains 33 exons encoding the Notch3 protein, which includes an extracellular domain that consists of 34 epidermal growth factor-like repeats (EGFr).[29] Most P/LP variants (89.29%, 50/56) of the *NOTCH3* gene in our cohort were located in exon 6 to exon 22, encoding EGFr 7–34, which results in milder phenotypes than mutations located in the region encoding EGFr 1–6.[29–32] Another example can be found in individuals with a V617F mutation in the *JAK2* gene, leading to essential thrombocythemia or polycythemia vera. These patients present with only an increased platelet count, which is easily confused with the increased platelet count secondary to stroke complications such as infection or anaemia. Additionally, aspirin is effective for the vascular symptoms caused by the V617F mutation in *JAK2*, which would also mask the clinical signs.[33 34] Diagnosis will be missed if the mutations lead to the occurrence of risk factors that then cause IS. For example, heterozygous mutations in *LDLR* result in familial hypercholesterolemia that can then cause IS.[35–37] Clinicians often ignore the differential diagnosis of hypercholesterolemia and do not differentiate between monogenetic and complex aetiologies.

The genetic screening for Mendelian cause of stroke is critical for correct aetiological diagnosis in adult stroke patients. Almost all causes of stroke are included, such as large-artery atherosclerotic, cerebral SVD, cardioembolic, as well as coagulation disturbances, vascular malformations, metabolic disorders and large-artery non-atherosclerotic, so the panel is suitable for molecular diagnosis of all-cause IS. However, due to the significantly higher proportion of Mendelian stroke detected in patients with undetermined aetiology compared with other CCS types of stroke, and the highest genotype–phenotype matching among Mendelian stroke patients with coagulation abnormalities and cerebral SVD types, these patients are the most beneficial population in the clinical setting.

This study had some limitations. We determined whether an individual with P/LP variants predicted to be at risk for monogenic disease had corresponding phenotypes by reviewing EHR data; however, not every phenotype would have been available in the EHR system from our registry, so most cases with systemic monogenic diseases, such as congenital heart diseases and pseudoxanthoma elasticum, were classified as having insufficient clinical information. We also used an automated interpretation tool (InterVar), based on the ACMG/AMP guidelines, to evaluate the pathogenicity of the variants by updating the gene list. Our pipeline only used 18 categories of ACMG/AMP criteria to classify the variants, while additional information such as familial segregation, family history and de novo status could not be obtained in this cohort for further analysis. Some variants of unknown significance (VUS) may therefore be pathogenic with inclusion of those additional criteria and may have been missed. In addition, some of the variants currently classified in ClinVar as VUS may actually be P/LP in future acquired data. Thus, the prevalence of monogenic stroke in this cohort may have been underestimated. Furthermore, copy number variants were not analysed. In addition, our current study used targeted NGS and would have missed genes associated with other Mendelian causes. For this reason, we performed further whole genome sequencing on these samples and the data analysis is currently ongoing.[38] We will explore the feasibility of following up with those monogenic stroke patients with insufficient or inconclusive clinical evidence, to either confirm or deny the genetic diagnosis of Mendelian causes through long-term medical observation.

In summary, 7.6% individuals carried at least one P/LP variant associated with monogenic disease with stroke. Moreover, 2.2% patients in the CNSR-III cohort had clinical evidence from EHR data to support their diagnosis of monogenic causes. The Mendelian causes of stroke are neglected in adult IS cohorts, mainly because of the late onset of symptomatic stroke, combined common vascular risks and no prominent family history.

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Contributors YW take responsibility for the overall content as the guarantor. YW accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. YW and WL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: YW, WL, HL Acquisition, analysis, or interpretation of data: WL, HL,CL, JZ, ZX, HG, QX, AW, ZL, MW Drafting of the manuscript: YW, WL, HL, CL, JZ, ZX,HX, BM Critical revision of the manuscript for important intellectual content: YW, WL, HL, CL, JZ, HX, BM Statistical analysis: JZ, HX, ZX, QX, MW Administrative, technical, or material support: YJ, HG, AW, XM, JL, JJ, ZL, WZ, Beijing Genomics institution Supervision: WL, HL, CL, JZ.

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Competing interests None declared.

Patient consent for publication Not applicable.

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all other research centres in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data that support the findings of this study are available from the corresponding author, YW, upon reasonable request.

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Supplemental Files

eMethods

NGS data analysis

Updating PVS1, PS1, PP2, and BP1 lists for InterVar

Since the publishing of InterVar software in 2017, a great deal of newly-found pathogenic mutations has been discovered. To incorporate these progresses, we updated the PVS1, PS1, PP2, and BP1 lists of InterVar using recently released ClinVar database (ClinVar 20200622 version). All of the updating process was conducted using the same pipeline of InterVar or under the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[1,2]

PVS1 gene list

Genes in PVS1 list harbored loss-of-function (LOF) mutations that were reported to be pathogenic. First, we extracted all of the pathogenic/likely pathogenic (PLP) and LOF mutations from ClinVar. The genetic variants in ClinVar 20200622 version were regarded to be PLP and LOF mutations if: 1) the variant was recorded by MedGen; 2) its minor allele frequency (MAF) < 5%; 3) it was not predicted or reported to be "benign", "likely benign", or "uncertain significance" in ClinVar; 4) the record of the mutation in ClinVar should not contain the string "conflicting"; 5) the mutations resulted in stopgain, stoploss, frameshift, destruction of canonical ±1 or 2 splice sites (dbscSNV≥0.6), loss of initiation codon, or deletion of single or multiple exons. The mutations that fulfill all of the above 5 criteria were regarded to be PLP and LOF mutations. We found 3312 genes that harbored these mutations, and these genes were included in updated PVS1 gene list.

Second, another part of PVS1 gene list were obtained by retrieving the LOF-mutation-intolerant genes from genomAD. A total of 3075 Genes with pLI ≥0.9 were identified and included in PVS1 gene list.

After integration and removing duplications for the 3312 and 3075 genes, a total of 5646 genes were resolved. This list was regarded to be the updated PVS1 gene list, and 150 out of the 181 genes were present in this list.

PS1 mutation list

PS1 list contained nonsynonymous mutations that were reported to be pathogenic. Therefore, we first extracted all of the PLP mutations from ClinVar. The genetic variants in ClinVar 20200622 version were regarded to be nonsynonymous PLP mutations if: 1) the variant was recorded by MedGen; 2) its minor allele frequency (MAF) < 5%; 3) it was not predicted or reported to be "benign", "likely benign", or "uncertain significance" in ClinVar; 4) the record of the mutation in ClinVar should not contain the string "conflicting"; 5) the mutations resulted in nonsynonymous mutation. We found 35767 genetic variants that fulfill all of the above 5 criteria, and they were allocated in the updated PS1 list.

PP2 gene list

In a certain gene, if >80% of the pathogenic variants were missense while <10% of missense variants were benign in ClinVar, the gene would be assigned to the PP2 gene list. Accordingly, the PP2 gene list was obtained through 2 steps. First, for each gene that was recorded by ClinVar, we counted the number of PLP variants and calculated the percentage of nonsynonymous mutations among the PLP variants. The genetic variants in ClinVar 20200622 version were regarded to be PLP mutations if: 1) the variant was recorded by MedGen; 2) its minor allele frequency (MAF) < 5%; 3) it was not predicted or reported to be "benign", "likely benign", or "uncertain significance" in ClinVar; 4) the record of the mutation in ClinVar should not contain the string "conflicting". The mutations that fulfill all of the above 4 criteria were regarded to be PLP mutations. Additionally, nonsynonymous PLP mutations should further fulfill a

5th criterion that the PLP variants would result in nonsynonymous mutations. Then the percentage of pathogenic variants that were missense was obtained for each gene.

In the second step, we counted the number of nonsynonymou variants and calculated the percentage of benign/likely benign (BLB) mutations in each gene. Genetic variants were applied in this calculation if: 1) the variant was recorded by MedGen; 2) its minor allele frequency (MAF) < 5%; 3) the mutations were nonsynonymous substitutions. For BLB variants, another 2 criteria should be fulfilled that: 4) the record of the mutation in ClinVar should not contain the string "conflicting"; 5) it was not predicted or reported to be "pathogenic", "likely pathogenic", or "uncertain significance" in ClinVar record. Then the percentage of nonsynonymous variants that were BLB was obtained for each gene.

Afterwards, based on the above 2 percentages, we 490 genes that fulfilled the criteria of PP2 genes, these genes made up the updated PP2 gene list. A total of 22 genes in the 181 candidate genes were present in the updated PP2 gene list.

BP1 gene list

In a certain gene, if >80% of the pathogenic variants were truncating mutation, the gene would be contained in BP1 gene list. Therefore, for each gene that was recorded by ClinVar, we counted the number of PLP variants and calculated the percentage of truncating mutations. The genetic variants in ClinVar 20200622 version were regarded to be PLP mutations if: 1) the variant was recorded by MedGen; 2) its minor allele frequency (MAF) < 5%; 3) it was not predicted or reported to be "benign", "likely benign", or "uncertain significance" in ClinVar; 4) the record of the mutation in ClinVar should not contain the string "conflicting". The mutations that fulfill all of the above 4 criteria were regarded to be PLP mutations.

Afterwards, we calculated the percentage of PLP mutations that resulted in stopgain, stoploss, frameshift, destruction of canonical ±1 or 2 splice sites (dbscSNV≥0.6), loss of initiation codon, or deletion of single or multiple exons, and the genes with this percentage>80% was rated as BP1 genes. In summary, we found 604 BP1 genes and 9 out of the 181 genes were contained in the updated BP1 gene list.

Phenotyping:

All individuals that harbored pathogenic/likely pathogenic variants that had an expected phenotype based off of the inheritance pattern of the disease, and were not given a clinical diagnosis were classified into the following four categories (Unlikely, Possible, Probable, Definite) based off of the criteria listed below after Electronic Health Record (EHR) review.

Dilated Cardiomyopathy (DCM):

Dilated cardiomyopathy is clinically diagnosed based on echocardiography. Its diagnostic criteria are as follows:[3] 1. The end-diastolic inner diameter of the left ventricle is greater than 5.5 cm in men and 5.0 cm in women. 2. The ejection fraction is less than 45%, or the left ventricular shortening rate is less than 25%. It is more scientific that the end-diastolic inner diameter of the left ventricle per square meter is greater than 2.7cm. Before diagnosing dilated cardiomyopathy, it is necessary to rule out heart enlargement caused by hypertension, coronary heart disease (CAD), valvular heart disease, congenital heart disease, alcoholic cardiomyopathy, etc.

Definite: N/A

Possible: The end-diastolic inner diameter of the left ventricle, greater than 5.5cm in men and 5.0cm in women

Or the ejection fraction is less than 45%;

Or the left ventricular shortening rate is less than 25%;

Or have heart failure in past history;

Or sudden cardiac death in family history;

Unlikely: Normal cardiac imaging (echocardiography or cardiac MRI) with EF>50% OR cardiomyopathy (EF<45%) with significant CAD*

*Significant CAD was defined as ≥75% stenosis in the left main, proximal left anterior descending coronary arteries, or ≥2 epicardial coronary arteries or history of myocardial infarction

Hypertrophic cardiomyopathy (HCM)

HCM is typically defined by the presence of unexplained left ventricular hypertrophy (LVH) with a maximum wall thickness ≥15 mm in adults or a z-score >3 in children.[4-6] If there is a family history of HCM, or if genetic testing confirms that a relative has inherited the family's pathogenic sarcomere variant, a maximum LV wall thickness ≥13 mm supports diagnosis. Such LVH occurs in a non-dilated ventricle in the absence of other cardiac or systemic disease capable of producing the observed magnitude of increased LV wall thickness, such as pressure overload or storage/infiltrative disorders.

- Definite: Septal wall thickness ≥ 1.5 cm on echocardiography with no hypertension, coronary heart disease (CAD), valvular heart disease, congenital heart disease, alcoholic cardiomyopathy.
- Possible: Septal wall thickness ≥ 1.3 cm on echocardiography or <1.3 cm and EF<45% in the absence of an ischemic etiology*
- Unlikely: Septal wall thickness < 1.3 cm on echocardiography and EF>50%

An additional requirement for classification was the presence of at least one echocardiography study

*Ischemic etiology was defined as ≥75% stenosis in the left main OR proximal left anterior descending coronary arteries OR ≥2 epicardial coronary arteries or a history of myocardial infarction

Fabry Disease

Suggestive Findings

Fabry disease should be suspected in males and females with the following clinical features:

Periodic crises of severe pain in the extremities (acroparesthesia)

Vascular cutaneous lesions (angiokeratomas)

Sweating abnormalities (anhidrosis, hypohidrosis, and rarely hyperhidrosis)

Characteristic corneal and lenticular opacities

Unexplained stroke

Unexplained left ventricular hypertrophy

Renal insufficiency of unknown etiology including unexplained proteinuria or microalbuminuria

The diagnosis of Fabry disease is established in **a male proband** by:

Identification of deficient alpha-galactosidase A (α-Gal A) enzyme activity in plasma, isolated leukocytes, and/or cultured cells. The test is a fluorometric assay and uses the substrate 4-methylumbelliferyl-α-D-galactopyranoside.

Males with classic Fabry disease have <1% α-Gal A enzyme activity.

Males with atypical Fabry disease have residual enzyme activity >1% of normal.

Identification of a hemizygous pathogenic variant in GLA by molecular genetic testing

Female proband. The diagnosis of Fabry disease is established in a female proband by identification of

a heterozygous pathogenic variant in GLA by molecular genetic testing.

- Definite: N/A
- Possible: unexplained left ventricular hypertrophy with a hemizygous pathogenic variant in GLA in Males or a heterozygous pathogenic variant in females.
- Unlikely: No above clinical features with a pathogenic variant in GLA.

Unexplained left ventricular hypertrophy

Familial Transthyretin (*TTR*) Amyloidosis:

Because there is no formal diagnostic criteria for Familial *TTR* amyloidosis, individuals were classified based on the number of neurologic and/or cardiac signs/symptoms that were documented in the EHR of the respective individual. Individuals that harbored pathogenic/likely pathogenic mutations associated with Familial *TTR* amyloidosis were classified into the four categories based off of the following criteria:[7]

- Definite: N/A
- Probable: One Cardiac and one Neurologic Manifestation
- Possible: One Cardiac or one Neurologic Manifestation
- Unlikely: Normal Cardiac Imaging and no documented Neurologic signs/symptoms

A cardiac manifestation is defined as documentation of at least one of the following:

- Left ventricular hypertrophy in the absence of an alternative cause
- Heart Failure with preserved ejection fraction
- Restrictive cardiomyopathy
- Conduction disease: Atrioventricular block on electrocardiogram (EKG)
- Presence of a pericardial effusion on echocardiography in the absence of an alternative cause

A neurologic manifestation is defined as documentation of at least one of the following:

- Sensory disturbances of unknown etiology
- Neuropathic pain
- Autonomic disturbances

Atrial fibrillation (AF)

Body surface electrocardiogram (ECG) or 24-hour Holter electrocardiogram shows irregular shape and size of f wave instead of P wave, frequency 350-600 beats/min, QRS complex form is standard form or with ventricular differential conduction and wide deformity, ventricular rate is absolute irregular

- Definite: ECG or 24 Holter showed AF signs and had AF history or AD family history.
- Possible: ECG or 24 Holter showed AF signs or other type of arrhythmia
- Unlikely: ECG or 24 Holter showed normal and no arrhythmia history.

Familial Hypercholesterolemia:

Individuals that harbored a pathogenic/likely pathogenic variant associated with familial hypercholesterolemia who were heterozygous for mutations in the LDLR gene were categorized according to the Simon-Broome criteria as follows:

- Definite: Serum LDL-C*≥190 mg/dL or Total Cholesterol (TC)*≥280 mg/dL
- Possible: After the LDL-C and TC values were corrected, Serum LDL-C*≥190 mg/dL or Total Cholesterol (TC)*≥280 mg/dL.
- Unlikely: Serum LDL-C*<190 mg/dL or Total Cholesterol*<280 mg/dL

*If the patient was on a statin, the LDL-C and TC values were corrected using LDL/0.7 and TC/0.8, respectively.

Marfan Syndrome:

Individuals that harbored pathogenic/likely pathogenic mutations associated with Marfan Syndrome were classified into the four categories based off of the Revised Ghent Nosology:[8]

- Definite: N/A
- Possible: Systemic Score between 4-6 and a causal *FBN1* mutation
- Unlikely: Normal Imaging with no mention of Ectopia Lentis or Systemic Score signs/symptoms

*Aortic Criterion: History of Aortic Dissection or an Aorta Z-score≥2. Z-scores calculated using the patient's aortic diameter, as measured by echocardiography, using the following Z-score calculator: https://www.marfan.org/dx/zscore.

Supravalvular Aortic Stenosis (SVAS):

Individuals that harbored pathogenic/likely pathogenic variants associated with restrictive cardiomyopathy were classified into the four categories as follows:

- Definite: After aortic valve prosthetic valve replacement surgery
- Possible: Moderate Aortic Stenosis gradient with Normal Aortic Valve on echocardiography
- Unlikely: Normal Imaging

Thoracic aortic aneurysms and aortic dissections (TAAD):

A thoracic aortic aneurysm is a permanent, localized dilatation of the thoracic aorta. Thoracic aortic aneurysms may involve different thoracic aortic segments. To evaluate for a thoracic aortic aneurysm, the aortic diameter is measured (perpendicular to the axis of blood flow) by echocardiography, CT, or MRI at reproducible anatomic locations.

- Definite: After aortic valve prosthetic valve replacement surgery,
- Possible: Moderate Aortic Stenosis gradient with Normal Aortic Valve on echocardiography
- Unlikely: Normal Imaging

Neurofibromatosis 1(NF1)

Suggestive Findings

Neurofibromatosis 1 (NF1) should be suspected in individuals who have any of the following findings:

• Six or more café au lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals

• Two or more neurofibromas of any type or one plexiform neurofibroma

• Freckling in the axillary or inguinal regions

• Optic glioma

• Two or more Lisch nodules (iris hamartomas)

• A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis

• A first-degree relative (parent, sib, or offspring) with NF1 as defined by the above criteria

Establishing the Diagnosis

The diagnosis of NF1 is established in a proband who meets the diagnostic criteria for neurofibromatosis 1 (NF1) developed by the National Institutes of Health [NIH 1988]. The NIH diagnostic criteria for NF1 are met in an individual who has two or more of the features listed in Suggestive Findings.[9]

- Definite: NA;
- Possible: Individuals with a pathogenic variants in the NF1 gene;
- Unlikely: NA

Polycythemia vera

Major criteria

1. Hemoglobin >16.5 g/dL in men or > 16 g/dL in women;or hematocrit >49% in men or > 48% in women or increased red blood cell mass
2. Presence of JAK2 mutation

Minor criterion

1.Bone marrow trilineage proliferation

2.Subnormal serum erythropoietin level

3. EEC growth

Bone marrow biopsy might not be needed in the presence of hemoglobin >18.5 g/dL (hematocrit 55.5%) in men or > 16.5 g/dL (hematocrit 49.5%) in women.

- Definite: both two major criteria + one minor criterion or the first major + two minor criteria;
- Possible: two major criteria;
- Unlikely: Nomal hemoglobin level

Essential thrombocythemia (ET)

Major criteria[10]

1. Platelets ≥450 x 10^9 /L
2. Bone marrow megakaryocyte proliferation and loose clusters
3. Not meeting WHO criteria for other myeloid neoplasms
4. JAK2/CALR/MPL mutated

- Definite: all four major criteria
- Possible: two major criteria;
- Unlikely: Nomal Platelets level

Polycystic kidney disease (PKD1 and PKD2)[11]

Definite:

The diagnosis of ADPKD is established in a proband with ANY of the following:

Age-specific ultrasound criteria and an affected first-degree relative with ADPKD

Age-specific MRI criteria and an affected first-degree relative with ADPKD

Identification of a heterozygous pathogenic variant in one of the genes listed in Table 3

Ultrasound Criteria for Diagnosis of ADPKD in Individuals at 50% Risk for ADPKD Based on Family History

Age	PKD1	PKD2	Unknown ADPKD Genotype
15-30 yrs	≥3 cysts [1] PPV = 100% SEN = 94.3%	≥3 cysts [1] PPV = 100% SEN = 69.5%	≥3 cysts [1] PPV = 100% SEN = 81.7%
30-39 yrs	≥3 cysts [1] PPV = 100% SEN = 96.6%	≥3 cysts [1] PPV = 100% SEN = 94.9%	≥3 cysts [1] PPV = 100% SEN = 95.5%
40-59 yrs	≥2 cysts in each kidney PPV = 100% SEN = 92.6%	≥2 cysts in each kidney PPV = 100% SEN = 88.8%	≥2 cysts in each kidney PPV = 100% SEN = 90%

Possible:

Multiple bilateral renal cysts and the absence of manifestations suggestive of a different renal cystic disease

Cysts in other organs, especially the liver, but also seminal vesicles, pancreas, and arachnoid membrane

Enlargement of the kidneys or liver on physical examination

Hypertension in an individual younger than age 35 years

An intracranial aneurysm

A family history of ADPKD

Unlikely: NA

Cerebral cavernous malformations-1(KRIT1)

- Intracranial thin-walled sinusoidal vessel (cavernous) malformations
- Seizures
- Headache
- Intracranial hemorrhage
- Focal neurologic deficits
- Intracranial calcifications
- Angiographically 'silent'
- MRI is best imaging modality to detect lesions

  - Definite: MRI showed intracranial thin-walled sinusoidal vessel (cavernous)
  - Possible: NA
  - Unlikely: Normal Imaging

Ehlers-Danlos syndrome (EDS)

Individuals that harbored pathogenic/likely pathogenic variants associated with Ehler-Danlos Syndrome (COL5A1,COL5A2, COL1A1, or COL1A2) were classified into the three categories as follows based off of the 2017 international classification of the Ehlers–Danlos syndromes[12]

- Definite: NA
- Possible: a proband with the minimal clinical diagnostic criteria (intracranial aneurysms and arteriovenous fistulae, may occur in the rare individual) and identification of a heterozygous pathogenic variant in COL1A1 or COL1A2
- Unlikely: None of the above clinical manifestations

Cerebral amyloid angiopathy, GSN-related

- Cranial neuropathy, esp. facial paresis
- Bulbar palsy
- Peripheral polyneuropathy, esp. vibration and touch loss
- Amyloid cardiomyopathy
- Renal failure
- Cutis laxa
-Corneal lattice dystrophy

- Definite: NA
- Possible: Diagnosed with CAA by imaging
- Unlikely: None of the above clinical manifestations

Thrombophilia due to thrombin defect duo to F2 defect

- Definite: NA
- Possible: Thrombosis, recurrent, cognitive function loss
- Unlikely: None of the above clinical manifestations

Hyperchylomicronemia, late-onset APOA5

- Definite: NA
- Possible: Decreased LDL and HDL, increased TG, stroke
- Unlikely: None of the above clinical manifestations

HTRA1-autosomal dominant disease

HTRA1 heterozygous mutations may lead to a late-onset syndrome characterized by gait disturbances, mood depression, cognitive impairment, stroke, migraine as well as WMHs on MRI.

- Definite: NA
- Possible: HTRA1 heterozygous mutations and a late-onset stroke as well as WMHs
- Unlikely: Just a HTRA1 heterozygous mutations with none of the above clinical manifestations.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)[13]

Clinical criteria

#1 Age at onset (clinical symptoms #2 or white matter lesions) ≤55 years old.

#2 At least two of the following clinical findings:

a. Either of subcortical dementia, long tract signs, or pseudobulbar palsy.

b. Stroke-like episode with a focal neurological deficit.

c. Mood disorder.

d. Migraine.

#3 Autosomal dominant inheritance.

#4 White matter lesions involving the anterior temporal pole by MRI or CT.

#5 Exclusion of leukodystrophy (Adrenoleukodystrophy, metachromatic leukodystrophy, etc.).

Genetic criteria

NOTCH3 mutations localize in exons 2–24 and result in the gain or loss of

cysteine residues in the epidermal growth factor-like repeat domain.
Cysteine-sparing variants should be carefully evaluated by skin biopsy and segregation studies
Pathological criteria
The pathological hallmark of CADASIL is granular osmiophilic material (GOM) detected by electron microscopy. Immunostaining of NOTCH3 extracellular domain is also useful.
Definite:
CADASIL is definite when the individual fulfills
(1) White matter lesions by MRI or CT.
(2) Clinical criteria #5
(3) Genetic criteria and/or pathological criteria
Possible:
CADASIL is possible when the individual has abnormal white matter lesions (Fazekas grade ≥2) and fulfills either of
(1) ≤55 years old
(2) At least one of the symptoms in clinical criteria #2
Unlikely:
No phenotype

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S)
Major features
#1 Vascular retinopathy typically manifesting as decreased visual acuity and/or visual field defects
#2 Focal neurologic signs can include but are not limited to hemiparesis, facial weakness, aphasia, and hemianopsia.
#3 Global brain dysfunction may manifest as progressive cognitive impairment.
#4 Brain MRI abnormalities are restricted to the white matter
(1)Focal, non-enhancing T2-hyperintense lesions scattered throughout the periventricular and deep white matter (at an age when nonspecific age-related white matter hyperintensities are infrequent)
(2)Punctate T2-hyperintense white matter lesions with nodular enhancement
(3)Hyperintense mass lesions on T2 and hypointense lesions on T1-weighted images, enhanced with gadolinium contrast, and often surrounded by extensive edema. Hemorrhages are rarely reported. Occasionally, restricted diffusion, most often centrally, is observed and is referred to as a "pseudotumor."
#5 Family history of middle-age onset of disease manifestations consistent with an autosomal dominant inheritance pattern.
#6 Exclusion of leukodystrophy AND brain tumor.
Supportive features
Calcifications on brain CT scan, typically not present in healthy controls
Nonspecific MRI white matter lesions that occur more frequently than expected given the age of the individual
Microvascular liver disease, manifested by modest elevations of alkaline phosphatase and gamma-glutamyltransferase
Microvascular kidney disease, typically manifested by a mild-to-moderate increase in serum creatinine or by proteinuria

Pathology

Histologic abnormalities have been demonstrated in all organs involved in RVCL-S, including the following.

(1)Retina: scattered microinfarcts, thickened hyalinized retinal arterial walls, focal areas of disruption of the ganglion cell layer and inner nuclear layer.

(2)Brain: Multiple – often confluent – foci of ischemic necrosis of white matter, Vasculopathy (vessel wall thickening and luminal stenosis; telangiectasias), a modest chronic inflammatory cell infiltrate in some individuals, focal calcifications and reactive astrocytosis, myelin loss.

(3)Kidney: renal arteriolosclerosis, focal or diffuse glomerulosclerosis

(4)Liver:Nodular regenerative hyperplasia, micro- and macrovesicular steatosis, periportal inflammation, bridging and portal fibrosis.

Definite:

RVCLS is definite when the individual fulfills

(1) fulfills either of Major features

(2) Clinical criteria #6

(3) Genetic criteria and/or pathological criteria

Possible:

RVSLS is possible when the individual has either of Major features or fulfills more than three of Supportive features

Unlikely:

No phenotype

<u>Brain small vessel disease with or without ocular anomalies (COL4A1)</u>

Major features

(1)Porencephaly

(2)Brain small-vessel disease with or without ocular anomalies

(3)HANAC (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps) syndrome

(4)Tortuosity of retinal arteries

(5)Nonsyndromic autosomal dominant congenital cataract

Definite:

(1) fulfills either of Major features and

(2) Genetic criteria and/or pathological criteria

Possbile:

Col4a1is possible when the individual has either of Major features

Unlikely:

No phenotype

<u>Brain small vessel disease 2</u> (COL4A2)

Major features

(1)Porencephaly

(2)Brain small-vessel disease with intracranial hemorrhage

(3)cerebellar and optic atrophy,cataracts, intracranial aneurysms, nephropathy, and myopathy .

Definite:

(1) fulfills either of Major features and

(2) Genetic criteria
Possbile:
Col4a1is possible when the individual has either of Major features
Unlikely:
No phenotype

MOYAMOYA (RNF213)
Diagnostic Criteria
(1) Cerebral angiography is considered essential for the diagnosis, and must show at least the follow-ing findings:
(i) Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery.
ii) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase.
(iii) Bilaterality of findings (i) and (ii).
(2)However, when magnetic resonance imaging(MRI) and magnetic resonance angiographic (MRA) findings meet all of the following criteria,cerebral angiography can be omitted. See the “Guidelines for Diagnostic Imaging by MRI and MRA”
(i) MRA shows stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery.
(ii) MRA shows abnormal vascular networks in the basal ganglia.
Note: When 2 or more visible flow voids are present in the basal ganglia on MRI, at least unilaterally, they can be deemed as representing an abnormal vascular network.
(iii) Bilaterality of findings (i) and (ii).
(3) Moyamoya disease is an illness of unknown etiology. The differential diagnosis of this disease includes similar cerebrovascular lesions associated with the following underlying diseases, which should, therefore, be excluded: (i) atherosclerosis, (ii) autoimmune disease, (iii) meningitis, (iv) brain tumors, (v) Down's syndrome, (vi) von Recklinghausen's disease, (vii) head injury, (viii) cerebrovascular lesions after head irradiation,and (ix) others.
Pathological findings that can be used as references for the diagnosis
Thickening of the arterial intima, mainly in the terminal portion of the internal carotid arteries, and narrowing or blockage of the lumen caused by this change, usually bilateral. Occasionally, lipid deposits are also present in the thickened intima.
Arteries such as the anterior, middle, and posterior cerebral arteries forming the circle of Willis occasionally show varying degrees of stenosis or occlusion associated with fibrocellular thickening of the intima,and thinning of the media.
Numerous small vascular channels (perforating and anastomotic barnches)can be seen around the circle of Willis.
Pia mater may also show reticular conglomerates of small vessels.
Diagnostic assessmemt:
Definite:
All criteria listed in(1)or(2) and in (3)should be met.
Possbile:
All criteria are fulfilled except item(1)(iii) and/or item(2)(iii) among the criteria of (1)or(2) and (3).
Unlikely:

No phenotype

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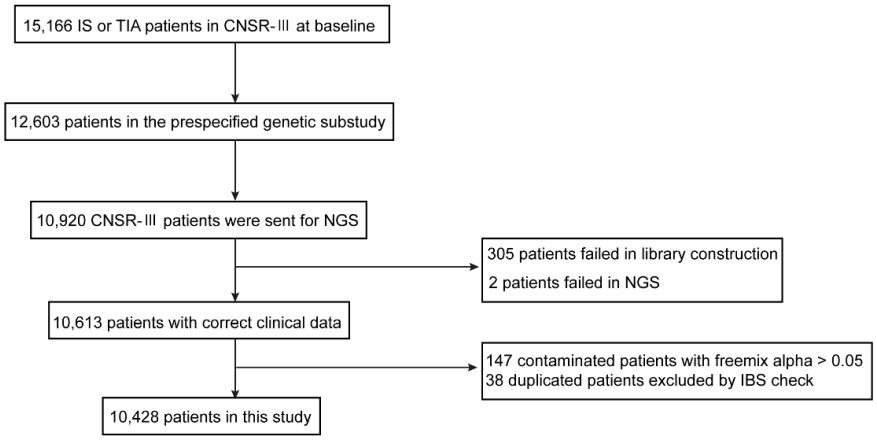

eFigure 1. Flow chart illustrating the patients screening process

eTable 1 The classification of the stroke etiology for each gene

Gene	Phenotype	Etiology of stroke
RBM20	Hereditary cardiomyopathies	Embolic stroke
ACTC1	Hereditary cardiomyopathies	Embolic stroke
LMNA	Hereditary cardiomyopathies	Embolic stroke
MYBPC3	Hereditary cardiomyopathies	Embolic stroke
ACTN2	Hereditary cardiomyopathies	Embolic stroke
PRKAG2	Hereditary cardiomyopathies	Embolic stroke
BAG3	Hereditary cardiomyopathies	Embolic stroke
DSG2	Hereditary cardiomyopathies	Embolic stroke
KCNA5	Hereditary cardiac dysrhythm	Embolic stroke
KCNJ5	Hereditary cardiac dysrhythm	Embolic stroke
SCN4B	Hereditary cardiac dysrhythm	Embolic stroke
KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke
GJA5	Hereditary cardiac dysrhythm	Embolic stroke
SCN5A	Hereditary cardiac dysrhythm	Embolic stroke
KCNJ2	Hereditary cardiac dysrhythm	Embolic stroke
KCNH2	Hereditary cardiac dysrhythm	Embolic stroke
KCNE2	Hereditary cardiac dysrhythm	Embolic stroke
SCN3B	Hereditary cardiac dysrhythm	Embolic stroke
NPPA	Hereditary cardiac dysrhythm	Embolic stroke
SCN2B	Hereditary cardiac dysrhythm	Embolic stroke
SCN1B	Hereditary cardiac dysrhythm	Embolic stroke
PRKAR1A	Carney complex, type 1	Embolic stroke
KRAS	Noonan syndrome 3	Embolic stroke
TLL1	Atrial septal defect	Embolic stroke
GJA1	Atrioventricular septal defect 3	Embolic stroke
GATA4	Tetralogy of Fallot	Embolic stroke
NKX2-5	Tetralogy of Fallot	Embolic stroke
ZFPM2	Tetralogy of Fallot	Embolic stroke
GDF1	Congenital heart defects, multiple types, 6	Embolic stroke
TTN	Hereditary cardiomyopathies	Embolic stroke
MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease
MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease
PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease
MYH11	Aortic aneurysm, familial thoracic 4	Large artery disease

eTable 1 Continued

Gene	Phenotype	Etiology of stroke
ACTA2	Aortic aneurysm, familial thoracic 6	Large artery disease
FBN1	Marfan syndrome	Large artery disease
ELN	Supravalvar aortic stenosis	Large artery disease
COL5A1	Ehlers-Danlos syndrome, classic type	Large artery disease
COL1A1	Combined osteogenesis imperfecta and Ehlers-Danlos syndrome 1	Large artery disease
COL1A2	Combined osteogenesis imperfecta and Ehlers-Danlos syndrome 2	Large artery disease
CETP	Hyperalphalipoproteinemia	Large artery disease
RNF213	Moyamoya disease	Large artery disease
LDLR	Hypercholesterolemia, familial, 1	Large artery disease
APOA5	Hyperchylomicronemia, late-onset	Large artery disease
F2	Thrombophilia due to thrombin defect	Prothrombotic state
JAK2	Thrombocythemia 3	Prothrombotic state
VWF	von Willebrand disease, type 1	Prothrombotic state
GP1BA	von Willebrand disease, platelet-type	Prothrombotic state
ETV6	Thrombocytopenia 5	Prothrombotic state
SERPIND1	Thrombophilia due to heparin cofactor II deficiency	Prothrombotic state
SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state
PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state
PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state
STIM1	Stormorken syndrome	Prothrombotic state
NOTCH3	CADASIL	Small vessel disease
HTRA1	HTRA1-autosomal dominant disease	Small vessel disease
COL4A2	Brain small vessel disease 2	Small vessel disease
COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease
TREX1	Vasculopathy, retinal, with cerebral leukoencephalopathy and systemic manifestations/RVCL-S	Small vessel disease
GSN	Amyloidosis, Finnish type	Small vessel disease
TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease
PRNP	Cerebral amyloid angiopathy, PRNP-related	Small vessel disease
PSEN1	Alzheimer's disease	Small vessel disease
GLA	Fabry Disease	Other disease (small and large artery disease)
NF1	Neurofibromatosis 1	Other disease (small and large artery disease)
ABCC6	Pseudoxanthoma elasticum	Other disease

eTable 1 Continued

Gene	Phenotype	Etiology of stroke
		(small and large artery disease)
PKD1	Polycystic kidney disease 1	Other disease (Cerebrovascular malformations)
PKD2	Polycystic kidney disease 2	Other disease (Cerebrovascular malformations)
KRIT1	Cerebral cavernous malformations-1	Other disease (Cerebrovascular malformations)
ACVRL1	Telangiectasia, hereditary hemorrhagic, type 2	Other disease (Cerebrovascular malformations)
ENG	Telangiectasia, hereditary hemorrhagic, type 1	Other disease (Cerebrovascular malformations)
FLCN	Birt-Hogg-Dube syndrome	Other disease (Unknown mechanism)
DYRK1B	Abdominal obesity-metabolic syndrome 3	Other disease (Unknown mechanism)
PDE4D	Acrodysostosis 2, with or without hormone resistance	Other disease (Unknown mechanism)
APOA1	Amyloidosis, 3 or more types	Other disease (Unknown mechanism)
VHL	Pheochromocytoma	Other disease (Unknown mechanism)
RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease (Unknown mechanism)
BMPR2	Pulmonary hypertension, primary	Other disease (Unknown mechanism)
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	Other disease (Unknown mechanism)
KIF1B	Pheochromocytoma	Other disease (Unknown mechanism)
TGIF1	Holoprosencephaly 4	Other disease (Unknown mechanism)

eTable 2 List of the 181 genes associated with Mendelian-stroke in custom-designed panel

Gene	Location	OMIM ID	Inheri-tance	Associated Mendelian Disorder
ABCA1	9q31.1	600046	AR	Tangier disease
ABCC6	16p13.11	603234	AR	Arterial calcification, generalized, of infancy, 2; Pseudoxanthoma elasticum
ACTA2	10q23.31	102620	AD	Moyamoya disease 5; Aortic aneurysm, familial thoracic 6; Multisystemic smooth muscle dysfunction syndrome
ACTC1	15q14	102540	AD	Atrial septal defect 5; Cardiomyopathy, dilated, 1R; Cardiomyopathy, hypertrophic, 11; Left ventricular noncompaction 4
ACTN2	1q43	102573	AD	Cardiomyopathy, dilated, 1AA, with or without LVNC; Cardiomyopathy, hypertrophic, 23, with or without LVNC; Myopathy, congenital with structured cores and Z-line abnormalities; Myopathy, distal, 6, adult onset
ACVRL1	12q13.13	601284	AD	Telangiectasia, hereditary hemorrhagic, type 2
ANK2	4q25-q26	106410	AD	Cardiac arrhythmia, ankyrin-B-related; Long QT syndrome 4
APOA1	11q23.3	107680	AD	Amyloidosis, 3 or more types
APOA5	11q23.3	606368	AD	Hyperchylomicronemia, late-onset
APP	21q21.3	104760	AD	Alzheimer disease 1, familial; Cerebral amyloid angiopathy, Dutch, Italian, Iowa, Flemish, Arctic variants
ATP7A	Xq21.1	300011	XLR	Menkes disease; Occipital horn syndrome; Spinal muscular atrophy, distal, X-linked 3
B4GALT1	9p21.1	137060	AR	Congenital disorder of glycosylation, type IId
BAG3	10q26.11	603883	AD	Cardiomyopathy, dilated, 1HH
BMPR2	2q33.1-q33.2	600799	AD	Pulmonary hypertension, familial primary, 1, with or without HHT; Pulmonary hypertension, primary, fenfluramine or dexfenfluramine-associated; Pulmonary venoocclusive disease 1
BRCC3	Xq28	300617	XLR	Moyamoya 4 X-link
CBL	11q23.3	165360	AD	juvenile myelomonocytic leukemia and Noonan syndrome-like disorder
CBS	21q22.3	613381	AR	Homocystinuria, B6-responsive and nonresponsive types; Thrombosis, hyperhomocysteinemic
CCER2	19q13.2	617634	AD	Moyamoya disease, susceptibility to
CCM2	7p13	607929	AD	Cerebral cavernous malformations 2
CDKN1C	11p15.4	600856	AD	Beckwith-Wiedemann syndrome; IMAGE syndrome
CECR1/ ADA2	22q11.1	615688	AR	Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome
CEP19	3q29	615586	AR	Morbid Obesity And Spermatogenic Failure
CETP	16q13	118470	AD	Hyperalphalipoproteinemia; High density lipoprotein cholesterol level QTL 10
COL1A1	17q21.33	120150	AD	Combined osteogenesis imperfecta and Ehlers-Danlos syndrome 1

eTable2 Continued

Gene	Location	OMIM ID	Inheri-tance	Associated Mendelian Disorder
COL1A2	7q21.3	120160	AD	Combined osteogenesis imperfecta and Ehlers-Danlos syndrome 2
COL3A1	2q32.2	120180	AD, AR	Ehlers-Danlos syndrome, vascular type; Polymicrogyria with or without vascular-type EDS
COL4A1	13q34	120130	AD	Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps; Brain small vessel disease with or without ocular anomalies; Anterior segment dysgenesis with cerebral involvement; Porencephaly 1; Retinal artery tortuosity
COL4A2	13q34	120090	AD	Brain small vessel disease 2
COL5A1	9q34.3	120215	AD	Ehlers-Danlos syndrome, classic type, 1; Fibromuscular dysplasia, multifocal
CPT2	1p32.3	600650	AR	CPT II deficiency
CST3	20p11.21	604312	AD	Cerebral amyloid angiopathy
CTC1	17p13.1	613129	AR	Cerebroretinal Microangiopathy With Calcifications And Cysts
CTSA	20q13.12	613111	AR	Galactosialidosis
CYP27A1	2q35	606530	AR	Cerebrotendinous xanthomatosis
DES	2q35	125660	AD	Cardiomyopathy, dilated, 1I;Scapuloperoneal syndrome, neurogenic, Kaeser type
DOCK8	9p24.3	611432	AR	Hyper-IgE recurrent infection syndrome, autosomal recessive
DSG2	18q12.1	125671	AD	Arrhythmogenic right ventricular dysplasia, familial, 10
DYRK1B	19q13.2	604556	AD	Abdominal obesity-metabolic syndrome 3
ELN	7q11.23	130160	AD	Cutis laxa, autosomal dominant; Supravalvar aortic stenosis
ENG	9q34.11	131195	AD	Hereditary hemorrhagic telangiectasia, type 1
ENPP1	6q23.2	173335	AD, AR	Arterial calcification, generalized, of infancy, 1;Cole disease
EPHX2	8p21.2-p21.1	132811	AD, AR	Hypercholesterolemia, familial, due to LDLR defect, modifier of
ETV6	12p13.2	600618	AD	Thrombocytopenia 5
F10	13q34	613872	AR	Factor X Deficiency
F13A1	6p25.1	134570	AR	Factor XIII Subunit A Deficiency
F13B	1q31.3	134580	AR	Factor XIII Subunit B Deficiency
F2	11p11.2	176930	AD, AR	Dysprothrombinemia; Hypoprothrombinemia; Thrombophilia due to thrombin defect;
F3	1p21.3	134390	NA	NA
F5	1q24.2	612309	AD, AR	Factor V deficiency; Thrombophilia due to activated protein C resistance; Thrombophilia, susceptibility to, due to factor V Leiden
F7	13q34	613878	AR	Factor VII Deficiency
F8	Xq28	300841	XLR	Hemophilia A
FBN1	15q21.1	134797	AD	Marfan syndrome
FGA	4q31.3	134820	AD, AR	Congenital Afibrinogenemia; Amyloidosis, familial visceral
FGB	4q31.3	134830	AR	Congenital Afibrinogenemia
FGG	4q32.1	134850	AR	Congenital Afibrinogenemia
FLCN	17p11.2	607273	AD	Birt-Hogg-Dube syndrome; Pneumothorax, primary spontaneous

eTable2 Continued

Gene	Location	OMIM ID	Inheri-tance	Associated Mendelian Disorder
GATA4	8p23.1	600576	AD	Atrial Septal Defect 2; Tetralogy of Fallot
GATA6	18q11.2	601656	AD	Atrial Septal Defect 9; Tetralogy of Fallot
GATAD1	7q21.2	614518	AR	Cardiomyopathy, dilated, 2B
GDF1	19p13.11	602880	AD	Congenital heart defects, multiple types, 6
GDF2	10q11.22	605120	AD	Hereditary hemorrhagic telangiectasia, type 5
GGCX	2p11.2	137167	AR	Vitamin K-Dependent Clotting Factors, Combined Deficiency of, 1
GJA1	6q22.31	121014	AD	Atrioventricular septal defect 3
GJA5	1q21.2	121013	AD	Atrial fibrillation, familial, 11
GLA	Xq22.1	300644	XL	Fabry disease; Fabry disease, cardiac variant
GP1BA	17p13.2	606672	AD, AR	Bernard-Soulier syndrome, type A2; von Willebrand disease, platelet-type
GP6	19q13.42	605546	AR	Bleeding Disorder Platelet Type 11
GSN	9q33.2	137350	AD	Amyloidosis, Finnish type
GUCY1A3	4q32.1	139396	AR	Moyamoya 6 with achalasia
HBB	11p15.4	141900	AR	Sickle cell anemia
HTRA1	10q26.13	602194	AD, AR	Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL); Cerebral arteriopathy, autosomal dominant, with subcortical infarcts and leukoencephalopathy, type 2
ITGA2	5q11.2	192974	NA	platelet disorder
ITGA2B	17q21.31	607759	AD, AR	Bleeding Disorder Platelet Type 16;Glanzmann thrombasthenia 1
ITGB3	17q21.32	173470	AD, AR	Bleeding disorder, platelet-type, 24, autosomal dominant; Glanzmann thrombasthenia 2
ITM2B	13q14.2	603904	AD	Retinal dystrophy with inner retinal dysfunction and ganglion cell abnormalities; Dementia
ITPKC	19q13.2	606476		Kawasaki disease, associated
JAG1	20p12.2	601920	AD	Tetralogy of Fallot; Alagille syndrome 1
JAK2	9p24.1	147796	AD	Thrombocythemia 3
KCNA5	12p13.32	176267	AD	Familial Atrial Fibrillation 7
KCNE1	21q22.12	176261	AD, AR	Long QT syndrome 5; Jervell and Lange-Nielsen syndrome 2
KCNE2	21q22.11	603796	AD	Familial Atrial Fibrillation 4; Long QT syndrome 6
KCNH2	7q36.1	152427	AD	Long QT syndrome 2; Short QT syndrome 1
KCNJ2	17q24.3	600681	AD	Familial Atrial Fibrillation 9; Short QT syndrome 3; Andersen syndrome
KCNJ5	11q24.3	600734	AD	Long QT syndrome 13; Hyperaldosteronism, familial, type III
KCNQ1	11p15.5-p15.4	607542	AD	Atrial fibrillation, familial 3; Long QT syndrome 1; Short QT syndrome 2
KIF1B	1p36.22	605995	AD	Pheochromocytoma; Charcot-Marie-Tooth disease, type 2A1
KRAS	12p12.1	190070	AD	Arteriovenous malformation of the brain, somatic; Cardiofaciocutaneous syndrome 2; Noonan syndrome 3; RAS-associated autoimmune leukoproliferative disorder
KRIT1	7q21.2	604214	AD	Cerebral cavernous malformations 1
LAMP2	Xq24	309060	XLD	Danon disease
LDLR	19p13.2	606945	AD, AR	Hypercholesterolemia, familial

eTable2 Continued

Gene	Location	OMIM ID	Inheri-tance	Associated Mendelian Disorder
LIPC	15q21.3	151670	AR	High density lipoprotein cholesterol level QTL 12; Hepatic lipase deficiency
LMBRD1	6q13	612625	AR	Methylmalonic aciduria and homocystinuria, cblF type
LMNA	1q22	150330	AD, AR	Charcot-Marie-Tooth disease, type 2B1; Cardiomyopathy, dilated, 1A
LPL	8p21.3	609708	AD, AR	Hepatic Lipase Deficiency; Combined hyperlipidemia, familial; High density lipoprotein cholesterol level QTL 11
MFAP5	12p13.31	601103	AD	Aortic aneurysm, familial thoracic 9
MMACHC	1p34.1	609831	AR	Methylmalonic aciduria and homocystinuria, cblC type
MPL	1p34.2	159530	AD, AR	Thrombocythemia 2; Thrombocytopenia, congenital amegakaryocytic
MTCP1	Xq28	300116	XLR	Moyamoya disease
MTHFR	1p36.22	607093	AR	Homocystinuria due to MTHFR deficiency
MTR	1q43	156570	AR	Homocystinuria-megaloblastic anemia, cblG complementation type
MTRR	5p15.31	602568	AR	Homocystinuria-megaloblastic anemia, cbl E type
MTTP	4q23	157147	AD, AR	Abdominal obesity-metabolic syndrome 1; Abetalipoproteinemia
MMUT	6p12.3	609058	AR	Methylmalonic aciduria, mut (0) type
MYBPC3	11p11.2	600958	AD	Cardiomyopathy, hypertrophic, 4; Cardiomyopathy, dilated, 1MM; Left ventricular noncompaction 10
MYH11	16p13.11	160745	AD	Aortic aneurysm, familial thoracic 4
MYH9	22q12.3	160775	AD	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss; Deafness, autosomal dominant 17
MYLK	3q21.1	600922	AD	Aortic aneurysm, familial thoracic 7
NF1	17q11.2	613113	AD	Neurofibromatosis, type 1
NKX2-5	5q35.1	600584	AD	Atrial Septal Defect 7, with or without AV Conduction Defects; Tetralogy of Fallot
NOS3	7q36.1	163729	AD	Alzheimer disease, type 1
NOTCH3	19p13.12	600276	AD	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL1)
NPPA	1p36.22	108780	AD	Familial Atrial Fibrillation 6
NUP155	5p13.2	606694	AR	Familial Atrial Fibrillation 15
P2RY12	3q25.1	600515	AR	Bleeding Disorder Platelet Type 8
PCNT	21q22.3	605925	AR	Microcephalic osteodysplastic primordial dwarfism, type II
PDCD10	3q26.1	609118	AD	Cerebral cavernous malformations 3
PDE4D	5q11.2-q12.1	600129	AD	Acrodysostosis 2, with or without hormone resistance
PGM1	1p31.3	171900	AR	Congenital disorder of glycosylation, type It
PHACTR1	6p24.1	608723	AD	Spontaneous Bilateral Cervical Internal Carotid and Vertebral Artery Dissection
PIGA	Xp22.2	311770	XLR	Multiple congenital anomalies-hypotonia-seizures syndrome 2
PITX2	4q25	601542	AD	Axenfeld-Rieger syndrome, type 1
PKD1	16p13.3	601313	AD	Polycystic kidney disease 1

eTable2 Continued

Gene	Location	OMIM ID	Inheri-tance	Associated Mendelian Disorder
PKD2	4q22.1	173910	AD	Polycystic kidney disease 2
PLA2G7	6p12.3	601690	AR	Platelet-Activating Factor Acetylhydrolase Deficiency
PLAU	10q22.2	191840	AD	Quebec Platelet Disorder
PLOD3	7q22.1	603066	AR	Lysyl hydroxylase 3 deficiency
PNP	14q11.2	164050	AR	Immunodeficiency due to purine nucleoside phosphorylase deficiency
POLD1	19q13.33	174761	AD	Mandibular Hypoplasia, Deafness, Progeroid Features, And Lipodystrophy syndrome
PRKAG2	7q36.1	602743	AD	Cardiomyopathy, hypertrophic 6;Glycogen storage disease of heart, lethal congenital; Wolff-Parkinson-White syndrome
PRKAR1A	17q24.2	188830	AD	Carney complex, type 1
PRKG1	10q11.2-q21.1	176894	AD	Aortic aneurysm, familial thoracic 8
PRNP	20p13	176640	AD	Cerebral amyloid angiopathy, PRNP-related
PROC	2q14.3	612283	AD, AR	Thrombophilia due to protein C deficiency
PROS1	3q11.1	176880	AD, AR	Thrombophilia due to protein S deficiency
PROZ	13q34	176895	NA	deep venous thrombolic disease, associated
PSEN1	14q24.2	104311	AD	Cardiomyopathy, dilated, 1U;Alzheimer disease, type 3
PSEN2	1q42.13	600759	AD	Cardiomyopathy, dilated, 1V;Alzheimer disease-4
RASA1	5q14.3	139150	AD	Capillary malformation-arteriovenous malformation
RBM20	10q25.2	613171	AD	Cardiomyopathy, dilated, 1DD
RET	10q11.21	164761	AD	Pheochromocytoma
RNF213	17q25.3	613768	AD, AR	Moyamoya disease 2, susceptibility to
RYR1	19q13.2	180901	AD, AR	Central core disease
RYR2	1q43	180902	AD	Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy 2; Ventricular arrythmias due to cardiac ryanodine receptor calcium release deficiency syndrome; Ventricular tachycardia, catecholaminergic polymorphic, 1
SCN1B	19q13.11	600235	AD	Atrial fibrillation, familial, 13
SCN2B	11q23.3	601327	AD	Atrial fibrillation, familial, 14
SCN3B	11q24.1	608214	AD	Atrial fibrillation, familial, 16;Brugada syndrome 7
SCN4B	11q23.3	608256	AD	Atrial fibrillation, familial,17; Long QT syndrome 10
SCN5A	3p22.2	600163	AD	Atrial fibrillation, familial, 10; Brugada syndrome 1; Cardiomyopathy, dilated, 1E
SERPINC1	1q25.1	107300	AD, AR	Thrombophilia due to antithrombin III deficiency
SERPIND1	22q11.21	142360	AD	Thrombophilia due to heparin cofactor II deficiency
SHOC2	10q25.2	602775	AD	Noonan-like syndrome and moyamoya disease
SLC19A2	1q24.2	603941	AR	Thiamine-Responsive Megaloblastic Anemia Syndrome

eTable2 Continued

Gene	Location	OMIM ID	Inheri-tance	Associated Mendelian Disorder
SLC2A10	20q13.12	606145	AR	Arterial tortuosity syndrome
SMAD3	15q22.33	603109	AD	Loeys-Dietz syndrome, type 3
SMAD4	18q21.2	600993	AD	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome
SMARCAL1	2q35	606622	AR	Schimke immunoosseous dysplasia
STIM1	11p15.4	605921	AD, AR	;Immunodeficiency 10
TALDO1	11p15.5	602063	AR	Transaldolase deficiency
TAZ	Xq28	300394	XLR	3-Methylglutaconic aciduria, type II (Barth syndrome)
TBX1	22q11.21	602054	AD	Tetralogy of Fallot
TBX20	7p14.2	606061	AD	Atrial septal defect 4
TBXA2R	19p13.3	188070	AD	Bleeding disorder, platelet-type, 13, susceptibility to
TCAP	17q12	604488	AD	Cardiomyopathy, hypertrophic, 25
TCN1	11q12.1	189905	NA	NA
TGFB2	1q41	190220	AD	Loeys-Dietz syndrome, type 4
TGFB3	14q24.3	190230	AD	Arrhythmogenic right ventricular dysplasia 1;Loeys-Dietz syndrome 5
TGFBR1	9q22.33	190181	AD	Loeys-Dietz syndrome, type 1A; Loeys-Dietz syndrome, type 2A
TGFBR2	3p24.1	190182	AD	Loeys-Dietz syndrome 2
TGIF1	18p11.31	602630	AD	Holoprosencephaly 4
THBD	20p11.21	188040	AD	Thrombophilia Due To Thrombomodulin Defect
TLL1	4q32.3	606742	AD	Atrial septal defect 6
TMEM173	5q31.2	612374	AD	STING-associated vasculopathy, infantile-onset
TREX1	3p21.31	606609	AD	Vasculopathy, retinal, with cerebral leukodystrophy
TTN	2q31.2	188840	AD	Cardiomyopathy, dilated, 1G
TTR	18q12.1	176300	AD	Amyloidosis, hereditary, transthyretin-related
VHL	3p25.3	608537	AD	von Hippel-Lindau syndrome
VKORC1	16p11.2	608547	AD	Vitamin K-Dependent Clotting Factors, Combined Deficiency of, 2; Warfarin resistance
VWF	12p13.31	613160	AD, AR	Von Willebrand Disease
YY1AP1	1q22	607860	AR	Grange syndrome
ZFPM2	8q23.1	603693	AD	Tetralogy of Fallot

eTable 3 Diagnoses of 759 individuals with 1 P/LP variant at risk for one monogenic diseases

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300069	F	58	ACTC1	Hereditary cardiomyopathies	Embolic stroke	NM_005159:exon3:c.T213A:p.Y71X	NA	P			Y	
CNSR302746	F	71	ACTC1	Hereditary cardiomyopathies	Embolic stroke	NM_005159:exon7:c.G1093A:p.D365N	NA	LP			Y	
CNSR301704	M	55	ACTN2	Hereditary cardiomyopathies	Embolic stroke	NM_001103:exon16:c.G1919A:p.R640H	LP	VUS			Y	
CNSR305213	M	63	ACTN2	Hereditary cardiomyopathies	Embolic stroke	NM_001103:exon16:c.G1919A:p.R640H	LP	VUS				Y
CNSR308476	F	64	ACTN2	Hereditary cardiomyopathies	Embolic stroke	NM_001103:exon14:c.C1618T:p.Q540X	NA	P			Y	
CNSR303363	M	63	BAG3	Hereditary cardiomyopathies	Embolic stroke	NM_004281:exon2:c.181-1G>A	NA	P			Y	
CNSR309438	M	52	DSG2	Hereditary cardiomyopathies	Embolic stroke	NM_001943:exon10:c.G1311A:p.W437X	NA	P			Y	
CNSR300880	M	51	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052.5(GATA4):c.997+103G>T	P	VUS			Y	
CNSR302453	M	84	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon6:c.G1075A:p.E359K	P	VUS			Y	
CNSR302668	F	80	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon6:c.G1075A:p.E359K	P	VUS			Y	
CNSR302724	F	53	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:c.997+103G>T	P	VUS			Y	
CNSR302956	M	53	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon7:c.C1325T:p.A442V	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303353	M	53	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon5:c.C946G:p.Q316E	P	VUS			Y	
CNSR303946	M	41	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon6:c.G1075A:p.E359K	P	VUS			Y	
CNSR305783	M	60	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:c.997+103G>T	P	VUS			Y	
CNSR306009	M	77	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:c.997+103G>T	P	VUS			Y	
CNSR309014	M	70	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon7:c.C1325T:p.A442V	P	VUS			Y	
CNSR309505	M	74	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon7:c.C1325T:p.A442V	P	VUS			Y	
CNSR309956	M	51	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:exon3:c.777delC:p.R260fs	NA	LP			Y	
CNSR309997	M	46	GATA4	Tetralogy of Fallot	Embolic stroke	NM_002052:c.997+103G>T	P	VUS			Y	
CNSR304597	M	47	GDF1	Congenital heart defects, multiple types, 6	Embolic stroke	NM_001492:exon7:c.159delC:p.P53fs	NA	LP			Y	
CNSR306192	M	71	GDF1	Congenital heart defects, multiple types, 6	Embolic stroke	NM_001492:exon7:c.289dupG:p.V97fs	NA	LP			Y	
CNSR307760	F	72	GDF1	Congenital heart defects, multiple types, 6	Embolic stroke	NM_001492:exon7:c.C262T:p.Q88X	NA	P			Y	
CNSR300610	F	72	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.A305T:p.K102M	NA	LP			Y	
CNSR304700	F	45	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.A305T:p.K102M	NA	LP			Y	
CNSR305166	F	77	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.G913C:p.A305P	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR305429	M	66	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.A305T:p.K102M	NA	LP			Y	
CNSR306575	M	83	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.A305T:p.K102M	NA	LP			Y	
CNSR310100	M	76	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.A524G:p.Y175C	NA	LP			Y	
CNSR300869	M	60	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.T269C:p.L90P	NA	LP			Y	
CNSR303120	F	66	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.T269C:p.L90P	NA	LP			Y	
CNSR303449	M	74	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.G1055T:p.R352M	NA	LP		Y		
CNSR305175	M	66	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.T686C:p.L229P	NA	LP		Y		
CNSR306594	F	62	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.G317C:p.R106P	NA	LP		Y		
CNSR309131	F	61	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.G1028A:p.R343H	NA	LP			Y	
CNSR309756	M	64	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.C316T:p.R106C	NA	LP		Y		
CNSR310261	F	89	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.T581C:p.V194A	NA	LP		Y		
CNSR300158	M	64	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR300624	F	43	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR301595	M	47	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR301642	M	45	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302182	M	70	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.G1828A:p.E610K	P	VUS		Y		
CNSR302320	M	56	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR302364	F	79	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS	Y			
CNSR304681	M	45	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.G1828A:p.E610K	P	VUS			Y	
CNSR305072	M	54	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR305124	M	60	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS	Y			
CNSR307143	M	59	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR307545	M	75	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR308123	M	66	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR308261	M	72	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.G1828A:p.E610K	P	VUS			Y	
CNSR303689	M	47	KCNE2	Hereditary cardiac dysrhythm	Embolic stroke	NM_172201:exon2:c.G205A:p.V69M	LP	VUS			Y	
CNSR304562	M	66	KCNE2	Hereditary cardiac dysrhythm	Embolic stroke	NM_172201:exon2:c.G205A:p.V69M	LP	VUS		Y		
CNSR305932	F	53	KCNE2	Hereditary cardiac dysrhythm	Embolic stroke	NM_172201:exon2:c.G205A:p.V69M	LP	VUS		Y		
CNSR303137	M	61	KCNH2	Hereditary cardiac dysrhythm	Embolic stroke	NM_000238:exon7:c.G1888A:p.V630I	LP	VUS			Y	
CNSR303306	M	53	KCNH2	Hereditary cardiac dysrhythm	Embolic stroke	NM_000238:exon2:c.G121A:p.V41I	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR305582	F	68	KCNH2	Hereditary cardiac dysrhythm	Embolic stroke	NM_000238:exon6:c.C1352T:p.P451L	LP	VUS			Y	
CNSR306897	M	57	KCNH2	Hereditary cardiac dysrhythm	Embolic stroke	NM_000238:exon2:c.G271T:p.E91X	NA	P			Y	
CNSR302460	F	70	KCNJ2	Hereditary cardiac dysrhythm	Embolic stroke	NM_000891:exon2:c.A971G:p.H324R	NA	LP			Y	
CNSR305866	M	52	KCNJ2	Hereditary cardiac dysrhythm	Embolic stroke	NM_000891:exon2:c.A593G:p.N198S	NA	LP			Y	
CNSR300301	M	44	KCNJ5	Hereditary cardiac dysrhythm	Embolic stroke	NM_000890:exon2:c.G862A:p.E288K	NA	LP			Y	
CNSR306658	M	58	KCNJ5	Hereditary cardiac dysrhythm	Embolic stroke	NM_000890:exon2:c.G532A:p.V178I	NA	LP			Y	
CNSR307982	M	33	KCNJ5	Hereditary cardiac dysrhythm	Embolic stroke	NM_000890:exon3:c.G1039T:p.D347Y	NA	LP			Y	
CNSR308486	F	81	KCNJ5	Hereditary cardiac dysrhythm	Embolic stroke	NM_000890:exon2:c.G632A:p.R211Q	NA	LP			Y	
CNSR300462	M	71	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon5:c.C758G:p.S253C	P	VUS	Y			
CNSR300983	F	71	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon3:c.C589T:p.P197S	LP	VUS			Y	
CNSR301428	M	42	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon6:c.G911A:p.W304X	NA	P		Y		
CNSR303201	F	48	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon7:c.C965T:p.T322M	P	VUS			Y	
CNSR303313	M	58	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon11:c.1489dupC:p.L496fs	NA	LP			Y	
CNSR303540	F	54	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon15:c.C1780T:p.R594X	P	LP		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303754	M	68	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon13:c.G1664A:p.R555H	P/LP	VUS		Y		
CNSR304030	F	53	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon7:c.C961T:p.Q321X	P	P			Y	
CNSR304199	M	71	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon13:c.C1630T:p.Q544X	NA	P			Y	
CNSR304883	M	83	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon3:c.C520T:p.R174C	P/LP	VUS			Y	
CNSR305135	F	59	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon16:c.1887dupC:p.G629fs	P/LP	VUS			Y	
CNSR305142	M	58	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon9:c.1148dupC:p.A383fs	NA	LP			Y	
CNSR305149	F	78	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon13:c.C1639T:p.Q547X	NA	P			Y	
CNSR306632	M	58	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon2:c.G436T:p.E146X	NA	P			Y	
CNSR306754	F	60	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon4:c.C674T:p.S225L	P/LP	VUS	Y			
CNSR308491	M	71	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon11:c.1445delC:p.T482fs	P	LP	Y			
CNSR308806	F	61	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_181798:exon1:c.5dupA:p.D2fs	NA	LP			Y	
CNSR300909	M	51	KRAS	Noonan syndrome 3	Embolic stroke	NM_033360:exon5:c.G463C:p.A155P	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR301758	M	69	KRAS	Noonan syndrome 3	Embolic stroke	NM_033360:exon5:c.T476C:p.L159S	NA	LP			Y	
CNSR303935	F	62	KRAS	Noonan syndrome 3	Embolic stroke	NM_033360:exon5:c.T467C:p.F156S	NA	LP			Y	
CNSR307860	M	47	KRAS	Noonan syndrome 3	Embolic stroke	NM_033360:exon5:c.T467C:p.F156S	NA	LP			Y	
CNSR300439	M	66	LMNA	Hereditary cardiomyopathies	Embolic stroke	NM_170707:exon6:c.G949A:p.E317K	P/LP	VUS		Y		
CNSR303884	F	30	LMNA	Hereditary cardiomyopathies	Embolic stroke	NM_170707:exon6:c.G1157A:p.R386K	P	VUS			Y	
CNSR306920	F	69	LMNA	Hereditary cardiomyopathies	Embolic stroke	NM_170707:exon11:c.G1745A:p.R582H	P	VUS			Y	
CNSR300696	M	57	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon32:c.3628-2A>G	NA	P			Y	
CNSR301225	M	59	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon13:c.1153_1168del:p.V385fs	P/LP	LP		Y		
CNSR301773	M	51	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon2:c.G109T:p.G37X	NA	P		Y		
CNSR301808	M	68	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256.3(MYBPC3):c.821+1G>A	P	P			Y	
CNSR303691	M	61	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon31:c.3624delC:p.K1209fs	P	LP		Y		
CNSR304072	M	19	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon22:c.2308+1G>C	NA	P		Y		
CNSR306521	M	81	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon15:c.1377delC:p.P459fs	P	LP	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307147	M	84	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon15:c.1377delC:p.P459fs	P	LP		Y		
CNSR308693	M	72	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon15:c.C1387T:p.Q463X	P	P		Y		
CNSR309002	F	80	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon13:c.1153_1168del:p.V385fs	P/LP	LP	Y			
CNSR310109	M	89	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon14:c.G1256A:p.R419H	LP	VUS			Y	
CNSR310251	M	58	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon13:c.G1187A:p.W396X	NA	P		Y		
CNSR310405	M	46	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon14:c.G1256A:p.R419H	LP	VUS			Y	
CNSR300926	F	48	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR301214	M	67	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR302885	F	62	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR303343	M	68	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.C349T:p.R117X	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303636	F	68	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR304524	M	54	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR309531	F	48	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR310093	F	44	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR310271	F	75	NKX2-5	Tetralogy of Fallot	Embolic stroke	NM_001166176:exon2:c.386delT:p.L129X	NA	LP			Y	
CNSR304051	F	34	NPPA	Hereditary cardiac dysrhythm	Embolic stroke	NM_006172:exon2:c.C319T:p.R107X	NA	LP			Y	
CNSR304789	F	81	NPPA	Hereditary cardiac dysrhythm	Embolic stroke	NM_006172:exon2:c.C181T:p.Q61X	NA	P			Y	
CNSR303354	M	45	PRKAG2	Hereditary cardiomyopathies	Embolic stroke	NM_016203:exon7:c.914delC:p.P305fs	NA	LP			Y	
CNSR304520	F	60	PRKAG2	Hereditary cardiomyopathies	Embolic stroke	NM_016203:exon4:c.G547A:p.E183K	P	VUS		Y		
CNSR308259	M	57	PRKAG2	Hereditary cardiomyopathies	Embolic stroke	NM_024429:exon7:c.445_446delinsAA:p.P149N	NA	LP			Y	
CNSR309141	M	60	PRKAG2	Hereditary cardiomyopathies	Embolic stroke	NM_016203:exon7:c.G922C:p.E308Q	NA	LP			Y	
CNSR309562	F	84	PRKAG2	Hereditary cardiomyopathies	Embolic stroke	NM_016203:exon13:c.A1402C:p.K468Q	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309699	F	52	PRKAG2	Hereditary cardiomyopathies	Embolic stroke	NM_016203:exon4:c.G547A:p.E183K	P	VUS			Y	
CNSR304696	M	49	PRKAR1A	Carney complex, type 1	Embolic stroke	NM_212472.2(PRKAR1A):c.709-7_709-2del	P	VUS			Y	
CNSR300155	M	38	RBM20	Hereditary cardiomyopathies	Embolic stroke	NM_001134363:exon2:c.471delA:p.A157fs	NA	LP			Y	
CNSR301927	M	51	RBM20	Hereditary cardiomyopathies	Embolic stroke	NM_001134363:exon2:c.699_702del:p.K233fs	NA	LP		Y		
CNSR306544	M	51	RBM20	Hereditary cardiomyopathies	Embolic stroke	NM_001134363:exon6:c.1668+1G>T	NA	P			Y	
CNSR310082	M	50	RBM20	Hereditary cardiomyopathies	Embolic stroke	NM_001134363:exon10:c.2615_2616insAG:p.E872fs	NA	LP			Y	
CNSR306204	F	77	SCN1B	Hereditary cardiac dysrhythm	Embolic stroke	NM_001037.5(SCN1B):c.590+1G>A	LP	VUS			Y	
CNSR304738	F	68	SCN2B	Hereditary cardiac dysrhythm	Embolic stroke	NM_004588:exon2:c.G172A:p.V58M	NA	LP	Y			
CNSR305339	M	84	SCN2B	Hereditary cardiac dysrhythm	Embolic stroke	NM_004588:exon2:c.C142G:p.L48V	NA	LP	Y			
CNSR306524	M	61	SCN2B	Hereditary cardiac dysrhythm	Embolic stroke	NM_004588:exon2:c.G172A:p.V58M	NA	LP		Y		
CNSR303696	M	61	SCN3B	Hereditary cardiac dysrhythm	Embolic stroke	NM_018400:exon3:c.A326G:p.N109S	NA	LP			Y	
CNSR300328	M	62	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon2:c.C140A:p.T47K	NA	LP			Y	
CNSR301522	M	72	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon5:c.G602A:p.C201Y	NA	LP		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302551	F	57	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon3:c.G373A:p.D125N	NA	LP			Y	
CNSR303785	M	71	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon4:c.G514A:p.G172R	NA	LP	Y			
CNSR305818	F	70	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon5:c.G607C:p.V203L	NA	LP			Y	
CNSR306117	F	82	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon2:c.C76T:p.P26S	NA	LP		Y		
CNSR309161	M	54	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon4:c.T565G:p.F189V	NA	LP			Y	
CNSR309232	M	65	SCN4B	Hereditary cardiac dysrhythm	Embolic stroke	NM_174934:exon4:c.T509C:p.V170A	NA	LP			Y	
CNSR302210	M	61	SCN5A	Hereditary cardiac dysrhythm	Embolic stroke	NM_198056:exon7:c.G845A:p.R282H	P	VUS			Y	
CNSR304301	M	66	SCN5A	Hereditary cardiac dysrhythm	Embolic stroke	NM_198056:exon24:c.4246delG:p.A1416fs	NA	LP			Y	
CNSR305555	F	53	SCN5A	Hereditary cardiac dysrhythm	Embolic stroke	NM_198056:exon16:c.C2440T:p.R814W	P/LP	VUS		Y		
CNSR305563	M	77	SCN5A	Hereditary cardiac dysrhythm	Embolic stroke	NM_198056:exon28:c.G4931A:p.R1644H	P	VUS			Y	
CNSR309188	M	40	SCN5A	Hereditary cardiac dysrhythm	Embolic stroke	NM_198056:exon28:c.G4931A:p.R1644H	P	VUS			Y	
CNSR300443	F	49	TLL1	Atrial septal defect	Embolic stroke	NM_012464:exon19:c.2566delC:p.P856fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300397	F	68	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon326:c.C76717T:p.R25573X	LP	P			Y	
CNSR300902	M	51	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.T13254G:p.Y4418X	NA	LP			Y	
CNSR300950	F	66	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon326:c.69869_69870insAAGA:p.D23290fs	NA	LP			Y	
CNSR301273	F	77	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon50:c.C14864G:p.S4955X	NA	P			Y	
CNSR301296	M	56	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon304:c.C62299T:p.Q20767X	NA	P			Y	
CNSR301340	M	66	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR301524	M	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.C11806T:p.R3936X	NA	LP			Y	
CNSR301692	F	81	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.T13254G:p.Y4418X	NA	LP			Y	
CNSR301708	M	51	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon322:c.C68449T:p.R22817X	P/LP	LP			Y	
CNSR301710	M	60	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon283:c.54989delC:p.T18330fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR301726	M	71	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon358:c.C104947T:p.Q34983X	LP	P			Y	
CNSR301743	F	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon61:c.G17856A:p.W5952X	NA	P			Y	
CNSR301816	F	61	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon240:c.44335delG:p.E14779fs	NA	LP			Y	
CNSR301883	M	38	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon266:c.49991delC:p.T16664fs	NA	LP			Y	
CNSR301922	M	80	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon62:c.C18055T:p.Q6019X	NA	P			Y	
CNSR302004	F	73	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon92:c.26483-1G>A	NA	P			Y	
CNSR302024	F	59	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon361:c.107377+1G>C	NA	P			Y	
CNSR302155	M	55	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon103:c.G29590T:p.E9864X	NA	P			Y	
CNSR302306	M	47	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.13482delC:p.A4494fs	NA	LP			Y	
CNSR302383	M	54	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302462	F	59	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.C14113T:p.R4705X	NA	LP			Y	
CNSR302468	M	53	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon143:c.33826+2T>A	NA	P		Y		
CNSR302498	F	63	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon314:c.T66159G:p.Y22053X	NA	LP			Y	
CNSR302527	F	28	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon338:c.G92001A:p.W30667X	NA	P			Y	
CNSR302655	F	43	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon92:c.26483-1G>A	NA	P			Y	
CNSR302687	F	62	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.T13254G:p.Y4418X	NA	LP			Y	
CNSR302703	F	63	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon332:c.88636_88637del:p.V29546fs	NA	LP			Y	
CNSR302733	M	76	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.14580delT:p.Y4860X	NA	LP			Y	
CNSR302739	M	42	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.13962delG:p.T4654fs	NA	LP			Y	
CNSR302803	M	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon346:c.96144delG:p.W32048X	NA	LP		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302812	M	84	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon360:c.G106945T:p.E35649X	NA	P			Y	
CNSR302836	F	56	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133378.4:c.59644+1G>A	LP	VUS			Y	
CNSR302853	M	55	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR302922	M	46	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon319:c.C67495T:p.R22499X	P/LP	P			Y	
CNSR303144	M	69	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon358:c.C104947T:p.Q34983X	LP	P		Y		
CNSR303232	M	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon265:c.G49659A:p.W16553X	NA	P			Y	
CNSR303373	M	45	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR303397	M	59	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon48:c.11884delG:p.V3962fs	NA	LP		Y		
CNSR303414	M	82	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon289:c.56275delA:p.T18759fs	NA	LP			Y	
CNSR303473	F	68	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon304:c.C63025T:p.R21009X	P/LP	P			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303486	M	70	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon52:c.G15304T:p.G5102X	NA	P			Y	
CNSR303552	F	60	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon45:c.C10405T:p.Q3469X	NA	P			Y	
CNSR303676	M	48	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon326:c.76397_76398del:p.I25466fs	P	LP			Y	
CNSR303961	M	82	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.13897dupC:p.Q4633fs	NA	LP			Y	
CNSR303985	F	75	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon159:c.G35500T:p.E11834X	NA	P			Y	
CNSR304024	M	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon138:c.33340+2T>C	NA	P			Y	
CNSR304056	F	51	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550.2:c.49345+2T>C	LP	VUS			Y	
CNSR304056	F	51	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.12571delA:p.T4191fs	NA	LP			Y	
CNSR304076	F	70	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon271:c.C51436T:p.Q17146X	P	P			Y	
CNSR304115	F	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon248:c.46201_46204del:p.T15401fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304236	M	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR304295	M	46	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon100:c.28907delG:p.C9636fs	NA	LP			Y	
CNSR304443	F	66	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon251:c.46821_46906del:p.P15607fs	NA	LP			Y	
CNSR304630	F	77	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon87:c.25083_25086del:p.F8361fs	NA	LP		Y		
CNSR304797	M	57	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.13550delT:p.M4517fs	NA	LP			Y	
CNSR305023	M	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon63:c.C18541T:p.R6181X	NA	P			Y	
CNSR305065	F	68	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.14463_14464del:p.T4821fs	NA	LP			Y	
CNSR305258	M	63	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550.2:c.49345+2T>C	LP	VUS			Y	
CNSR305258	M	63	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.12571delA:p.T4191fs	NA	LP			Y	
CNSR305322	F	53	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_003319:exon45:c.11505_11506insAATTAATTCATTAACA:p.V3836_E3837delinsNX	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR305448	M	61	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon45:c.C10405T:p.Q3469X	NA	P			Y	
CNSR305694	M	60	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon55:c.16112delA:p.N5371fs	NA	LP			Y	
CNSR305735	M	62	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon352:c.98381delG:p.G32794fs	NA	LP			Y	
CNSR305812	M	71	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon163:c.35813delA:p.K11938fs	NA	LP			Y	
CNSR306351	M	57	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550.2:c.49345+2T>C	LP	VUS			Y	
CNSR306351	M	57	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.12571delA:p.T4191fs	NA	LP			Y	
CNSR306385	F	67	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon56:c.C16404A:p.C5468X	NA	P			Y	
CNSR306470	M	70	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon358:c.C104947T:p.Q34983X	LP	P			Y	
CNSR306608	M	48	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon63:c.C18541T:p.R6181X	NA	P			Y	
CNSR307049	M	79	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon280:c.C54067T:p.R18023X	LP	P			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307096	M	78	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon92:c.26483-2A>G	NA	P		Y		
CNSR307169	M	61	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.11782_11783del:p.M3928fs	NA	LP			Y	
CNSR307344	F	70	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.11416_11419del:p.I3806fs	NA	LP			Y	
CNSR307493	F	68	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon347:c.96504delA:p.G32168fs	NA	LP			Y	
CNSR307561	M	55	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon322:c.68527+1G>T	NA	P			Y	
CNSR307677	M	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.T13254G:p.Y4418X	NA	LP			Y	
CNSR307734	M	63	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550.2:c.49345+2T>C	LP	VUS			Y	
CNSR307734	M	63	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.12571delA:p.T4191fs	NA	LP			Y	
CNSR307750	M	52	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon339:c.A92854T:p.R30952X	NA	P			Y	
CNSR307875	M	73	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308005	M	48	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.C10735T:p.Q3579X	NA	P			Y	
CNSR308032	M	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP		Y		
CNSR308096	M	58	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR308211	M	87	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon91:c.G26254T:p.E8752X	NA	P			Y	
CNSR308221	M	75	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon137:c.33247+1G>A	NA	P			Y	
CNSR308406	F	80	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon324:c.69179_69180insTTAC:p.T23060fs	NA	LP			Y	
CNSR308440	F	58	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon360:c.G106914A:p.W35638X	NA	P			Y	
CNSR308503	F	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon343:c.95246delA:p.E31749fs	NA	LP			Y	
CNSR308517	M	47	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon328:c.87432delT:p.P29144fs	NA	LP			Y	
CNSR308532	M	59	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon93:c.26979dupT:p.G8994fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308562	M	78	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.14236delA:p.T4746fs	NA	LP			Y	
CNSR308731	F	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon82:c.23896_23897del:p.S7966fs	NA	LP			Y	
CNSR308774	M	73	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon87:c.25113delG:p.E8371fs	NA	LP			Y	
CNSR308791	M	64	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon7:c.1205delC:p.A402fs	NA	LP			Y	
CNSR309122	M	50	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon11:c.1732dupG:p.E578fs	NA	LP			Y	
CNSR309205	M	72	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.15075delT:p.V5025fs	NA	LP			Y	
CNSR309225	F	53	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.C11806T:p.R3936X	NA	LP			Y	
CNSR309332	M	52	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon354:c.C99052T:p.Q33018X	NA	P			Y	
CNSR309344	M	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550.2:c.49345+2T>C	LP	VUS			Y	
CNSR309344	M	65	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.12571delA:p.T4191fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309386	F	71	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR309744	M	48	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon335:c.90597delA:p.G30199fs	NA	LP			Y	
CNSR309871	M	46	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR310007	M	61	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.C10522T:p.Q3508X	NA	LP			Y	
CNSR310370	M	58	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon46:c.G10819T:p.E3607X	NA	LP			Y	
CNSR310422	M	62	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.T13254G:p.Y4418X	NA	LP			Y	
CNSR302718	M	66	ZFPM2	Tetralogy of Fallot	Embolic stroke	NM_012082:exon6:c.739+1G>A	NA	P			Y	
CNSR310062	M	60	ZFPM2	Tetralogy of Fallot	Embolic stroke	NM_012082:exon7:c.G779A:p.R260Q	P	VUS			Y	
CNSR303911	M	82	ACTA2	Aortic aneurysm, familial thoracic 6	Large artery disease	NM_001613:exon3:c.170delG:p.G57fs	NA	LP	Y			
CNSR300368	M	64	APOA5	Hyperchylomicronemia, late-onset	Large artery disease	NM_052968:exon2:c.G30A:p.W10X	NA	P			Y	
CNSR307179	F	50	APOA5	Hyperchylomicronemia, late-onset	Large artery disease	NM_052968:exon2:c.G30A:p.W10X	NA	P		Y		
CNSR300355	F	79	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR301124	M	75	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR301461	F	53	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon6:c.G537A:p.W179X	NA	P			Y	
CNSR301827	M	35	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR302864	F	64	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR303299	M	51	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR303732	F	48	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon11:c.1102delC:p.P368fs	NA	LP			Y	
CNSR304614	M	62	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.786dupC:p.L262fs	NA	LP			Y	
CNSR304790	F	73	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR305067	M	55	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.786delC:p.L262fs	NA	LP			Y	
CNSR305247	M	76	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR305437	M	77	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.C853T:p.R285X	NA	LP			Y	
CNSR305830	M	45	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR305982	M	75	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon11:c.982-1G>C	NA	LP			Y	
CNSR306316	F	46	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon14:c.1321+1G>A	P	P			Y	
CNSR306620	F	54	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon12:c.1208delA:p.D403fs	NA	LP			Y	
CNSR306695	M	59	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR306834	M	85	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR307652	M	70	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR307689	M	50	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR307818	M	88	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR307964	M	47	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon14:c.1321+1G>A	P	P			Y	
CNSR308010	M	82	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.C160T:p.R54X	NA	LP			Y	
CNSR308189	M	64	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR308467	F	81	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309068	M	56	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR309319	F	75	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR309412	F	76	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR309459	M	46	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon11:c.1102delC:p.P368fs	NA	LP			Y	
CNSR309700	M	27	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR310111	F	79	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon9:c.783_786del:p.D261fs	NA	LP			Y	
CNSR304557	F	56	COL1A1	CeAD,FMD,TAA,AAA	Large artery disease	NM_000088:exon5:c.441delC:p.P147fs	P	LP		Y		
CNSR306617	M	49	COL1A1	CeAD,FMD,TAA,AAA	Large artery disease	NM_000088:exon37:c.G2594A:p.R865H	LP	VUS			Y	
CNSR306717	F	63	COL1A1	CeAD,FMD,TAA,AAA	Large artery disease	NM_000088:exon5:c.386_388delinsT:p.G129Lfs*39	NA	P			Y	
CNSR309324	M	52	COL1A1	CeAD,FMD,TAA,AAA	Large artery disease	NM_000088:exon21:c.1354-1G>C	NA	P		Y		
CNSR305489	F	77	COL1A2	CeAD,FMD,TAA,AAA	Large artery disease	NM_000089:exon19:c.G946A:p.G316S	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR306054	M	49	COL1A2	CeAD,FMD,TAA,AAA	Large artery disease	NM_000089:exon17:c.G874A:p.G292S	P	VUS		Y		
CNSR306112	M	69	COL1A2	CeAD,FMD,TAA,AAA	Large artery disease	NM_000089:exon5:c.207delC:p.G69fs	NA	LP		Y		
CNSR304228	M	72	COL5A1	Ehlers-Danlos syndrome, classic type,	Large artery disease	NM_000093:exon66:c.T5486G:p.F1829C	LP	VUS			Y	
CNSR306147	F	67	COL5A1	Ehlers-Danlos syndrome, classic type,	Large artery disease	NM_001278074:exon64:c.C5095T:p.Q1699X	NA	P			Y	
CNSR308149	M	71	COL5A1	Ehlers-Danlos syndrome, classic type,	Large artery disease	NM_000093:exon48:c.G3781A:p.G1261R	LP	VUS			Y	
CNSR300432	M	48	ELN	SVAS	Large artery disease	NM_000501:exon14:c.686-2A>G	NA	P			Y	
CNSR300818	M	83	ELN	SVAS	Large artery disease	NM_000501:exon24:c.1621+1G>A	LP	P			Y	
CNSR301992	M	72	ELN	SVAS	Large artery disease	NM_000501:exon14:c.686-2A>G2A>G	NA	P			Y	
CNSR302656	M	50	ELN	SVAS	Large artery disease	NM_000501:exon14:c.686-2A>G	NA	P			Y	
CNSR305968	F	78	ELN	SVAS	Large artery disease	NM_001278939:exon26:c.1933+2T>A	NA	P		Y		
CNSR306387	M	55	ELN	SVAS	Large artery disease	NM_001278939:exon26:c.1933+2T>A	NA	P		Y		
CNSR307595	M	60	ELN	SVAS	Large artery disease	NM_000501:exon14:c.686-2A>G	NA	P			Y	
CNSR308754	M	39	ELN	SVAS	Large artery disease	NM_000501:exon11:c.571+1G>A	NA	P			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR310118	M	45	ELN	SVAS	Large artery disease	NM_000501:exon24:c.1621+1G>A	LP	P	Y			
CNSR300886	M	75	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon22:c.A2613C:p.L871F	P	VUS			Y	
CNSR301821	M	64	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon63:c.T7754C:p.I2585T	P/LP	VUS		Y		
CNSR302393	M	51	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon22:c.A2613C:p.L871F	P	VUS			Y	
CNSR303067	F	58	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon22:c.A2613C:p.L871F	P	VUS			Y	
CNSR304747	M	73	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon22:c.A2613C:p.L871F	P	VUS			Y	
CNSR305922	M	50	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon22:c.A2613C:p.L871F	P	VUS			Y	
CNSR309171	M	78	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon10:c.G1091A:p.R364Q	NA	LP			Y	
CNSR300049	M	53	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon9:c.C1216A:p.R406R	P	VUS			Y	
CNSR300051	F	42	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon11:c.A1691G:p.N564S	LP	VUS	Y			
CNSR300104	F	65	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon11:c.T1592A:p.M531K	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300212	F	48	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon11:c.T1592A:p.M531K	NA	LP			Y	
CNSR300289	M	62	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon10:c.A1454T:p.H485L	NA	LP		Y		
CNSR300310	M	41	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon4:c.510delC:p.D170fs	P	LP	Y			
CNSR300371	F	76	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon4:c.C516A:p.D172E	NA	LP			Y	
CNSR300418	M	58	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon16:c.A2344T:p.K782X	P	LP		Y		
CNSR300451	F	81	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon10:c.A1525G:p.K509E	LP	VUS	Y			
CNSR300867	F	73	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon13:c.G1879A:p.A627T	P/LP	VUS			Y	
CNSR301304	M	57	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon11:c.T1592A:p.M531K	NA	LP		Y		
CNSR301669	F	70	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon11:c.A1691G:p.N564S	LP	VUS		Y		
CNSR301850	M	67	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon7:c.T1016C:p.L339P	LP	VUS	Y			
CNSR302713	M	42	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon4:c.C487T:p.Q163X	P	LP	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303264	M	60	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon13:c.C1880T:p.A627V	LP	VUS	Y			
CNSR303708	F	69	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon13:c.G1864T:p.D622Y	NA	LP			Y	
CNSR304012	M	82	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon11:c.T1592A:p.M531K	NA	LP			Y	
CNSR304637	F	70	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon13:c.G1879A:p.A627T	P/LP	VUS		Y		
CNSR304929	M	79	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon6:c.A924T:p.E308D	LP	VUS			Y	
CNSR305027	F	64	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon9:c.G1247A:p.R416Q	P/LP	VUS	Y			
CNSR305733	M	59	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon4:c.T400C:p.C134R	P/LP	VUS			Y	
CNSR306253	M	83	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon14:c.G2026C:p.G676R	LP	VUS	Y			
CNSR306440	M	62	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon7:c.C1048T:p.R350X	P	LP	Y			
CNSR306967	M	56	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon7:c.G1049A:p.R350Q	P	VUS			Y	
CNSR307020	F	52	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_001195798.2:c.313+1dup	P/LP	VUS		Y		
CNSR307426	M	54	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon9:c.G1247A:p.R416Q	P/LP	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307613	F	71	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon14:c.G2026C:p.G676R	LP	VUS	Y			
CNSR307649	M	49	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon12:c.1745_1746del:p.L582fs	P	LP	Y			
CNSR307861	M	66	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon10:c.1570_1582del:p.V524fs	NA	LP		Y		
CNSR308053	M	69	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon14:c.G2026C:p.G676R	LP	VUS			Y	
CNSR308235	M	52	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon9:c.C1216A:p.R406R	P	VUS	Y			
CNSR308766	M	61	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon4:c.G502A:p.D168N	P/LP	VUS			Y	
CNSR309242	M	53	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon2:c.T100G:p.C34G	P/LP	VUS			Y	
CNSR309264	M	42	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon5:c.G796C:p.D266H	NA	LP		Y		
CNSR309633	M	69	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon6:c.908delG:p.R303fs	NA	LP			Y	
CNSR300114	M	77	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon3:c.C88T:p.R30X	LP	VUS			Y	
CNSR301352	M	45	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR301444	M	41	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR302503	F	68	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302574	M	77	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR303517	F	65	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon9:c.338dupT:p.L113fs	NA	LP			Y	
CNSR305631	M	65	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR306162	M	57	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR306421	F	53	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR300828	M	73	MYH11	Aortic aneurysm, familial thoracic 4	Large artery disease	NM_002474:exon28:c.T3791A:p.L1264Q	NA	LP			Y	
CNSR306393	M	44	MYH11	Aortic aneurysm, familial thoracic 4	Large artery disease	NM_002474:exon19:c.A2254T:p.K752X	NA	P			Y	
CNSR307728	M	48	MYH11	Aortic aneurysm, familial thoracic 4	Large artery disease	NM_002474:exon26:c.G3466T:p.E1156X	NA	P			Y	
CNSR300206	M	54	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon16:c.C2371T:p.Q791X	NA	P			Y	
CNSR302047	F	73	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon18:c.2463-2A>G	NA	P			Y	
CNSR304181	F	64	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon12:c.1517-2A>G	NA	P			Y	
CNSR305870	F	61	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon18:c.C2692T:p.R898X	NA	P			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307523	F	67	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon14:c.C1915T:p.Q639X	NA	P			Y	
CNSR307730	M	56	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon18:c.C2665T:p.Q889X	NA	P			Y	
CNSR309070	M	61	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon6:c.422+1G>A	NA	P			Y	
CNSR309296	M	58	MYLK	Aortic aneurysm, familial thoracic 7	Large artery disease	NM_053025:exon10:c.1228dupG:p.D410fs	NA	LP			Y	
CNSR300785	M	76	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon13:c.T1473A:p.H491Q	NA	LP			Y	
CNSR302491	F	48	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon2:c.A320G:p.D107G	NA	LP			Y	
CNSR303483	M	72	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon8:c.T962C:p.I321T	NA	LP			Y	
CNSR303769	M	65	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon2:c.A320G:p.D107G	NA	LP			Y	
CNSR304124	F	58	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon3:c.T541C:p.F181L	NA	LP			Y	
CNSR305284	F	68	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon8:c.T962C:p.I321T	NA	LP			Y	
CNSR305514	F	80	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon2:c.A350G:p.D117G	NA	LP			Y	
CNSR305685	F	57	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon3:c.T539C:p.V180A	NA	LP			Y	
CNSR306077	F	65	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon8:c.T962C:p.I321T	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR306372	M	60	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon2:c.G391A:p.V131M	NA	LP			Y	
CNSR307814	M	60	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon10:c.1128delC:p.N376fs	NA	LP			Y	
CNSR309202	F	44	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_001098512:exon1:c.A257C:p.K86T	NA	LP			Y	
CNSR309352	F	49	PRKG1	Aortic aneurysm, familial thoracic 8	Large artery disease	NM_006258:exon2:c.A320G:p.D107G	NA	LP		Y		
CNSR300151	M	61	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR300449	F	65	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR300542	M	65	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR300570	F	60	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR300650	M	71	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR301176	M	60	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR301302	M	66	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR301408	M	70	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR301446	M	57	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR301456	F	46	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR301695	M	45	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR301768	M	62	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR302170	M	37	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS				Y
CNSR302455	F	27	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR302619	M	65	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR302741	F	67	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR302775	M	35	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303338	M	65	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR303394	M	54	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS				Y
CNSR303404	M	57	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR303451	F	53	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR303695	F	70	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR304133	F	54	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR304137	F	60	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR304305	M	61	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR304368	M	56	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR304370	M	67	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304477	M	69	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS				Y
CNSR304840	M	30	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR305285	M	52	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR305511	M	45	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR305688	F	51	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR305701	F	58	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR305969	F	67	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR306018	M	79	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR306251	F	48	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR306474	M	51	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS				Y

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR306719	F	56	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR307009	F	65	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS				Y
CNSR307043	M	62	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR307110	M	62	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR307307	M	72	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR307323	M	66	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR307418	F	68	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR307541	F	61	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR308107	M	51	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR308482	M	53	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308599	M	59	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR308643	M	60	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR308924	F	44	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR309034	M	58	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR309437	F	51	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR309554	F	53	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR309631	M	62	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS	Y			
CNSR310183	M	41	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR310309	M	51	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR303114	M	71	ETV6	Thrombocytopenia 5	Prothrombotic state	NM_001987:exon2:c.C115T:p.R39X	NA	P			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300244	F	60	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon10:c.C1195T:p.R399C	NA	LP			Y	
CNSR300779	M	60	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon13:c.G1679A:p.R560Q	NA	LP			Y	
CNSR301431	M	49	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon4:c.G290A:p.R97Q	NA	LP			Y	
CNSR302043	M	75	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.A715G:p.S239G	NA	LP			Y	
CNSR302610	F	62	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.A715G:p.S239G	NA	LP			Y	
CNSR302706	M	65	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon4:c.G290A:p.R97Q	NA	LP			Y	
CNSR302815	F	64	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.C683T:p.T228I	NA	LP			Y	
CNSR302834	M	54	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon11:c.G1307A:p.R436Q	NA	LP			Y	
CNSR303002	M	53	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon4:c.G290A:p.R97Q	NA	LP			Y	
CNSR303616	M	70	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.A715G:p.S239G	NA	LP			Y	
CNSR303837	M	68	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon2:c.A136G:p.T46A	NA	LP			Y	
CNSR304831	M	45	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon4:c.G290A:p.R97Q	NA	LP			Y	
CNSR304932	M	64	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon10:c.G1196T:p.R399L	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR305605	M	66	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon4:c.G290A:p.R97Q	NA	LP			Y	
CNSR306073	M	51	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.A715G:p.S239G	NA	LP		Y		
CNSR306469	M	69	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.C677A:p.A226E	NA	LP			Y	
CNSR306519	F	71	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon11:c.G1299T:p.R433S	NA	LP			Y	
CNSR306646	F	81	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon5:c.419_420insTGAG:p.P140fs	NA	LP			Y	
CNSR306759	M	44	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon11:c.G1299T:p.R433S	NA	LP			Y	
CNSR307305	M	45	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon11:c.C1306T:p.R436X	NA	P			Y	
CNSR307437	M	82	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon2:c.G119A:p.R40Q	NA	LP			Y	
CNSR307824	M	76	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon9:c.G1054A:p.E352K	P	LP			Y	
CNSR307908	M	58	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon10:c.C1147T:p.R383W	NA	LP			Y	
CNSR308145	F	74	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon4:c.G290A:p.R97Q	NA	LP			Y	
CNSR308905	M	56	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.A715G:p.S239G	NA	LP			Y	
CNSR308999	M	62	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon8:c.G1003A:p.D335N	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309128	M	52	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon11:c.G1299T:p.R433S	NA	LP			Y	
CNSR310389	M	53	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.A715G:p.S239G	NA	LP			Y	
CNSR310428	M	60	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon2:c.C239T:p.T80M	NA	LP			Y	
CNSR301130	F	87	GP1BA	von Willebrand disease, platelet-type	Prothrombotic state	NM_000173:exon2:c.A449G:p.N150S	LP	VUS			Y	
CNSR300210	M	54	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR300974	F	61	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR301140	F	67	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR301453	M	74	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR301596	M	81	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR301724	F	53	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR301871	M	70	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302013	F	62	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR302241	M	76	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR302246	F	43	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR302755	F	59	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR302832	M	63	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR302950	F	60	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR303845	M	61	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR303914	F	51	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR304686	M	64	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR306131	F	76	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR306885	M	65	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR306975	M	53	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR306992	F	62	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR307039	M	66	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR307258	M	73	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR307566	F	62	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR308276	M	67	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR308823	M	67	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS			Y	
CNSR308929	M	79	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS			Y	
CNSR309106	M	77	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309615	F	79	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS			Y	
CNSR309872	M	75	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR310420	M	69	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR305210	M	58	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:exon9:c.G889C:p.D297H	P	VUS			Y	
CNSR306872	F	64	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:exon3:c.G199C:p.E67Q	NA	LP			Y	
CNSR307697	M	58	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:c.678+9C>T	P	VUS			Y	
CNSR307931	M	29	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:exon7:c.C658T:p.R220W	P	VUS			Y	
CNSR309298	F	64	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:exon3:c.G76C:p.V26L	NA	LP			Y	
CNSR310362	M	74	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:exon9:c.G889C:p.D297H	P	VUS			Y	
CNSR303734	M	40	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon10:c.C1063T:p.R355C	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303874	M	48	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon6:c.A586G:p.K196E	P	VUS			Y	
CNSR304216	M	65	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon14:c.T1680A:p.Y560X	LP	LP			Y	
CNSR304306	F	61	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon10:c.C1063T:p.R355C	P	VUS			Y	
CNSR305014	F	67	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon10:c.C1063T:p.R355C	P	VUS			Y	
CNSR307585	M	56	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon14:c.1753delG:p.E585fs	NA	LP			Y	
CNSR307679	M	63	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon10:c.C1063T:p.R355C	P	VUS			Y	
CNSR308628	F	59	PROS1	Thrombophilia due to protein S deficiency	Prothrombotic state	NM_000313:exon12:c.1427_1428insA:p.L476fs	NA	LP			Y	
CNSR300805	M	53	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon2:c.C218T:p.P73L	P/LP	VUS			Y	
CNSR301590	M	70	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon3:c.T442C:p.S148P	P	VUS			Y	
CNSR305745	M	71	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon3:c.T442C:p.S148P	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR305890	F	41	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon3:c.A572G:p.Q191R	LP	VUS			Y	
CNSR306312	M	50	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon2:c.C235T:p.R79C	LP	VUS			Y	
CNSR309720	M	60	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon3:c.A572G:p.Q191R	LP	VUS			Y	
CNSR300699	F	69	SERPIND1	Thrombophilia due to heparin cofactor II deficie	Prothrombotic state	NM_000185:exon2:c.657_660del:p.R219fs	NA	LP			Y	
CNSR302505	M	54	SERPIND1	Thrombophilia due to heparin cofactor II deficie	Prothrombotic state	NM_000185:exon2:c.C415T:p.R139X	NA	P			Y	
CNSR304069	M	62	SERPIND1	Thrombophilia due to heparin cofactor II deficie	Prothrombotic state	NM_000185:exon2:c.556_557del:p.F186fs	NA	LP			Y	
CNSR305242	F	70	SERPIND1	Thrombophilia due to heparin cofactor II deficie	Prothrombotic state	NM_000185:exon3:c.949_950del:p.E317fs	NA	LP			Y	
CNSR307508	M	55	SERPIND1	Thrombophilia due to heparin cofactor II deficie	Prothrombotic state	NM_000185:exon3:c.917delA:p.E306fs	NA	LP			Y	
CNSR309254	M	66	SERPIND1	Thrombophilia due to heparin cofactor II deficie	Prothrombotic state	NM_000185:exon2:c.668_677del:p.D223fs	NA	LP			Y	
CNSR305747	M	62	STIM1	Stormorken syndrome	Prothrombotic state	NM_001277961:exon11:c.1621_1624del:p.S541fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300050	M	60	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR300111	M	59	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.2289dupG:p.S764	NA	LP			Y	
CNSR300534	M	68	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon14:c.C1677A:p.C559X	NA	LP			Y	
CNSR300609	F	74	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR300627	F	67	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.C4135T:p.R1379C	P	VUS			Y	
CNSR301287	M	48	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR301361	M	62	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon32:c.5462delC:p.T1822	NA	LP			Y	
CNSR301580	M	74	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.C4696T:p.R1566X	P	P			Y	
CNSR301972	M	66	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR302390	M	54	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon43:c.C7390T:p.R2464C	P/LP	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302557	F	67	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR303068	M	73	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.C3797A:p.P1266Q	LP	VUS			Y	
CNSR303106	M	60	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR303246	F	64	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.C2372T:p.T791M	LP	VUS			Y	
CNSR303642	M	64	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR303701	M	77	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR303871	M	63	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon44:c.C7464T:p.G2488G	LP	VUS			Y	
CNSR304193	M	68	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR304338	F	57	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.C3797A:p.P1266Q	LP	VUS			Y	
CNSR304493	M	64	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304667	M	52	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR304733	M	75	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon20:c.2658delC:p.P886fs	NA	LP			Y	
CNSR304865	M	50	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR305150	M	63	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon43:c.G7332A:p.W2444X	NA	P			Y	
CNSR306284	M	68	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR306560	M	76	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR306641	F	70	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon44:c.C7464T:p.G2488G	LP	VUS			Y	
CNSR306919	M	68	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon20:c.G2561A:p.R854Q	P/LP	VUS			Y	
CNSR307271	M	63	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon39:c.C6835T:p.Q2279X	NA	P			Y	
CNSR308117	F	79	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308135	M	53	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.T3774A:p.Y1258X	NA	LP			Y	
CNSR308576	M	25	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon18:c.G2303A:p.R768Q	LP	VUS			Y	
CNSR308978	F	75	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon7:c.C813G:p.Y271X	NA	LP			Y	
CNSR309553	M	62	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.G3970A:p.G1324S	P	VUS			Y	
CNSR309563	M	50	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.4094delT:p.L1365fs	NA	LP			Y	
CNSR310361	M	62	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon30:c.G5235A:p.W1745X	NA	P			Y	
CNSR301005	M	51	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon6:c.G343A:p.G115S	NA	LP	Y			
CNSR302264	M	73	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon9:c.G502A:p.G168R	NA	LP	Y			
CNSR302968	F	81	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon50:c.G4718A:p.G1573E	NA	LP	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302973	M	58	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon15:c.G823A:p.G275	NA	LP			Y	
CNSR303061	F	55	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon9:c.G502A:p.G168R	NA	LP			Y	
CNSR303631	F	79	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon21:c.G1277T:p.G42	NA	LP	Y			
CNSR303650	F	88	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon27:c.G1937C:p.G646A	NA	LP	Y			
CNSR304740	M	52	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon40:c.3407-1G>A	NA	P			Y	
CNSR304947	M	43	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon37:c.C3187T:p.R1063X	NA	LP	Y			
CNSR305943	M	70	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon6:c.G343A:p.G115S	NA	LP	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR306510	M	78	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon49:c.G4471A:p.G1491S	NA	LP			Y	
CNSR307106	M	58	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon23:c.G1420A:p.G474R	NA	LP	Y			
CNSR308031	M	70	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon27:c.G1937C:p.G646A	NA	LP		Y		
CNSR308223	F	69	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon25:c.G1640C:p.G547A	NA	LP			Y	
CNSR309282	F	76	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001303110:exon15:c.G823C:p.G275R	NA	LP			Y	
CNSR310132	F	81	COL4A1	Brain small vessel disease with or without ocular anomalies/PADMAL	Small vessel disease	NM_001845:exon39:c.G3379A:p.G1127S	NA	LP	Y			
CNSR300117	M	75	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon33:c.G2954T:p.G985V	NA	LP	Y			
CNSR300633	M	64	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon28:c.G2105C:p.G702A	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300646	M	65	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon37:c.3420delA:p.G1140fs	NA	LP			Y	
CNSR300683	F	79	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon19:c.G1180A:p.G394R	NA	LP		Y		
CNSR301611	M	53	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon36:c.G3338A:p.G1113E	NA	LP			Y	
CNSR301656	M	57	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon48:c.G4909A:p.G1637S	NA	LP	Y			
CNSR301698	M	60	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon19:c.G1180A:p.G394R	NA	LP			Y	
CNSR301913	F	68	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon33:c.G2954T:p.G985V	NA	LP			Y	
CNSR302077	M	44	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon48:c.G4906A:p.G1636S	NA	LP			Y	
CNSR302272	F	61	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon20:c.1306delC:p.P436fs	NA	LP	Y			
CNSR302290	F	72	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon46:c.G4465A:p.G1489S	NA	LP	Y			
CNSR302556	M	57	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon5:c.220delC:p.P74fs	NA	LP		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302914	F	70	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon44:c.C4228T:p.R1410	NA	P		Y		
CNSR303301	M	61	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon7:c.G451A:p.G151S	NA	LP			Y	
CNSR303811	M	68	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon39:c.G3589A:p.G1197S	NA	LP	Y			
CNSR303908	M	47	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon22:c.G1525A:p.G509R	NA	LP			Y	
CNSR305035	F	75	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon20:c.1306delC:p.P436fs	NA	LP	Y			
CNSR305298	M	67	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon28:c.G2105C:p.G702A	NA	LP			Y	
CNSR305789	M	59	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon34:c.G3088A:p.G1030S	NA	LP			Y	
CNSR306020	M	52	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon18:c.G1078A:p.G360S	NA	LP			Y	
CNSR306307	F	76	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon17:c.G995A:p.G332E	NA	LP			Y	
CNSR306619	M	58	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon25:c.G1778A:p.G593D	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307166	M	72	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon12:c.G719A:p.G240D	NA	LP	Y			
CNSR307249	M	62	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon42:c.G3985A:p.G1329R	NA	LP				Y
CNSR307401	M	64	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon44:c.4269delC:p.G1423fs	NA	LP	Y			
CNSR307591	F	53	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon20:c.1306dupC:p.G43	NA	LP		Y		
CNSR307722	M	71	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon20:c.C1291T:p.R431X	NA	P	Y			
CNSR308082	F	67	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon34:c.G3071C:p.G1024A	NA	LP		Y		
CNSR308217	M	70	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon25:c.G1792A:p.G598S	NA	LP	Y			
CNSR308251	M	65	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon33:c.G2954T:p.G985V	NA	LP	Y			
CNSR308728	F	72	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon39:c.G3589A:p.G1197S	NA	LP	Y			
CNSR309273	M	67	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon23:c.G1597T:p.G533X	NA	P	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309581	M	68	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon34:c.G3088A:p.G1030S	NA	LP				Y
CNSR309645	M	59	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon22:c.G1525A:p.G509R	NA	LP		Y		
CNSR309799	F	52	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon40:c.G3649A:p.G1217R	NA	LP			Y	
CNSR309962	M	62	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon7:c.G451A:p.G151S	NA	LP			Y	
CNSR310003	M	53	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon39:c.G3607A:p.G1203S	NA	LP	Y			
CNSR301748	F	52	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon7:c.G1034A:p.W345X	NA	P			Y	
CNSR303348	M	63	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon12:c.1736dupT:p.V579fs	NA	LP		Y		
CNSR303408	M	52	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon11:c.C1534T:p.Q512X	NA	P			Y	
CNSR303542	M	72	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon13:c.1899_1909del:p.A6	NA	LP			Y	
CNSR303781	F	71	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon10:c.1408delG:p.G470fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303822	M	50	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon10:c.1408delG:p.G470fs	NA	LP			Y	
CNSR304726	F	55	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon2:c.349+1G>T	NA	P			Y	
CNSR306001	M	71	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_000177:exon10:c.G1349A:p.W450X	NA	P				Y
CNSR309374	M	54	GSN	Amyloidosis, Finnish type	Small vessel disease	NM_001127663:exon3:c.85dupT:p.L28fs	NA	LP		Y		
CNSR305312	F	58	HTRA1	CARASIL	Small vessel disease	NM_002775:exon2:c.G517A:p.A173T	NA	LP	Y			
CNSR307080	M	59	HTRA1	CARASIL	Small vessel disease	NM_002775:exon4:c.778-2A>G	NA	P	Y			
CNSR309218	F	45	HTRA1	CARASIL	Small vessel disease	NM_002775:exon7:c.C1156T:p.R386X	NA	P			Y	
CNSR300221	F	69	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon17:c.G2687T:p.C896F	NA	LP	Y			
CNSR300468	M	75	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR300673	M	74	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon15:c.C2299T:p.R767C	NA	LP		Y		
CNSR300768	M	43	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300946	M	42	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon21:c.C3427T:p.R1143C	NA	LP	Y			
CNSR301247	M	55	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon13:c.A2129G:p.Y710C	NA	LP	Y			
CNSR301511	M	37	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon20:c.G3313T:p.G1105C	NA	LP	Y			
CNSR301757	M	46	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon18:c.C2898A:p.C966X	NA	P	Y			
CNSR301888	F	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon16:c.G2459T:p.C820F	NA	LP	Y			
CNSR301929	M	65	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			
CNSR301933	M	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon13:c.C2038T:p.R680C	NA	LP	Y			
CNSR302163	M	46	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon15:c.C2299T:p.R767C	NA	LP	Y			
CNSR302623	M	46	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon4:c.T547A:p.C183S	NA	LP	Y			
CNSR302884	M	55	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302919	M	53	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon12:c.C1918T:p.R640C	NA	LP			Y	
CNSR303044	M	58	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon17:c.G2689T:p.G897C	NA	LP	Y			
CNSR303149	M	58	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			
CNSR303251	F	64	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR303417	F	81	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon22:c.C3601T:p.R1201C	NA	LP	Y			
CNSR303714	F	67	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			
CNSR303980	F	56	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon12:c.C1918T:p.R640C	NA	LP	Y			
CNSR304138	F	46	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon5:c.G798C:p.W266C	NA	LP	Y			
CNSR304414	F	66	NOTCH3	disease	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR304488	M	54	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon3:c.G260T:p.C87F	NA	LP	Y			
CNSR304558	F	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon10:c.G1547T:p.C516F	NA	LP	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304990	M	45	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon14:c.C2149T:p.R717C	NA	LP	Y			
CNSR305140	M	59	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon22:c.C3568T:p.R1190C	NA	LP	Y			
CNSR305147	M	50	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon14:c.C2182T:p.R728C	LP	VUS	Y			
CNSR305228	M	56	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon20:c.C3298T:p.R1100C	NA	LP	Y			
CNSR305245	F	63	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P			Y	
CNSR305301	M	57	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR305508	M	57	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR305632	M	79	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon21:c.C3427T:p.R1143C	NA	LP	Y			
CNSR306139	F	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon16:c.T2498G:p.F833C	NA	LP	Y			
CNSR306600	M	52	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR306663	F	68	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon15:c.C2353T:p.R785C	NA	LP	Y			
CNSR306806	F	56	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon6:c.889_894delinsTG	NA	P			Y	
CNSR306879	M	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR306929	M	39	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR306956	M	82	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon15:c.C2353T:p.R785C	NA	LP	Y			
CNSR307019	F	63	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon12:c.T1931A:p.V644D	NA	LP	Y			
CNSR307044	F	52	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon4:c.G671A:p.C224Y	P	VUS	Y			
CNSR307182	M	44	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			
CNSR307435	M	74	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon18:c.2984delC:p.P99	NA	LP				Y
CNSR307912	M	65	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR308185	M	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon4:c.C619T:p.R207C	P/LP	VUS		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308416	F	75	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			
CNSR308638	F	52	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon9:c.1488delC:p.P496	NA	LP			Y	
CNSR308656	M	65	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P		Y		
CNSR308967	M	63	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1819T:p.R607C	P/LP	VUS	Y			
CNSR309724	M	49	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR310191	M	61	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	P	Y			
CNSR310413	M	75	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon21:c.C3427T:p.R1143C	NA	LP			Y	
CNSR300708	F	67	PRNP	Cerebral amyloid angiopathy, PRNP-related	Small vessel disease	NM_000311:exon2:c.G538A:p.V180I	P/LP	VUS			Y	
CNSR301128	M	76	PRNP	Cerebral amyloid angiopathy, PRNP-related	Small vessel disease	NM_000311:exon2:c.G538A:p.V180I	P/LP	VUS			Y	
CNSR304209	M	71	PRNP	Cerebral amyloid angiopathy, PRNP-related	Small vessel disease	NM_000311:exon2:c.G628A:p.V210I	P	VUS			Y	
CNSR304380	M	69	PSEN1	Alzheimer's disease	Small vessel disease	NM_000021:exon7:c.C658T:p.R220X	NA	P			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307124	F	71	TREX1	Vasculopathy, retinal, with cerebral leukoencephalopathy and systemic manifestations/RVCL-S	Small vessel disease	NM_016381:exon1:c.1024_1041del:p.342_347del	P	VUS			Y	
CNSR308620	M	70	TREX1	Vasculopathy, retinal, with cerebral leukoencephalopathy and systemic manifestations/RVCL-S	Small vessel disease	NM_016381:exon1:c.G832A:p.A278T,TR	LP	VUS			Y	
CNSR300109	F	67	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon3:c.A326G:p.E109G	NA	LP			Y	
CNSR300873	M	69	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.C347G:p.T116R	NA	LP		Y		
CNSR300907	M	45	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	
CNSR301040	M	74	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.T119C:p.V40A	NA	LP			Y	
CNSR301165	F	54	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	
CNSR302353	M	78	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP		Y		

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR303371	M	37	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	
CNSR304525	M	46	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.G424A:p.V142I	P/LP	VUS			Y	
CNSR304550	F	57	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon3:c.A287G:p.K96R	NA	LP			Y	
CNSR305919	M	61	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon3:c.G307A:p.G103S	NA	LP				Y
CNSR306558	F	45	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon3:c.G241A:p.E81K	P	VUS			Y	
CNSR306867	M	70	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	
CNSR307119	M	64	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.C347G:p.T116R	NA	LP			Y	
CNSR307312	F	64	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.T119C:p.V40A	NA	LP			Y	
CNSR307403	F	60	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon3:c.A287G:p.K96R	NA	LP			Y	
CNSR307497	M	60	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR307816	M	71	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	
CNSR307956	M	58	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP			Y	
CNSR308636	F	64	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.C419T:p.A140V	NA	LP			Y	
CNSR309004	M	62	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.G361A:p.G121S	NA	LP			Y	
CNSR310000	M	45	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.G349T:p.A117S	P/LP	VUS			Y	
CNSR310227	F	62	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.G361A:p.G121S	NA	LP			Y	
CNSR310334	M	47	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.G148A:p.V50M	P	LP			Y	
CNSR310356	M	69	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon4:c.C413T:p.T138I	NA	LP			Y	
CNSR302278	F	75	ACVRL1	Telangiectasia, hereditary hemorrhagic, type 2	Other disease	NM_000020:exon7:c.C936A:p.H312Q	NA	LP				Y
CNSR302466	M	55	ACVRL1	Telangiectasia, hereditary hemorrhagic, type 2	Other disease	NM_000020:exon6:c.G682A:p.V228I	LP	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304271	M	68	ACVRL1	Telangiectasia, hereditary hemorrhagic, type 2	Other disease	NM_001077401:exon6:c.817_818delinsTG:p.L273W	NA	LP			Y	
CNSR300263	M	79	APOA1	Amyloidosis, 3 or more types	Other disease	NM_000039:exon3:c.127dupG:p.V43fs	NA	LP			Y	
CNSR304280	F	47	APOA1	Amyloidosis, 3 or more types	Other disease	NM_000039:exon3:c.116_117insTGGC:p.A39fs	NA	LP			Y	
CNSR302473	M	61	BMPR2	Pulmonary hypertension, primary	Other disease	NM_001204:exon2:c.77-1G>C	NA	P			Y	
CNSR303094	M	62	BMPR2	Pulmonary hypertension, primary	Other disease	NM_001204:exon12:c.G1687A:p.V563M	P	VUS			Y	
CNSR306598	M	76	BMPR2	Pulmonary hypertension, primary	Other disease	NM_001204:exon12:c.G1687A:p.V563M	P	VUS			Y	
CNSR310185	M	44	BMPR2	Pulmonary hypertension, primary	Other disease	NM_001204:exon12:c.G1687A:p.V563M	P	VUS			Y	
CNSR301648	M	64	CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	Other disease	NM_005188:exon13:c.2153+1G>T	NA	P				Y
CNSR308533	F	65	CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	Other disease	NM_005188:exon8:c.T1111C:p.Y371H	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR309022	F	51	DYRK1B	Abdominal obesity-metabolic syndrome 3	Other disease	NM_004714:exon10:c.C1462T:p.R488X	NA	P			Y	
CNSR309338	F	69	DYRK1B	Abdominal obesity-metabolic syndrome 3	Other disease	NM_004714:exon3:c.149_150del:p.V50fs	NA	LP			Y	
CNSR303561	M	60	ENG	Telangiectasia, hereditary hemorrhagic, type 1	Other disease	NM_000118:exon2:c.G219A:p.T73T	P	VUS			Y	
CNSR304704	M	45	FLCN	Birt-Hogg-Dube syndrome	Other disease	NM_144997:exon12:c.1381dupA:p.S461fs	NA	LP			Y	
CNSR307128	M	72	FLCN	Birt-Hogg-Dube syndrome	Other disease	NM_144997:exon4:c.7delG:p.A3fs	NA	LP			Y	
CNSR309913	F	58	FLCN	Birt-Hogg-Dube syndrome	Other disease	NM_144997:exon11:c.1285dupC:p.H429fs	P	LP			Y	
CNSR309961	M	47	FLCN	Birt-Hogg-Dube syndrome	Other disease	NM_144997:exon11:c.1285dupC:p.H429fs	P	LP			Y	
CNSR310041	M	61	FLCN	Birt-Hogg-Dube syndrome	Other disease	NM_144997:exon9:c.C1015T:p.Q339X	NA	P			Y	
CNSR304882	F	44	GLA	Fabry Disease	Other disease	NM_000169:exon3:c.514delT:p.C172fs	NA	LP		Y		
CNSR306744	M	76	GLA	Fabry Disease	Other disease	c.639+919G>A	P	VUS		Y		
CNSR301291	F	84	KIF1B	Pheochromocytoma	Other disease	NM_015074:exon6:c.C463T:p.R155X	NA	P			Y	
CNSR308367	M	84	KIF1B	Pheochromocytoma	Other disease	NM_183416:exon21:c.1996delG:p.G666fs	NA	LP			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300249	M	56	KRIT1	Cerebral cavernous malformations-1	Other disease	NM_194454:exon13:c.G1391A:p.W464X	P	P	Y			
CNSR302326	F	51	KRIT1	Cerebral cavernous malformations-1	Other disease	NM_194456:exon8:c.457dupA:p.T153fs	NA	LP			Y	
CNSR304825	F	60	KRIT1	Cerebral cavernous malformations-1	Other disease	NM_194456:exon6:c.262+1G>A	NA	P			Y	
CNSR305230	M	63	KRIT1	Cerebral cavernous malformations-1	Other disease	NM_194456:exon5:c.T33G:p.Y11X	NA	LP			Y	
CNSR309657	M	51	KRIT1	Cerebral cavernous malformations-1	Other disease	NM_194456:exon9:c.T585A:p.Y195X	NA	LP			Y	
CNSR305024	M	52	NF1	Neurofibromatosis 1	Other disease	NM_000267:exon41:c.C6349T:p.Q2117X	NA	P		Y		
CNSR305340	M	53	NF1	Neurofibromatosis 1	Other disease	NM_000267:exon18:c.2027dupC:p.T676fs	P	LP		Y		
CNSR307410	M	73	NF1	Neurofibromatosis 1	Other disease	NM_000267:exon4:c.G479A:p.R160K	LP	VUS		Y		
CNSR304809	M	53	PDE4D	Acrodysostosis 2, with or without hormone resistance	Other disease	NM_001165899:exon3:c.G94T:p.G32X	NA	P			Y	
CNSR304838	F	62	PDE4D	Acrodysostosis 2, with or without hormone resistance	Other disease	NM_001197223:exon1:c.18_21del:p.Y6fs	NA	LP			Y	
CNSR300154	M	60	PKD1	ADPKD	Other disease	NM_001009944.3(PKD1):c.7065+9C>T	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300265	M	53	PKD1	ADPKD	Other disease	NM_001009944:exon10:c.1987delC:p.Q663fs	NA	LP		Y		
CNSR301236	M	69	PKD1	ADPKD	Other disease	NM_001009944:exon44:c.G12036A:p.W4012X	P	P		Y		
CNSR301587	F	64	PKD1	ADPKD	Other disease	NM_001009944:exon29:c.C9829T:p.R3277C	P/LP	VUS			Y	
CNSR304664	F	49	PKD1	ADPKD	Other disease	NM_001009944:exon11:c.T2534G:p.L845W	NA	LP			Y	
CNSR306045	F	56	PKD1	ADPKD	Other disease	NM_001009944:exon19:c.G7494A:p.W2498X	NA	P			Y	
CNSR306128	M	65	PKD1	ADPKD	Other disease	NM_001009944:exon34:c.10499+1G>A	NA	P			Y	
CNSR309549	M	47	PKD1	ADPKD	Other disease	NM_001009944:exon11:c.T2534C:p.L845S	P/LP	VUS			Y	
CNSR309966	F	50	PKD1	ADPKD	Other disease	NM_001009944:exon45:c.G12391T:p.E4131X	P	P			Y	
CNSR301946	M	67	PKD2	ADPKD	Other disease	NM_000297:exon3:c.779delC:p.T260fs	NA	LP			Y	
CNSR301999	F	54	PKD2	ADPKD	Other disease	NM_000297:exon4:c.C958T:p.R320X	P	P	Y			
CNSR303365	M	53	PKD2	ADPKD	Other disease	NM_000297:exon4:c.1094+1G>C	NA	P	Y			

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304191	F	57	PKD2	ADPKD	Other disease	NM_000297:exon14:c.C2533T:p.R845X	P	P	Y			
CNSR308318	M	59	PKD2	ADPKD	Other disease	NM_000297:exon12:c.G2305T:p.E769X	LP	P	Y			
CNSR308733	F	63	PKD2	ADPKD	Other disease	NM_000297:exon6:c.T1506G:p.Y502X	NA	P	Y			
CNSR301009	F	76	RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease	NM_020975:exon14:c.G2410A:p.V804M	P/LP	VUS			Y	
CNSR301675	M	62	RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease	NM_020975:exon14:c.G2410A:p.V804M	P/LP	VUS			Y	
CNSR303165	F	61	RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease	NM_020975:exon14:c.G2410A:p.V804M	P/LP	VUS			Y	
CNSR305395	M	60	RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease	NM_020975:exon13:c.G2370T:p.L790F	P	VUS			Y	
CNSR309526	F	64	RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease	NM_020975:exon13:c.G2370T:p.L790F	P	VUS			Y	
CNSR310343	M	68	RET	Medullary thyroid carcinoma or Pheochromocytoma	Other disease	NM_020975:exon14:c.G2410A:p.V804M	P/LP	VUS			Y	
CNSR303341	M	44	TGIF1	Holoprosencephaly 4	Other disease	NM_173208:exon3:c.C83T:p.S28F	NA	LP			Y	
CNSR308090	F	71	TGIF1	Holoprosencephaly 4	Other disease	NM_173208:exon4:c.A451G:p.T151A	P	VUS			Y	

eTable 3 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308126	M	66	TGIF1	Holoprosencephaly 4	Other disease	NM_173208:exon4:c.A451G:p.T151A	P	VUS			Y	
CNSR304572	M	62	VHL	Pheochromocytoma	Other disease	NM_000551:exon3:c.A479G:p.E160G	NA	LP				Y

eTable 4 Diagnoses of 29 individuals harbored more than 2 P/LP variants in different genes

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR300094	M	70	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.C160T:p.R54X	NA	LP			Y	
CNSR300094	M	70	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon28:c.C4909T:p.Q1637X	NA	P		Y		
CNSR300101	M	68	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon3:c.497delinsGGATCCCCCAGCTGCATCCCCCAG:p.A166GfsX48	LP	VUS		Y		
CNSR300101	M	68	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR300197	F	67	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR300197	F	67	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon2:c.C235T:p.R79C	LP	VUS			Y	
CNSR300499	F	82	ELN	SVAS	Large artery disease	c.639+919G>A	NA	P			Y	
CNSR300499	F	82	GLA	Fabry Disease	Other disease	NM_000501:exon14:c.686-2A>G	P	VUS		Y		
CNSR300830	M	64	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon3:c.T560C:p.L187P	P/LP	VUS		Y		
CNSR300830	M	64	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR301010	M	55	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon5:c.G796A:p.D266N	P/LP	VUS			Y	

eTable 4 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR301010	M	55	PDE4D	Acrodysostosis 2, with or without hormone resistance	Other disease	NM_001197220:exon1:c.65+1G>A	NA	P			Y	
CNSR301223	M	53	SCN2B	Hereditary cardiac dysrhythm	Embolic stroke	NM_004588:exon2:c.C142G:p.L48V	NA	LP			Y	
CNSR301223	M	53	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon5:c.G805A:p.G269S	P/LP	VUS	Y			
CNSR301496	M	47	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS	Y			
CNSR301496	M	47	NF1	Neurofibromatosis 1	Other disease	NM_000267:exon25:c.3240delA:p.L1080fs	NA	LP		Y		
CNSR301738	F	64	FBN1	Marfan syndrome	Large artery disease	NM_000138:exon27:c.C3268G:p.P1090A	NA	LP			Y	
CNSR301738	F	64	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS		Y		
CNSR301797	M	77	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon11:c.G1303A:p.E435K	NA	LP			Y	
CNSR301797	M	77	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon44:c.G7450A:p.V2484I	LP	VUS			Y	
CNSR302006	M	46	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR302006	M	46	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR302050	F	76	KCNQ1	Hereditary cardiac dysrhythm	Embolic stroke	NM_000218:exon6:c.G815A:p.G272D	P	VUS	Y			
CNSR302050	F	76	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon326:c.C85223G:p.S28408X	NA	P			Y	

eTable 4 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR302050	F	76	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon13:c.G1898T:p.R633L	NA	P	Y			
CNSR302176	M	63	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon2:c.T222G:p.Y74X	NA	LP			Y	
CNSR302176	M	63	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon7:c.G691A:p.G231R	NA	LP			Y	
CNSR303412	F	70	GJA1	Atrioventricular septal defect 3	Embolic stroke	NM_000165:exon2:c.G158A:p.R53H	NA	LP			Y	
CNSR303412	F	70	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	
CNSR303485	M	50	JAK2	Thrombocythemia 3	Prothrombotic state	NM_004972:exon14:c.G1849T:p.V617F	P	VUS			Y	
CNSR303485	M	50	DYRK1B	Abdominal obesity-metabolic syndrome 3	Other disease	NM_004714:exon8:c.C1072T:p.R358X	NA	P			Y	
CNSR303619	M	65	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon11:c.1115_1127del:p.Q372fs	NA	LP			Y	
CNSR303619	M	65	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon39:c.G3589A:p.G1197S	NA	LP			Y	
CNSR303839	M	55	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_001267550:exon324:c.69145delA:p.I23049fs	NA	LP		Y		
CNSR303839	M	55	SERPINC1	Thrombophilia due to antithrombin III deficiency	Prothrombotic state	NM_000488:exon3:c.T442C:p.S148P	P	VUS			Y	
CNSR303839	M	55	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon14:c.1614delC:p.P538	NA	LP			Y	
CNSR304342	M	53	KCNA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_002234:exon1:c.C1727T:p.A576V	P	VUS			Y	

eTable 4 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR304342	M	53	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.C13231T:p.Q4411X	NA	LP			Y	
CNSR306238	F	74	CETP	Hyperalphalipoproteinemia	Large artery disease	NM_000078:exon13:c.1225_1226insAGACT:p.K409fs	NA	LP			Y	
CNSR306238	F	74	PRNP	Cerebral amyloid angiopathy, PRNP-related	Small vessel disease	NM_000311:exon2:c.G538A:p.V180I	P/LP	VUS		Y		
CNSR306857	M	74	TTN	Hereditary cardiomyopathies	Embolic stroke	NM_133379:exon46:c.13109delC:p.S4370X	NA	LP			Y	
CNSR306857	M	74	RNF213	Moyamoya disease	Large artery disease	NM_001256071:exon60:c.G14429A:p.R4810K	P	VUS			Y	
CNSR306857	M	74	F2	Thrombophilia due to thrombin defect	Prothrombotic state	NM_000506:exon2:c.T80C:p.V27A	NA	LP			Y	
CNSR306857	M	74	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon20:c.G2561A:p.R854Q	P/LP	VUS			Y	
CNSR307276	M	53	PROC	Thrombophilia due to protein C deficiency, autos	Prothrombotic state	NM_000312:exon9:c.G1000A:p.G334S	P	VUS			Y	
CNSR307276	M	53	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon30:c.2577_2578insGG	NA	LP				Y
CNSR307448	M	64	MFAP5	Aortic aneurysm, familial thoracic 9	Large artery disease	NM_003480:exon10:c.C472T:p.R158X	P	VUS			Y	
CNSR307448	M	64	TGIF1	Holoprosencephaly 4	Other disease	NM_173208:exon4:c.A451G:p.T151A	P	VUS			Y	
CNSR307803	M	64	VWF	von Willebrand disease, type 1	Prothrombotic state	NM_000552:exon22:c.C2965T:p.Q989X	NA	P			Y	
CNSR307803	M	64	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1759T:p.R587C	NA	LP	Y			

eTable 4 Continued

Code_n	Gender	Age	Gene	Phenotype	Etiology of stroke	Mutation	Clinvar	ACMG	Definite	Possible	Undetermined	Insufficient Information
CNSR308769	M	58	ELN	SVAS	Large artery disease	splicing	P	P			Y	
CNSR308769	M	58	LDLR	Hypercholesterolemia, familial, 1	Large artery disease	NM_000527:exon10:c.G1567A:p.V523M	P	VUS		Y		
CNSR308831	M	42	COL4A2	Brain small vessel disease 2	Small vessel disease	NM_001846:exon12:c.G701T:p.G234V	NA	LP			Y	
CNSR308831	M	42	PKD1	ADPKD	Other disease	NM_001009944:exon45:c.G12391T:p.E4131X	P	P			Y	
CNSR309790	M	57	RBM20	Hereditary cardiomyopathies	Embolic stroke	NM_001134363:exon2:c.870delA:p.S290fs	NA	LP			Y	
CNSR309790	M	57	TTR	Amyloidosis, hereditary, transthyretin-related	Small vessel disease	NM_000371:exon2:c.C170A:p.A57D	NA	LP				Y
CNSR310131	M	60	MYBPC3	Hereditary cardiomyopathies	Embolic stroke	NM_000256:exon12:c.1042_1043insCGGCA:p.M348fs	P	LP			Y	
CNSR310131	M	60	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon11:c.C1630T:p.R544C	P/LP	VUS	Y			
CNSR310244	M	53	GATA4	Tetralogy of Fallot	Embolic stroke	NM_001308093:c.1000+103G>T	P	VUS			Y	
CNSR310244	M	53	NF1	Neurofibromatosis 1	Other disease	NM_000267:exon14:c.1541_1542del:p.Q514fs	P	LP		Y		
CNSR310283	M	59	GJA5	Hereditary cardiac dysrhythm	Embolic stroke	NM_005266:exon2:c.C292T:p.H98Y	NA	LP		Y		
CNSR310283	M	59	NOTCH3	CADASIL	Small vessel disease	NM_000435:exon3:c.C328T:p.R110C	P	VUS	Y			

eTable 5 Four individuals with 2 P/LP variants in the *ABCC6* gene

Code	Gender	Age	Gene	Mutation	Clinvar	ACMG	Phenotype
CNSR309580	F	66	ABCC6	NM_001171: exon26: c.C3703T: p.R1235W	P	VUS	Pseudoxanthoma elasticum
CNSR301384	M	53	ABCC6	NM_001171: exon31: c.4404-1G>A	NA	P	Pseudoxanthoma elasticum
CNSR301384	M	53	ABCC6	NM_001171: exon24: c.C3490T: p.R1164X	P	P	Pseudoxanthoma elasticum
CNSR309564	M	37	ABCC6	NM_001171: exon26: c.C3703T: p.R1235W	P	VUS	Pseudoxanthoma elasticum
CNSR309564	M	37	ABCC6	NM_001171: exon28: c.G3892A: p.V1298I	NA	LP	Pseudoxanthoma elasticum
CNSR310336	M	48	ABCC6	NM_001171: exon26: c.3735+1G>T	NA	P	Pseudoxanthoma elasticum
CNSR310336	M	48	ABCC6	NM_001171: exon23: c.C3304T: p.Q1102X	NA	P	Pseudoxanthoma elasticum

eTable 6 Characteristics of the Patients with one MGD in C3 cohort

Characteristic	**ToTal (N=759)**	**Embolic stroke (N=245, 32.28)**	**Large artery disease (N=184, 24.24)**	**Prothrombotic state (N=124, 16.34)**	**Small vessel disease （N=148, 19.50)**	**Other disease (N=58, 7.64)**
Age at time of study entry, mean±SD	61.53±11.50	61.91±12.23	60.43±12.22	62.78±10.54	61.52±10.59	60.71±10.05
⩽45 yr	66 (8.70)	21 (8.57)	21 (11.41)	8 (6.45)	13 (8.78)	4 (6.90)
> 45 yr	693 (91.30)	226 (92.24)	163 (88.59)	116 (93.55)	135 (91.22)	54 (93.10)
Male, n (%)	504 (66)	162 (66.12)	119 (64.67)	89 (71.77)	98 (66.22)	36 (62.07)
Medical history, n (%)						
Ischaemic stroke	193 (25.43)	56 (22.86)	42 (22.83)	30 (24.19)	47 (31.76)	18 (31.03)
Coronary heart diseases	98 (12.91)	36 (14.69)	15 (8.15)	17 (13.71)	22 (14.86)	8 (13.79)
Atrial fibrillation	64 (8.43)	25 (10.20)	14 (7.61)	10 (8.06)	9 (6.08)	6 (10.35)
Hypertension	452 (59.55)	139 (56.73)	119 (64.67)	71 (57.26)	81 (54.73)	42 (72.41)
Diabetes mellitus	177 (23.32)	57 (23.27)	45 (24.46)	29 (23.39)	28 (18.92)	18 (31.03)
Dyslipidemia	68 (8.96)	26 (10.61)	10 (5.43)	8 (6.45)	18 (12.12)	6 (10.35)
Stroke type						
IS	718 (94.60)	233 (95.10)	171 (92.93)	119 (95.97)	142 (95.95)	53 (91.38)
TIA	41 (5.40)	12 (4.90)	13 (7.07)	5 (4.03)	6 (4.05)	5 (8.62)
Family history of Stroke	97 (12.78)	38 (15.51)	24 (13.04)	13 (10.48)	15 (10.14)	7 (12.07)
CCS						
Large artery atherosclerosis	220 (28.99)	66 (26.94)	70 (38.04)	33 (26.61)	40 (27.03)	11 (18.97)
Cardioaortic embolism	57 (7.51)	27 (11.02)	10 (5.43)	6 (4.84)	8 (5.41)	6 (10.35)
Small arterial occlusion	191 (25.16)	66 (26.94)	36 (19.57)	27 (21.77)	43 (29.05)	19 (32.76)
Other etiologies	11 (1.45)	1 (0.41)	6 (3.26)	1 (0.81)	3 (2.03)	0 (0.00)
Undetermined etiology	280 (36.89)	85 (34.69)	62 (33.70)	57 (45.97)	54 (36.49)	22 (37.93)

eTable 7 The characteristics of individuals who had been diagnosed monogenic stroke before gene testing

Code_n	Mendelian caused of stroke through EHR reviewed	Gene	Age	Gender
CNSR301140	Thrombocythemia	JAK2;exon11:c.G1402T:p.V468F,	67	Female
CNSR301496	Thrombocythemia	JAK2;exon11:c.G1402T:p.V468F,	47	Male
CNSR302832	Thrombocythemia	JAK2;exon11:c.G1402T:p.V468F,	63	Male
CNSR307039	Thrombocythemia	JAK2;exon11:c.G1402T:p.V468F,	66	Male
CNSR307566	Thrombocythemia	JAK2;exon11:c.G1402T:p.V468F,	62	Female
CNSR309872	Thrombocythemia	JAK2;exon11:c.G1402T:p.V468F,	75	Male
CNSR303251	Small vessel disease，CADASIL	NOTCH3;exon11:c.C1630T:p.R544C	64	Female
CNSR305508	Small vessel disease，CADASIL	NOTCH3;exon11:c.C1630T:p.R544C	57	Male
CNSR306929	Small vessel disease，CADASIL	NOTCH3;exon11:c.C1630T:p.R544C	39	Male
CNSR307912	Small vessel disease，CADASIL	NOTCH3;exon11:c.C1630T:p.R544C	65	Male
CNSR308967	Small vessel disease，CADASIL	NOTCH3;exon11:c.C1819T:p.R607C	63	Male
CNSR301757	Small vessel disease，CADASIL	NOTCH3;exon18:c.C2898A:p.C966X	46	Male
CNSR310283	Small vessel disease，CADASIL	NOTCH3;exon3:c.C328T:p.R110C	59	Male
CNSR307044	Small vessel disease，CADASIL	NOTCH3;exon4:c.G671A:p.C224Y	52	Female
CNSR302455	Moyamoya	RNF213;exon60:c.G14429A:p.R4810K	27	Female
CNSR304840	Moyamoya,PFO?	RNF213;exon60:c.G14429A:p.R4810K	30	Male
CNSR306251	Moyamoya	RNF213;exon60:c.G14429A:p.R4810K	48	Female