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Review Article

Genetic risk of Spontaneous intracerebral hemorrhage: Systematic review and future directions

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ABSTRACT

Background: Although highly heritable, few genes have been linked to spontaneous intracerebral hemorrhage (SICH), which does not currently have any evidence-based disease-modifying therapy. Individuals of African ancestry are especially susceptible to SICH, even more so for indigenous Africans. We systematically reviewed the genetic variants associated with SICH and examined opportunities for rapidly advancing SICH genomic research for precision medicine.

Method: We searched the National Human Genome Research Institute-European Bioinformatics Institute (NHGRI–EBI) Genome Wide Association Study (GWAS) catalog and PubMed for original research articles on genetic variants associated with SICH as of 15 June 2019 using the PRISMA guideline.

Results: Eight hundred and sixty-four articles were identified using pre-specified search criteria, of which 64 met the study inclusion criteria. Among eligible articles, only 9 utilized GWAS approach while the rest were candidate gene studies. Thirty-eight genetic loci were found to be variously associated with the risk of SICH, hematoma volume, functional outcome and mortality, out of which 8 were from GWAS including *APOE, CR1, KCNK17, 1q22, CETP, STYK1, COL4A2* and *17p12*. None of the studies included indigenous Africans.

Conclusion: Given this limited information on the genetic contributors to SICH, more genomic studies are needed to provide additional insights into the pathophysiology of SICH, and develop targeted preventive and therapeutic strategies. This call for additional investigation of the pathogenesis of SICH is likely to yield more discoveries in the unexplored indigenous African populations which also have a greater predilection.

1. Introduction

Spontaneous intracerebral hemorrhage (SICH) refers to non-traumatic bleeding into the brain parenchyma [1] of which up to about 80% are non-lobar [2]. About half of stroke-deaths are due to SICH which has no disease-modifying treatment (unlike ischemic stroke) [3] and accounts for huge societal costs [4,5]. Developing interventions to mitigate its devastating outcomes requires a better understanding of its risk factors and pathophysiology [6,7]. With heritability of SICH estimated to be as high as 44% [8], genomic studies constitute a powerful tool in unravelling the pathobiology of this devastating disease [9,10]. Despite this broad understanding that genetic variations contribute substantially to the pathogenesis of SICH,[5] only a few risk variants have been identified or validated, with none discovered so far in continental Africans in whom it is four times more common [8,11–16].

The objective of this systematic review is to document genetic variants currently reported to be associated with SICH with the goal of exploring their role in the pathophysiology of the disease while proposing future directions.

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2. Methods

2.1. Search strategy

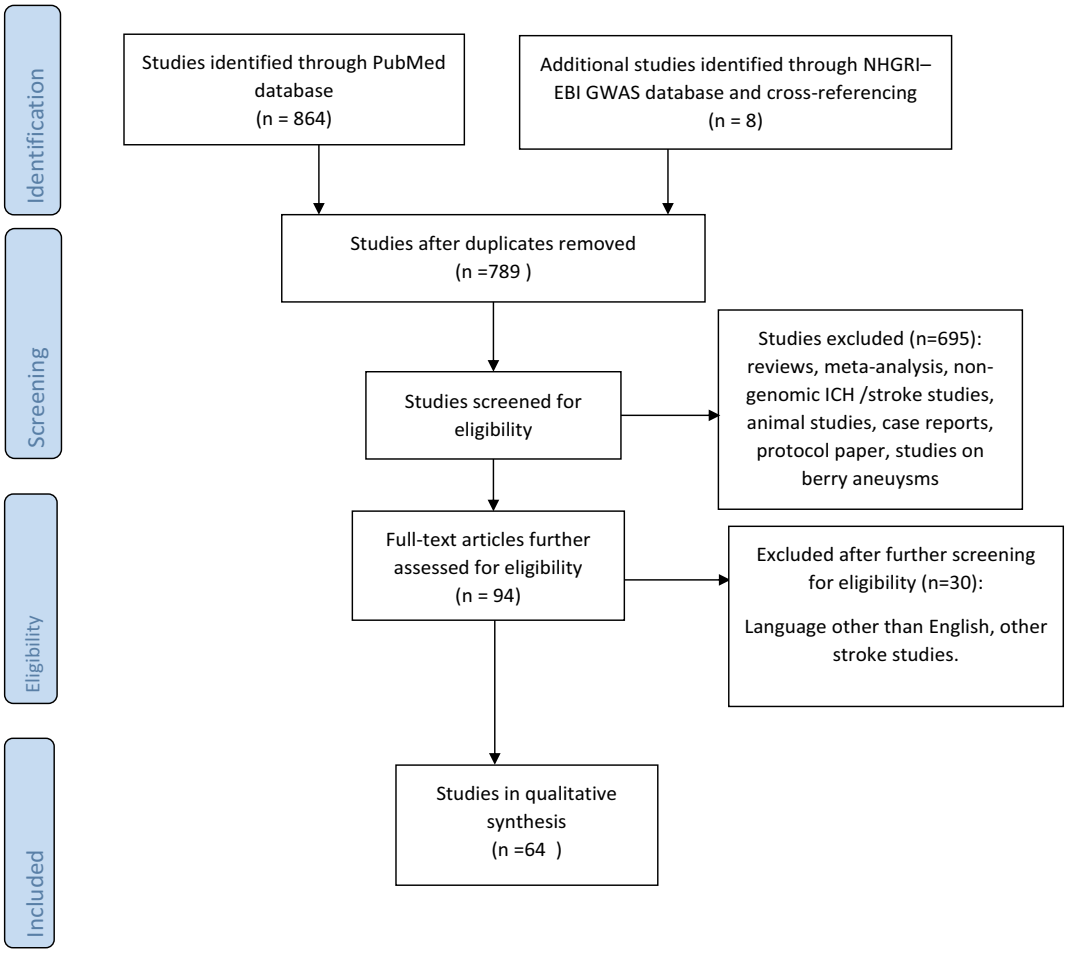
We searched PubMed and the National Human Genome Research Institute-European Bioinformatics Institute (NHGRI–EBI) GWAS catalog up till 15 June 2019 using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. The search terms were "spontaneous", "intracerebral", "hemorrhage", "stroke", "genetic", "genomic", "risk" and "variant". In the first round of search, spontaneous intracerebral hemorrhage was variously combined with genetic risk, genomics and genetic variants while in the second round, haemorrhagic stroke was variously combined with genetic risk, genomics and genetic variants. Additional articles were obtained through cross-referencing. All articles identified were further scrutinized for eligibility while duplicates were removed. No additional articles were found from Google Scholar.

2.1.1. Eligibility criteria

Included were GWAS and candidate gene studies published up till 15 June 2019. All studies were full length original research articles that were published in English language. We excluded review articles, stroke studies of ischemic or subarachnoid hemorrhage type, studies of SICH that were not on genomics, animal studies, case reports and the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study protocol paper [17], which was the only protocol paper in the search results. Fig. 1 shows the PRISMA flow diagram.

3. Results

Initial search returned 864 articles comprising 856 from PubMed, 3 from NHGRI-EBI GWAS database and 5 from cross-referencing. These were further scrutinized, resulting in identification of 75 duplicates which were removed from further analysis, leaving 789 articles. Of the remaining 789 articles, only 64 (11 in African Americans) met the eligibility criteria for the systematic review and these were included in the data synthesis. Only 10 of the 64 articles utilized GWAS (Table 1) while the rest utilized candidate gene approach (Table 2). Tables 1 and 2 describe all the included studies including their year of publication, susceptibility risk locus/gene name, genetic variant locus, odd ratio, sample ancestry, and sample size. Overall, 38 genetic loci were found to be variously associated with the risk of SICH, haematoma volume, functional outcome, recurrence and mortality, out of which 8 were from GWAS (*i.e. APOE, CR1, KCNK17, 1q22, CETP, STYK1, COL4A2* and *17p12)* (Table 1). Several other loci were identified from candidate gene analyses as shown in Table 2. Of all the genetic variants identified, 22 of the 62 studies which reported significant associations (35.5%) have small to moderate effect sizes with odd ratio (OR) < 1.5. Caucasians, Hispanics, African Americans and Orientals were variously included in all these studies which reported various degrees of associations of genetic variants with risk and outcome of SICH but none included indigenous Africans.



NHGRI – EBI: National Human Genome Research Institute- European Bioinformatics Institute

Fig. 1. PRISMA flow diagram.

Table 1
Genetic variants associated with Spontaneous intracerebral hemorrhage from Genome Wide Association Studies (GWAS).

First author	Year	Susceptibility risk locus/ Gene name	Genetic variant locus (allele)	OR	Study population/ Ancestry	Sample size (Cases/ Control)	Technique/Approach	Comment
Biffi [34]	2010	*APOE*	*APOE Ɛ2*	1.82 (95% CI 1.50–2.23)	European	6230 (2189/4041)	GWAS with meta-analysis	Associated with the risk of lobar SICH
			APOE Ɛ4	2.20 (95% CI 1.85–2.63)				
			APOE Ɛ4	1.21 (95% CI 1.08–1.36)				Associated with the risk of deep SICH
Biffi [62]	2011	*APOE*	*APOE Ɛ2*	1·50 (95% CI 1·23–1·82)	European/African American	2025 (849 lobar & 1176 deep SICH)	GWAS: replication and meta-analysis	Associated with mortality, but not SICH location
			APOE Ɛ2	1·52 (95% CI 1·25–1·85)				Associated with poor outcome, but not SICH location
Biffi [63]	2012	*CR1*	rs6656401	1.61 (95% CI 1.19–2.17)	Non-Hispanic white (n = 1001), others (n = 131)	878 (554/324)	GWAS	Associated with Cerebral amyloid angiopathy-related SICH
Ma Q [26]	2013	*KCNK17*	rs10947803	1.65 (95% CI 1.04–2.62)	Chinese	322 (166/156)	GWAS	Associated with SICH
Woo [11]	2014	*1q22*	*rs2984613*	1.24 (95% CI 1.09–1.40)	Caucasian/African American	6968 (3226/3742)	GWAS: replication and meta-analysis	Associated with deep SICH
Anderson [3]	2016	*CETP*	*rs173539*	1.25 (SE 0.06)	Caucasian	2387 (1149/1238)	GWAS with replication	Associated with increased risk of SICH
Yamada [28]	2017	*STYK1*	*rs138533962*	111.3 (95% CI 33.0–694.6)	Japanese	9831 (673/9158)	GWAS	Associated with increased risk of SICH
Rannikmae [14]	2017	*COL4A2*	*rs4771674*	1.28 (95% CI 1.13–1.44)	European	2708(1878/2830)	GWAS with meta-analysis	Associated with deep SICH
Marini [42]	2018	*17p12*	rs11655160	0.17 (SE 0.60) for aGCS 1.94 (SE 0.33) for 3-month MRS	European	534 (294/240)	GWAS	Associated with admission level of consciousness and 3-month functional outcome in lobar ICH
Marini [27]	2019	*APOE*	*APOE Ɛ2*	1.49 (95% CI 1.24–1.80)	White, Black & Hispanic	13,124 (6195/9929)	GWAS with meta-analysis	Associated with lobar SICH in Whites and Hispanics
			APOE Ɛ4	1.51 (95% CI 1.23–1.85)				

APOE = Apolipoprotein E; CR1 = Complement receptor type 1; COL1A2 = Type I collagen alpha 2; CETP = cholesteryl ester transfer protein; KCNK17 = potassium channel, subfamily K, member17; STYK = Tyrosine-protein kinase.

Table 2
Genetic Variants Associated with Spontaneous Intracerebral Hemorrhage from Candidate Gene Studies.

First author	Year	Susceptibility risk locus/ Gene name	Genetic variant locus (allele)	OR	Study population/ Ancestry	Sample size (Cases/Control)	Technique/ Approach	Comment
Alberts [64]	1997	*Endoglin*	*Endoglin*	4.8 (95% CI 1.28–21.601)	White/African American	305 (103/202)	Candidate gene	Mutated in cases of hereditary hemorrhagic telangiectasia (HHT)-associated SICH"
Rosand [65]	2000	*APOE*	APOE Ɛ2	3.8 (95% CI 1.0–14.6)	Unspecified (study in Boston, USA)	107 (41/66)	Candidate gene	Associated with warfarin-associated SICH in patients with CAA
Gemmati [66]	2001	*Factor XIIIA*	*Val34Leu*	1.70 (CI 95% 1.16–2.51)	Unspecified (study in Ferrara, Italy)	260 (130/130)	Candidate gene	Increases risk of SICH
Dou [67]	2004	*Alpha Adducin*	*ADD1 G/W460*	1.38 (95% CI 1.01–1.88)	Chinese	910 (456/454)	Candidate gene	Associated with SICH, independent of hypertension
Slowik [25]	2004	*ACE*	ACE DD genotype	2.46 (95% CI 1.14–5.31)	Polish	174 (58/116)	Candidate gene	Associated with SICH
Woo [68]	2005	*APOE*	*APOE Ɛ4*	2.25 (95% CI 1.18–4.28)	White/African American	312 (107/205)	Candidate gene	Independently associated with lobar SICH
Pawlikowska [40]	2006	*APOE*	*APOE Ɛ2*	5.09 (95% CI 1.46–17.7)	White/African American	284 (18 with new SICH)	Candidate gene	Increases the risk of SICH in patients with brain AVM
Navarro-Núñez [69]	2007	*Beta-1 tubulin*	*TUBB1 Q43P*	2.78 (95% CI 1.16–6.63)	White/Asian	708 (259/449)	Candidate gene	Increases risk of SICH in young men
Pera [33]	2008	*Glutathione peroxidase 1 (GPX1)*	*C593T GPX1*	2.36 (95% CI 1.31–4.26)	White	389 (192/197)	Candidate gene	Associated with lobar SICH
Yamada [30]	2008	*LIMK1*	*rs710968*	0.51 (95% CI 0.32–0.78)	White (Japanese)	3765 (333/3432)	Candidate gene	A allele is protective against SICH
Kim [41]	2009	*Interleukin-1β*	*rs16944* *rs1143627*	2.6 (95% CI 1.1–6.5) 2.7 (95% CI 1.1–6.6)	White/African American	486 (231/255) 488 (235/253)	Candidate gene with replication	Increase risk of SICH in patients with brain AVM
Reuter [70]	2009	*TIMP-2*	*261G/A*	2.020 (95% CI 1.115–3.661)	White	609 (356/253)	Candidate gene with replication	Homozygosity for allele A is associated with SICH
Chen [21]	2009	*APOE*	APOE Ɛ2Ɛ3	43 (95% CI 4.0–535.0)	Taiwanese	497 (217/280)	Candidate gene	Deep SICH more common in carriers of APOE Ɛ2Ɛ3 allele who also consume alcohol
Yoshida [71]	2010	*ERLIN1*	*rs1324694*	0.59 (95% CI 0.39–0.88)	Japanese	4304 (582/3722)	Candidate gene	Associated with SICH
		TRAPPC9	*rs12679196*	0.19 (95% CI 0.03–0.60)				
		WNK2	*rs16936752*	1.59 (95% CI 1.10–2.38)				
Chen [72]	2010	*TNF-α*	*T-1031C*	1.9 (95% CI 1.1–3.4)	Taiwanese	628 (260/368)	Candidate gene	Associated with increased risk of SICH in males
			C-863A	0.5 (95% CI 0.2–0.9)				Protective against SICH in females
			G-308A	2.6 (95% CI 1.3–5.3)				Associated with increased risk of SICH in males
Samarajan BI [73]	2010	*ACT*	*rs4934*	0.40 (95% CI 0.196–0.825)	Indians	381 (193/188)	Candidate gene	No association with SICH
Kalita [22]	2011	*ACE*	*rs4646994*	7.04 (95% CI 3.44–14.42)	Indians	302 (104/198)	Candidate gene	Genotype DD associated with non-lobar SICH
Somarajan [74]	2011	*MTHFR*	*C677 T TT Genotype*	1.85 (CI 0.46–7.40)	Indians	403 (215/188)	Candidate gene	No association with SICH
Lim [75]	2011	*TGFBR2*	*rs2228048*	1.7 (95% CI 1.20–2.42)	Koreans	522 (127/395)	Candidate gene	C allele found at higher frequency in patients with SICH
Gong [76]	2011	*VEGFA*	*rs1547651*	2.11 (95% CI 1.01–4.42)	Chinese	311	Candidate gene	Increased risk of SICH in brain AVM
Kim [77]	2011	*ALOX5AP*	*rs17222919-1316 T/G*	1.95 (95% CI 1.20–3.17)	Korean	594 (196/398)	Candidate gene	Associated with SICH
Appelboom [46]	2011	*CFH Y402H*	rs1061170)	7.62 (95% CI 1.40–41.6)	White, African American, Asian, Hispanic	82	Candidate gene	Independently predicted short term mortality and survival at 6 months.

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Table 2 (*continued*)

First author	Year	Susceptibility risk locus/ Gene name	Genetic variant locus (allele)	OR	Study population/ Ancestry	Sample size (Cases/Control)	Technique/ Approach	Comment
Zhang [78]	2012	*APOE*	*APOE Ɛ4*	3.00 (95% CI 1.76–5.13)	Chinese	360 (180/180)	Candidate gene	Associated with SICH
Gao [79]	2012	*MTHFR*	*677 T*	1.38 (95% CI 1.17–1.62)	Caucasian/Asian	5985 (1828/4067)	Candidate gene with meta-analysis	Associated with increased risk of SICH
Liu [80]	2012	*COL1A2*	*rs42524*	2.261 (95% CI 1.482–3.451)	Chinese	879 (393/486)	Candidate gene	Associated with SICH
Martini [23]	2012	*APOE*	APOE Ɛ2	2.28 (95% CI 1.50–3.46);	European American, African American	2145 (597/1548)	Candidate gene	Associated with lobar SICH
			APOE Ɛ4	1.43 (95% CI 1.03–1.99)				
Brouwers [45]	2012	*APOE*	APOE Ɛ2	2.72 (95% CI 1.19–6.23)	European	510 (lobar 265; deep 245)	Candidate gene	Increased risk of hematoma expansion in those with lobar SICH.
Qin [81]	2013	*ACE I/D*	*rs4646994*	1.80 (95% CI 1.39–2.33)	Caucasian/Asian	6418 (2806/3612)	Candidate gene with meta-analysis	Associated with SICH in Asians, not Caucasians
Sun [82]	2013	*ACE I/D*	*rs4646994*	1.58 (95% CI1.07–2.35)	Caucasian/Asian	2446 (805/1641)	Candidate gene with meta-analysis	Associated with SICH in Asians, not Caucasians
Appelboom [44]	2013	*von Willebrand factor*	rs216321	Not reported	European American	82	Candidate gene	Independently predicted relative hematoma enlargement.
Misra [83]	2013	*APOE*	APOE Ɛ2	4.32 (95% CI 1.65–11.28)	Indians	322 (134/188)	Candidate gene	Associated with recurrent SICH
			APOE Ɛ4	11.33 (95% CI 5.37–23.02)				
Wang [84]	2014	*TIMP-1*	*rs2070584*	1.535 (95% CI 1.025–2.300)	Chinese	715 (410/305)	Candidate gene	Associated with SICH in Chinese male population
Kim [85]	2014	*IFNE*	*rs2039381, Gln71Stop*	1.61 (95% CI 1.14–2.26)	Korean	665 (264/401)	Candidate gene	Associated with SICH
Zhang [86]	2014	*APOE*	*APOE Ɛ4*	1.42 (95% CI 1.21–1.67)	Caucasian/Asian	4813 (1238/3575)	Candidate gene with meta-analysis	Associated with SICH
Kumar [12]	2014	*Beta-2 AR*	*Gln27Glu*	2.9 (95% CI 1.04–8.0)	Indian	212 (106/106)	Candidate gene	Associated with increased risk of SICH
Jagiełła J [29]	2014	*FGA Thr312Ala*	FGA Thr312Ala	2.30 (95% CI 1.10–4.80)	Polish, Greek	1277(503/774)	Candidate gene	Protective against SICH
Das [87]	2015	*ACE*	*DD*	2.46 (95% CI 1.43–4.21)	Indian	400 (200/200)	Candidate gene	Associated with SICH
Kumar [88]	2014	*ACE*	*DD*	2.0 (1.02–3.8)	Indian	212 (106/106)	Candidate gene: meta-analysis with replication	Associated with SICH
Ou [89]	2014	*MTHFR*	*rs1801133*	1.48 (95% CI 1.16–1.89)	Chinese	2660 (1280/1380)	Candidate gene	Associated with SICH
Falcone GH [90]	2014	*APOE*	*APOE Ɛ2*	2.47 (95% CI 1.08–5.66)	European	1093 (63/1030)	Candidate gene with replication	Increased risk of lobar SICH with use of warfarin
			APOE Ɛ4	2.71 (95% CI 1.40–5.23)				
Das [91]	2014	*E selectin*	*S128R*	1.73 (95% CI 1.2–2.5)	Indian	500 (250/250)	Candidate gene	CC genotype associated with SICH
He [31]	2014	*KCNK17*	*rs12214600*	0.56 (95% CI 0.35–0.90)	Chinese	2581 (1356/1225)	Candidate gene	Associated with reduced risk of SICH
Roy [92]	2014	*CCL11*	*rs4795895-1382A > G*	3.5 (95% CI 2.16–5.82)	Indian	440 (220/220)	Candidate gene	Associated with SCIH
Raffeld [93]	2015	*APOE*	*APOE Ɛ4*	1.31 (95% CI 1.02–2.69)	Caucasian/African American	363 cases	Candidate gene	Associated with recurrence of non-lobar SICH

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Table 2 (*continued*)

First author	Year	Susceptibility risk locus/ Gene name	Genetic variant locus (allele)	OR	Study population/ Ancestry	Sample size (Cases/Control)	Technique/ Approach	Comment
Chen [32]	2015	*TIMP-2*	rs7503607 C > A	2.45 (95% CI 1.37–4.38)	Taiwanese	772 (396/376)	Candidate gene	Associated with deep SICH
		MMP-2	rs2285053 TT	2.91 (95% CI 1.02–8.31)				
Ho M [2]	2015	*MMP-9*	rs3787268	0.48 (95% CI 0.27–0.86	Taiwanese	765 (326/439)	Candidate gene	Both genes associated with deep SICH: rs4898 in males ≥65 years & rs2250889 in males < 65 years
		TIMP-1	rs4898	0.35 (95% CI 0.15–0.81)				
Kumar [94]	2016	*TGF-β1*	*G800A*	9.07 (95% CI 2.3–35.6)	Indian	200 (100/100)	Candidate gene	Associated with increased risk of SICH
			T869C	5.1 (95% CI 1.9–13.2)				
Tian [95]	2016	*COL1A2*	*rs42524*	12.01 (2.89–106.75)	Chinese	454 (227/227)	Candidate gene	Associated with development of hypertensive SICH
Dardiotis EV [96]	2017	*ITGAV*	*rs7565633*	0.56 (95% CI 0.37–0.86)	Greek, Polish	1015 (443/572)	Candidate gene	Independently associated with risk of SICH
Park [97]	2017	*TNF*	*rs1799724*	1.60 (95% CI 1.14–2.24)	Korean	599 (144/455)	Candidate gene	Associated with increased risk of SICH
Gong QR [20]	2017	*CD36*	rs1194182	0.674 (95% CI 0.457–0.992)	Chinese	590 (292/298)	Candidate gene	Polymorphism in the CD36 gene associated with SICH in those with hypertension
Yang [98]	2018	*ROCK*	*rs288980*	1.144 (95% CI 1.006–1.310)	Chinese	3050 (607/2443)	Candidate gene	Associated with SICH
			rs7237677	1.150 (1.010–1.309				
El Husseini [43]	2018	*gp130 (G/A)*	rs10940495	0.16 (95%CI 0.03–0.87)	European American, African American, Hispanic	54	Candidate gene	Associated with 6-month functional outcome
Lin [19]	2018	*COL4A1*	rs544012 AC	1.854 (95% 1.067–3.221)	Chinese	378 (181/197)	Candidate gene	Independently associated with the risk of developing SICH
			rs679505 AA	2.772 (95% 1.437–5.348)				

APOE = Apolipoprotein E; CR1 = Complement receptor type 1; ACE = Angiotensin Converting Enzyme; I/D = Insertion/Deletion polymorphism; CFH = Complement Factor H; ACT = alpha1 antichymotrypsin; FGA = Fibrinogen; TIMP = Tissue Inhibitor of Metalloproteinase; MMP = Metalloproteinase; KCNK = Potassium Channel, Subfamily K; COL1A2 = Type I collagen alpha 2; CETP = cholesteryl ester transfer protein; COL4A1 = Type IV collagen alpha 1; AVM = Arteriovenous malformation; ALOX5AP = Arachidonate 5-lipoxygenase activating protein; VEGFA = Vascular Endothelial Growth Factor A; TGFBR2 = Transforming growth factor, beta receptor II; TNF = Tumor Necrosis Factor; MTHFR = Methylenetetrahydrofolate reductase; IFNE = Interferon-ε; AR = Adrenergic receptor; KCNK17 = potassium channel, subfamily K, member17; CCL11 = Eotaxin-1; TGF-β1 = Transforming growth factor-β1; ITGAV = integrin AV; CETP = cholesteryl ester transfer protein; STYK = Tyrosine-protein kinase; EWAS = exome wide association study; ROCK = Rho Kinase.

4. Discussion

4.1. Genetic loci associated with SICH

As there is no definitive treatment for SICH at the moment, identification of genetic variants associated with the condition will represent a great leap forward in the efforts toward understanding the pathophysiology of this devastating condition with the ultimate goal of facilitating the development of appropriate personalized treatment and preventive modalities [18]. Although genetic factors may contribute to the pathobiology of SICH, our results showed that few risk alleles have been reported till date. SICH is a polygenic disorder with variable combinations of environmental and genetic factors in its causation. Also, possibility of gene-gene interaction exists, especially interaction between the genetic variants associated with hypertension and stroke.

Our review shows that the genetic loci associated with increased susceptibility to SICH include *APOE, COL4A1, COL4A2, CD36, TIMP-1, TIMP-2, MMP-2, MMP-9, KCNK17, CR1,STYK1, ACE*, *1q22,* and *CETP* among others [2,3,11,14,19–28]. In contrast *FGA Thr312Ala, LIMK1* and *KCNK17,* were found to be protective against the disease [29–31]. In terms of location, the genetic variants associated with lobar SICH include *APOE Ɛ2, Ɛ4*,Ɛ2/Ɛ3 and *GPX1,* while *APOE Ɛ4, 1q22, COL4A2, TIMP-1, TIMP-2, MMP-2, MMP-9* and *ACE* are associated with deep SICH [2,11,14,21,23,24,32–34]. These associations have implication for deepening the understanding of the pathophysiology of SICH. For instance, *COL4A1, TIMP-1, TIMP-2 and ACE* are involved in the maintenance of vascular integrity. ACE converts angiotensin I to angiotensin II which is a potent vasoconstrictor and is also involved in the degradation of bradykinin, a potent vasodilator [24,35]. Both angiotensin II and bradykinin are involved in blood pressure regulation. Likewise, *COL4A1* gene encodes type IV collagen α proteins, which are the main constituents of basement membranes [19], while *TIMPs 1&2* inhibit MMPs 2 & 9 which are endopeptidases whose biological effects involve digestion of both the extracellular matrix and the basal lamina with resultant breakdown of blood-brain barrier and activation of an inflammatory reaction [36,37]. The underlying problem in many cases of deep SICH is rupture of Charcot-Bouchard aneurysms which results from a compromise of the deep penetrating vessels due to inadequate deposition of collagen. It is thus conceivable that a mutation in any of these genes involved in maintenance of vascular integrity can lead to a compromise of the functions of their proteins which in turn will lead to an increase in the risk of developing deep SICH. It has been shown that deep SICH is commonly associated with hypertensive vasculopathy [8].

Lobar SICH is associated with *APOE* which transports lipoproteins, fat-soluble vitamins, and cholesterol, in addition to its involvement in cell membrane maintenance and repair [38]. *APOE Ɛ2 or Ɛ4* alleles are responsible for deposition of β-amyloid protein which tend to augment the activation of vascular injury pathways and result in impaired vascular physiology which are the underlying pathological changes in cerebral amyloid angiopathy, the major cause of lobar SICH [39]. CR1 and APOE Ɛ2 were also found to be associated with cerebral amyloid angiopathy-related SICH while Interleukin-1β and APOE Ɛ2 are implicated in arteriovenous malformation-related SICH [40,41].

Genetic loci *17p12, gp130 (G/A), von Willebrand factor (rs216321), LIMK1, APOE Ɛ2, CFH Y402H*, and *KCNK17* are potential prognostic biomarkers in SICH because they are variously associated with hematoma expansion, admission level of consciousness and functional outcome [42–46]. These findings would be of importance in the design of personalized treatment and prevention plan for this devastating disease with no established treatment.

4.2. Opportunities in SICH genomics research in indigenous Africans

Whole genome sequencing (WGS) which is at least 20 times more expensive than GWAS, has so far been disappointing in complex polygenic diseases including stroke probably due to the small sample size [47]. GWAS is a good study design to establish genetic associations in complex human diseases with common variants [48]; when combined with Trans-omics approaches, biological mechanisms of SICH could be unraveled [10]. However, to achieve this goal, adequately powered discovery and replication studies are needed. Thus, a population with high burden of the disease will be invaluable in this context. The substantially higher heritability and ethnic predilection of SICH in African populations, [49] along with the genomic diversity and unique high allelic frequencies of certain variants in Africans (due to ecologic adaptations) [50,51], make it compelling to design GWAS in this population. In addition, the low linkage disequilibrium observed in Africans will facilitate fine-mapping of discovered loci in Europeans and Asian ancestry populations [52,53]. Another compelling reason for conducting such GWAS in Africans is the co-existing high burden of SICH, small vessel disease [41] and hypertension, a dominant risk factor for both ischemic stroke and SICH in these populations [54].

However, only 11 (18.0%) of the 61 eligible studies in this systematic review included African Americans as participants while none included indigenous Africans in whom the burden of SICH is disproportionately high [8,11,13,16,55]. It is also instructive to note that only one out of the 864 screened studies was in an indigenous African population but the article was not included in our analysis because it did not meet the eligibility criteria. The latter study was by Abidi *et al* and found no significant relationship between *MTHFR* gene and SICH among 113 patients and 323 healthy controls in Morocco, North Africa [56]. We previously reported that among individuals aged > 45 years, intracerebral hemorrhage was more common in indigenous Africans (27%) compared to African Americans (8%) and European Americans (5.4%) and that they also have a higher prevalence of hypertension as a stroke risk factor compared to other ancestry groups in the SIREN-REGARDS Collaboration (Stroke Investigative Research and Educational Network–Reasons for Geographic and Racial Differences in Stroke) [57].

So far, single-trait and multi-trait GWAS have identified *TARID/TCF21, LLPH/TMBIM4* and *FRMD3* as novel genetic loci associated with hypertension in people of African ancestry [54]. Leveraging high burden of SICH on the genomic diversity of indigenous Africans will most likely result in discovery and replication of newer genes that will improve our understanding and treatment of this devastating disease. Considering the high resolution in the African only analyses in a study by Asimit et al., "it may be beneficial to include a few small African cohorts (e.g., size 1000 each) rather than an additional couple of large European cohorts (e.g., size 10 000). The possibility of deriving benefits that have a global impact may therefore be more likely by developing the capacity for genomic sciences in Africa, such that an increased number of African-focused GWASs may be performed. This includes enabling and empowering more African researchers to carry out such studies in their populations." [58] Continental Africans have shown strong willingness toward genetic testing for stroke [59] and this demonstrates a huge potential translational impact of new discoveries in ameliorating the very huge burden of SICH in populations of African ancestry [60] and extended benefit to other global populations.

4.3. Role of Omics in understanding the pathophysiology of SICH and future directions

Although GWAS is robust, a reasonable combination of emerging tools of genomics, including whole genome sequencing and next generation whole exome sequencing with functional omics will be imperative to understand the pathophysiology of SICH. Thus, transcriptomics, epigenomics, proteomics and metabolomics can be variously combined with the emerging tools of genomics in order to improve the understanding of the pathophysiology of this condition. The high burden of hypertension in Africans [61], which could be an intermediate phenotype for SICH, makes application of omics a potentially rewarding endeavour in an attempt to have a clearer

understanding of the pathways involved in the development of SICH. This is already being achieved for hypertension itself. For instance, a recent study in African ancestry population identified three novel genomic regions associated with blood pressure and went further to use transomics techniques to unravel the associated pathways, which have not been reported before in studies involving other ancestry populations [54]. Similar techniques can help decipher the genetic underpinnings of SICH and provide a clearer understanding of its pathophysiologic mechanisms.

4.4. Conclusion

There is a need to conduct more genetic studies including GWAS to discover and replicate new loci associated with SICH. It is imperative that such studies include Africans in view of the high burden of the disease in these populations. By focusing on African populations, these studies will take advantage of the high burden of disease, substantially higher heritability, genomic diversity and high allelic frequencies of certain variants in these populations. In all, advocated genomic studies followed by transomics techniques promise to contribute to our understanding of the pathophysiology of SICH and development of appropriate personalized preventive and therapeutic modalities.

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NHGRI – EBI: National Human Genome Research Institute-European Bioinformatics Institute.

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