# Identifying missing genes involved in Moyamoya cerebral angiopathy

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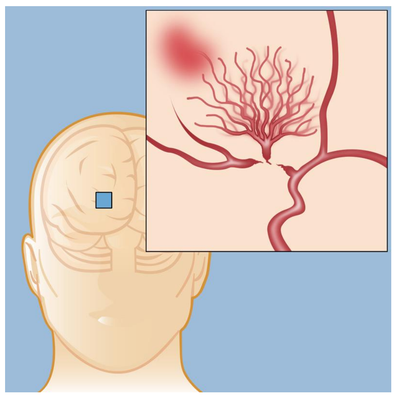
## Background

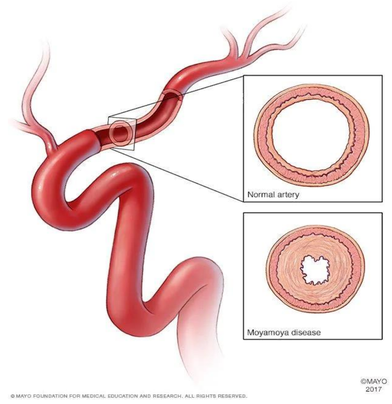


Collateral neoangiogenic vessels

*Weillcornellbrainandspine.org*

MoyaMoya Angiopathy (MMA) is a rare vascular dysplasia characterized by a progressive stenosis of the terminal part of the supraclinoid internal carotid arteries (ICA) and the compensatory development of abnormally fragile collateral neoangiogenic vessels at the base of the brain that can lead to ischemic stroke or cerebral hemorrhages in both children and adult-patients. MMA may be the sole manifestation of the disease (moyamoya disease /MMD) or it may be associated with other manifestations (moyamoya syndromes / MMS). The molecular etiology and pathogenesis of MMA are totally unknown, precluding the development of preventive and curative treatments.

However, MMD and MMS have a genetic background. A very strong association of MMD with an *RNF213* variant (R4810K) has been found in the East Asian population. This strongly associated variant has a low penetrance (1/150) and is absent in Caucasians. RNF213 should therefore be considered as a susceptibility gene. In addition, 16 MMS genes have been discovered, some of which being involved in highly penetrant conditions. Several pathways have been identified such as the RasMAPK or the NO pathway. However, in the vast majority of MMA patients , none of the known MMA genes have been involved.



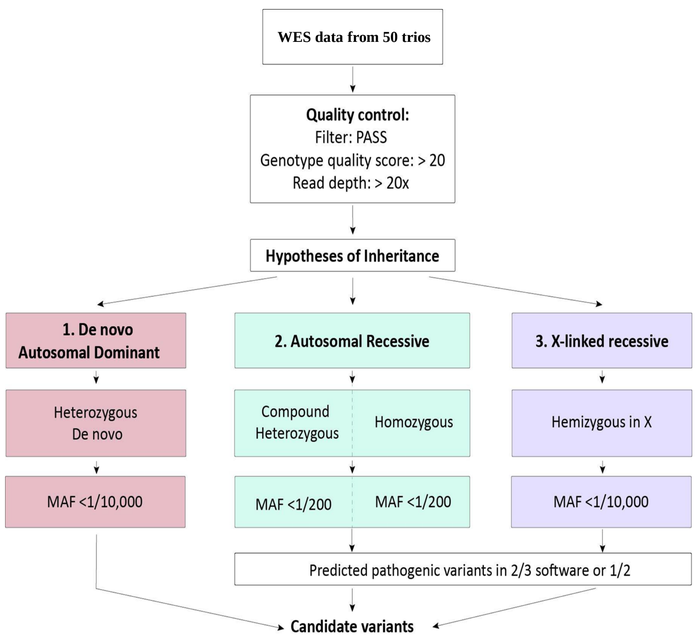

Stenosis of the internal carotid arteries

*mayoclinic.org*

## Methods

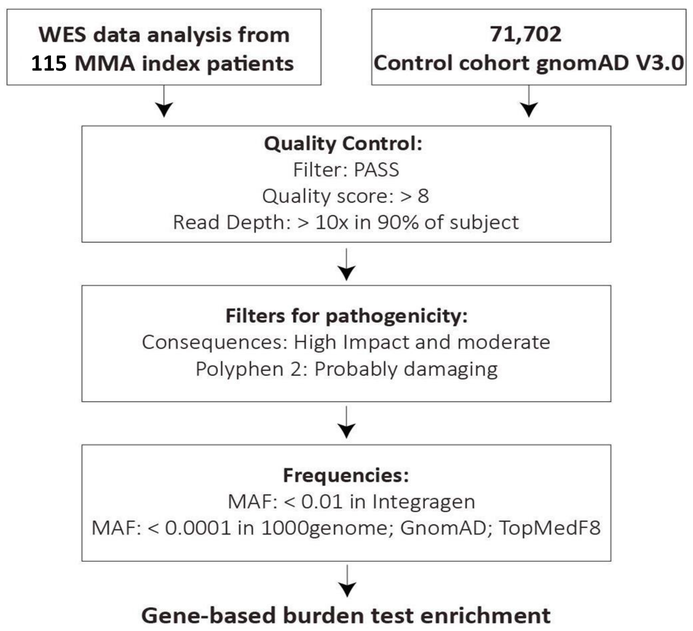
Our aims are to identify MMA missing genes and pathways. In order to achieve it, we will analyze Whole Exome Sequencing data from 50 MMA child-parents' trios and 115 unrelated probands and some of their relatives with different approaches,

### Mendelian inheritance approach



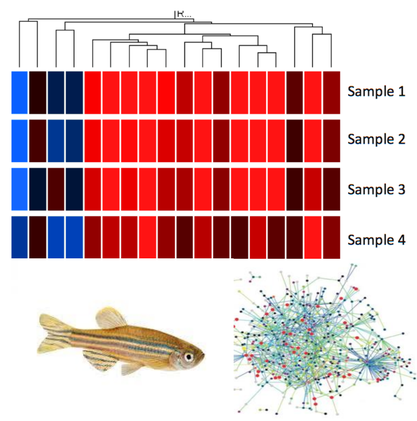

- Searching variants leading to a possible Mendelian MMA using Child/parents trios
  - De novo occurrence
  - Autosomal recessive inheritance
  - X-linked inheritance

### Gene-based burden tests approach




- Searching rare variants enrichment in patients versus controls
  - Collapsing all qualifying variants located in a given gene
  - Statistical analysis (Fisher exact)

### Gene prioratizing




- Knowledge extracted from litterature:
  - Nature/potential consequences of variants
  - Candidate gene expression pattern
  - Animal models phenotypes
- Interaction data with known MMA genes and networks
- In vitro experiments for top ranked genes

## Importance of the results

Molecular basis of most MMA remains unknown in patients. Furthermore, identification of MMA genes/pathways could provide us new diagnostic tools, improve genetic counseling and provide clues to pharmaceutical intervention in this disease.