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# Genetic determinants in ischaemic stroke subtypes: Seven year findings and a review

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ABSTRACT

Stroke is a global health problem and a leading cause of disability worldwide. There have been numerable studies undertaking research on different aspects of ischaemic stroke employing various epidemiological, clinical and molecular parameters. Nevertheless ischaemic stroke being a complex disorder with different subtypes demands equal attention towards its subtypes too. Since there has been enough evidence that disposition to certain subtype is genetically determined and there is a distinct mechanism that influences its development, association studies should focus on subtypes simultaneously while studying specific genes. Data from such studies will thus provide better and intricate findings with regard to heterogenous ischaemic stroke. In the present review we discuss the genes studied by our group over a period of seven years in association with stroke subtypes in a South Indian population and correlate the findings with similar genetic studies from other populations so as to provide an overview of various genes involved in the pathogenesis of ischaemic stroke subtypes.

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## 1. Introduction

Stroke has been recognised as a multi-factorial polygenic and complex disease resulting from a combination of vascular, environmental and genetic factors (Della-Morte et al., 2012). Approximately 80–90% of strokes are ischaemic (IS), which happens when a blood vessel (artery) supplying the blood to an area of the brain becomes blocked by a blood clot (Bonita, 1992; Flossmann et al., 2004; Brown et al., 1996). The role of genetic determinants in ischaemic stroke has been demonstrated in a number of reports which include twin, family and animal model studies (Wang et al., 1997). Recent technological advancements and two major international projects i.e. 'Human Genome Project' and 'HapMap Project' have tremendously contributed in the discovery of genes associated with various complex diseases. The discovery of SNPs in the first project and the development of haplotype map of human genome in the latter have greatly influenced the role of association studies in complex diseases including cardiovascular diseases and stroke. Among the several genes reported to be associated with stroke only a few have been replicated which could be attributed to complex genetic aetiology and many loci influencing the pathophysiology of stroke. Nevertheless, the association of several identified genes with stroke still remains controversial and differences in ethnicity/race further add up to the underlying complexity of the disease, its risk and prognosis. Apart from these etiological factors ischaemic stroke is also characterised by different subtypes that have distinct pathophysiological mechanisms and different classification systems have been proposed for establishing the distinct stroke subtypes. These include The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, Stop-Stroke Study TOAST (SSS-TOAST) classification, the Causative Classification System (CCS), A-S-C-O (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other causes) classification and OSCP (Oxfordshire Community Stroke Project) classification (Adams et al., 1993; Ay et al., 2005, 2007; Amarenco et al., 2009; Bamford et al., 1991).

Among these the TOAST classification has been extensively used in majority of the studies, and it is also the first system based on stroke mechanism and currently the most preferred one, although with certain limitations. It classifies ischaemic stroke into 5 categories: large artery atherosclerosis (occlusion or stenosis with ≥50% diameter reduction of a brain-supplying artery with location and morphology typical of atherosclerosis); small artery occlusion (the presence of one of the traditional lacunar syndromes — pure motor stroke, pure sensory stroke, sensory motor stroke, ataxic hemiparesis, and dysarthria-clumsy hand syndrome additionally infarction <1.5 cm of diameter or normal CT/MRI examination, the absence of acute cerebral cortical dysfunction,

*Abbreviations:* TOAST, The Trial of ORG 10172 in Acute Stroke Treatment; CCS, Causative Classification System; OSCP, Oxfordshire Community Stroke Project; RAAS, Renin Angiotensin Aldosterone System; CT, computed tomography; MRI, magnetic resonance imaging; LAA, large artery atherosclerosis; ILA, intracranial large artery; ELA, extracranial large artery; SAO, small artery occlusion; CE, cardioembolism; ODA, other determined aetiologies; UDA, undetermined aetiology.

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and the absence of signs of cardiac embolisms); cardio-embolism (the presence of a high- or medium-risk source of cardiac embolism); other determined aetiologies (show some rare causes of stroke e.g. non-atherosclerotic vasculopathies, hypercoagulable states or haematologic disorders, genetic disorders and metabolic disorders and moreover diagnostic procedures, including blood tests or arteriography should reveal one of the unusual causes of stroke) and stroke of undetermined aetiology. The undetermined category is a heterogeneous group with no cause found despite proper investigation. Although a recent study undertaken by Marnane et al. (2010) found both the CCS and ASCO system to be good enough when compared with TOAST, they do suggest for a feasible single combined classification system (Marnane et al., 2010). Such a system if well-established will provide a uniform platform to harmonise the heterogenous ischaemic stroke to an extent and also for optimising the stroke treatment.

The genetic contribution to multifactorial stroke is polygenic. However, identifying the underlying genes has been a major challenge. Most studies have focussed on polymorphic variants promoting stroke, predisposing phenotypes or mediators. The polyetiologic ischaemic stroke shows marked variation in its subtypes, therefore studies focussing on genetic risk factors should equally pay attention to aetiological ischaemic stroke subtypes.

Significant research is being conducted to establish the relationship between the functional variants of a number of genes including genes involved in Renin Angiotensin Aldosterone System (RAAS), homocysteine metabolising gene, nitric oxide synthase metabolising gene, lipid metabolising gene, fibrinolytic/thrombotic genes, pro-inflammatory/anti-inflammatory genes and other classes of genes. However, very few studies have evaluated the role of various candidate genes in the development of specific stroke subtypes. Therefore, in the present study we aim to document the various genes involved in progression of different stoke subtypes in a South Indian population from Andhra Pradesh and also review the genes involved in the pathogenesis of stroke subtypes reported in other populations.

## 2. Materials and methods

### 2.1. Subjects

One thousand and five hundred ischaemic stroke patients (males: females = 1069:431) presenting with new stroke evaluated in the neurology department of Nizam's Institute of Medical Sciences (NIMS), Hyderabad (A.P., India) between June 2007 and March 2014 were enrolled for the study. The study was approved by the ethical committee of the study hospital as well as the Institutional Ethical Committee. All the patients were examined by a qualified stroke neurologist and ischaemic stroke was differentiated by computed tomography (CT) scans and magnetic resonance imaging (MRI). All the patients underwent CT scan as well as MRI. Patients with major cardiac, renal, hepatic, endocrinological disorders, skeletal disorders and cancerous diseases were excluded from this study. As a control group healthy individuals matched for sex and age were recruited from the same geographic area with no clinical evidence of any cerebrovascular disease. Information on demographic characteristics and risk factors was collected using a structured questionnaire. Samples were collected only after obtaining the written informed consent. The ischaemic stroke was classified into subtypes according to the TOAST classification (Adams et al., 1993) and hypertension, alcohol use, diabetes and smoking were defined as reported previously (Munshi et al., 2008).

### 2.2. DNA isolation and genotyping

A total of 5 ml of blood was collected in EDTA tubes and genomic DNA was extracted from blood samples using standard phenol–chloroform method. The polymorphisms in various genes reported in this study were detected as reported earlier (Munshi et al., 2008, 2009a, 2009b, 2010a, 2010b, 2010c, 2010d, 2011, 2012a, 2012b, 2012c; Babu et al., 2012; Das et al., 2014a; Roy et al., 2014b; Sharma et al., 2013).

### 2.3. Statistical analysis

Hardy–Weinberg equilibrium was tested for the various gene polymorphisms and the association between genotypes and ischaemic stroke was examined by odds ratio with 95% confidence interval (CI) and chi-square analysis using Open EPI6 software (Open Epi Version 2.3.1 from the Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA). Allelic frequencies were calculated according to the number of different alleles observed and the total number of alleles examined. Statistical significance was defined as $p < 0.05$.

## 3. Results

A total of 1500 ischaemic stroke patients were collected over a period of seven years. The clinical characteristics of all the patients have been given in Table 1. The mean age was 54.6 years for ischaemic stroke patients and the profiles of the patients for the various risk factors revealed hypertension in 57.5%, diabetes in 47.9%, smoking in 47.1%, alcohol use in 42.8% and family history of stroke in 21.6% of patients. The distribution of patients belonging to different subtypes according to TOAST classification has been given in Table 2. A total of 669 (44.6%) patients were found to be diagnosed with large artery atherosclerosis (LAA) of which 431 (64.4%) and 238 (35.6%) patients were found to be classified as intracranial and extracranial large artery respectively (ILA and ELA). Small artery occlusion (lacunar) (SAO) was diagnosed in 232 (15.5%), cardioembolism (CE) in 206 (13.7%), other determined aetiologies (ODA) in 82 (5.5%) and undetermined aetiology (UDA) in 311 (20.7%) of ischaemic stroke patients.

We have been studying the association of various candidate genes involved in various pathways with stroke and its subtypes for the past seven years (Munshi et al., 2008, 2009a, 2009b, 2010a, 2010b, 2010c, 2010d, 2011, 2012a, 2012b, 2012c; Babu et al., 2012; Das et al. 2014a; Roy et al. 2014b; Sharma et al., 2013). In the present study we have given a holistic picture of all these genes in association with stroke subtypes and have also evaluated all the 1500 IS samples because the sample size in some of our previous studies was low (Munshi et al., 2008, 2009b, 2010a, 2010b, 2010c, 2010d, 2012b; Das et al. 2014a). The various genes found to be associated with IS subtypes from different pathways in multiple ethnicities have been depicted in Figs. 1 and 2. The different genes studied in association with IS subtypes by us have been summarised in Table 3. The genes studied in RAAS system include ACE and CYP11B2. In ACE the I/D polymorphism studied revealed a significant association with subtype ILA [p = 0.007, OR = 1.78 (95% CI; 1.05–3.03)]. On the other hand the -344C/T polymorphism of

**Table 1**
Clinical characteristics of ischaemic stroke patients.

| Characteristics | Patients (n = 1500) |
|---|---|
| Age | 54.6 (16.4) |
| Male:female | 1069:431 |
| Systolic BP (mm Hg) (mean ± S.D.) | 149 (14.8) |
| Diastolic BP (mm Hg) (mean ± S.D.) | 90.7 (17.6) |
| Total cholesterol (mean ± S.D.) | 198.56 (40.2) |
| Triglycerides (mean ± S.D.) | 181.6 (39.42) |
| Random glucose (mean ± S.D.) | 132.7 (9.4) |
| HDL cholesterol (mean ± S.D.) | 58.3 (20.6) |
| Hypertension | 57.5% |
| Diabetes | 47.9% |
| Smoker | 47.1% |
| Alcohol use | 42.8% |
| Family history of stroke | 21.6% |

Age, systolic BP, diastolic BP, total cholesterol, high density lipoprotein (HDL) cholesterol, random glucose and triglycerides are given as mean (SD).

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**Table 2**
Distribution of ischaemic stroke subtypes classified according to TOAST classification.

| TOAST classification | Total no. of patients (1500) |
|---|---|
| Large artery atherosclerosis | 669 (44.6%) |
| A) Intracranial large artery | 431 (64.4%) |
| B) Extracranial large artery | 238 (35.6%) |
| Small artery occlusions (lacunar) | 232 (15.5%) |
| Cardioembolism | 206 (13.7%) |
| Other determined aetiologies | 82 (5.5%) |
| Undetermined aetiology | 311 (20.7%) |

CYP11B2 was found to be associated with ILA [$p < 0.001$, OR = 3.07 (95% CI; 1.55–5.95)], SAO [$p < 0.001$, OR = 4.00 (95% CI; 1.67–9.20)] and CE [$p < 0.001$, OR = 3.82 (95% CI; 1.09–9.50)]. The MTHFR gene which is involved in homocysteine metabolism, has been well studied in different ethnic populations, the C677T polymorphism of MTHFR evaluated in the study population was found to be associated with subtypes ILA [$p < 0.05$, OR = 1.6 (95% CI; 1.3–2.7)], SAO [$p < 0.05$, OR = 1.4 (95% CI; 1.12–3.01)] and UDA [$p < 0.05$, OR = 0.7 (95% CI; 0.28–0.95)]. The eNOS gene which plays an active role in the maintenance of vascular haemostasis was however, found not to be associated with any of the stroke subtypes. The LPL gene HindIII polymorphism which is involved in lipid metabolism was found to be associated with ILA [$p = 0.0003$, OR = 3.33 (95% CI; 1.54–7.23)] and SAO [$p = 0.07$, OR = 2.21 (95% CI; 0.92–5.59)]. The various genes studied in fibrinolytic and thrombotic genes were found to be associated with different stroke subtypes. The tPA C-7351T polymorphism showed a negative association whereas the I/D polymorphism was found to be associated with subtype ILA [$p < 0.001$, OR = 3.06 (95% CI; 1.68–4.73)] and UDA [$p = 0.004$, OR = 2.66 (95% CI; 1.35–5.05)]. However, the other two variants studied in this system i.e. PAI-1 gene, 4G/5G polymorphism and prothrombin gene G2021A polymorphism did not show a significant association with any specific stroke subtype. In pro-inflammatory/anti-inflammatory pathways G+448A polymorphism of TNF-α gene was found to be associated with ILA [$p = 0.026$, OR = 1.77 (95% CI; 1.16–3.10)], ELA [$p = 0.008$, OR = 2.65 (95% CI; 1.25–5.35)], CE [$p = 0.007$, OR = 2.34 (95% CI; 1.25–5.22)] and UDA [$p < 0.001$, OR = 3.29 (95% CI; 1.60–6.05)] but -1612 5A/6A polymorphism of MMP-3 gene and G1059C variant of CRP gene did not show a significant association with IS. On the other hand G-1082A polymorphism of IL-10 was found to be associated with subtypes ELA [$p = 0.01$, OR = 2.76 (95% CI; 1.14–4.64)] and UDA [$p = 0.0009$, OR = 3.8 (95% CI; 1.92–3.59)]. E-selectin S128R polymorphism was associated significantly with subtype ILA [$p < 0.001$, OR = 9.39 (95% CI; 5.35–16.9)] and SAO [$p < 0.001$, OR = 9.61(95% CI; 4.94–19.6)]. The -1382G polymorphism of CCL-11 gene was found to be associated with subtype ILA [$p < 0.0001$, OR = 9.3 (95% CI; 5.49–16.6)] and SAO [$p < 0.0001$, OR = 9.56 (95% CI; 4.77–19.7)]. Analysis of ALOX5AP gene for polymorphism SG13S114T/A showed association with subtype ILA [$p < 0.001$, OR = 2.07 (95% CI; 1.29–3.35)] and CE [$p = <0.001$, OR = 4.76 (95% CI; 2.9–8.5)]. Other genes which could not be grouped into particular system like CYP4F2 gene, G1347A polymorphism showed association with CE subtype of stroke [$p < 0.001$, OR = 4.28 (95% CI; 1.62–5.24)]. For the ESR1 gene, analysis of PvuII polymorphism showed positive association with subtypes ELA [$p = 0.002$, OR = 3.62 (95% CI; 1.35–5.74)], SAO [$p = 0.0005$, OR = 4.76 (95% CI; 2.52–9.91)], CE [$p = 0.0003$, OR = 3.29 (95% CI; 1.33–4.72)] and UDA [$p = 0.012$, OR = 3.02 (95% CI; 1.53–5.16)]. However, the other variant XbaI did not show a significant association with IS and its subtypes. For PDE4D gene SNPs 32 and 87 were reported to be negatively associated whereas, SNP 83 was found to be associated with subtypes ILA [$p < 0.0001$, OR = 2.95 (95% CI; 2.01–4.26)], ELA [$p = 0.034$, OR = 0.35 (95% CI; 0.09–1.08)] and SAO [$p < 0.0001$, OR = 3.08 (95% CI; 1.84–5.12)]. SNP 41 was found to be significantly associated with subtypes ILA [$p < 0.001$, OR = 3.16 (95% CI; 1.86–5.05)], ELA [$p = 0.002$, OR = 2.68 (95% CI; 1.32–5.07)], SAO [$p = 0.029$, OR = 2.21 (95% CI; 1.16–4.44)] and CE [$p = 0.044$, OR = 0.32 (95% CI; 0.18–1.06)]. On the other hand SNP 56 was found to be associated with all the subtypes ILA [$p < 0.001$, OR = 3.15 (95% CI; 1.9–5.55)], ELA [$p <$

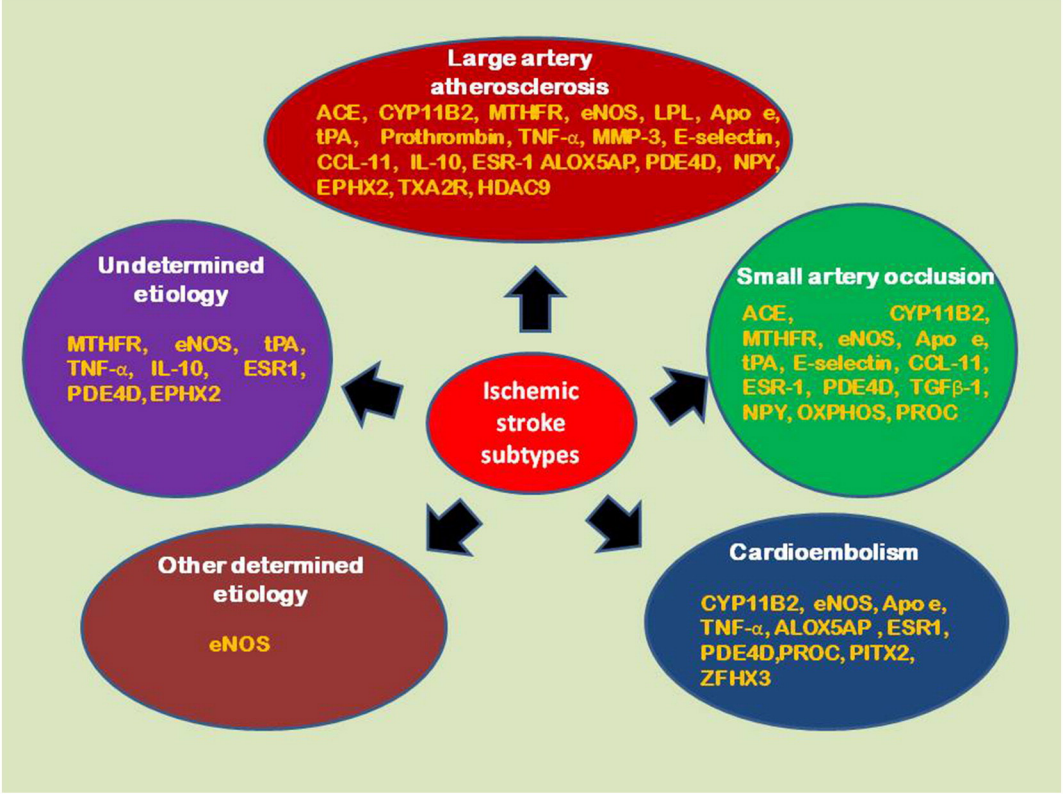


**Fig. 1.** Genes found to be associated with ischaemic stroke subtypes (TOAST classification).

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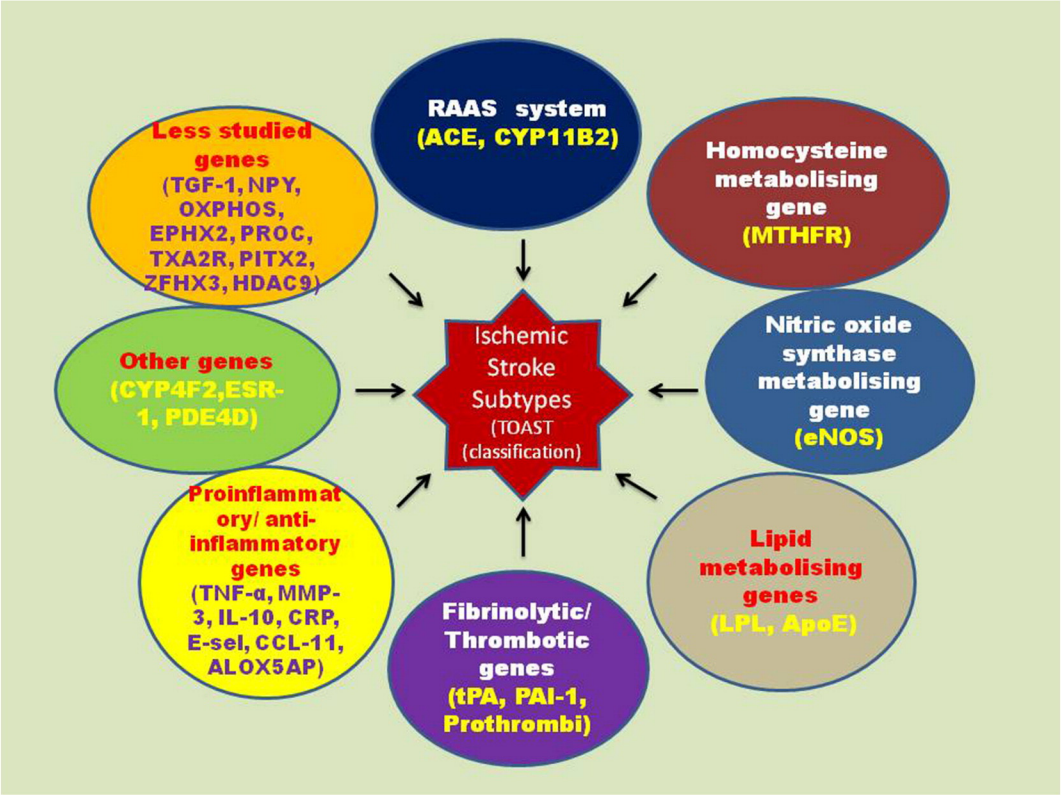


**Fig. 2.** Various genes from different pathways reported to be associated with ischaemic stroke subtypes.

0.001, OR = 3.17 (95% CI; 1.7–6.14)] SAO [$p < 0.001$, OR = 4.74 (95% CI; 2.85–8.56)], ODA [$p < 0.001$, OR = 6.74 (95% CI; 2.76–15.36)] and UDA [$p < 0.001$, OR = 3.98 (95% CI; 2.75–6.67)].

## 4. Discussion

This study by our group is a population based case–control prospective study carried over a period of seven years from 2007 to 2014 in a South Indian population from Andhra Pradesh. The association of various candidate genes with IS and its subtypes classified according to TOAST classification has been evaluated. As IS is a major cause of morbidity, mortality and an economic burden on developing countries multiple research is being carried out on different risk factors of stroke like genetic, molecular, biochemical, cytological, and epidemiological. In the present study however, we have tried to present a consolidated account of different genes studied in association with IS subtypes globally and also discuss the subtypes found to be significantly associated with different genes involved in various pathways, studied so far by us. Such a review in our opinion will convey the idea of need for increase in stroke subtype research.

### *4.1. Renin Angiotensin Aldosterone System (RAAS) genes*

#### *4.1.1. Angiotensin Converting Enzyme (ACE)*

This gene plays an important role in hypertension and cerebrovascular diseases (CVD) and is involved in cardiac and vascular fibrosis (Holtz, 1993; Ruiz-Ortega et al., 2001). ACE is a rate-limiting enzyme and the most widely studied gene of this system involved in vascular remodelling and atherosclerosis (Slowik et al., 2004). Our study involving ACE gene I/D polymorphism revealed a significant association of DD genotype only with ILA (Table 3) (Munshi et al., 2008). This might be because ILA was the most frequent IS subtype in our study (Table 2). Most noted difference of the stroke registry of NIMS (the study hospital) from western registries was the predominance of ILA rather than ELA of LAA. However, association with risk of lacunar infarction has been reported in a Japanese population with no effect in atherothrombotic and cardioembolic infarction (Mizuno et al., 2003). Markus et al. also reported a positive association of D allele with lacunar infarction (Markus et al., 1995). In contrast to this, another study from Japan reported the association with thrombotic brain infarction (Doi et al., 1997). Similar association was also found in a study involving 29 case–control studies from China that documents the DD genotype to be a risk factor for cerebral infarction (Tao et al., 2009). A meta-analysis involving 11 studies by Rao et al., suggests the DD genotype to be a greater risk factor for small vessel when compared with large vessel disease (Rao et al., 2009). In contrast to these findings a study involving Polish population could not establish an association of this polymorphism with any of the etiological ischaemic stroke subtypes (Pera et al., 2006).

#### *4.1.2. Aldosterone synthase gene (CYP11B2)*

The other well-studied gene of RAAS is aldosterone synthase gene CYP11B2. We found a positive association of -344C/T polymorphism of this gene with ILA, SAO and CE (Munshi et al., 2010a) (Table 3). Similar results were also observed by two other independent studies among Tunisian Arabs and Chinese Han population (Saidi et al., 2010; Yan and Wang, 2012). In contrast to these a recent meta-analysis by Pi et al. reports no such significant association for the polymorphism with IS (Pi et al., 2013). Q14

Nevertheless studies focussing on other related genes from RAAS excluding ACE gene have been less and therefore a great amount of focus is needed on them.

### *4.2. Homocysteine metabolising gene*

#### *4.2.1. Methylene tetrahydrofolate reductase (MTHFR)*

Elevated level of homocysteine is an independent risk factor for IS. Increasing concentration of homocysteine leads to elevated levels of S-adenosyl homocysteine which is an inhibitor for methyl transferases

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**Table 3**
Summary of different genes studied by us in South Indian population in ischaemic stroke subtypes.

| S. no | Gene | SNP | Association | Subtype | OR | 95% CI | p value | No. of positive cases (mutants) specific to subtype (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | ACE | I/D | Positive | Intracranial large artery | 1.78 | (1.05–3.03) | =0.007 | 73 (16.9%) |
| 2 | CYP11B2 | -344C/T | Positive | Intracranial large artery | 3.07 | (1.55–5.95) | <0.001 | 212 (49.2%) |
| | | | | Lacunar stroke | 4.00 | (1.67–9.20) | <0.001 | 140 (60.3%) |
| | | | | Cardioembolic stroke | 3.82 | (1.09–9.50) | <0.001 | 88 (28.3%) |
| 3 | MTHFR | C677T | Positive | Intracranial large artery | 1.6 | (1.3–2.7) | <0.05 | 21 (4.9%) |
| | | | | Lacunar stroke | 1.4 | (1.12–3.01) | <0.05 | 14 (6.03%) |
| | | | | Undetermined aetiology | 0.7 | (0.28–0.95) | <0.05 | 6 (1.9%) |
| 4 | eNOS | Intron 4b/a | Positive | No specific subtype | | | | |
| 5 | LPL | HindIII | Positive | Intracranial large artery | 3.33 | (1.54–7.23) | =0.0003 | 240 (55.7%) |
| | | | | Lacunar stroke | 2.21 | (0.92–5.59) | =0.07 | 142 (61.2%) |
| 6 | tPA | C-7351T | Negative | Intracranial large artery | 3.06 | (1.68–4.73) | <0.001 | 86 (19.9%) |
| | | I/D | Positive | Undetermined aetiology | 2.66 | (1.35–5.05) | =0.004 | 49 (15.7%) |
| 7 | PAI-1 | 4G/5G | Negative | | | | | |
| 8 | Prothrombin | G2021A | Negative | | | | | |
| 9 | TNF-α | G+448A | Positive | Intracranial large artery | 1.77 | (1.16–3.10) | =0.026 | 67 (15.5%) |
| | | | | Extracranial large artery | 2.65 | (1.25–5.35) | =0.008 | 64 (26.9%) |
| | | | | Cardioembolism | 2.34 | (1.25–5.22) | =0.007 | 44 (21.3%) |
| | | | | Undetermined aetiology | 3.29 | (1.60–6.05) | <0.001 | 71 (22.8%) |
| 10 | MMP-3 | -1612 5A/6A | Negative | | | | | |
| 11 | IL-10 | G-1082A | Positive | Extracranial large artery | 2.76 | (1.14–4.64) | =0.01 | 68 (28.6%) |
| | | | | Undetermined aetiology | 3.8 | (1.92–3.59) | =0.0009 | 84 (27%) |
| 12 | CRP | G1059C | Negative | | | | | |
| 13 | E-selectin | S128R | Positive | Intracranial large artery | 9.39 | (5.35–16.9) | <0.001 | 22 (5%) |
| | | | | Lacunar stroke | 9.61 | (4.94–19.6) | <0.001 | 4 (1.72%) |
| 14 | CCL-11 | A-1382G | Positive | Intracranial large artery | 9.3 | (5.49–16.6) | <0.0001 | 374 (86.7%) |
| | | | | Lacunar stroke | 9.56 | (4.77–19.7) | <0.0001 | 177 (76.3%) |
| 15 | ALOX5 | SG13S114 | Positive | Intracranial large artery | 2.07 | (1.29–3.35) | <0.001 | 116 (26.9%) |
| | | T/A | | Cardioembolism | 4.76 | (2.9–8.5) | <0.001 | 95 (46.1%) |
| 16 | CYP4F2 | G1347A | Positive | Cardioembolic stroke | 4.28 | (1.62–5.24) | <0.001 | 92 (44.7%) |
| 17 | ESR1 | PvuII (rs2234693) | Positive | Extracranial large artery | 3.62 | (1.35–5.74) | =0.002 | 57 (23.9%) |
| | | | | Lacunar stroke | 4.76 | (2.52–9.91) | =0.0005 | 47 (20.2%) |
| | | | | Cardioembolism | 3.29 | (1.33–4.72) | =0.0003 | 60 (29.1%) |
| | | XbaI (rs9340799) | Negative | Undetermined aetiology | 3.02 | (1.53–5.16) | =0.012 | 56 (18%) |
| 18 | PDE4D | SNP 32 | Negative | Intracranial large artery | 2.95 | (2.01–4.26) | <0.0001 | 87 (20.2%) |
| | | SNP 87 | Negative | Extracranial large artery | 0.35 | (0.09–1.08) | =0.034 | 9 (3.8%) |
| | | SNP 83 | Positive | Lacunar stroke | 3.08 | (1.84–5.12) | <0.0001 | 53 (22.8%) |
| | | SNP 41 | Positive | Intracranial large artery | 3.16 | (1.86–5.05) | <0.001 | 130 (30.1%) |
| | | | | Extracranial large artery | 2.68 | (1.32–5.07) | =0.002 | 60 (25.2%) |
| | | | | Lacunar stroke | 2.21 | (1.16–4.44) | =0.029 | 47 (20.2%) |
| | | | | Cardioembolism | 0.32 | (0.18–1.06) | =0.044 | 17 (8.2%) |
| | | SNP 56 | Positive | Intracranial large artery | 3.15 | (1.9–5.55) | <0.001 | 90 (20.9%) |
| | | | | Extracranial large artery | 3.17 | (1.7–6.14) | <0.001 | 55 (23.1%) |
| | | | | Lacunar stroke | 4.74 | (2.85–8.56) | <0.001 | 58 (25%) |
| | | | | Other determined aetiologies | 6.74 | (2.76–15.36) | <0.001 | 48 (58.5%) |
| | | | | Undetermined aetiology | 3.98 | (2.75–6.67) | <0.001 | 91 (29.3%) |

that alters methylation of genes and thus modulates gene expression changes (Yi et al., 2000). Among the genes involved in the metabolism of homocysteine, methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism plays a pivotal role by decreasing the activity of MTHFR and increasing homocysteine levels (Weisberg et al., 1998). Choi et al. and They-They et al. suggest the C677T polymorphism to be a risk factor for SAO and atherothrombotic stroke respectively (Choi et al., 2003; They-They et al., 2011). A large case–control study from China also reported the polymorphism to be responsible for cerebral thrombotic stroke (Li et al., 2003). Hassan et al. document the C677T polymorphism to be associated with ischaemic leukoaraiosis (cerebral small vessel disease causing lacunar infarction) among Caucasians (Hassan et al., 2004a, 2004b). We studied polymorphism C677T in association with IS subtypes and found the CT genotype to be a strong risk factor for ILA, SAO and UDA (unpublished data) (Table 3). Studies analysing the homocysteine metabolising genes with respect to stroke subtypes are very few since majority of the studies have focussed on homocysteine levels in association with the variant genotype.

### 4.3. Nitric oxide synthase metabolising gene

#### 4.3.1. Endothelial nitric oxide synthase gene (eNOS)

NOS family of genes generates nitric oxide (NO) in blood vessels and regulates vascular function and maintenance of vascular homeostasis. Reduction in the activity of vascular endothelial nitric oxide synthase leads to impaired endothelium dependent vasodilation that is implicated in stroke (Stagliano et al., 1997). Our study on eNOS 4b/a variable number tandem repeat (VNTR) polymorphism of eNOS gene, revealed a significant association with IS but it did not associate with any specific stroke subtype (Munshi et al., 2010b) (Table 3). Study by Hassan et al., involving T-786C and intron 4b/a polymorphism reported the combination of -786C and intron 4a alleles to be protective in lacunar infarction suggesting this haplotype to have a particular functional role. One potential explanation suggested for this effect is that intron 4, 27-bp repeat element has a *cis* regulatory role that enhances the transcription activity at the -786 locus (Hassan et al., 2004a, 2004b; Wang et al., 2002) but contrary to this finding Hou et al. found the 4a allele to be a risk factor for all stroke subtypes (Hou et al., 2001). Although, we did not study the mutation T-786C in our samples we could not reach any conclusive results on IS subtype association with variant eNOS 4b/a despite being positive for IS.

### 4.4. Lipid metabolising genes

#### 4.4.1. Lipoprotein lipase gene (LPL)

Lipoprotein and lipid metabolising genes have been implicated in the pathogenesis of ischaemic, cerebrovascular diseases and atherosclerosis. The lipoprotein lipase (LPL) gene is known to play an important

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role in plasma lipoprotein metabolism. We evaluated HindIII polymorphism of the gene in association with stroke subtypes and a significant association with IS subtype ILA was observed (Munshi et al., 2012a) (Table 3). A possible explanation for this could be that SAO is due to atherosclerosis, microatheroma and hemodynamic perfusion but no such atherosclerotic role exists for CE stroke because it is due to embolism in patients with nonvalvular arterial fibrillation (Shimo-Nakanishi et al., 2001). The study by Shimi-Nakanishi et al., involving HindIII, PvuII and Ser447Stop mutations documented the association of only HindIII polymorphism with atherothrombotic cerebral infarction (Shimo-Nakanishi et al., 2001). In contrast to this, study by Xu et al., among the Chinese suggested the association of PvuII polymorphism and Ser447Stop mutation and not HindIII polymorphism with cerebral infarction (Xu et al., 2008). However, we are yet to evaluate the PvuII and Ser447Stop mutations in the study population.

#### 4.4.2. Apolipoprotein E gene (ApoE)

This gene plays a major role in lipid transport and metabolism and is a common gene studied in neurodegenerative diseases (Eichner et al., 2002). This glycoprotein has three isoforms 2, 3 and 4 which gives rise to 6 genotypes. A majority of studies report 4 allele to be associated with high LDL cholesterol levels and cardiovascular/cerebrovascular disease (Lenzen et al., 1986; McCarron et al., 1999). There have been significant studies evaluating the gene in different ethnicities. Lai et al. reported the 3/4 genotype to be significantly associated with SAO among the Chinese (Lai et al., 2007) whereas Kokubo et al. suggested 2 to be a risk factor for atherothrombosis and CE (Kokubo et al., 2000). However, a study by Kang et al. found no difference in the genotypes between LAA and SAO (Kang and Lee, 2006). The association of apo 4 with large vessel disease was also reported by Saidi et al., among the Tunisians and by Kessler et al., among the Germans (Saidi et al., 2009; Kessler et al., 1997). Abboud et al. from Belgium also reported the association of apo 4 genotype with intracranial atherosclerosis (Abboud et al., 2008). However, in contrast to these findings, the large Italian cohortstudy by Cerrato et al., could not establish any significant difference in the frequency of apo 4 genotypes between cases and controls (Cerrato et al., 2005). However as far as the association of ApoE gene variants with stroke and its subtypes in the study population is concerned, the research is still going on and therefore could not be included in the current paper.

### 4.5. Fibrinolytic/thrombotic genes

Abnormalities in fibrinolytic and thrombotic genes have been implicated in atherosclerotic diseases like myocardial infarction and stroke. A delicate interplay between these genes tremendously affects the pathological process and the insult to vascular regions of brain in IS.

#### 4.5.1. Tissue pasminogen activator gene (tPA)

It is a serine protease and endothelium-derived tPA is the primary mediator of local intravascular fibrinolysis. The two polymorphisms studied by us in this gene are tPA I/D and -7351C>T. Only the former revealed a positive association with IS subtypes ILA and UDA (Babu et al., 2012) (Table 3). A recent meta-analysis also found -7351C>T to be a significant risk factor among East Asians when compared with Caucasians and South Asians and after stratification the association was more prominent in LAA rather than in SAO and CE (Sun et al., 2013). However, Jannes et al. (2004) and Geng et al. (2008) found this polymorphism to be associated with lacunar infarction classified according to OSCP (Oxfordshire Community Stroke Project) classification. This disparity in association with subtypes could be attributed to different classification systems, since TOAST classification is based on clinical symptoms and OSCP classification system is based on initial symptoms.

#### 4.5.2. Plasminogen activator inhibitor type-1 (PAI-1) gene

This gene is known to regulate the function of thrombin and is the main inhibitor for tPA. However, we could not establish an association of 4G/5G polymorphism with stroke in our study group (Babu et al., 2012) (Table 3) but there are reports that show positive association with atherothrombotic stroke (Bang et al., 2001; Wiklund et al., 2005).

#### 4.5.3. Prothrombin gene

This is also called as factor II and is a vitamin-K dependent glycoprotein that coverts fibrinogen to fibrin. The G2021A mutation in this gene was found not to be a risk factor for IS in our population (Munshi et al., 2009a) (Table 3) because this polymorphism is reported to be uncommon among Indians (Garewal et al., 2003; Gupta et al., 2003; Ghosh et al., 2001; Rees et al., 1999) and it also has a low prevalence among Caucasians (Franco et al., 1998). However, a recent report by They-They et al. suggested it to be a risk factor for large artery stroke subtype among Moroccans (They-They et al., 2012).

### 4.6. Pro-inflammatory/anti-inflammatory genes

#### 4.6.1. Tumour necrosis factor-α (TNF-α)

This is a potent pro-inflammatory cytokine implicated in stroke (Feuerstein et al., 1994). Our study involving the +448G/A variant revealed significant association with subtypes ILA, ELA, CE and UDA (Munshi et al., 2011) (Table 3) but there are hardly any other reports on the role of TNF-α gene variants in association with stroke subtypes.

#### 4.6.2. Matrix metalloproteinases (MMPs)

MMPs are a family of zinc dependent proteinases that mediate remodelling, capillary permeability and play an important role in tissue and vascular homeostasis (Nagase and Woessner, 1999). MMP-3 or stromelysin-1 gene variant -1612 (5A/6A) studied by our group was not found to be associated with IS in our population (Munshi et al., 2011) (Table 3). This is in accordance with a study by Kaplan et al. (2008). However, there are reports that suggest this polymorphism to be significantly associated with atherosclerotic cerebral infarction and LAA among the Chinese (Huang et al., 2008; Ma et al., 2013).

#### 4.6.3. Interleukin 10 (IL-10)

IL-10 is a multifunctional anti-inflammatory cytokine and is known to counterbalance the harmful effects of TNF-α and other pro-inflammatory molecules (Perini et al., 2001). -1082G/A variant studied by us revealed the A allele to be an important risk factor for IS and associated significantly with ELA and UDA (Munshi et al., 2010c) (Table 3). However, we did not find any other study reporting its association with stroke subtypes.

#### 4.6.4. C-reactive protein (CRP)

CRP is an acute phase reactant and its levels increase pronouncingly after tissue injury or inflammation. A lot of studies have concentrated on the levels of CRP in IS and its subtypes but there are very few reports studying its variants associated with stroke. Our study on 1059G>C polymorphism revealed no mutants among controls and IS patients (Das et al., 2014) (Table 3). A study evaluating association of this variant with venous thromboembolism (VTE) in Chinese Han population also found no significant difference in alleles among cases and controls (Mahemuti et al., 2012).

#### 4.6.5. E-selectin (E-sel)

E-selectin is known to mediate leukocyte activation that travels across endothelial cells, reaches brain parenchyma, triggers other inflammatory mediators and damages the vascular regions of the brain (Kozuka et al., 2002). The S128R variant of the gene is known to provide a link for the development of diseases like atherosclerosis and stroke (Rao et al., 2002). Our study involving this variant found a significant association with ILA and SAO subtypes (Roy et al., 2014) (Table 3).

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However, studies on E-selectin variants in association with IS and its subtypes are negligible.

#### 4.6.6. Eotaxin-1 (CCL-11)

Eotaxin-1 acts as a chemoattractant for leukocytes and directs them towards site of inflammation (Chalouhi et al., 2013). The -1382A>G variant studied by us revealed a significant association with IS subtypes ILA and SAO stroke (Unpublished data) (Table 3). A study among Chinese involving various variants of CCL-11 gene suggested a strong association of this variant with IS (Zhao et al., 2012) but there are no reports on its association with IS subtypes.

#### 4.6.7. Arachidonate 5-lipoxygenase activating protein (ALOX5AP)

This gene is a main regulator for the synthesis of leukotrienes which are secreted by inflammatory cells at the injured sites and thus plays an important role in atherosclerosis and other vascular damages (Spanbroek et al., 2003). Evaluating the association of SG13S114T/A variant of ALOX5AP1 gene with IS and its subtypes, we found significant association with ILA and CE (Sharma et al., 2013) (Table 3). Zhang et al. reported a 1.62 fold increase in thrombotic stroke among the patients having SG13S114AA genotype (Zhang et al., 2012).

### 4.7. Other genes

#### 4.7.1. Cytochrome P450 (CYP) gene

CYP4F2 gene is a subfamily of CYP450 enzymes and is involved in the metabolism of 20-hydroxyeicosatetraenoic acid (20-HETE). 20-HETE is a potent vasoconstrictor involved in the constriction of cerebral blood vessel and is involved in the pathogenesis of IS and its subtypes (Deng et al., 2010). Very few studies have been carried out evaluating its association with IS. Our study revealed significant association with CE stroke in our population (Munshi et al., 2012b) (Table 3) however, there are no studies evaluating its role in IS subtypes.

#### 4.7.2. Oestrogen receptor-α (ESR1)

Oestrogen, a sex steroid influences reproductive, cardiovascular and skeletal systems in both men and women by binding to specific oestrogen receptors of target cells (Deroo and Korach, 2006). The evaluation of ESR1 PvuII (-397T/C) and XbaI (-351A/G) polymorphisms by Molvarec et al., Markoula et al. and Kunnas et al., did not find any association among ischaemic stroke or its subtypes in both the genders (Molvarec et al., 2007; Markoula et al., 2008; Kunnas et al., 2010). Our study however, found a positive association of the pp genotype of PvuII in both women and men afflicted with stroke but could not establish the same for the XbaI variant (Munshi et al., 2010d). Significant association was also established by us in stroke subtypes ELA, SAO, CE and UDA (Table 3). However studies by Zhang et al. and Shearman et al., reported the TC and CC genotypes to be associated with stroke respectively (Zhang et al., 2002; Shearman et al., 2005). A recent meta-analysis too supports the association of only PvuII variant and not XbaI with stroke but none of the studies have evaluated association of ESR1 gene variants with stroke subtypes (Li et al., 2012).

#### 4.7.3. Phosphodiesterase 4D (PDE4D)

This gene belongs to a superfamily of phosphodiesterases (PDE4 family) that is implicated in the degradation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and codes for cAMP specific 3′ 5′-cyclic phosphodiesterase 4D which has indirect effects on cardiovascular and stroke biomarkers (Worrall and Mychaleckyj, 2006; Schubert et al., 2000). After Gretarsdottir et al., recognised this gene and its SNPs 83, 32 and 87 to be independent risk factors for stroke, a dozen of studies comprising of cohorts from different ethnicities have studied its various SNPs in PDE4D gene in association with stroke (Gretarsdottir et al., 2003). The study by our group involving SNPs 83, 32, 87, 41, and 56 and a novel SNP at position 59736747T>G revealed SNPs 83, 41 and 56 to be significantly associated with IS and its subtypes (Munshi et al., 2009b, 2012c). SNP 83 in our study was found to be associated with ILA, ELA and SAO subtypes (Table 3) whereas it was found to be associated with CE stroke in an American population (Meschia et al., 2005). SNP 87 on the other hand was found to be associated with CE stroke among both blacks and whites by Woo et al. (2006). The meta-analysis carried out by Bevan et al., although did not find significant association of SNP 56 but they did report its association with CE (Bevan et al., 2008) whereas Gretarsdottir et al., in Icelandic population reported SNP 56 to be associated with stroke of UDA (Gretarsdottir et al., 2003). Further, SNP 41 was reported to be associated with ILA, ELA, lacunar stroke and CE while SNP 56 was positively associated with ILA, ELA, lacunar stroke, ODA and UDA in our study (Table 3).

### 4.8. Less studied genes

#### 4.8.1. Transforming growth factor β1 gene (TGF-β1)

With regard to stroke subtypes we found only one study that suggests the C869T variant to be strongly associated with small vessel occlusion (SVO) particularly among the females (Kim and Lee, 2006).

#### 4.8.2. Neuropeptide Y gene (NPY)

The study by Lee et al., suggested the C4112T variant to be associated with LAA and the haplotype TA or CC of C4112T and A6411C variants to be associated with LAA and SVO among the other subtypes (Lee and Kong, 2007).

#### 4.8.3. Oxidative phosphorylation gene (OXPHOS)

The study by Anderson et al., in IS and its subtypes reports the genes from complexes I and IV of OXPHOS to be associated with SVO (Anderson et al., 2013).

#### 4.8.4. Epoxide hydrolase gene (EPHX2)

This gene was found to be associated with large vessel disease and stroke of UDA (Gschwendtner et al., 2008).

#### 4.8.5. Protein C gene (PROC)

A three-nucleotide duplication/deletion variant (c.574_576del) was identified and was found to be significantly associated with IS and its subtypes SAO and CE stroke by Lu et al. (2013).

#### 4.8.6. Thromboxane A2 receptor gene (TXA2R)

The study by Zhao et al., among the Chinese showed the rs768963 to be significantly associated with LAA (Zhao et al., 2013).

#### 4.8.7. Genome wide association studies suggested genes

The Genome Wide Association Studies (GWAS) have suggested paired-like homeodomain transcription factor 2 (PITX2) and zinc finger homeobox 3 (ZFHX3) to be associated with CE which could be due to association of these loci with atrial fibrillation responsible for cardiac embolism (Gretarsdottir et al., 2008a, 2008b; Gudbjartsson et al., 2009). Q17 Additionally the GWAS by International Stroke Genetics Consortium (ISGC) and Wellcome Trust Case Control Consortium 2 (WTCCC2) found histone deacetylase 9 (HDAC9) within chromosome 7p21 to be associated with large vessel stroke (Bellenguez et al. 2012). Further, a Q18 locus on chromosome 9p21 and the rs1906591 variant on chromosome 4q25 have been suggested to be associated with large vessel disease and CE subtype respectively (Gschwendtner et al., 2009; Lemmens et al., 2010; Gretarsdottir et al., 2008a, 2008b).

## 5. Conclusion

Since stroke has been classified as a complex disorder, deciphering the exact cause of stroke has proved to be complicated. Stroke research has provided us with extensive knowledge on roles of several substantial candidate genes however, a clear picture still remains unestablished.

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Further the different subtypes in IS which have a genetic predisposition too, fuels up the complexity of the disease. Though a positive association for various genes with IS have been reported, they however, do not focus on subtypes of IS and therefore, a limited information is available with respect to the role of genetic variation associated with stroke subtypes. Majority of the genes studied by our group show association with ILA among South Indians (Asians) which could be due to large amount of ILA patients in the population This observation can be justified by the difference in the distribution of carotid atherosclerosis which has a racial/geographical tendency. It is known that Caucasians are more prone to extracranial atherosclerosis whereas among Asians and blacks intracranial atherosclerosis is common. However, Kumar et al., found the distribution of atherosclerosis among Indians to be midway between Asians and Caucasians (Kumar et al., 2010). Further, the underlying reason for the association of specific gene with specific stroke subtype is also currently unknown.

In conclusion, we propose that genetic association studies in IS can well contribute to the understanding of distribution of IS subtypes in different ethnicities globally. Such outcomes can substantially contribute in better understanding of pathophysiology of IS and help in pharmacogenetic research of stroke, thus providing new therapeutic targets and better protection from damages caused due to IS. The genetics of IS subtypes is one of most promising research frontiers and the identification of molecular biomarkers of preclinical IS subtypes will alert the individuals who are at the highest risk. This will eventually lead to novel therapeutic approaches for IS and its subtypes.

## Conflict of interest

None declared.

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