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Genetics in Stroke

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Disclosures

- I have consulted and received honoraria and/or travel reimbursement from:
  Amgen, Biomarin, Ultragenyx, Otsuka, Chiesi, Mirum, Amicus, PTC Therapeutics, Arcturus.
- I participate in sponsored clinical trials for:
  NGGT, Otsuka, Biomarin, Travere, Moderna
- I have no conflict related to commercial laboratories or genetic testing products
- I do not endorse or specifically recommend any specific commercial lab or testing product. Any reference to a specific laboratory or test is meant for example purposes only
- No off-label use of any drug will be discussed

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Learning Objectives

- Recognize the most common monogenetic forms of stroke
- Identify phenotypes more likely to have a genetic causes
- Differentiate types of genetic tests and their limitations

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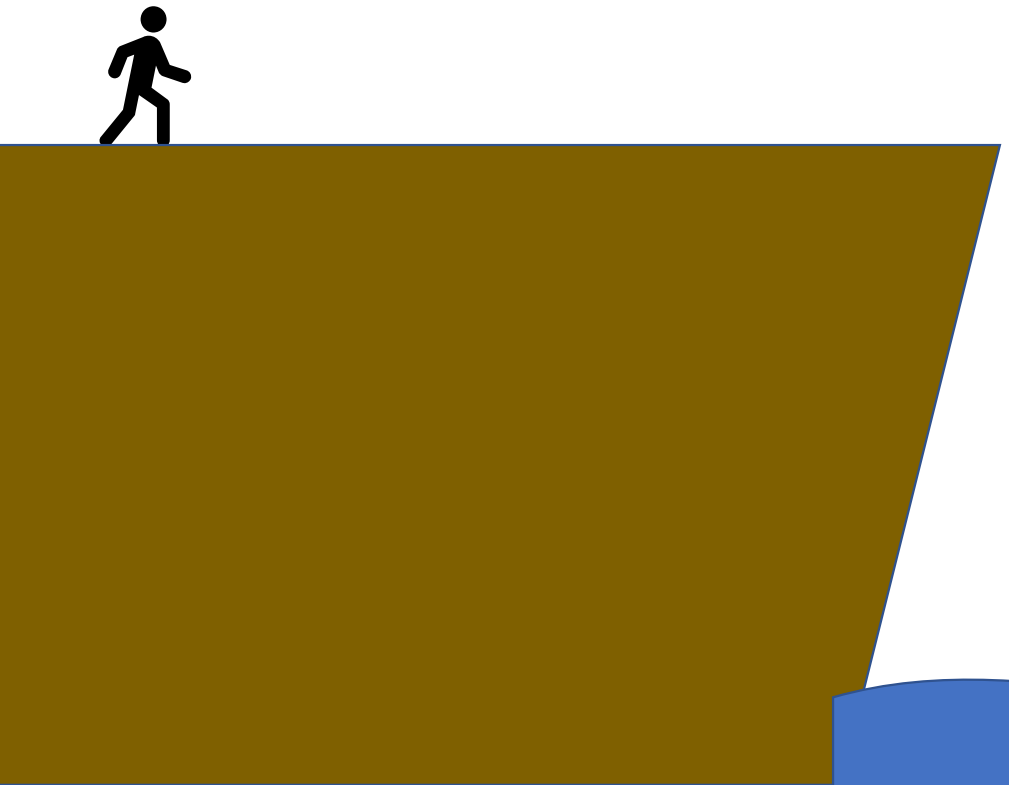
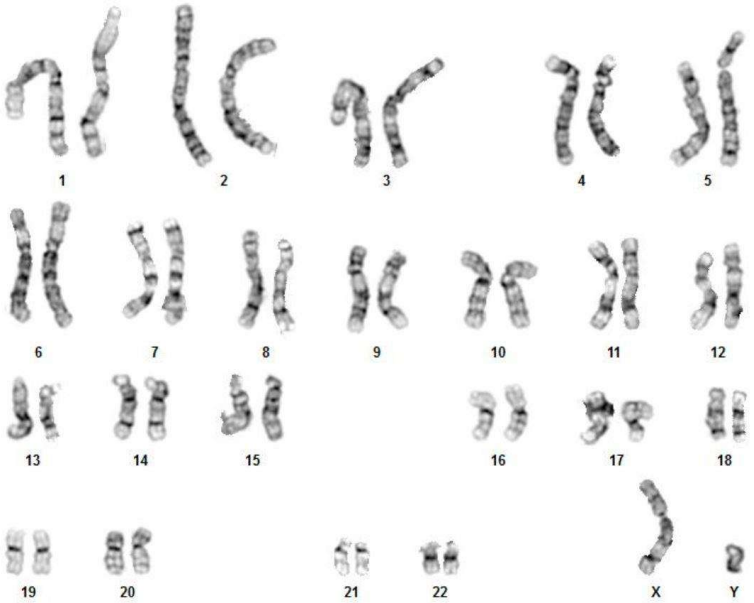
Genetic variation and disease



1. Mendelian disease
2. Genetics risk factors
   - Major
   - Minor
3. Environmental factors
   - Major
   - Minor

Genetics by the Numbers



- ~3,000,000,000 bases (letters)
- ~20,000 genes (instructions)
- 5,033 genes with possible disease link
- 7,660 diseases with a known genetic alteration
- 2% of the U.S. population have ‘genetic disease’ (excluding cancer)
- 16,000-17,000 base mitochondrial genome with 37 genes

http://omim.org/satistics/geneMap 11/23/25

Hall 1978 Am J Med Genet 1:417-436

Baird 1988 Am J Hum Genet 42:677-693-436

McCandless 2004 Am J Hum Genet 74:121-127

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Genetics and Stroke Statistics

- About 25% of stroke patients have a family history (15-52%)

  https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106074

- A monogenetic cause is identified in 1-5% of cases

  https://doi.org/10.3390/genes12121855

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Categories of Monogenetic Stroke Disorders

Ischemic Stroke Disorders

Small Vessel Disease
- CADASIL
- CARASIL
- CARASAL
- COL4 disease

Large Artery Disease
- Familial Hypercholesterolemia
- Vascular EDS
- Marfan and Marfan-like disease (Aortopathy)

Small and Larger Artery Disease
- Sickle cell disease
- Fabry Disease
- Hyperhomocyteinemia
- Neurofibromatosis type 1
- Pseudoxanthoma elasticum

Embolic
- HHT
- Hereditary cardiomyopathy
- Hereditary arrhythmias
- Aortopathy

Metabolic
- MELAS
- Mitochondrial disease NOS

Hemorrhagic Stroke Disorders

Small Vessel Disease
- Hereditary Cerebral amyloid angiopathy
- COL4 disease
- CARASAL

Large Artery Disease
- Primary Moya-Moya
- Secondary Moya-Moya (Fabry, Sickle cell)

Vascular Malformations
- Hereditary Hemorrhagic Telangiectasia (HHT)
- Cerebral cavernous Malformation (CCM)
- Autosomal dominant polycystic kidney disease

* This list is not comprehensive

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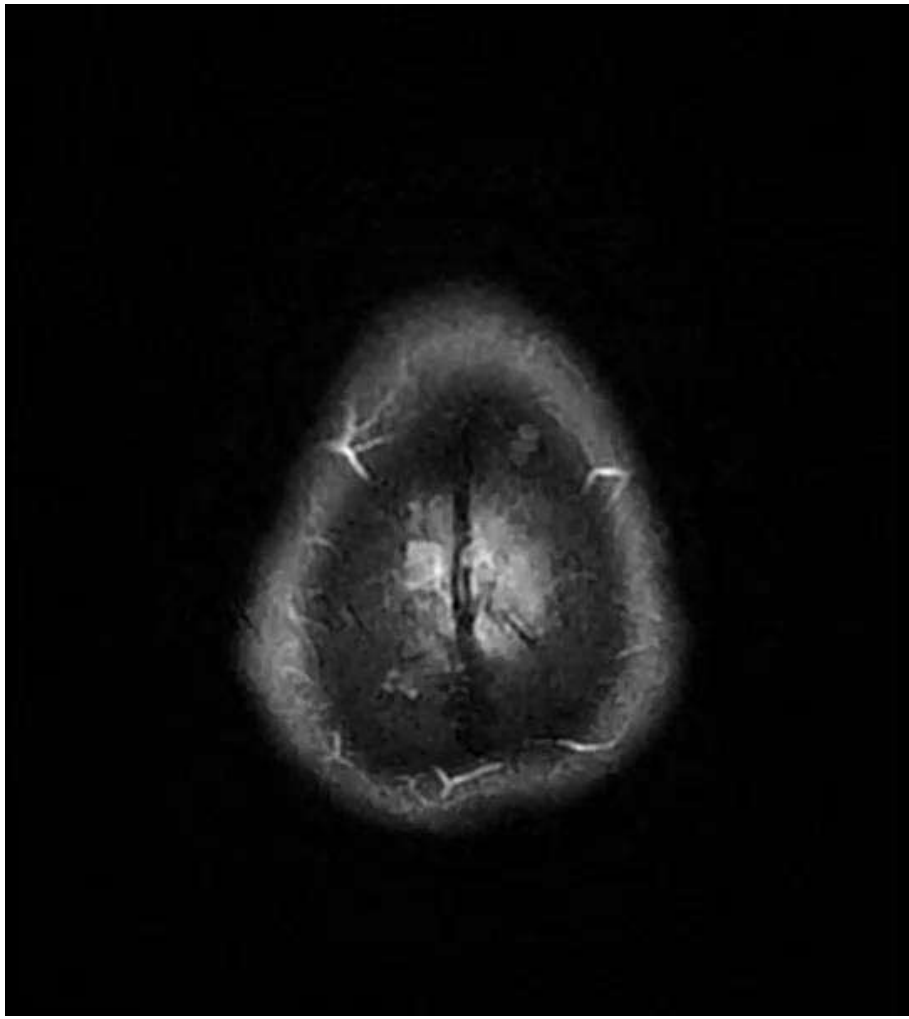
CADASIL

Cerebral **A**utosomal **D**ominant **A**rteriopathy with **S**ubcortical **I**nfarcts and **L**eukoencephalopathy

- *NOTCH3*
- Most common monogenic small-vessel stroke (1:25000)
- Lacunar strokes (30s–50s), migraine with aura
- Psychiatric disease, cognitive decline
- MRI: External capsule + anterior temporal lobe involvement

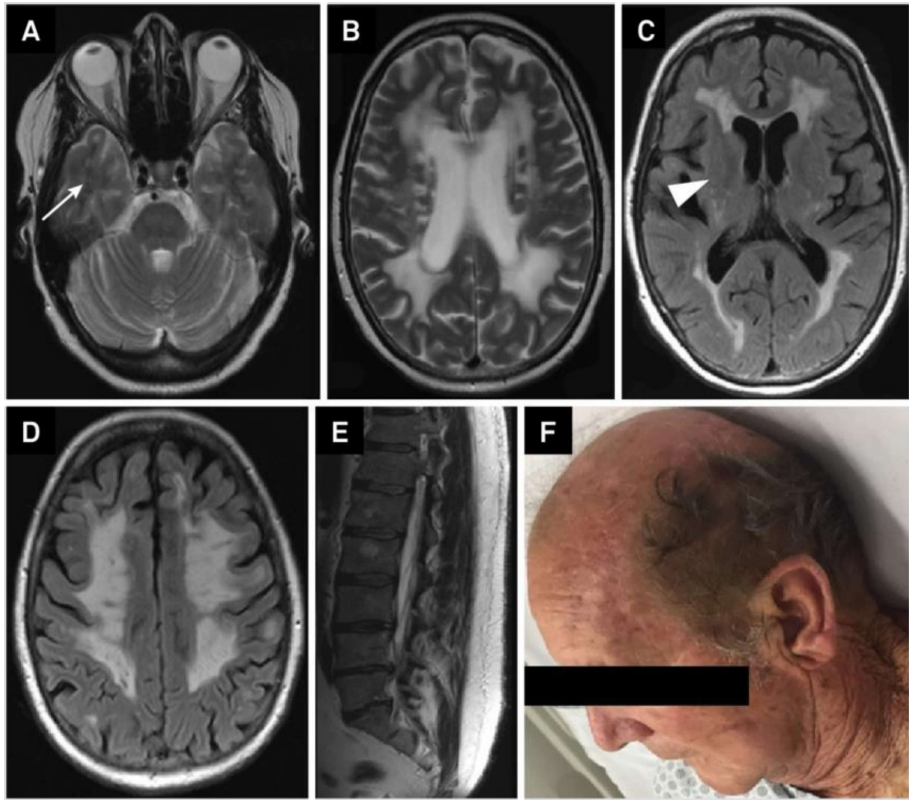


https://doi.org/10.53347/rID-1027

CARASIL

Cerebral **A**utosomal **R**ecessive **A**rteriopathy with **S**ubcortical **I**nfarcts and **L**eukoencephalopathy

- *HTRA1*
- Rare (50 cases), earlier onset(20s)
- The most frequent initial symptom is slowly progressive gait disturbance
- Alopecia, low-back pain/spondylosis
- TGF-β pathway dysregulation
- Dominant *HTRA1* form also exists



Arquivos de Neuro-Psiquiatria. 74. 599-600. 10.1590/0004-282X20160076.

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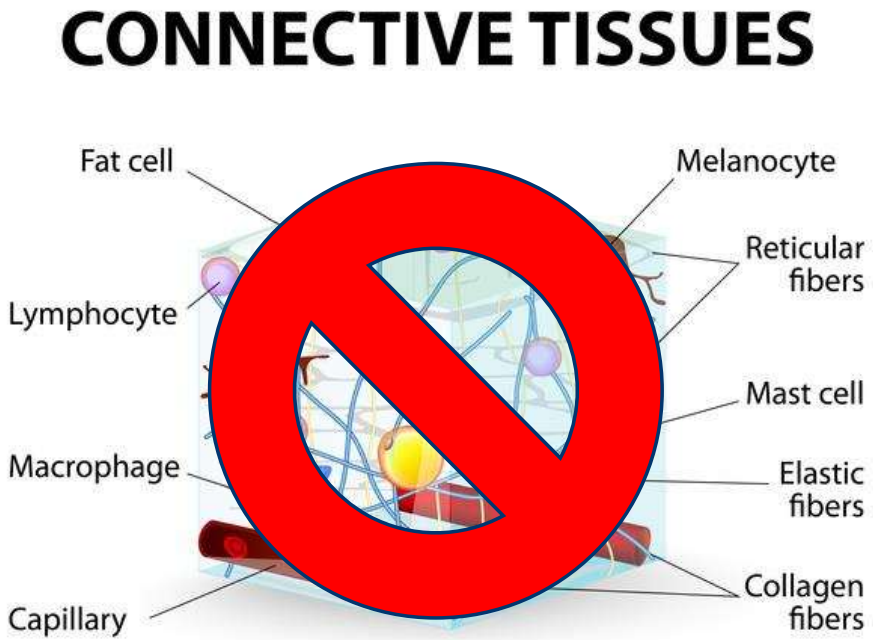
Connective Tissue Defects



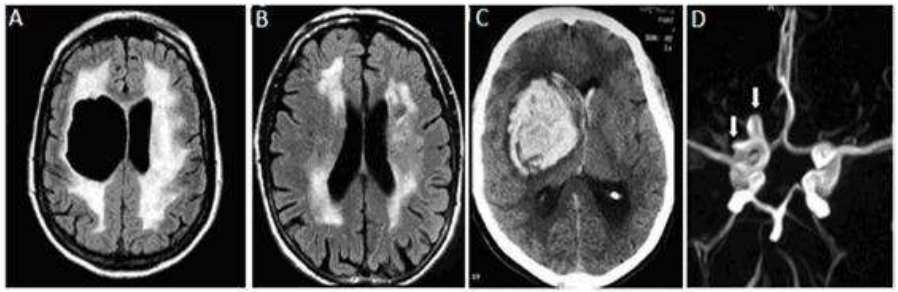
- Marfan Syndrome
- Loeys-Dietz syndrome
- Thoracic aortic aneurysm and dissection (TAAD) (~20 genes)
- Collagen defects

https://ghr.nlm.nih.gov/condition/loeys-dietz-syndrome

COL4 disease

COL4A1, COL4A2

- Autosomal dominant
- Basement membrane defects → fragile vessels
- Ischemic + hemorrhagic small-vessel disease
- Ocular abnormalities, kidney disease, muscle cramps
- HANAC (*h*ereditary *a*ngiopathy with *n*ephropathy, *a*neurysms, and muscle *c*ramps)
- ~100 families

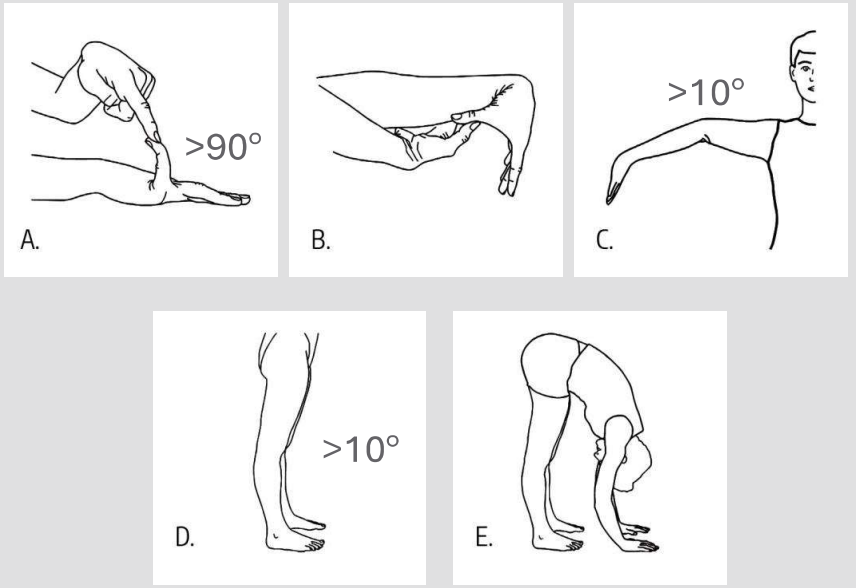


https://www.ncbi.nlm.nih.gov/sites/books/NBK7046/

Vascular EDS

COL3A1

- Ehlers-Danlos Syndrome
  - 13 subtypes (12 monogenic)
  - >20 genes
  - Skin extensibility, Joint hypermobility, tissue fragility
- Autosomal dominant
- 1:100,000
- Mild and severe form
- Vascular aneurysms and rupture
- Organ rupture



Joint Hypermobility

- Assessed with Beighton Criteria
- 1 point for each assessment
- 9 points possible
- >=5 generalized hypermobility
- 15-30% of general population

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HHT = Hereditary Hemorrhagic Telangiectasia

- Autosomal dominant
- Affects all genetic backgrounds
- Approximately 1.4 million people worldwide
- At least 1:5,000 (uncommon, but *not* rare)

GENE	HHT TYPE	CLINICAL MANIFESTATION DIFFERENCES	% of HHT
ENG	HHT 1	Pulmonary AVM and Cerebral AVM more frequent	44
ACVRL1	HHT 2	Liver VM more frequent and possibly GI bleeding	52
SMAD4	HHT/JP	Pulmonary AVM may be more frequent, Juvenile polyposis (JP) syndrome, aortic dilatation/dissection	1

https://doi.org/10.3390/jcm9113571

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Curasao Criteria for HHT

Definite: 3 or 4 criteria are present
Possible: 2 criteria are present
Unlikely: < 2 criteria are present

- Nosebleeds: spontaneous, recurrent
- Telangiectasias: multiple, at characteristic sites - mouth, face, hands
- AVMs: lung, brain, liver, gastrointestinal tract
- Family history: 1st degree relative with HHT

PMID: 10751092

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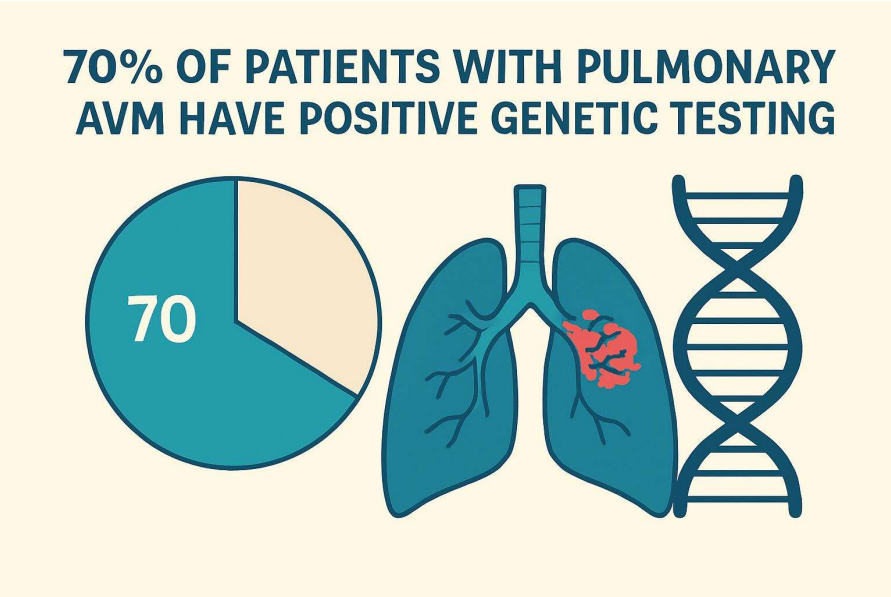
Stroke in HHT

- Rate: 10-20% of HHT patients
- Hemorrhagic – 10-20% have brain AV malformation
- Embolic – 40% have pulmonary AVM



https://doi.org/10.3390/jcm9061927

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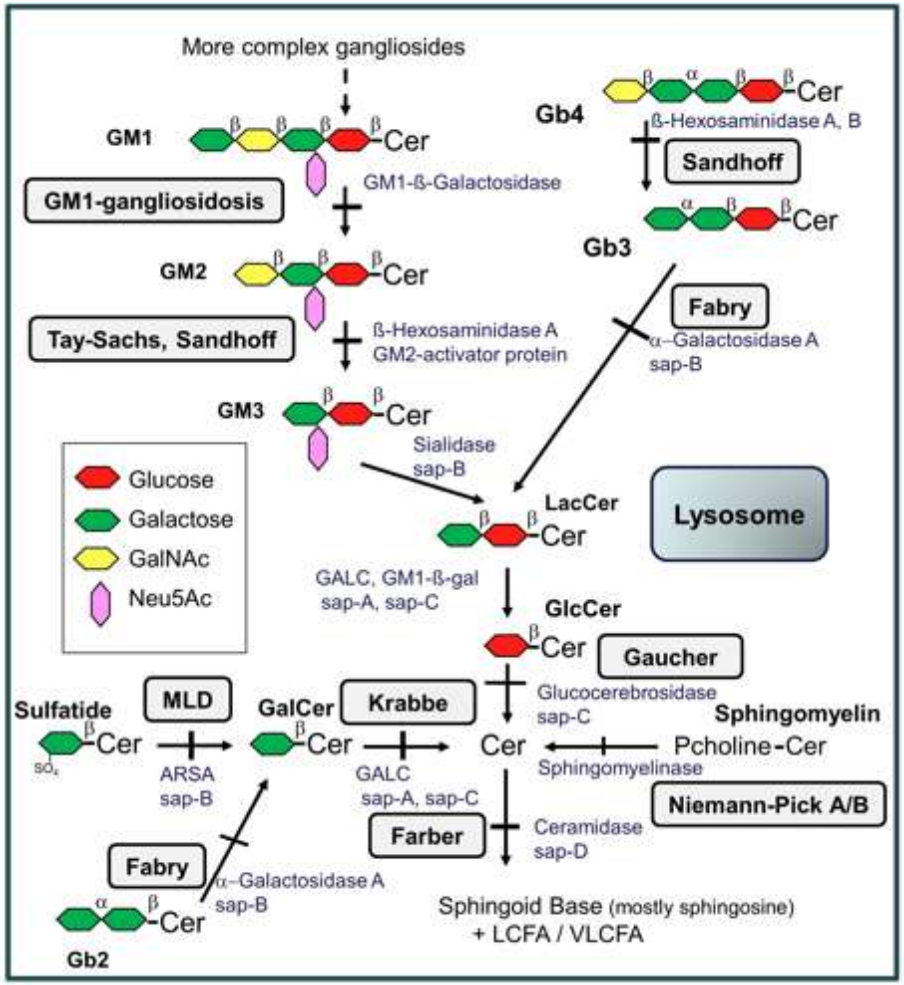
Fabry Disease

- X-Linked Sphingolipidosis
- Deficiency of lysosomal alpha-galactosidase
- 1:40000 prevalence (classic males)
- Treatment with enzyme replacement therapy or oral chaperone

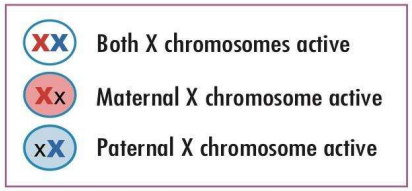


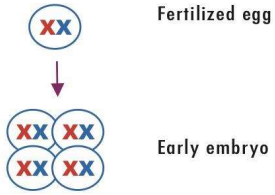
From M Vannier in IMD 6th JM Saudubray et al 2016

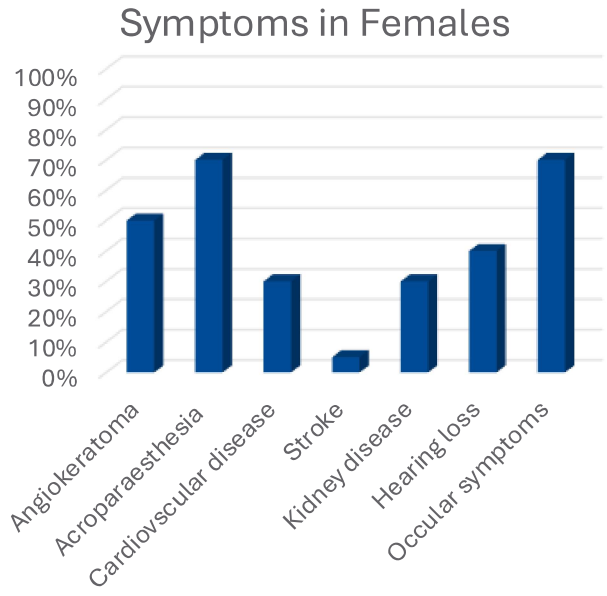
Fabry: A rainbow of severity

Feature		Classic
Age at onset		4-8 yrs
Average age of death		41 yrs
Manifestation	Angiokeratoma	++
	Acroparesthesia	++
	Hypohidrosis/anhidrosis	++
	Corneal/lenticular opacity	+
	Cardiac disease	LVH/ischemia
	Cerebrovascular disease	TIA/stroke
	Renal disease	ESRD
	Residual α-Gal A enzyme activity	<1%

Fabry in Females: X Inactivation







https://www.ncbi.nlm.nih.gov/sites/books/NBK1292/

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Slide adapted from Greenwood Genetics Center

Stroke in Fabry

- 5.4% of Males, 4.7% of females
- First stroke median age 37.9 (M) vs 45.4 years (F)
- 70% small vessel, 87% ischemic
- For late-onset Fabry, stroke occurred prior to diagnosis in 68%(M) vs 91.7%(F)
- Out of 721 German adults that had cryptogenic stroke and underwent Fabry screening, 4.9% of males and 2.4% of females diagnosed with Fabry
- ERT treatment reduces stroke risk (HR ~0.5, registry data)

https://doi.org/10.1016/S0140-6736(05)67635-0
https://doi.org/10.1016/j.ymgme.2023.107780

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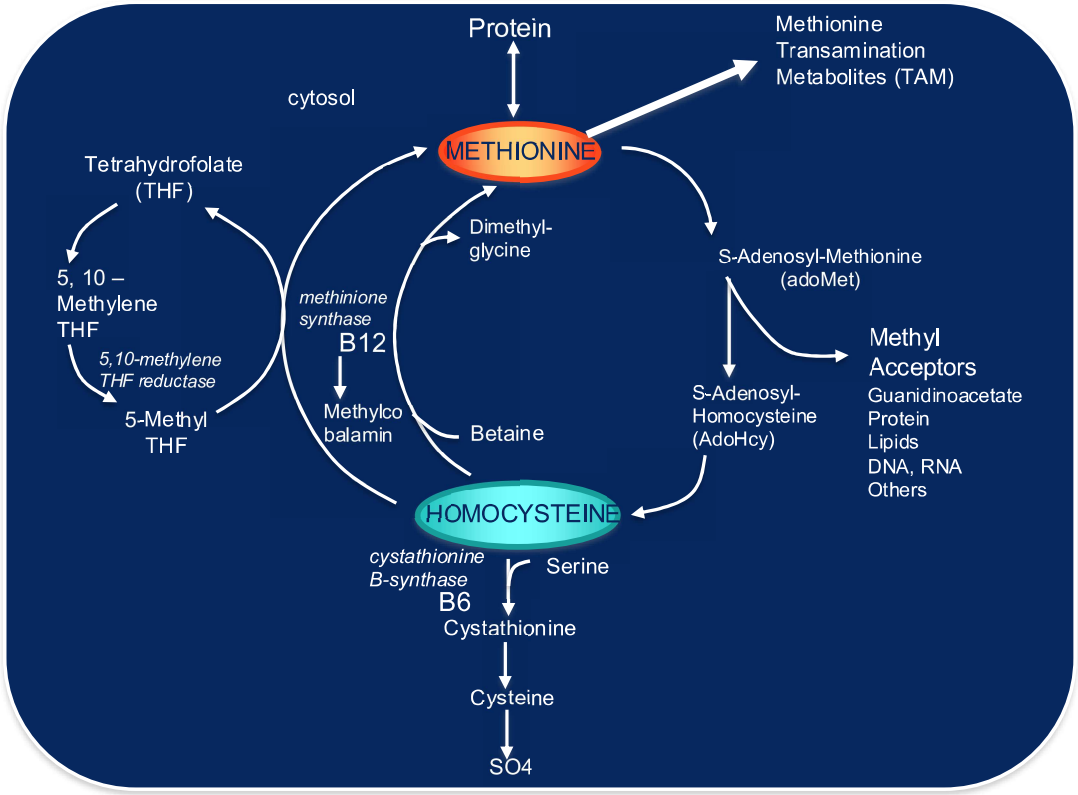
Hyperhomocyteinemia

- Hyperhomocyteinemia has been associated with stroke and CAD
- Classical homocystinuria (*CBS* deficiency)
- *MTHFR* deficiency
- Intracellular Cobalamin defects
  - *MMACHC* (*cblC*)
  - *MMADHC* (*cblD*-combined and *cblD*-homocystinuria)
  - *MTRR* (*cblE*)
  - *LMBRD1* (*cblF*)
  - *MTR* (*cblG*)
  - *ABCD4* (*cblJ*)
  - *THAP11*(*cblX*-like), *ZNF143*(*cblX*-like), *HCFC1* (*cblX*)

Methionine Metabolism



Yaghmai R et al. Am J Med Genet 2001;108:57

Slide courtesy SIMD-NAMA

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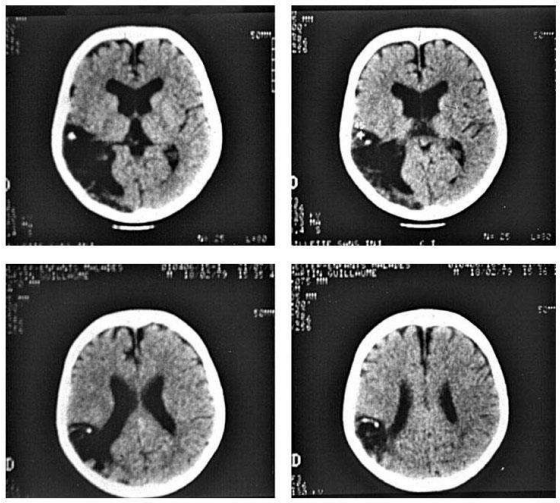
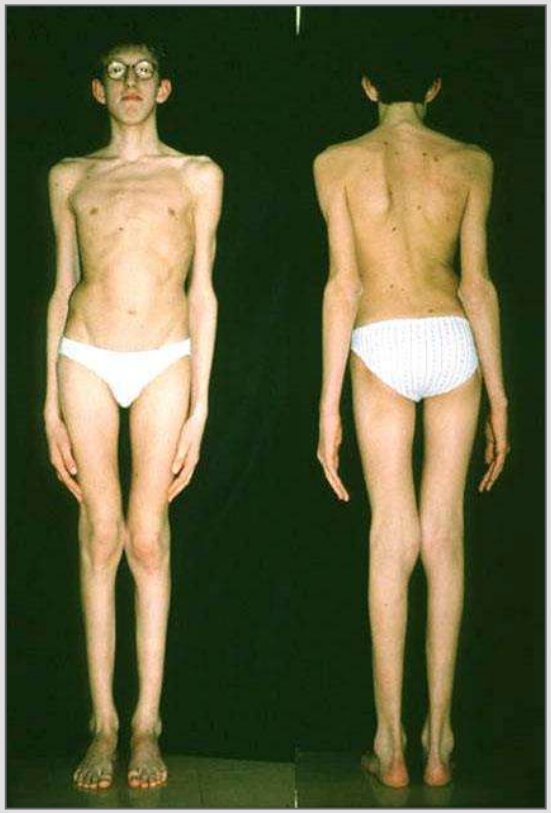
Classical homocystinuria

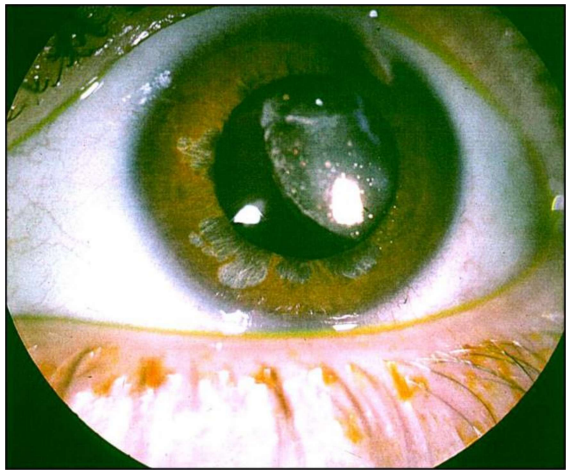
- Skeletal malformations
- Eye abnormalities (ectopia lentis, high myopia)
- Developmental disability, neuropsychiatric symptoms
- 50% Vascular event risk by age 30
- Treatment reduces risk by 90%

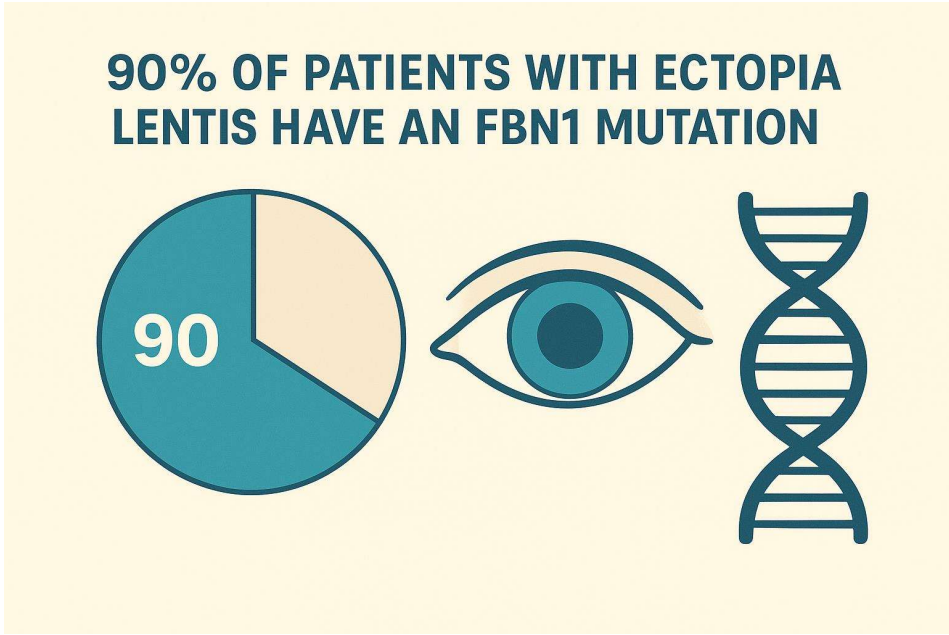




Ectopia Lentis

- Marfan Syndrome (75%)
- Homocystinuria (70-90%)
- MTHFR deficiency





https://doi.org/10.1167/iovs.65.1.20

MTHFR

- 5,10-methyl THF reductase
- Complete loss of function causes homocystinuria
- Two common variants:
  - c.665C>T (p.Ala222Val), historically C677T, Thermolabile form
  - c.1286A>C (p.Glu429Ala)
- Some asserted associations from the literature (all contested)

thromboembolic disease
stroke
aneurysm
peripheral artery disease
migraine
hypertension

recurrent pregnancy loss
male infertility
risk for offspring with neural tube defects
certain cancers
neuropsychiatric disease
chemotherapy toxicity

MTHFR Common Variants

Testing is not recommended

- There is not substantial evidence to support usefulness of MTHFR testing for any indication
- MTHFR testing changes management in no disease
- Internet information is misleading
- MTHFR testing is available in over 50 labs
- 2013 CMS data shows for MTHFR:
  - 150,000 tests ordered
  - ~$13 Million paid

https://pubmed.ncbi.nlm.nih.gov/23288205/

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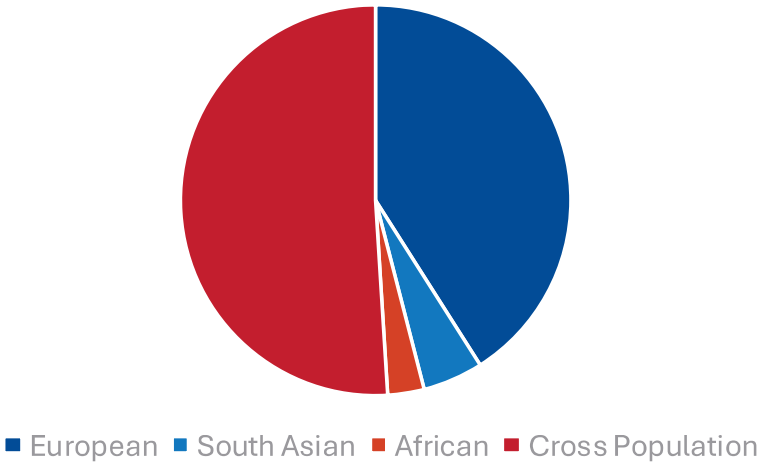
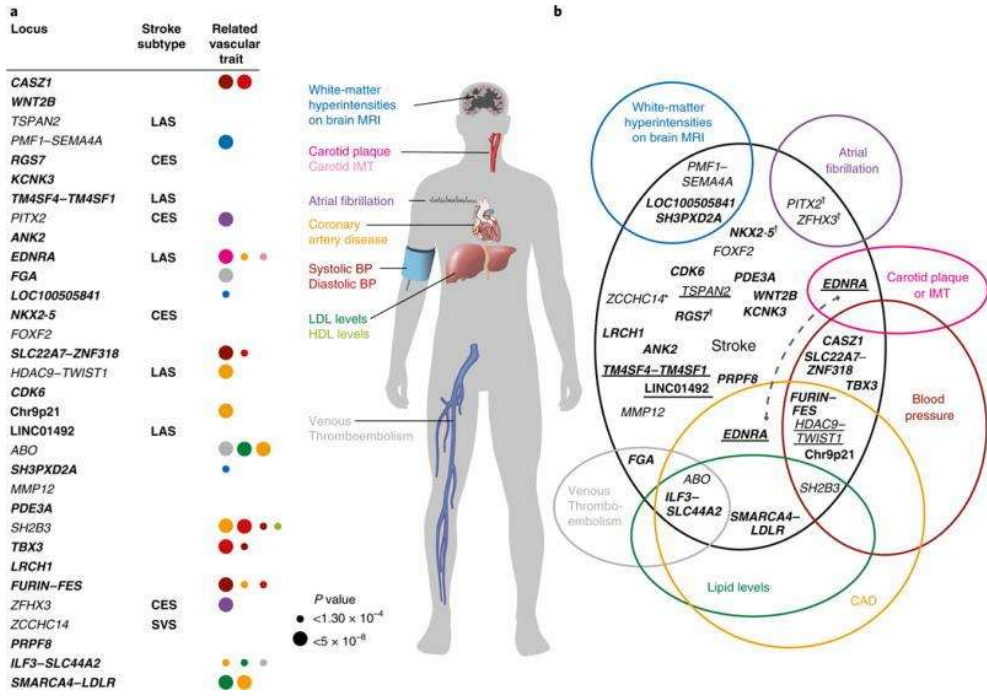
GWAS and Stroke

- 56 Loci identified since 2007
- Most participants of European descent

Ethnic Associations

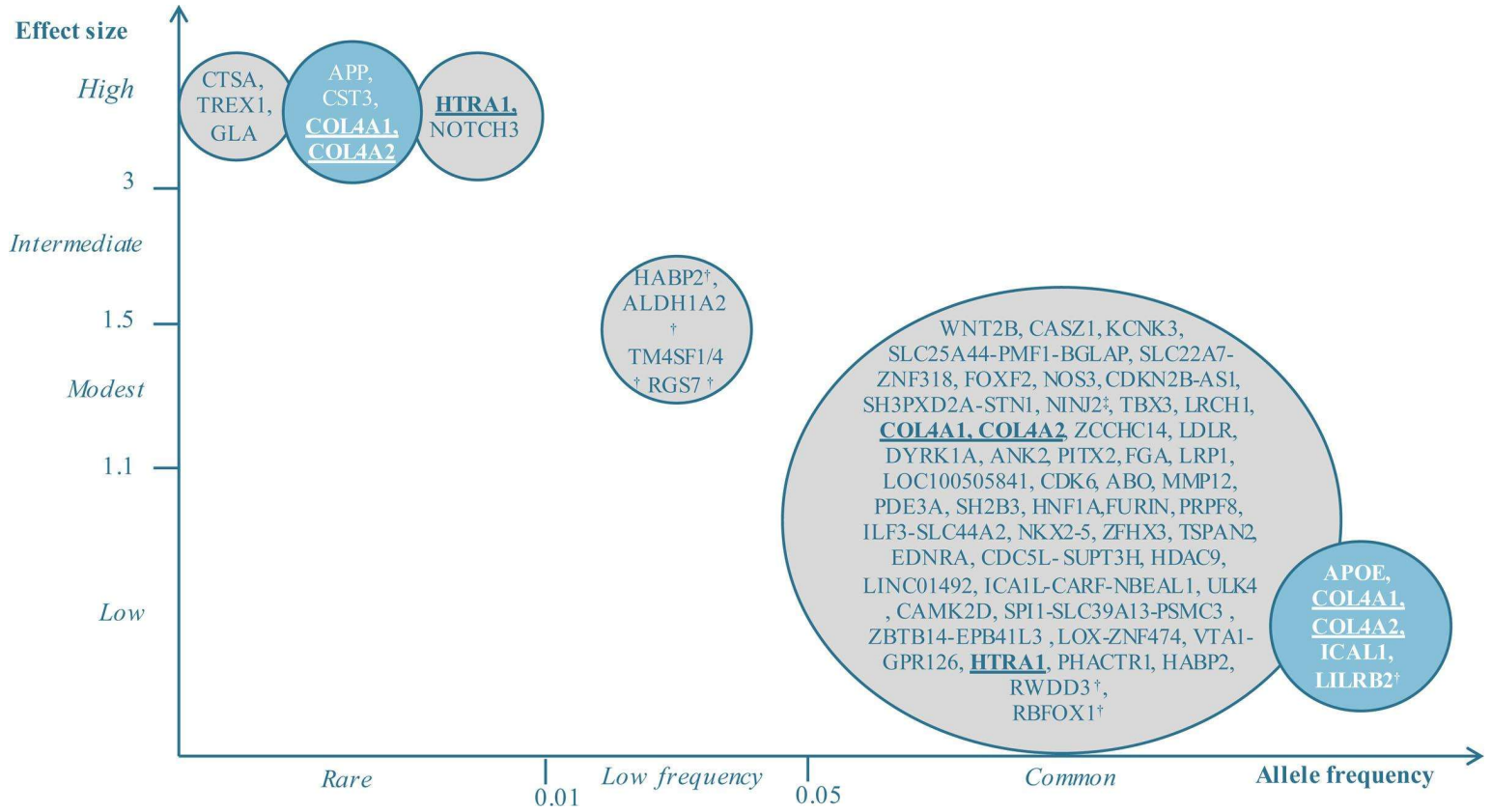




LAS: large-artery atherosclerotic stroke
CES: cardioembolic stroke
SVS: small-vessel stroke

https://doi.org/10.1038/s41588-018-0058-3

GWAS Loci and Monogenic Stroke



https://doi.org/10.1161/CIRCRESAHA.122.319950

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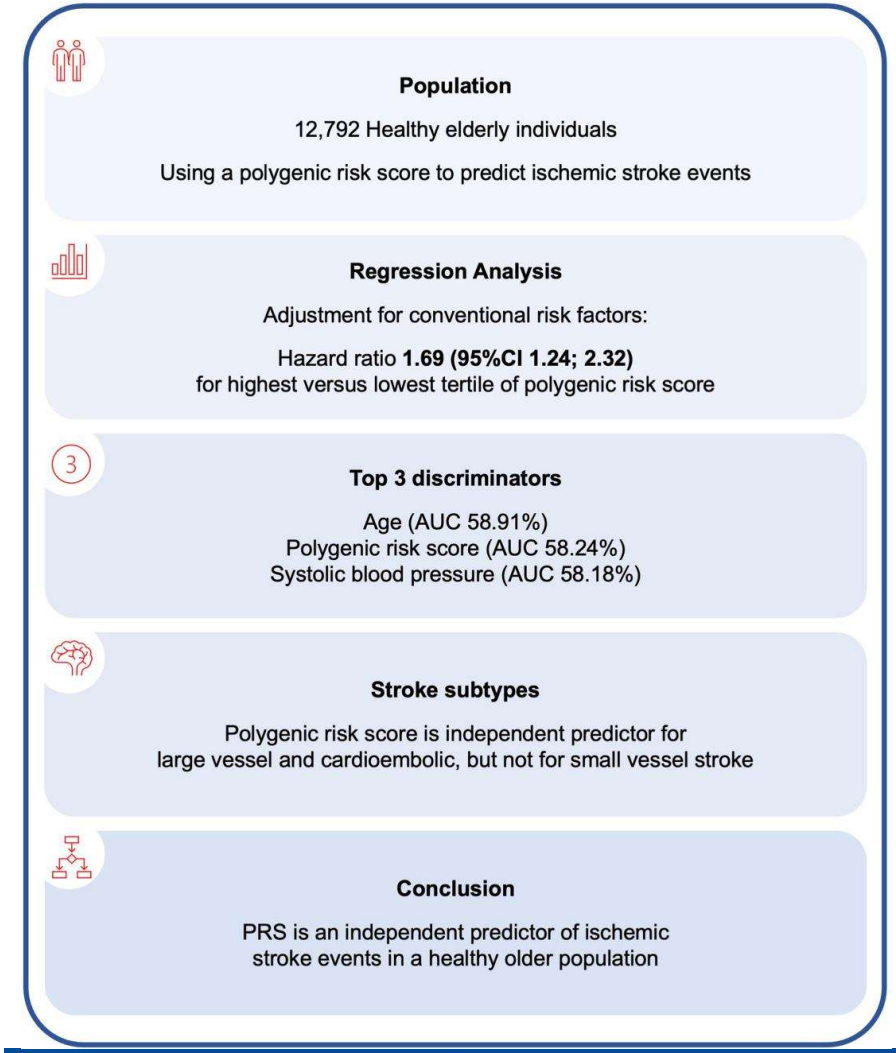
PRS and Stroke

- Predominantly European Cohort
- Predictive Performance of a Polygenic Risk Score for Incident Ischemic Stroke in a Healthy Older Population. *Stroke*. 2021;52(9):2882-2891. doi:10.1161/STROKEAHA.120.033670



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Pharmacogenomics and Stroke

- Pharmacogenomics assesses common variants in metabolic enzymes
- There are limited Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines
- Very limited data on impact to outcomes

https://cpicpgx.org/guidelines/

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Phenotypes with possible genetic cause

- **1. Personal or Family History Features**
  - **Stroke at a young age** (<50–55 years), especially ischemic stroke without traditional risk factors.
  - **Multiple family members** across generations with stroke, aneurysms, or early vascular disease.
  - **Recurrent strokes** in the same individual without clear acquired cause.
  - Family history of **migraine with aura**, psychiatric disease, or progressive cognitive decline (suggestive of CADASIL or other small-vessel diseases).
  - Family history of **sudden death** or **cardiac disease** that points to heritable arrhythmias or cardiomyopathy that can embolize.
- **2. Clinical Clues Suggesting a Specific Genetic Syndrome**
  - **Small-vessel disease on MRI** (multiple lacunes, anterior temporal lobe lesions, external capsule involvement) → CADASIL (NOTCH3 mutation).
  - **Recurrent early venous thrombosis**, miscarriages, or thrombophilia → inherited coagulation disorders (e.g., factor V Leiden, prothrombin gene mutation, protein C/S deficiency).
  - **Skin findings** (livedo reticularis, café-au-lait macules, connective tissue laxity) → connective tissue disorders or vasculopathies.
  - **Lens dislocation, long limbs, aortic root dilation** → Marfan syndrome → risk of cardioembolic stroke from aortic disease.
  - **Seizures + stroke-like episodes + lactic acidosis** → mitochondrial disorders (e.g., MELAS).
  - **Hypertension + renal disease at a young age** → COL4A1/2 vasculopathy or other inherited angiopathies.

Phenotypes with possible genetic cause

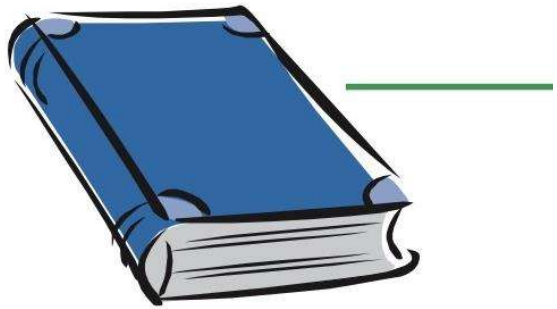
- **3. Stroke Mechanism Suggesting Genetic Etiology**
  - **Ischemic stroke due to arterial dissection** in young people → may be linked to connective-tissue disorders.
  - **Intracerebral hemorrhage** at a young age, especially lobar or recurrent → possible familial cerebral amyloid angiopathy or COL4A1/2.
  - **Multiple aneurysms or AVMs** → hereditary hemorrhagic telangiectasia (HHT) or other vascular malformation syndromes.
- **4. Absence of Traditional Risk Factors**
  - Genetic etiologies are more strongly considered when stroke occurs **without**:
  - hypertension
  - diabetes
  - hyperlipidemia
  - smoking
  - atrial fibrillation
  - significant atherosclerosis

Genetic Testing: 3 levels of Detail

BIG

Medium

small



Aneuploidy

Turner, Down, Klinefelter
Trisomy 13, 18
Balanced translocation

Microdeletion/duplication

Williams, DiGeorge

Single gene disorders

Most genetic disease

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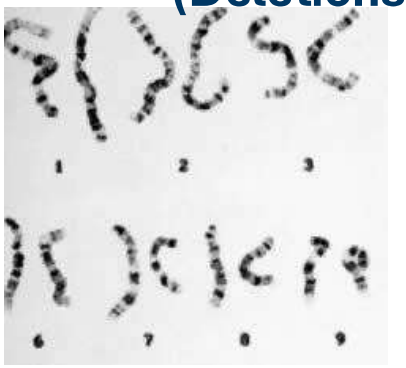
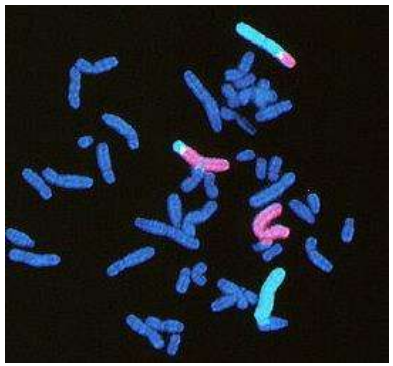
Genetic Testing: 3 levels of Detail

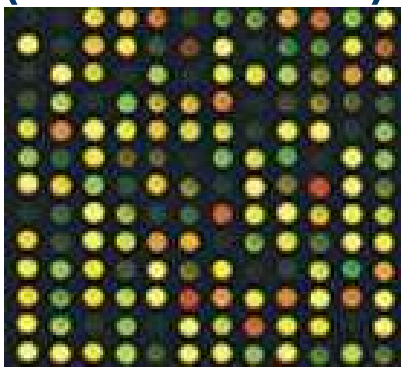
BIG **KARYOTYPE**
(Deletions >5 Mb



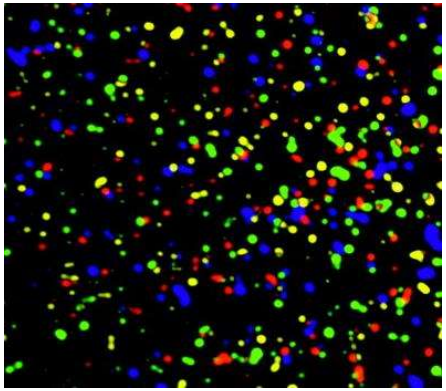
FISH
(Targeted Analysis)
>200 kb



Medium
Microarray (CMA)
(Deletions >5 kb)



small
Sequencing
(single base)



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Next-Generation Sequencing (NGS) – Short Read

- Multi-gene panels (MGP)
  - Usually by phenotype or disease
    - Small-vessel panel
    - Connective Tissue disorder panel
    - Mitochondrial panel
- Exome sequencing (ES or WES)
  - All coding regions of genes
  - ~1.5% of the total DNA
- Genome sequencing (GS or WGS)
  - All currently sequencable DNA
  - ~85% of total DNA

NGS Sequencing – Limitations/Advantages

- Lots of data
- Cost effective
- Can detect deletion/duplications
  - Except 1-3 exons in size
- **Difficulty in interpretations of all variants**
- **Variant classification is dynamic**
- Cannot distinguish pseudogenes or gene conversions
- Cannot diagnose all repeat expansion disorders (except certain genomes)
- Incidental findings in ES/GS

How much variation can there be?

- 5-10 million SNPs (varies by population)
  - 25,000-50,000 rare variants (private mutations or seen previously in < 0.5% of individuals tested)
- 75 new base pair mutations not detected in parental genomes
- 3-7 new CNVs involving ≈500 kb of DNA
- 200,000-500,000 indels (1-50 bp) (varies by population)
- 500-1000 deletions 1-45 kb, overlapping ≈200 genes
- 150 in-frame indels
- 200-250 shifts in reading frame
- 175-500 rare nonsynonymous variants
- 1-3 new nonsynonymous mutation
- 100 premature stop codons
- 40-50 splice site-disrupting variants
- 250-300 genes with likely loss-of-function variants
- 25 genes predicted to be completely inactivated

Nussbaum, R, et al. 2015. Thompson & Thompson genetics in medicine.

Cost and Turnaround (Self-Pay)

- G-banded karyotyping (with FISH)
  - $400 ($800)
  - 72 (24) hours
- Chromosomal microarray
  - $600
  - 10-14 days
- Exome
  - $800 ($2400 trio)
  - 4 weeks
- Genome
  - $1000
  - 6 weeks
- Targeted NGS panel
  - $250-$600
  - 2 weeks

Institutional and insurance bill prices can be much higher!!!!

There are many (rapidly changing) options

- Different labs have widely different billing policies and patient assistance programs.
- Labs have different panel offerings and approaches with limitations
  - Some are exome based
  - Some include mitochondrial genes
  - Some include non-coding pathogenic variants
  - Intronic depths differ
- All commercial labs have genetic counselors available to help with test selection
- Insurers may have specific requirements for genetic testing
- Self-pay may be cheapest option
- Sponsored testing is available in some cases
- Results can affect insurability

Genetic Counseling!

https://findageneticcounselor.nsgc.org/

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Summary

- There is a large genetic differential for stroke
- A genetic cause is identified in <5% of stroke cases
- The falling cost of genetic testing lowers the testing threshold
- Consider referral for testing for anyone with features suggestive of a genetic disorder
- Pre-test genetic counseling should be performed when feasible
- Gene panel testing targeting the phenotype is first-line
- Prioritize testing for potential treatable causes

Thank You

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