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Mini Review

The Role of Genetic Variation in Haemorrhagic Stroke: An Update

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Abstract

Diseases are known to have a genetic background and some diseases can be rare to common or even restricted to one's family/ lineage/ethnicity. Stroke is more of a heterogeneous disorder owing to multiple factors affecting its sudden appearance. Research on ischemic stroke and hemorrhagic stroke has suggested genetic variations in different genes along with few established risk factors to lead to its development. However, hemorrhagic stroke is associated with greater morbidity and mortality as compared to other stroke subtypes therefore in this review we present an overview on the genetics of hemorrhagic stroke. The role of some major genes, other associated genes, environmental risk factors that can possibly contribute to progression of hemorrhagic stroke has been discussed.

Keywords: Hemorrhagic stroke; Recurrence stroke; Intracerebral hemorrhage; Subarachnoid hemorrhage; Lobar; Non- lobar intracerebral hemorrhage

Introduction

Stroke is a complex disorder resulting from an interaction between a person's genetic background and various environmental factors. Latest statistics find it to be a leading cause of adult disability and the fifth leading cause of death with nearly 40% deaths occurring only among males. Hence, identification of markers for stroke is required both for risk prediction as well as for intervention to avert future events. Earlier molecular genetic studies were conducted by employing linkage studies and using markers such as microsatellites to identify areas of risk. Stroke is a heterogeneous condition and is divided into two types called as the ischemic stroke and hemorrhagic stroke. These 2 types are further divided into various subtypes.

Hemorrhagic stroke

Of the two forms of stroke attack, hemorrhagic stroke is perceived to be more complex since clinically a well-defined classification for it is still underway. Nevertheless, few groups have focused on studying it and report hemorrhagic stroke to be a more deadly form of stroke. It accounts for almost 13%-20% of all strokes and is associated with a mortality rate four times higher than that of ischemic stroke. Depending on the location of hemorrhage this is further subdivided into extradural, subdural, subarachnoid, intraventricular and intracerebral hemorrhage. Primary Intracerebral Hemorrhage (ICH) originates from rupture of small vessels damaged by chronic hypertension, whereas, secondary intracerebral hemorrhage is commonly associated with Subarachnoid Hemorrhage (SAH) due to ruptured intracranial aneurysms or ruptured arteriovenous malformations. Thus, effects of stroke depend on site and severity of brain injury with a severe stroke resulting in sudden death. Extensive progress has been made in understanding the monogenic forms of stroke but underlying pathogenesis suggests most of the strokes to be multifactorial in origin. Stroke cases have been reported to be clustered in families and it is found that 10% of patients suffering with ICH have a positive family history of hemorrhagic stroke [1]. Having a first degree relative with ICH has been suggested to be a high risk factor for developing the disease and individuals having a first degree relative with SAH are at seven-fold increased risk of developing SAH [2,3].

Genetics of hemorrhagic stroke

A considerable number of genetic association studies have identified a number of candidate genes but there is lack of reproducibility and uncertainty about the nature and number of genes involved in hemorrhagic stroke [4]. Additionally, there is a concern on positive associations being spurious and negative associations to be a result of inadequate statistical power due to small sample size or other methodological shortcomings [5,6]. Both candidate gene approaches and Genome Wide Association Studies (GWAS) have dissected the role of genetic components in ICH risk. However, GWAS has emerged as a more relevant tool to study ICH to conduct large scale genetic investigations. Along with it novel technologies such as next-generation sequencing provide an additional avenue for interesting discoveries regarding genetic contributions to hemorrhagic stroke.

Recent studies suggest on possible genetic links with ICH but in clinical terms there has been a lack of proper explanation for it. ICH is more of an acute manifestation of a chronic vasculopathy therefore, genetic contribution to Cerebral Amyloid Angiopathy (CAA) and hypertension is more relevant to study while analysing hemorrhagic stroke genetics [7]. Nevertheless, owing to devastating consequences of hemorrhagic stroke, it is essential to study the genetic variants that increase risk of ICH such that knowledge emerging from it assists in preventive strategies and helps define new therapeutic approaches.

The strongest evidence for genetic association of ICH comes from a recent GWAS that drew data on SNPs and Neuroimaging data in a cohort of 791 individuals with ICH and 876 healthy controls and found a heritability estimate of 44% for overall ICH risk. A substantial

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difference in heritability for lobar and deep ICH risk was estimated to be 73% and 34% respectively. Further, 15% of heritability was found to be mediated by variants in gene encoding Apolipoprotein E *(APOE)* and 29% of heritable ICH risk was related to non-*APOE* loci [8]. The results from the study on heritability estimates were comparable to earlier studies made in twin and pedigree studies [9,10]. *APOE* E2 and *APOE* E4 alleles were found to be associated with increased risk of ICH attributed to CAA (CAA-ICH) [11-13]. Another large scale genetic association study involving 2189 cases and 4041 controls reported increased risk of lobar ICH at genome wide significance level while meta-analysis studies have found *APOE* E4 to be associated with risk of deep ICH [14].

Potential reigning hypothesis linking *APOE* with the pathogenetic mechanism states that *APOE* E4 enhances Aβ deposition in the cerebral vasculature and that *APOE* E2 is a risk factor for hemorrhage from the amyloid-laden vessels. Studies suggest *APOE* E4 carriers to be a risk factor for early age hemorrhage as compared to non-carriers and also responsible for both CAA and CAA-ICH. *APOE* E4 has been lined with acceleration of vascular damage resulting from amyloid deposition which leads to rupture [11]. The mechanism by which *APOE* E4 increases risk of ICH is multifactorial because it is also responsible for risk of hypertension, a well-known risk factor for ICH. Additionally E4 allele carriers have an increased total cholesterol level which is yet another vascular stressor and E2 allele bearers are at an increased risk of vasculopathic changes such as fibrinoid necrosis that increases the possibility of ICH. In cases of recurrent ICH, E4 results in a striking 26 fold increase in recurrent risks as compared to E3 carriers and further an accompanied modulation by circulating lipid levels especially low-density lipoprotein mediates an essential role in progression [15-18]. A recent study by Woo, et al. 2013 also states that statin use conferred a higher risk for lobar ICH among E4/E4 and E2/E4 genotype carriers [19]. Further, a genetic association study by Das, et al. 2016 reports association for certain genotypic models of *APOE* with hemorrhagic stroke *vs.* controls and hemorrhagic stroke *vs.* ischemic stroke [20].

Angiotensin Converting Enzyme *(ACE)* is yet another gene in which the Insertion-Deletion polymorphism (I/D) has a shown great link with hemorrhagic stroke. A recent meta-analysis involving 33 studies reports an association of this polymorphism among Asians (Chinese, Japanese and Indian) but not among the white population [21]. *ACE* I/D polymorphism is known to elevate serum *ACE* levels that increase ICH risk by promoting hypertension but a clear cut mechanistic link between the polymorphism and its role in ICH is still not clear [22-24]. The DD polymorphism has been linked with Vasculitides that can damage blood vessels through inflammatory mechanisms [25]. Few other studies have also linked accumulation of Aβ particles and elevated risk of ICH owing to possible role in amyloid pathology [26]. A large meta-analysis reported the positive association of MTHFR (C677T) gene with ICH and the possible mechanism might be by accelerating atherosclerosis and promoting plaque rupture *via* excessive inflammation and endothelial wall stress [27,28]. Study among a South Indian population also found significant association for MTHFR (C677T) CT genotype with hemorrhagic stroke and ischemic stroke but analysis between the two types of stroke revealed no difference [29]. Apart from these three major genes other candidates from case-control studies have suggested genes like *TUBB1, FGA, LDLR, LPA, IL6, TNF, TGFβ2, ENG, IFNE, ERLIN1, TRAPPC* and *WNK2* to be associated with risk or conferred protection against ICH risk by participating in different pathological mechanisms [30-34]. Our group specifically has studied genetic association between ischemic stroke and hemorrhagic stroke for a few number of genes and found significant difference in genotype and allele frequencies for *APOE* (E2, E3 and E4), *ACE* (I/D), CCL-11 (1382A>G), MTHFR (C677T) and E-selectin (S128R) but found negative association for CRP (1059G>C) [20,24,29,35-37].

Apart from genes and their heritability, environmental factors that include modifiable risk factor i.e. Blood Pressure (BP) plays a pivotal role in ICH. A recent study suggests inadequate BP control to associate with both lobar and non-lobar ICH recurrence and CAA-related ICH [38,39]. Experimental evidence for hypertension in CAA- related ICH has been demonstrated in a transgenic mouse model Tg2576 exhibiting Alzheimer's–like pathology. Tg2576 mice developed signs of stroke with shorter latency with increase in systolic pressure when treated with angiotension II and L^G –nitroarginine methyl ester. This study design combined hypertension with human Aβ presence that served as a valuable tool to understand the interaction between two clinical factors in leading to spontaneous ICH [40]. Further, patients who have suffered ICH develop cognitive impairment at a higher rate and dementia early after ICH seems prevalent which is strongly associated with hematoma size and location [41]. ICH as such has no specific therapy but expansion of initial hematoma is a marker for poor prognosis. The biological mechanism of hematoma expansion is not clear but so far the only marker amenable for treatment in ICH is hematoma expansion thus serving it as a potential therapeutic target [42]. Smoking is yet another modifiable risk factor linked to aneurysmal Subarachnoid Haemorrhage (aSAH) and levels of circulating lipids i.e. serum total cholesterol and low-density lipoproteins have been found to be declining 6 months preceding primary ICH independent of statin or alcohol use. This finding in rate of change in serum lipids suggests lipid levels to be a potential biomarker for impending cerebral injury [43,44]. Additionally, differences in underlying vascular disease has been attributed to etiological factors like age and sex and studies that find such relevant information can help in providing more specific treatment options [45]. Thus, it can be said that although genetic factors do provide certain answers but modulation of these by environment/lifestyle plays quite an important role in pathogenesis of hemorrhagic stroke. Hence, studies employing gene-environment and gene-gene interaction studies have been suggested to introduce a new approach for evaluating the pathogenesis [46].

Further, major difference in genetics of hemorrhagic stroke and other forms of stroke has been demonstrated in a study by Dykstra –Aiello, et al. (2015). This study describes genes with Differential Alternative Splicing (DAS) and pathways unique for ICH as compared to other ischemic stroke etiologies like cardioembolism, large vessel atherosclerosis and lacunar stroke. Genes that differentiated ICH from ischemic stroke aetiologies were reported to be *INPP5D, ITA4, NAV1, PDGFC, CCM2, EXOSC1, EXOSC9* and *DGCR8*. The biological functions and networks represented by genes with differentially expressed exons in each disease group varied and pathways that ICH genes were mostly related with were protein transport and localization. Whereas, cardioembolic stroke genes were found to be associated

with ion binding/transport and cellular assembly, large vessel stroke with cell death, transcription and chromatin and lacunar stroke with cellular compromise, cell cycle, cell death and survival [47]. However, yet another study by Radmanesh, et al. (2015) employing exome sequencing found no rare coding variants to be associated with ICH but suggested studies with larger sample size for stronger power [48]. Another study in a rat model reports expression of LncRNAs to be significantly different as compared to control group which suggests that LncRNAs to be important in pathophysiological process of SAH. However, their role in humans needs to be explored for LncRNAs to act as potential biological prognostic markers [49]. A similar role for other non-coding RNAs i.e. microRNAs (miRNAs) was explored in cerebral arteries of rats following SAH. miR-30a and miR-143 were found to differ with time and with control group of sham- operated rats [50]. Although these set of experiments in humans and rats respectively provide a new direction of understanding in molecular genetics of stroke there replication or consistency in enough human samples/cohorts remains to be researched owing to spatial and temporal difference that can vary from patient to patient.

Conclusion

Nevertheless, despite these findings the integrated omics approach like transcriptomics, epigenomics, proteomics and metabolomics needs to be explored for further understanding the mechanisms underlying hemorrhagic stroke [7]. Identification of transcriptome variants, epigenetic changes, proteome profile and microRNAS can reveal ICH pathogenesis and individual genetic vulnerability at a better level and reveal better therapeutic targets. Thus, a few recent studies have already ventured into these areas but massive efforts that can consolidate overall knowledge from single positive association studies, GWAS, whole-genome sequencing with other possible molecular biology realms in diverse cohorts can help to elucidate a better pathogenesis of ICH. Currently genetics of hemorrhagic stroke hasn't received much attention and therefore, a fertile new area of investigation in neurology is open to both clinicians and basic researchers. To achieve this, an international massive collaborative effort that can provide more comprehensive and translating data is the call of time.

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