Genetics in vascular dementia

Raquel Manso-Calderón^{*,1,2}¹Department of Neurology, University Hospital of Salamanca, Salamanca 37007, Spain²Institute of Biomedical Research of Salamanca (IBSAL), University of Salamanca, Salamanca 37007, Spain*Author for correspondence: rmanso@saludcastillayleon.es

Vascular dementia (VaD) is a common disorder that encompasses heterogeneous entities, which creates challenges in order to reach a global consensus for diagnostic criteria. While the genetic basis for sporadic VaD remains poorly understood, the identification of causal genes in monogenic forms of VaD sheds light on the pathophysiological mechanisms of VaD. This special report describes progress in genetic research on monogenic and sporadic VaD, as well as on associated phenotypes, such as cerebral small vessel disease, stroke and Alzheimer's disease. Methodological issues (e.g., small-size studies) and strategies to overcome these problems (e.g., collaborative consortiums, endophenotypes) are discussed. Lastly, future perspectives in the field and how such work could benefit patients and clinicians are mentioned.

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Vascular dementia: an evolving concept

Vascular dementia (VaD) represents the more severe form of vascular cognitive impairment (VCI), an umbrella term that encompasses a heterogeneous group of disorders causing cognitive decline due to cerebrovascular disease (CVD) [1].

The concept VaD has evolved in the last decades. In 1974, Hachinski introduced the term multi-infarct dementia. Later on, the appearance of neuroimaging techniques yielded to the observation that chronic ischemia of small vessels (leukoaraiosis) constitutes the most frequent cause of cognitive impairment of vascular origin. In the 1990s, four sets of diagnostic criteria for VaD were agreed by national institutions or research networks using a definition of dementia based on clinical features of Alzheimer's disease (AD): the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria; the Alzheimer's Disease Diagnostic and Treatment Centers criteria; the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria; and the International Statistical Classification of Diseases, 10th revision criteria. However, disturbance in executive functions rather than in episodic memory is often the predominant feature of VaD; thereby VaD requires its own criteria [2]. In addition, studies comparing these protocols showed they were not interchangeable [3]. In the last years, some guidelines that introduce the concept of VCI, including all forms of cognitive decline from mild cognitive impairment of vascular origin to VaD as well as different CVD mechanisms (e.g., genetically related CVD and even combinations with AD and other neurodegenerative disorders), have been proposed. These comprise the American Heart Association/American Stroke Association and the International Society of Vascular Behavioral and Cognitive Disorders statements and the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition [2,4,5]. Noteworthy, a global consensus for the diagnosis of VaD is lacking today.

The lack of a consensuated definition for VaD creates challenges for research. This is one of the reasons why, although VaD is the second most common form of dementia, its genetic component remains poorly understood in comparison with AD [6]. Recently, a large multinational group of clinicians and researchers participated in a two-phase Vascular Impairment of Cognition Classification Consensus Study (VICCCS) to elaborate principles (VICCCS-1) and protocols (VICCCS-2) for diagnosis of VCI [7]. They recognized four major subtypes of VaD: poststroke dementia; subcortical ischemic VaD (SIVaD); multi-infarct (cortical) dementia (MID); and mixed dementias (further subdivided according to additional neurodegenerative pathologies) and suggested standardized use

of the National Institute of Neurological Disorders–Canadian Stroke Network recommendations on neuropsychological and imaging assessment for diagnosis of VCI so as to promote research collaboration [7,8].

Monogenic disorders

A supporting evidence for a genetic basis of VaD is the fact that mutations in single genes can lead to the development of VaD [6]. Albeit rare, the discovery of causal genes involved in monogenic forms of VaD contributes to the understanding of the pathogenic processes underlying them [9].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most frequent heritable form of VaD. Common manifestations are migraine with aura, recurrent strokes and psychiatric disturbances. It results from mutations of the *NOTCH3* gene (19q12). A great majority – so far over 230 pathogenic mutations reported – are missense mutations (exon 2–24), but deletions, duplications, splice site mutations and deletion/insertions have been described. All these mutations reside within the tandem EGF-like repeat region of Notch3 receptor and generate a gain or a loss of a cysteine residue, thus affecting the function of vascular smooth muscle cells [10,11]. Whether noncysteine variants and mutations causing loss of function (frame-shift deletion or nonsense mutations) can induce CADASIL is still debated [12]. Interestingly, white matter hyperintensities (WMHs) burden in CADASIL has been related to multiple genetic variants with small effect in a genome-wide association study (GWAS) performed in 466 European CADASIL patients, instead of being related to the different *NOTCH3* mutations [13].

Another hereditary form of VaD was observed in some cases of cerebral amyloid angiopathy (CAA). CAA is a group of biochemical and genetic diverse disorders sharing the deposit of amyloid proteins in the walls of vessels provoking leukoaraiosis, small cortical infarcts, lobar intracerebral hemorrhages (ICH) and/or microbleeds. Familial CAA comprises the following amyloid proteins and gene mutations: amyloid β -protein in *APP* (21q21.3) and presenilin (*PSEN 1*, 14q24.3; *PSEN2*, 1q42.13), transthyretin (ATTR) in *TTR* (18q12.1), cystatin C (ACys) in *CST3* (20p11.21), gelsolin (AGel) in *GSN* (9q33), prion protein (PrPSc) in *PRNP* (20p13) and ABri (ADan) amyloid proteins in *ITM2B* (13q14.3) [14].

Fabry disease is a disorder of glycosphingolipid metabolism owing to an absent or reduced lysosomal α -galactosidase activity due to mutations in the *GLA* gene (Xq22). This enzymatic deficiency promotes accumulation of globotriaosylceramide in the vascular endothelium of several organs, which can induce stroke (mostly lacunar but also large vessel and cardioembolic) and VaD [6,15].

Other more rarely described single-gene entities causing VaD include: cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, due to missense, nonsense and splice site mutations in the *HTRA1* gene (10q25); retinal vasculopathy with cerebral leukodystrophy, due to frame-shift *TREX1* mutations (3p21) that results in a DNase III (three prime repair exonucleases) impairment, multilaminated vascular basement membranes, cerebral small vessel disease (CSVD) and, in some cases, pseudotumoral lesions with surrounding oedema; and collagen type IV, alpha 1 (COL4A1)-related disorders, due to missense mutations – most of which affect glycine residue – in the *COL4A1-A2* genes (13q34), that are accompanied by small vessel arteriopathy and ICH [6,9,10,15,16].

Noteworthy, a meta-analysis of six familial CSVD genes (*COL4A1*, *COL4A2*, *NOTCH3*, *HTRA1*, *TREX1* and *CECRI*) carried out in 1878 ICH cases versus 2830 controls and 19,569 ischemic stroke (IS) – lacunar, cardioembolic, large vessel disease – cases versus 37,853 controls showed association between a locus in *COL4A2* and a single nucleotide polymorphism in *HTRA1* and both lacunar IS and deep ICH, suggesting common pathophysiologic mechanisms of distinct ischemic and hemorrhagic CSVD stroke phenotypes, offering new insights into the causal mechanisms of CSVD [17].

Sporadic VaD

Sporadic VaD has been suggested to result from a complex combination of multiple genetic variants with small effects and vascular risk factors, which are partly genetically determined [6]. Linkage analyses in VaD are based on a single Italian study that reports a significant association between the rs1333049 polymorphism in 9p21.3 and VaD [18]. However, genetic research in VaD has focused mainly on association studies with candidate genes involved in stroke and AD and/or in pathophysiological mechanisms critical to VaD [6,19]. Most of them have shown so far slightly significant associations with VaD ($0.01 < p < 0.05$), and scarcely have been replicated [15].

The genes involved in lipid metabolism, especially the *APOE* gene (19q13.2), have been the main research object. A recent meta-analysis including 44 studies (2481 cases, 7490 controls) corroborated a significant association

between $\epsilon 4$ allele carriers and higher risk of VaD, irrespective of ethnicity. Nevertheless, neither $\epsilon 2$ and $\epsilon 3$ allele carriers nor the APOE promoter T-427C increased risk for VaD [6,20,21]. In addition, two polymorphisms (Q192R and L55M) of *PON1* (7q21.3) were found to increase risk of VaD in Indian and French populations, but other two European studies did not confirm these findings for Q192R [6,21,22]. On the contrary, two meta-analyses failed to demonstrate association between an intron 16 insertion/deletion variant of *ACE* (17q23.3), a gene implicated in vascular reactivity, and VaD in both Europeans (six studies: 349 cases, 738 controls) and Asians (four studies: 497 cases, 478 controls) [19,21,23]. Only one report in Indians (80 cases, 170 controls) observed an increased risk of VaD in D allele carriers [24].

Several genes related to inflammation have also been related to VaD, including single nucleotide polymorphisms C-889T and C4845T of *IL-1 α* gene (2q14) in Taiwanese, C-511T of *IL-1 β* (2q14) in Japanese-Americans, G-174C of *IL-6* (7p21) in Italians and Indians, C-857T of *TNF- α* (6p21.3) in Europeans and T-1031C in Asians, and C+29T of *TGF- β 1* (19q13.1) in two Asian reports [6,15,19,20]. Finally, the variant C677T of *MTHFR* (1p36.3), which influences the level of homocysteine, proved to be associated with VaD in Asians (two studies: 178 cases, 250 controls), and more recently also showed stronger evidence in Europeans (two studies: 830 cases, 3438 controls) [21,25,26]. Another meta-analysis (two studies: 822 cases, 962 controls) failed to show association between A-16C of *PSEN-1* (14q24.3) and VaD [21,26].

Relatively few studies focused on the interaction between genes, so-called epistasis. Some examples are the combined polymorphisms *MTHFR* (C677T) and *IL6* (G-174C), *HSP 70-1* (A-110C) and *TNF- α* (T-1031C), *TGF- β 1* (C+29T) and *AGT* (T235M), and *FAM134B* (rs10041159) and *TNFRSF19* (rs9317882) [27–30].

On the other hand, three GWAS for VaD have been carried out. Two of them detected genetic associations near the androgen receptor gene on the X chromosome (rs12007229) and *RPGRIP1L* (rs16952362) in Dutch (67 patients, 5700 controls) and Korean (207 patients, 207 controls) populations, respectively. The first association was replicated in a German population (221 cases, 213 controls). *RPGRIP1L* regulates thromboxaneA2, which plays a role in vasoconstriction, platelet aggregation and thrombus formation [31,32]. Later on, functional studies have suggested an association between splicings of the *SYK* and the *PHLDB2* genes and VaD [33,34]. Specifically, *RPGRIP1L* and *PHLDB2* implications in strategic and SIVaD have been proposed as both are expressed in basal nuclei and caudate nucleus [32,34].

The role of associated phenotypes

A novel approach is based on genes identified through GWAS of stroke and AD, which overlap clinically in the realm of VaD. As part of the International Stroke Genetics Consortium, the METASTROKE collaboration, the NIH-funded SiGN initiative and the CHARGE consortium, several GWAS have been performed in tens of thousands of stroke patients and hundreds of thousands of controls [6]. A common variant at the *FOXF2/FOXQ1* locus was found to be associated with any stroke (ischemic + hemorrhagic) and WMHs [35]. However, most GWAS are largely restricted to certain IS subtypes: *HDAC9*, *SERPINA1* and *TSPAN2* were associated with large artery atherosclerosis stroke (LAS), whereas *PITX2* and *ZFHX3* associate with cardioembolic stroke (CES), and *ALDH2* with small artery stroke (SVS) [35–38]. Despite lower sample sizes, GWAS in ICH have revealed two replicated associations on 1q21 (for nonlobar ICH) and 12q21 (for lobar ICH) [39]. Moreover, low-frequency genetic variants (allele frequency <5%) *GUCY1A3* and *GCH1* enhanced risk of LAS and SVS, respectively [40]. Likewise, more than 20 novel susceptibility loci have been identified in AD by using GWAS and five rare genetic variants – *TREM2*, *PLD3*, *UNC5C*, *AKAP9* and *TM2D3* – (allele frequency <1%) discovered through next-generation sequencing [41,42]. Although these novel genes play mainly a major role in known AD pathways involving amyloid or tau processing, genes like *APOE*, *CLU*, *ABCA7* and *SLC24A4* were involved in the cholesterol pathway [43]. Notwithstanding, these genes have yet to be investigated for their relation with VaD.

Another line of research has been to consider some intermediate phenotypes – also called endophenotypes – that are more common and easier to quantify than the final disease expression [44]. Thus, endophenotypes increase the power of genetic studies by favoring the compilation of genetic and phenotypic data from multiple populations. Indeed, VaD subtype-specific genetic associations reported (e.g., *IL6* and MID, *TGFB1* and SIVaD, *NOS3*, *GCLM* or *ACT* and poststroke dementia) highlight the importance of define phenotypes according to the different etiologies of VaD, similarly to stroke [15,45]. For instance, GWAS have identified *ZHX2*, *APOC1* and *PINX1* as genes related to carotid intima-media thickness, and *PINK3CG* and *EDNRA* to carotid plaque presence, both serving as endophenotypes for LAS [46]. Atrial fibrillation, a major cause of CES, has been associated with up to 25 genome-wide significant loci [47]. Silent brain infarcts or lacunes, dilated perivascular spaces and

cerebral microbleeds are considered endophenotypes for SVS [48]. This also applies to WMHs, for which a recent meta-analysis evidenced genome-wide signals in *TRIM65*, *SH3PXD2A*, *EFEMP1*, *PMF1* and *HAAO* [49].

Benefits of understanding the genetics of VaD

Identification of individuals and families carrying causal genes involved in monogenic forms of VaD is important to provide appropriate genetic counseling and implement preventive measures [50]. The discovery of genetic variants in sporadic VaD should also imply diagnostic and prognostic advantages in order to optimize selection and stratification according to disease risk of persons for clinical trials in drug development studies [6,51]. For instance, an algorithm combining *APOE* and *TOMM40* genes, with predictive value for AD, has been used in the TOMMORROW randomized control trial [52]. An additional potential application for VaD genetics is to aid in the categorization of VaD subtypes, particularly those secondary to strokes labeled as cryptogenic or of undetermined cause after standard testing [50].

Moreover, both casual genes in monogenic disorders and susceptibility genes in sporadic disease, unraveled through GWAS and meta-analyses on cases and controls, serve for the generation of new targets and drug development [6,50]. For example, the discovery of mutations in *APP*, *PSEN1* and *PSEN2* genes in familial AD promoted the amyloid cascade hypothesis and anti-amyloid clinical trials [6]. In a similar way, the evidence that *HDAC9* variant increased atherosclerosis – particularly at the carotid bifurcation – and LAS conducted to assess sodium valproate treatment, which inhibits histone deacetylase 9 – the protein product of *HDAC9* [50].

Another interesting clinical application will be to use pharmacogenetics to personalize therapeutic decision making [50]. Pharmacogenetics refers to the interindividual genome-wide DNA variations and potential interactions that correlate with drug efficacy and safety [6]. In this sense, the knowledge of antihypertensive drugs that up- or downregulate VaD-associated genes (*MTHFR*, *SYK*, *AGT*, *RPGRIP1L*, *MMP9*, *VEGFA*) could be used for VaD prevention and treatment [53]. In stroke, up to 35% of variability noted in the response to warfarin in CES due to atrial fibrillation was related to *VKORC1* and *CYP2C9* variants [54]; reduced concentrations of clopidogrel in blood with increased risk of cardiovascular events were related to *CYP2C19*2* variant [55]; whereas hemorrhagic transformation and in-hospital death after treatment with alteplase for IS was associated with *A2M* and *F12* variants, respectively [56]; and *ABCB1* and *CES1* variants were shown to reduce the concentration of dabigatran in blood and risk of any bleeding [57].

Conclusion

Unraveling single genes causing monogenic forms of VaD or genetic variant-modifying traits of these well-defined phenotypes increase our understanding on the pathogenesis of VaD. For sporadic VaD, there have been several replicated candidate gene studies, but data available on GWAS are too small to yield convincing results. Future research requires larger sample sizes and more homogenous subgroups, being endophenotypes helpful for this purpose. Elucidate genetics in VaD will allow personalized therapeutic decision-making.

Future perspective

Although recent research progress observed in the knowledge of genetic basis on monogenic VaD, the field of sporadic VaD genetics faces several challenges because of the expected modest contribution to the disease of thousands of unknown variants. Larger sample sizes and replication in independent cohorts are mandatory. A method to overcome this issue is to join collaborative efforts via the creation of consortiums as happens in stroke or AD [8,45,58]. Another important challenge is the heterogeneity of phenotype definitions for VaD. Furthermore, mixed pathologies are frequent above the age of 75 and need to be taken into account. The introduction of endophenotypes constitutes an appealing strategy to advance in investigation on VaD [8,44]. The focus has so far been on WMHs and brain infarcts, but other neuroimaging traits with demonstrated heritability have yet to be analyzed in depth [6,59]. Interestingly, cerebral microbleeds (from T2*-weighted or susceptibility-weighted MRI) and enlarged perivascular spaces are markers for both ischemic and hemorrhagic pathology, whereas white matter integrity (from diffusion imaging) represents a previous stage in the development of WMHs underlying CSVD and hence VaD [60–62].

Beyond candidate genes studies and GWAS, the development of novel technologies (whole-exome and whole-genome sequencing) permits analysis of the risk burden of rare variants across a gene or region of interest in polygenic disorders [15]. Likewise, other types of genetic variation (e.g., copy number variations, telomere length) and epigenetic modifications – with a potential role in gene–environment interactions in VaD (e.g., DNA methylation

through epigenome-wide association studies) can be studied by means of existing collections of samples with matched phenotypic data [63–65]. Conversely, the evaluation of RNA (e.g., miRNAs) requires the collection of new samples to be used in by dedicated RNA processing pipelines. But miRNAs represent an emerging approach that is gaining focus in the last years, because of a suggested role in the pathogenesis of stroke, and its complications and outcomes [66]. In fact, miR-409-3p, miR-502-3p, miR-486-5p and miR-451a have been reported as biomarkers for small vessel VaD [67]. Therefore, promoting or suppressing expression of miRNAs by specific pharmaceutical and nonpharmaceutical therapies could represent an important target for treatment and preventive strategies in VaD [68].

Executive summary

Vascular dementia: an evolving concept

- Vascular cognitive impairment (VCI) comprises a heterogeneous group of disorders with diverse causes (ischemic, hemorrhagic, monogenic, plus AD) and manifestations (from mild cognitive impairment of vascular origin to vascular dementia [VaD]).
- Currently, a global consensus for the diagnosis of VaD is lacking.

Monogenic disorders

- The discovery of single-genes causing monogenic VaD contributes to the understanding of the pathogenic processes underlying them.
- Unraveling genetic variants in monogenic VaD can be helpful to shed light on pathophysiological mechanisms underlying sporadic VaD.

Sporadic vascular dementia

- Several genetic variants with small effects involved in different biological processes can predispose to VaD, being *APOE* e4 and *MTHFR* the most consistently replicated.
- To date, genome-wide association studies (GWAS) in VaD are scarce.

The role of associated phenotypes

- GWAS of stroke and Alzheimer's disease could be helpful for VaD due to shared pathways.
- Endophenotypes (e.g., white matter hyperintensities or microbleeds) can facilitate the identification of genetic risk factors in subcortical ischemic VaD.

Benefits of understanding the genetics of vascular dementia

- Novel genetic variants discovered in VaD could be used as diagnostic, prognostic and treatment biomarkers.
- Pharmacogenetics in VaD constitutes a hopeful point to improve drug efficacy and safety.

Conclusion

- The identification of causal genes remains limited to monogenic VaD, with findings for sporadic VaD less robust.
- Larger sample sizes and more homogenous subgroups are required.

Future perspective

- Endophenotypes emerge as a strategy to advance in genetic investigation on VaD.
- Beyond candidate gene analyses and GWAS, future research seems to focus also in rare variants, epigenetic modifications and miRNAs.

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