Genetics of Cerebrovascular Disease

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# Genetic loci associated with Mendelian cerebrovascular conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mode of inheritance</th>
<th>Underlying gene(s)</th>
<th>Stroke mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mendelian conditions mostly manifesting with ischaemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CADASIL</td>
<td>Autosomal dominant</td>
<td>NOTCH3</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>CARASIL</td>
<td>Autosomal recessive</td>
<td>HTRA1</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>CARASAL</td>
<td>Autosomal dominant</td>
<td>CTSA</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>Fabry's disease</td>
<td>X-linked</td>
<td>GLA</td>
<td>Small vessel disease, large artery disease, cardioembolism</td>
</tr>
<tr>
<td>PADMAL</td>
<td>Autosomal dominant</td>
<td>COL4A1</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>RVCL-S</td>
<td>Autosomal dominant</td>
<td>TREX1</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>Sickle-cell disease</td>
<td>Autosomal recessive</td>
<td>HBB</td>
<td>Prothrombotic state, large artery disease</td>
</tr>
<tr>
<td>FOXC1 deletion-related angiopathy</td>
<td>Autosomal dominant</td>
<td>FOXC1</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>DADA2</td>
<td>Autosomal recessive</td>
<td>ADA2 (CECR1)</td>
<td>Small vessel vasculitis</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>Autosomal recessive</td>
<td>ABCG6</td>
<td>Large artery disease, small vessel disease</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Autosomal recessive</td>
<td>CBS and others (eg, MTHFR)</td>
<td>Large artery disease, cardioembolism, small vessel disease, arterial dissection</td>
</tr>
<tr>
<td>Marfan's syndrome</td>
<td>Autosomal dominant</td>
<td>FBN1</td>
<td>Cardioembolism, arterial dissection</td>
</tr>
<tr>
<td>Vascular Ehlers-Danlos syndrome</td>
<td>Autosomal dominant</td>
<td>COL3A1</td>
<td>Arterial dissection</td>
</tr>
<tr>
<td>MELAS</td>
<td>Maternal</td>
<td>Mitochondrial DNA</td>
<td>Microvascular and neuronal factors</td>
</tr>
<tr>
<td>Hereditary haemorrhagic telangiectasia</td>
<td>Autosomal dominant</td>
<td>ENG or ALK1 in about 85% of cases</td>
<td>Arteriovenous malformations</td>
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<tr>
<td><strong>Mendelian conditions mostly manifesting with haemorrhagic stroke</strong></td>
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<tr>
<td>COL4A1 or COL4A2-related angiopathies</td>
<td>Autosomal dominant and de novo</td>
<td>COL4A1, COL4A2</td>
<td>Small vessel disease</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>Autosomal dominant</td>
<td>APP, CST3</td>
<td>Cerebral amyloid angiopathy</td>
</tr>
<tr>
<td>Cerebral cavernous malformations</td>
<td>Autosomal dominant</td>
<td>KRT1 (CCM1), MGC4607 (CCM2), PDCD10 (CCM3)</td>
<td>Cerebral cavernous malformations</td>
</tr>
</tbody>
</table>

CARASAL=cathepsin A-related arteriopathy with strokes and leukoencephalopathy. PADMAL=pontine autosomal dominant microangiopathy with leukoencephalopathy. RVCL-S=retinal vasculopathy with cerebral leukoencephalopathy. DADA2=deficiency of adenosine deaminase 2. MELAS=mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.
MEGASTROKE: Multiancestry GWAS of stroke and stroke subtypes in 521,612 subjects

29 studies = 67,162 cases/454,450 controls
~8 M variants imputed using 1000G or UK10K/HRC

Central QC: −5 < j < 5; Imp > 0.5; MAF > 0.01; EAC/study > 10

Ancestry-specific FE meta-analysis:
AS, AIS, LAS, CES, SVS

EUR
17 studies
40,585/406,111
AFR
5 studies
5,541/15,154
EAS
2 studies
17,368/28,195
SAS
3 studies
2,437/6,707
ASN
1 study
365/333
LAT
1 study
865/692

Transancestral meta-analysis

FE meta-analysis: $P < 5 \times 10^{-8}$, $P_{\text{het}} < 5 \times 10^{-8}$

MANTRA: $\log_{10}(\text{BF}) > 6$ & $PP_{\text{het}} < 0.95$

22 new stroke-associated loci identified

Malik et al. Nat Genetics.2018
MEGASTROKE: Single Marker Results

- 22 common novel loci with small effect sizes (OR 1.05 - 1.20)
- Significant correlations of risk-allele frequencies and ORs between populations
- Estimated phenotypic variance explained: 0.6% - 1.8%

Malik et al. Nat Genetics.2018
Genetic overlap with vascular traits

Malik et al. Nat Genetics. 2018
Shared genetic contribution between CVD and related vascular traits (wGRS; LD-score regression)
Metaanalysis of MEGASTROKE (European) and UKB

- 72,147 cases; 823,869 controls
- NOS3 genetically associated with HTN and coronary artery disease; MR analyses suggest that effects of variants in the NOS3 on stroke risk are in part mediated through blood pressure
- \textit{COL4A1} associated with Mendelian in small vessel disease (strongest association in MEGASTROKE with SVS)
- \textit{DYRK1A} encodes a dual-specificity tyrosine-phosphorylation–regulated kinase 1A that has been shown to regulate angiogenic responses in vascular endothelial cells

Malik et al. Ann Neurol 2018
MRI-defined extremes of SVD (general population)

- 3C-Dijon WES study (n=1497), replication in CHARGE (n=2,868, n (extremes) = 956)
- NOTCH3, HTRA1, COL4A1, COL4A2 and TREX1
- rare and common intronic variants in HTRA1 (rs2293871) and NOTCH3 (rs1043997)
- two participants carrying heterozygote genotypes at known pathogenic variants in NOTCH3 and HTRA1; both with extensive SVD on brain imaging, but mild clinical expression
- suggests that pathogenic variants known to cause rare Mendelian forms of SVD are more frequent in general population than previously suspected

Mishra et al. Brain 2019
Limitations

- Heterogeneous measurements across sites
- Heterogeneity of phenotype ("any stroke"; "any ischemic stroke"); limited sample size for more homogeneous subtype analyses
- Limited power to detect rare variants
- Limited sample size for several ancestral populations
Common genetic variants associated with AD

- **Pathways:**
  - Immune response
  - Endocytosis
  - Lipid metabolism
  - Tau binding
  - APP metabolism

- Enrichment for rare variants

- Limited overlap with CVD loci

Kunkle et al. Nature Genetics 2019

Columbia University Alzheimer’s Disease Research Center (ADRC)
• Ongoing efforts in the ADGC and several ADGC & ADSP related projects to look at shared genetic contribution between AD and CVD

• Complicated/limited by heterogeneity of CVD measurements across sites, available (endo)phenotype & biomarker data, and limited sample sizes for minority populations
Conclusions

- Large proportion of phenotypic variance of CVD still unexplained: likely involvement of a significant number of additional rare, common and structural variants
- Sporadic CVD shares genetic contribution with various vascular traits in particular blood pressure and coronary artery disease, but there are also CVD loci that have not been mapped to any of these traits (CVD-subtype specific? Power?)
- Overlap between Mendelian and sporadic CVD (Notch3, HTRA1, COL4A1); frequency of specific Mendelian variants likely higher than expected
- Limited genetic overlap with known AD loci

Need sufficiently large sample sizes (including biomarker, neuroimaging and neuropathological measures of CVD) across different ethnic groups to detect lower frequency variants, subtype-specific variants, ancestry-specific variants, and dissect genetic overlap with AD
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