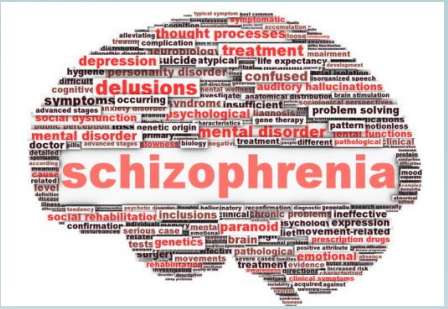
AJO-DK-00028







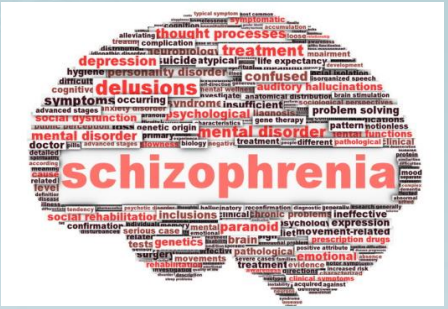


# GENETICS OF MIGRAINE

## Genetic aspects and latest findings

**Aarno Palotie**









# Genetics Strategy:

Uncover disease mechanisms

# Disclousures

**Chief Scientific officer for the FInnGen project that includes 13 pharma companies as members**

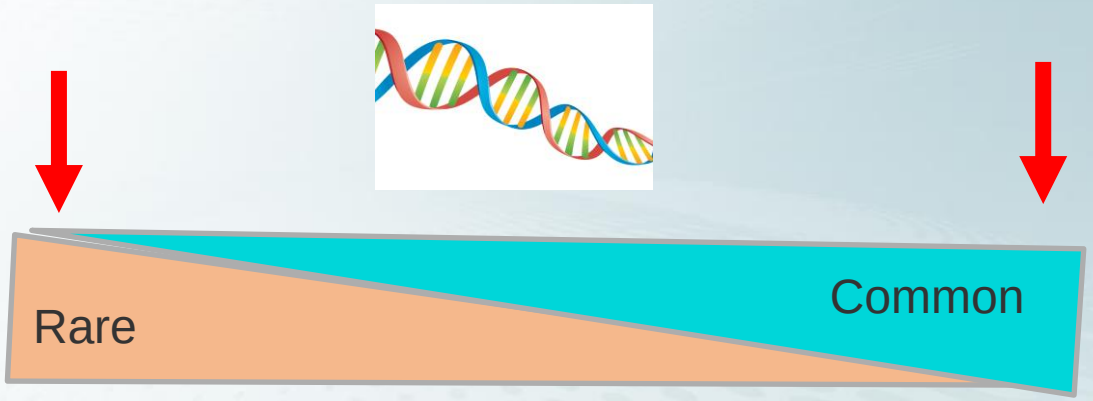
# Genetics Mission

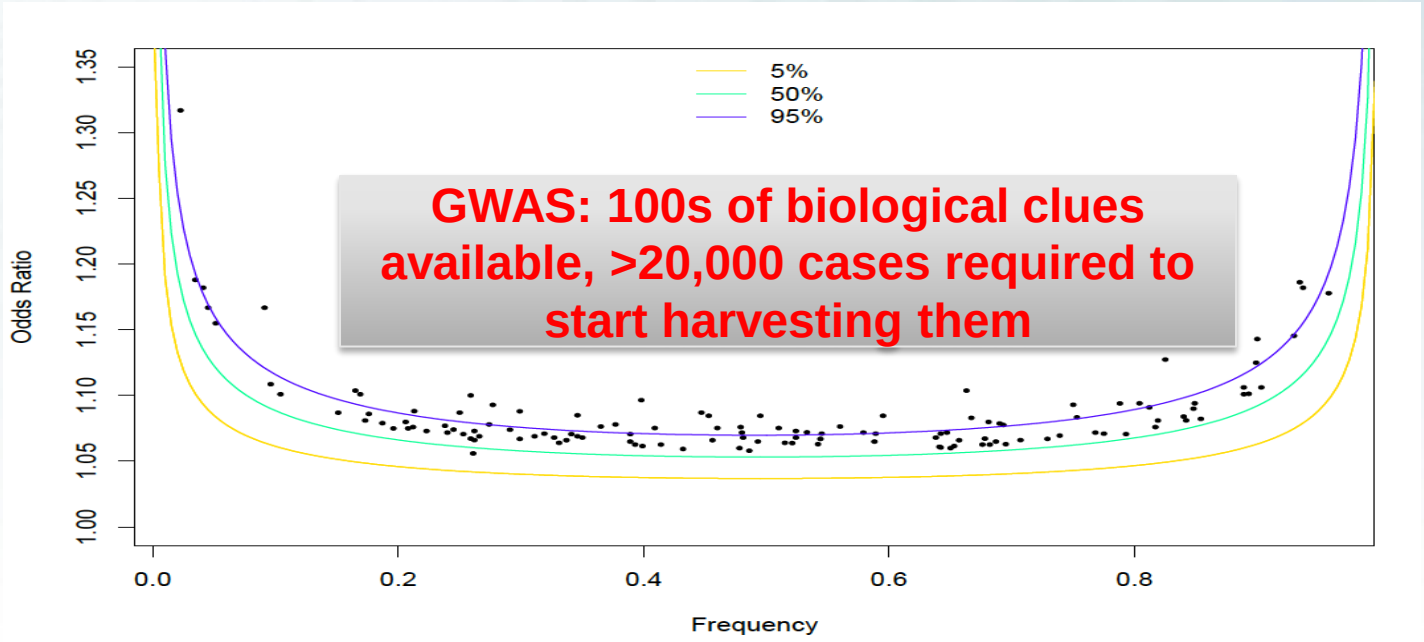
- Genetics is about generating a knowledgebase for biological insight and therapeutic development

- To that end, our genetics strategy is aimed at definitively establishing
  - specific genes and variants as associated,
  - interpreting their specific phenotypic consequence,
  - Glean insight about the cells and molecular pathways involved in order to seed and inform the design of experiments

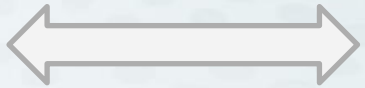
Courtesy of Mark Daly

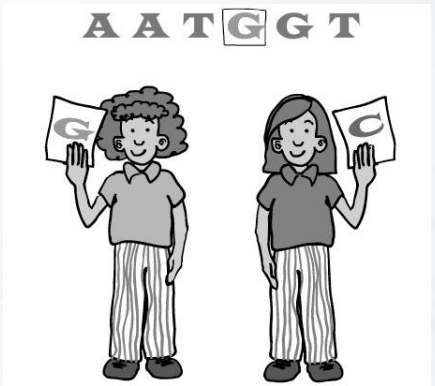
# Common and rare variants

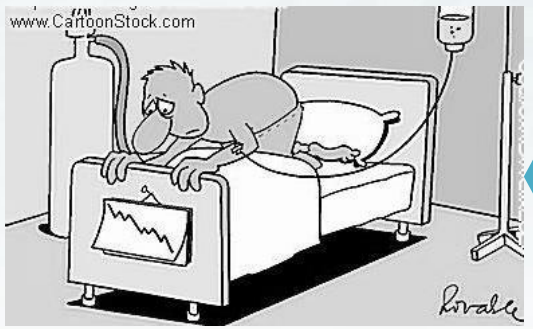



**GWAS: 100s of biological clues available, >20,000 cases required to start harvesting them**

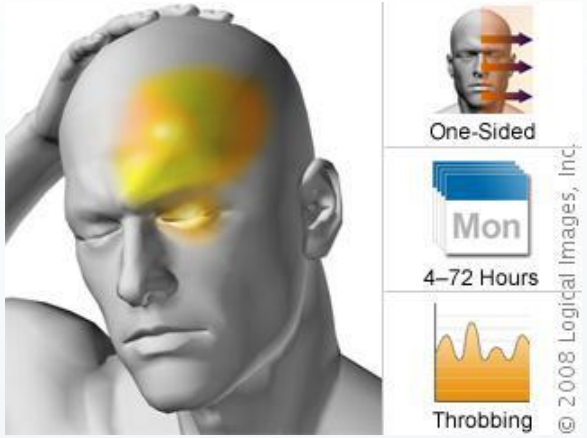
RARE  COMMON





# EACH GENE VARIANT HAS A SMALL EFFECT



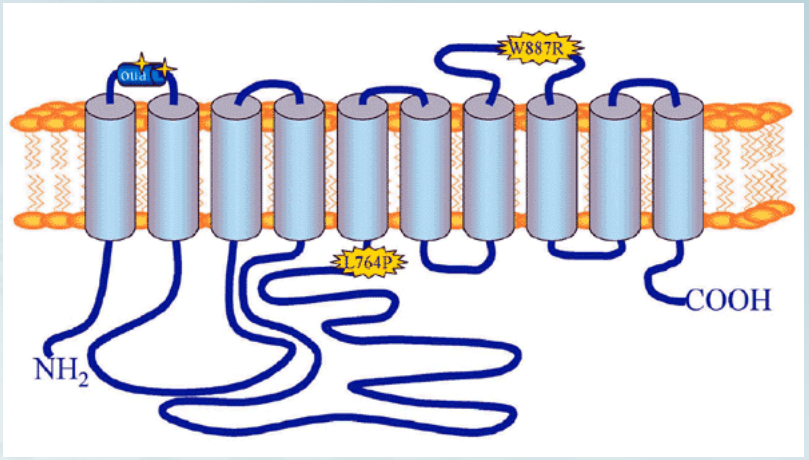

RARE ⟺ COMMON

# Rare forms of migraine
# Familial hemiplegic migraine

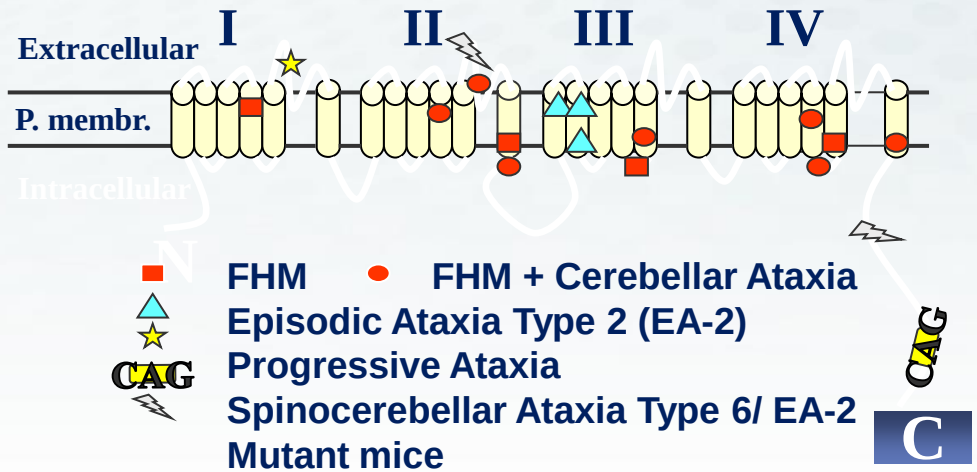
# Mendelian forms of migraine

## Familial hemiplegic migraine (FHM)

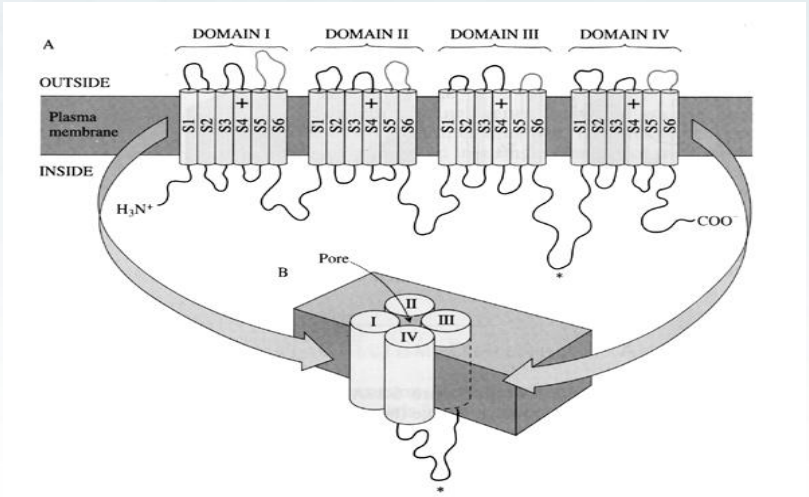
FHM2 1q ATP1A2




FHM1 19p CACNA1A




FHM3 2q SCN1A






Lancet Neurol. 2015;14(1):65-80.

FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

11-Dec-2020

# Genome-wide analysis of 102,084 cases identifies 123 migraine risk loci and subtype-specific risk alleles

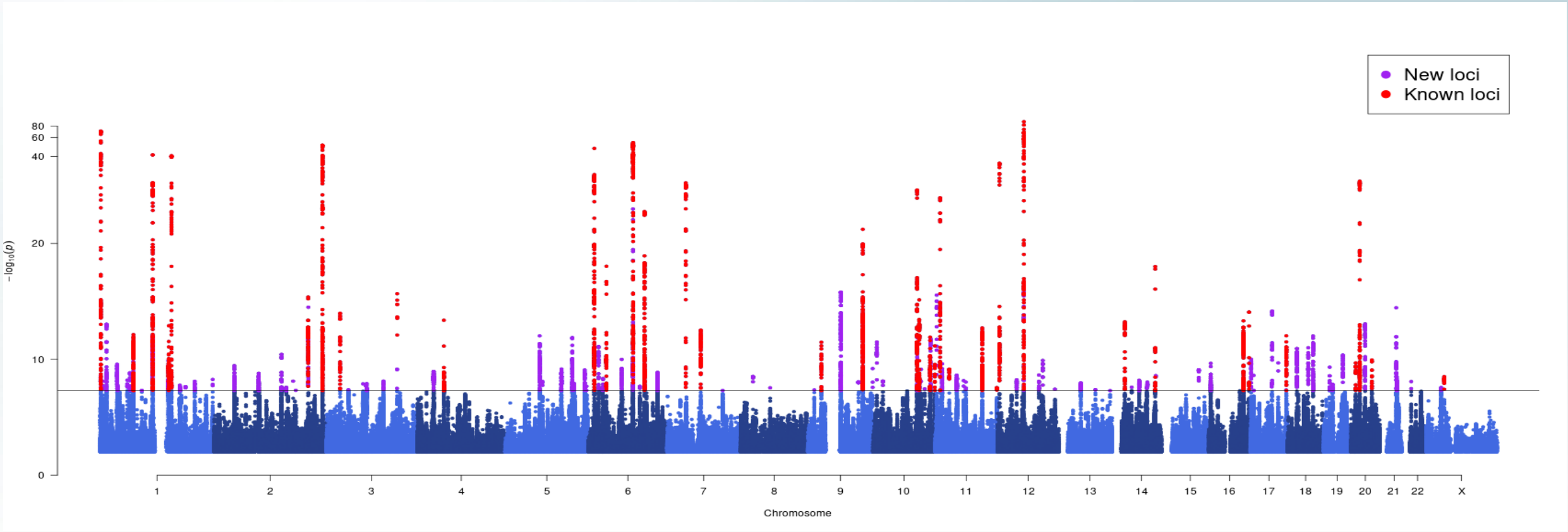
Hautakangas et al. Nature Genetics in press

Heidi Hautakangas
Matti Pirinen

Table 1. Five migraine study collections included in the meta-analysis

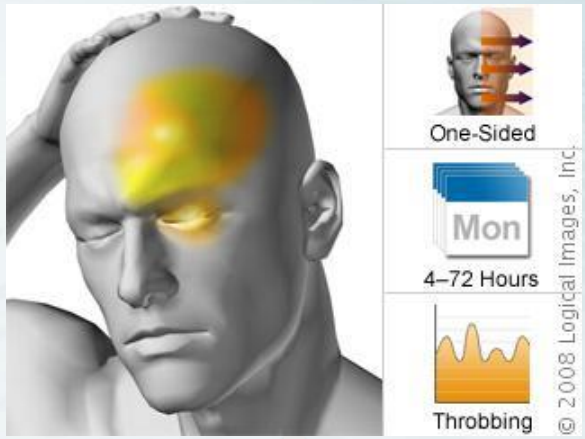
| Abbreviation | Full Name | Ethnicity | Cases | Controls | Case % | Migraine Definition |
|---|---|---|---|---|---|---|
| IHGC2016* | Gormley et al. 2016 (no 23andMe) | European descent | 29,209 | 172,931 | 14.4 | Self-reported and ICHD-II |
| 23andMe | 23andMe, Inc. (23andMe.com) | European descent | 53,109 | 230,876 | 18.7 | Self-reported |
| UKBB | UK Biobank (ukbiobank.ac.uk) | European, British | 10,881 | 330,170 | 3.2 | Self-reported |
| GeneRISK | GeneRISK (generisk.fi) | European, Finnish | 1,084 | 4,857 | 18.2 | Self-reported |
| HUNT | Nord-Trøndelag Health Study (ntnu.edu/hunt) | European, Norwegian | 7,801 | 32,423 | 19.4 | Self-reported migraine or fulfilling modified ICHD-II criteria |

*IHGC2016 is a meta-analysis of 21 studies listed in Supplementary Table 1. Some studies of IHGC2016 determined migraine status through clinical phenotyping while migraine status in other studies is based on self-reported information. ICHD-II = the International Classification of Headache Disorders 2nd edition.




123 loci: 86 new, 37 previously reported, at $P < 5e\text{-}8$.

# Migraine subtypes




## Migraine

- Recurrent, unilateral headache
- Pulsating pain
- 4-72 hours
- 2-3x more common in women than men
- Heritability ~ 60%
- Prevalence ~15%

Migraine sub-types

1 in 3 cases

Migraine ***with*** Aura

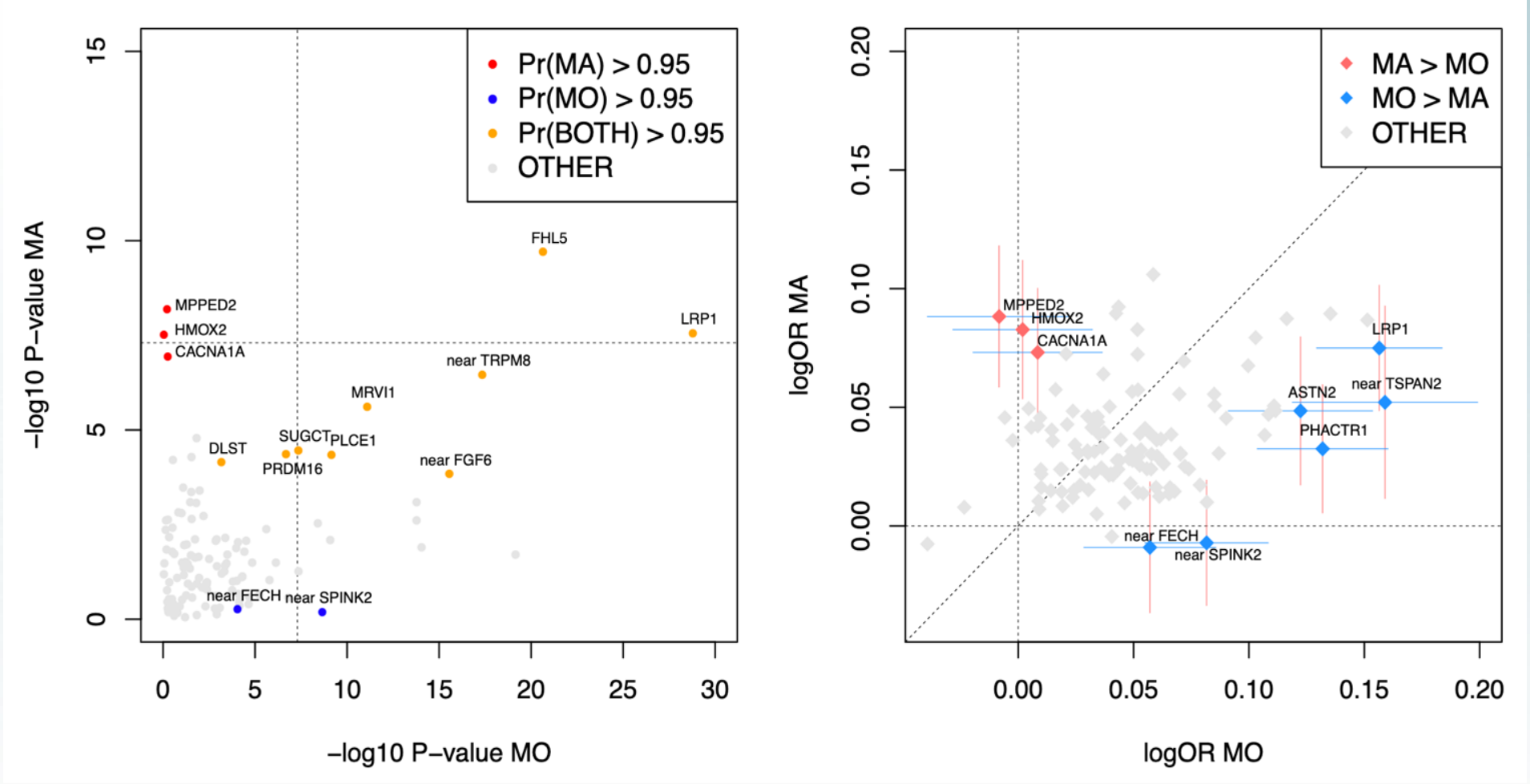
Migraine ***without*** Aura

2 in 3 cases

Table 2. Study collections included in MO and MA subtype analyses.

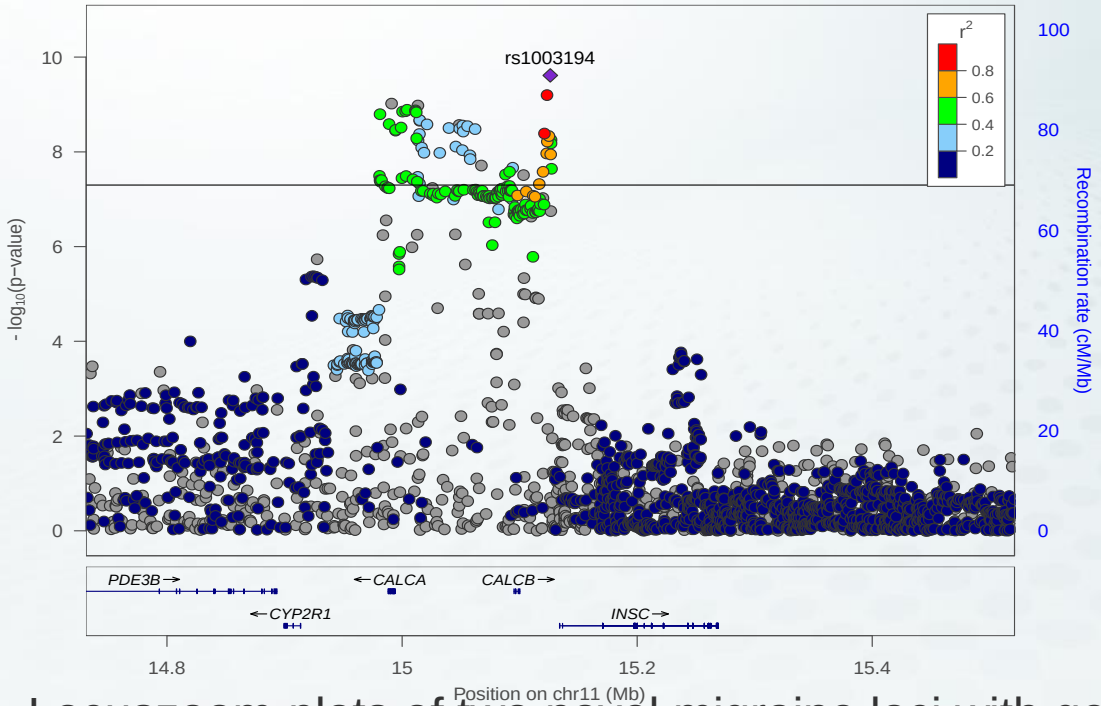
| Abbreviation | Full Name | Ethnicity | Subtype | Cases | Controls |
|---|---|---|---|---|---|
| IHGC2016* | Gormley et al. | European descent | MO | 8,348 | 139,622 |
| | | | MA | 6,332 | 144,883 |
| UKBB | UK Biobank (ukbiobank.ac.uk) | European, British | MO | 187 | 320,139 |
| | | | MA | 1,333 | 320,139 |
| deCODE | deCODE Genetics Inc. | European, Icelandic | MO | 1,648 | 193,050 |
| | | | MA | 2,297 | 209,338 |
| DBDS | Danish Blood Donor Study | European, Danish | MO | 3,756 | 28,045 |
| | | | MA | 3,938 | 28,045 |
| LUMINA | LUMINA migraine without aura or with aura | European, Dutch | MO | 1,115 | 1,445 |
| | | | MA | 741 | 1,447 |

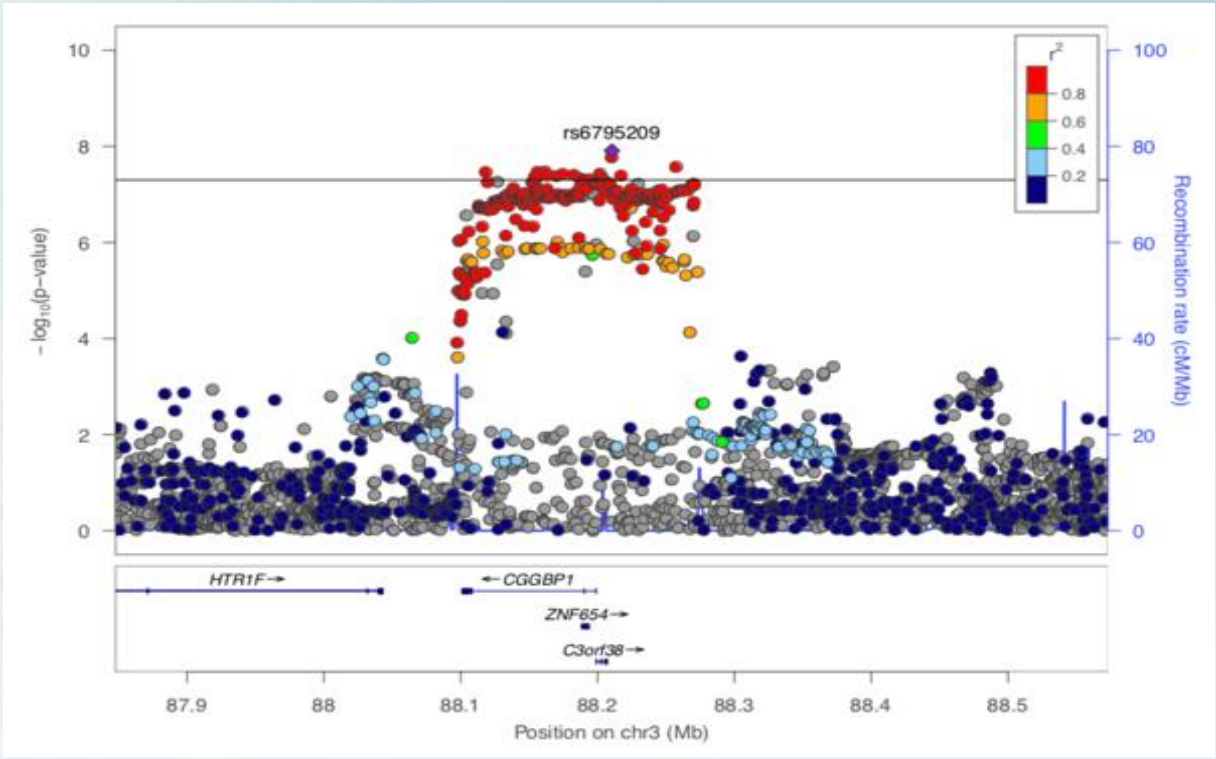
# Migraine lead variants show shared and distinct effects between the two subtypes




Lead variants stratified by migraine subtype for risk loci with minor allele frequency > 5%.
a) Axes show the negative log10 P-value of MO (X-axis) and MA (Y-axis) analyses. Symbols that are colored and annotated indicate > 95% posterior probability that a non-zero effect is present in both MO and MA (model BOTH), or that the effect is present only in MO or only in MA but not both (models MO and MA, respectively). Variants with a probability less than 95% for each of the three models are shown as gray.
b) Axes show logarithm of odds ratios for MO (X-axis) and MA (Y-axis) calculated for the migraine risk allele. The effects at variants that have been colored and annotated differ between the subtypes at significance level of 0.0004 = 0.05/123. The 95% confidence intervals are shown for the annotated variants.
MO = migraine without aura, MA = migraine with aura.

# Loci with known drug targets




Locuszoom-plots of two novel migraine loci with genes that are targets of recent migraine specific drugs.
(A) Locus containing *CALCA* and *CALCB* genes which encode CGRP, that is the target of preventive and
acute therapies via monoclonal antibodies and gepants.
(B) Locus containing *HTR1F* gene that encodes a serotonin $5 - HT_{1F}$ receptor that is the target of acute therapies via ditans.

# From locus to gene to function

- How much can we extrapolate from GWAS to functional consequences?

- Which is the causeative gene:
  - Several genes under the locus peak, proximity is not always the best predictor of the right gene
- Which is the causative variant:
  - Most lead variants are in regulatory regions
  - If the lead variant is a coding variant, helps to guide towards functional studies
- Which is the relevant target tissue?

Table 3. LDSC-SEG results that are significant at FDR 5%.

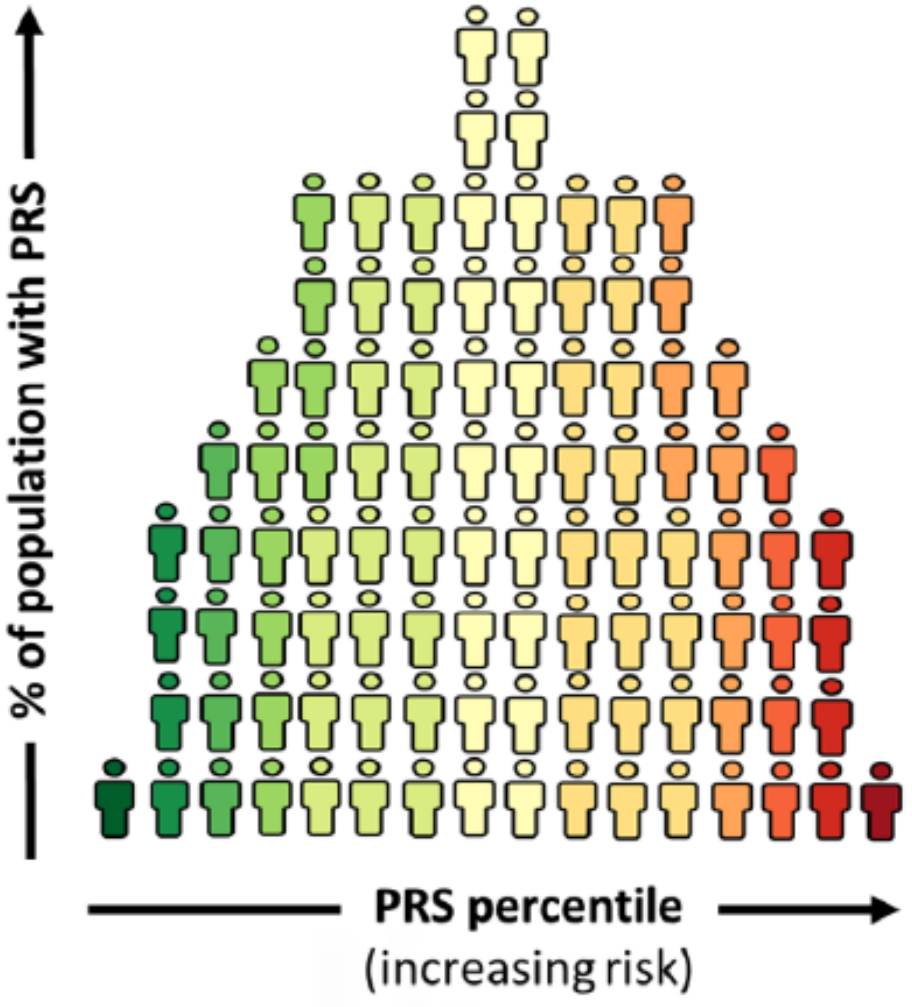
| Tissue/Cell type and histone mark | Tissue category | P-value | FDR |
|---|---|---|---|
| **Multi-tissue gene expression data** | | | |
| Aorta | Cardiovascular | 1.78E-04 | 0.029 |
| Tibial Artery | Cardiovascular | 3.60E-04 | 0.029 |
| Coronary Artery | Cardiovascular | 4.29E-04 | 0.029 |
| **Gene expression data of 13 brain regions from GTEx** | | | |
| Caudate (basal ganglia) | Central nervous system | 6.00E-04 | 0.008 |
| **Multi-tissue chromatin annotation data** | | | |
| Fetal Brain Female, H3K4me3 | Central nervous system | 2.49E-05 | 0.012 |
| Brain Dorsolateral Prefrontal Cortex, H3K27ac | Central nervous system | 8.43E-05 | 0.018 |
| Brain Dorsolateral Prefrontal Cortex, H3K4me3 | Central nervous system | 1.11E-04 | 0.018 |
| Aorta, H3K4me1 | Cardiovascular | 2.57E-04 | 0.031 |
| Stomach Mucosa, H3K36me3 | Digestive | 3.36E-04 | 0.032 |
| Aorta, H3K27ac | Cardiovascular | 4.40E-04 | 0.032 |
| Artery-Tibial ENTEX, H3K4me1 | Cardiovascular | 4.53E-04 | 0.032 |
| Ganglion Eminence derived primary cultured neurospheres, H3K4me3 | Central nervous system | 6.53E-04 | 0.04 |
| Brain Germinal Matrix, H3K4me3 | Central nervous system | 8.42E-04 | 0.043 |
| Aorta ENTEX, H3K27ac | Cardiovascular | 1.11E-03 | 0.043 |
| Artery-Coronary ENTEX, H3K4me3 | Cardiovascular | 1.13E-03 | 0.043 |
| Cortex derived primary cultured neurospheres, H3K36me3 | Central nervous system | 1.14E-03 | 0.043 |
| Ovary, H3K27ac | Other | 1.15E-03 | 0.043 |
| Cortex derived primary cultured neurospheres, H3K4me3 | Central nervous system | 1.29E-03 | 0.045 |
| Aorta ENTEX, H3K4me1 | Cardiovascular | 1.39E-03 | 0.045 |
| Stomach Smooth Muscle, H3K4me3 | Musculoskeletal/Connective | 1.55E-03 | 0.047 |

"Migraine is neurovascular"

Hautakangas et al. Nature Genetics in press

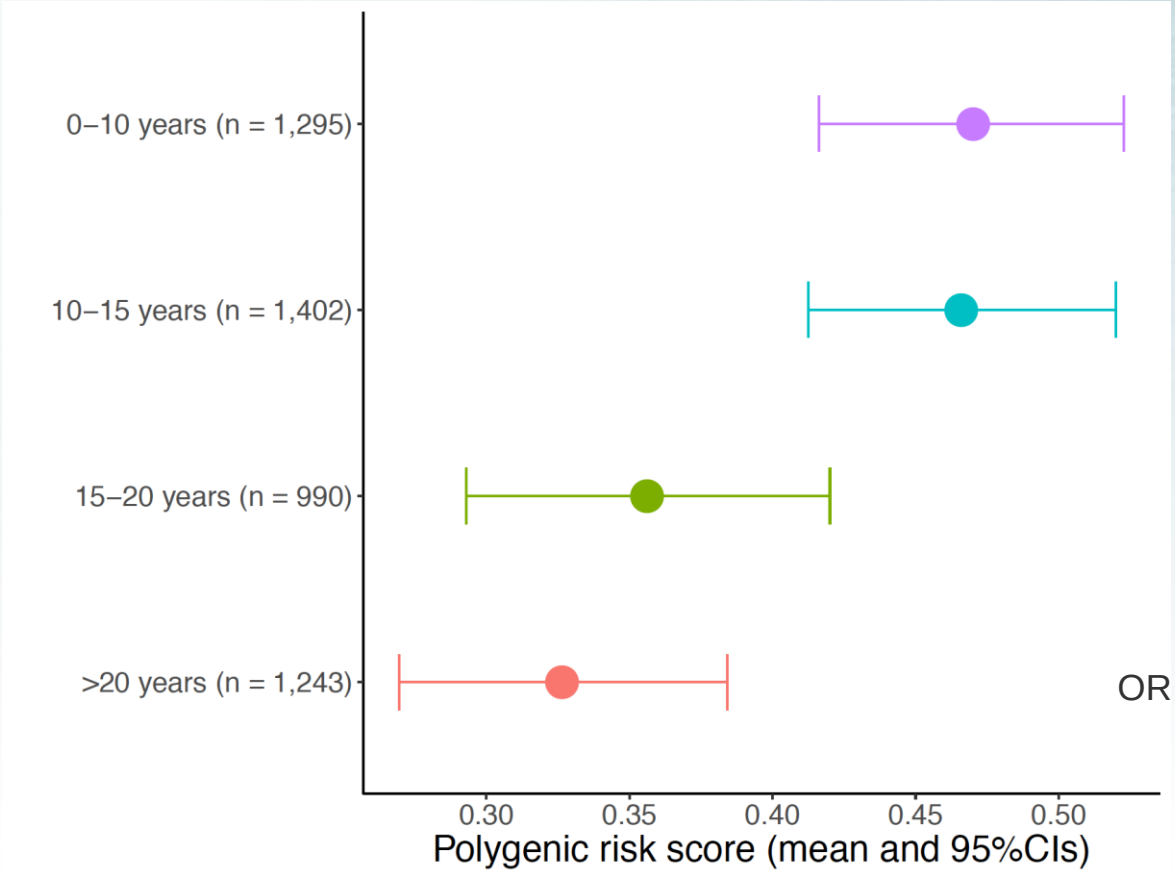
# Polygenic Risk Score PRS

| PRS percentile | Risk of disease vs. reference group |
|---|---|
| 0-1 | Lowest |
| 1-5 | |
| 5-10 | |
| 10-20 | |
| 20-40 | |
| **40-60 (reference)** | 1 |
| 60-80 | |
| 80-90 | |
| 90-95 | |
| 95-99 | |
| 99-100 | Highest |



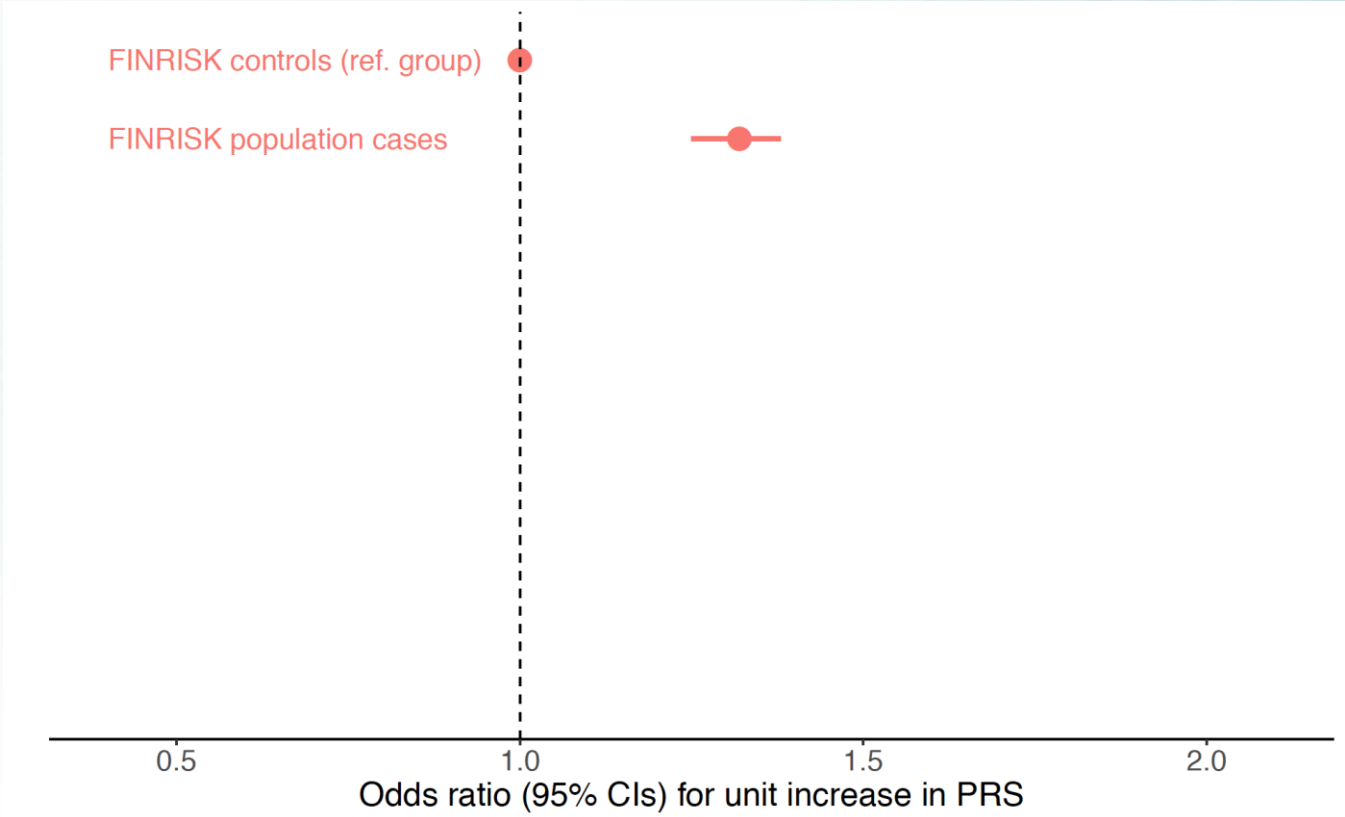

*Source: RGA*

# Earlier age of onset of headaches corresponds to higher PRS



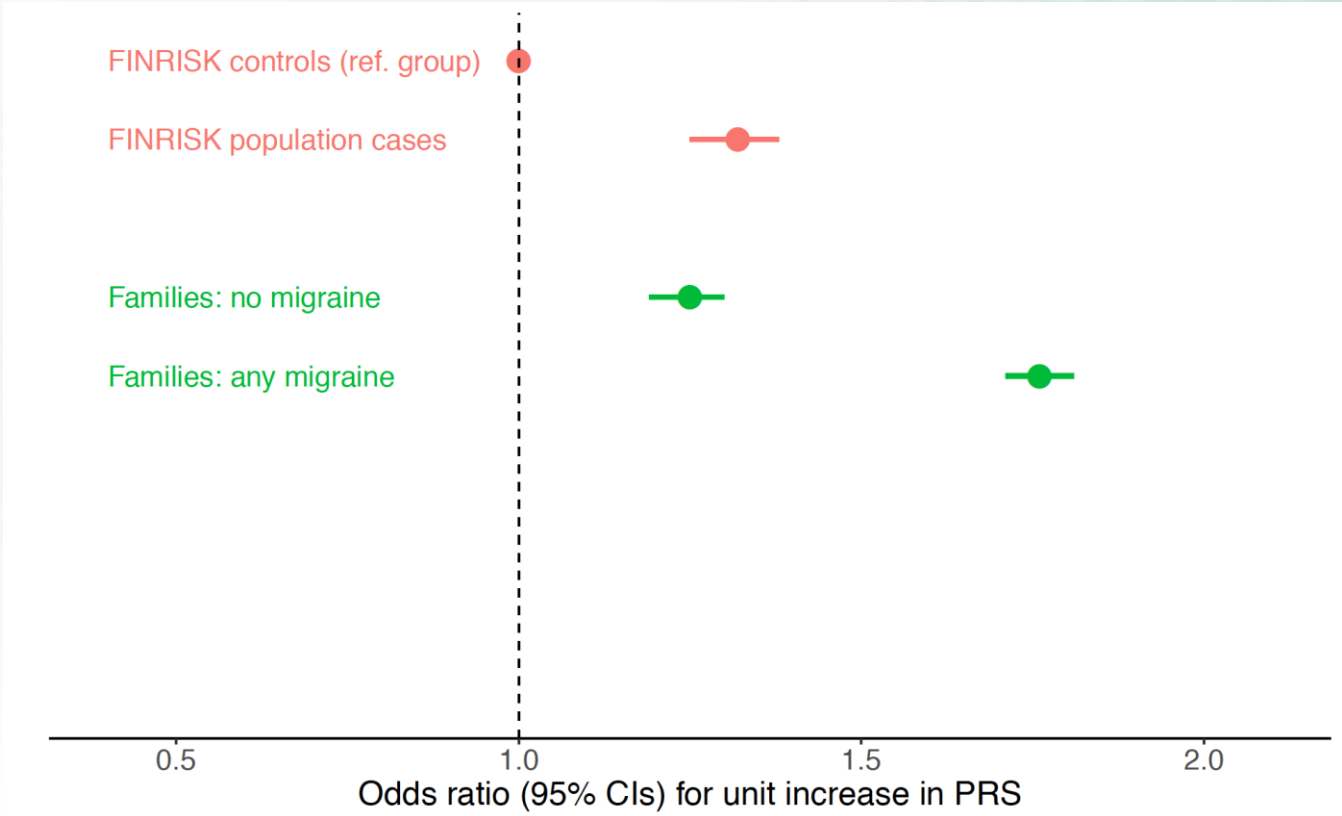

OR = 1.11, *P*-value = $8.2\times10^{-4}$

# Population sample –
# Cases associated with increased burden of common variation



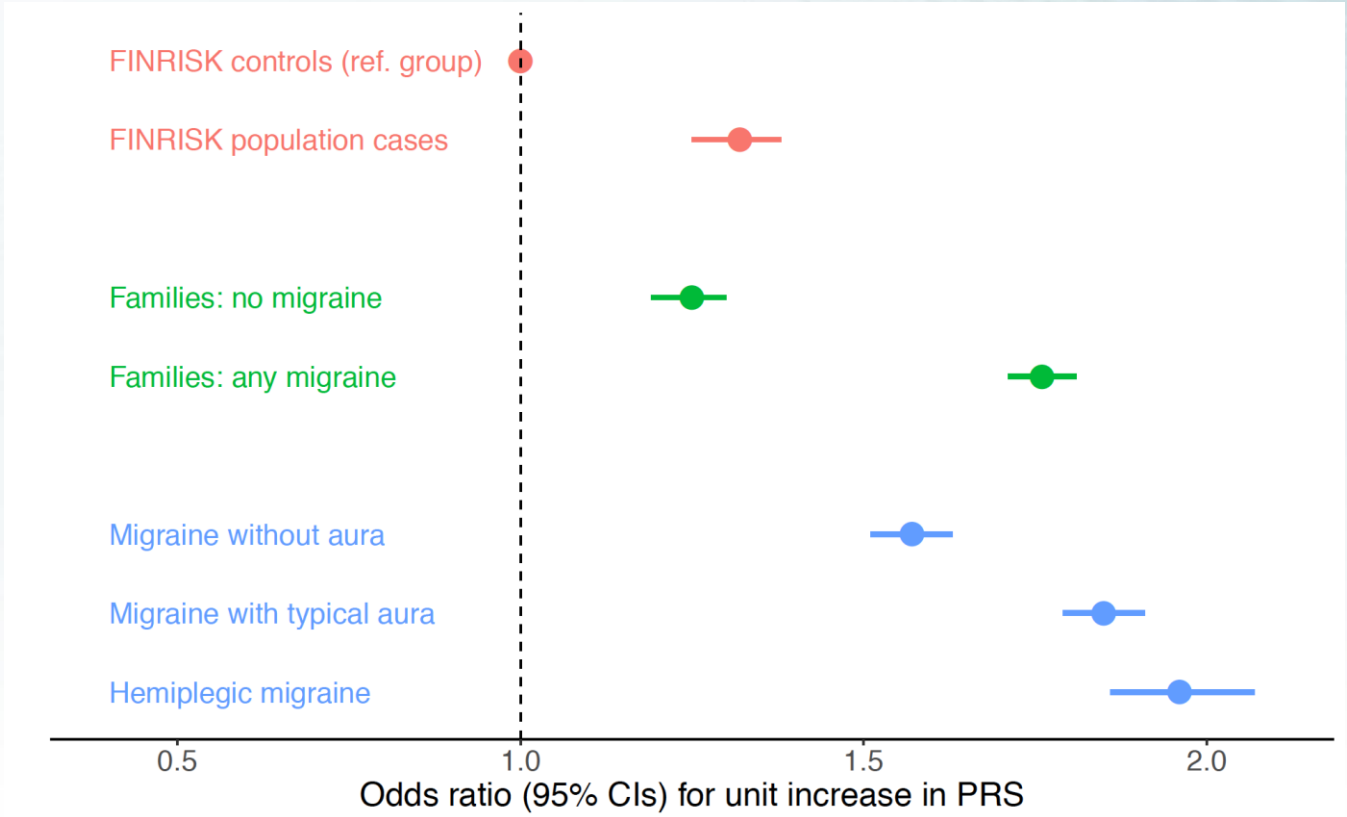

| | N | OR | *P*-value |
|---|---|---|---|
| FINRISK controls (ref. group) | 13,369 | NA | NA |
| FINRISK population cases | 1,101 | 1.32 | $7.2\times10^{-17}$ |

# Family sample –
# Familial cases significantly higher polygenic load than population cases



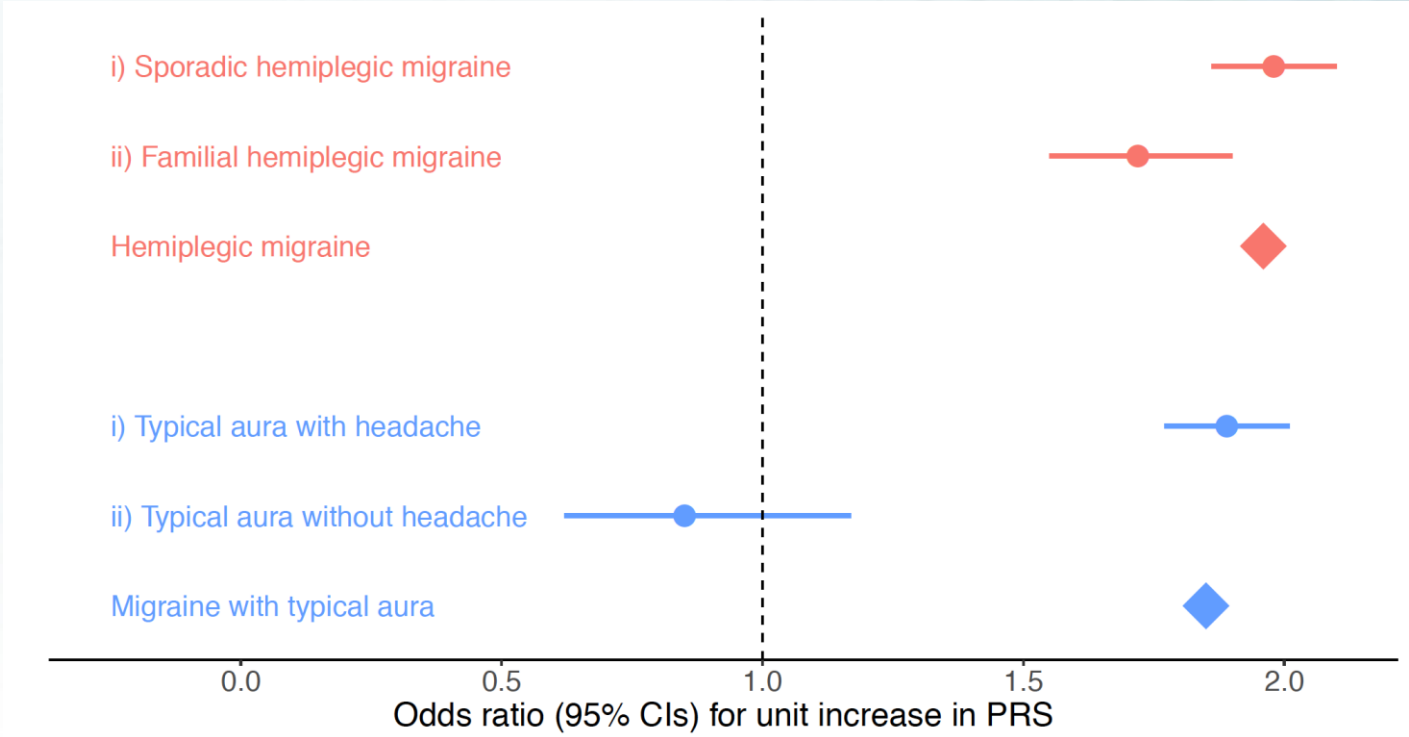

| | N | OR | *P*-value |
|---|---|---|---|
| FINRISK controls (ref. group) | 13,369 | NA | NA |
| FINRISK population cases | 1,101 | 1.32 | $7.2\times10^{-17}$ |
| Families: no migraine | 3,002 | 1.25 | $3.2\times10^{-15}$ |
| Families: any migraine | 5,317 | 1.76 | $1.7\times10^{-109}$ |

# Subtypes –
# aura subtypes have higher enrichment than migraine without aura



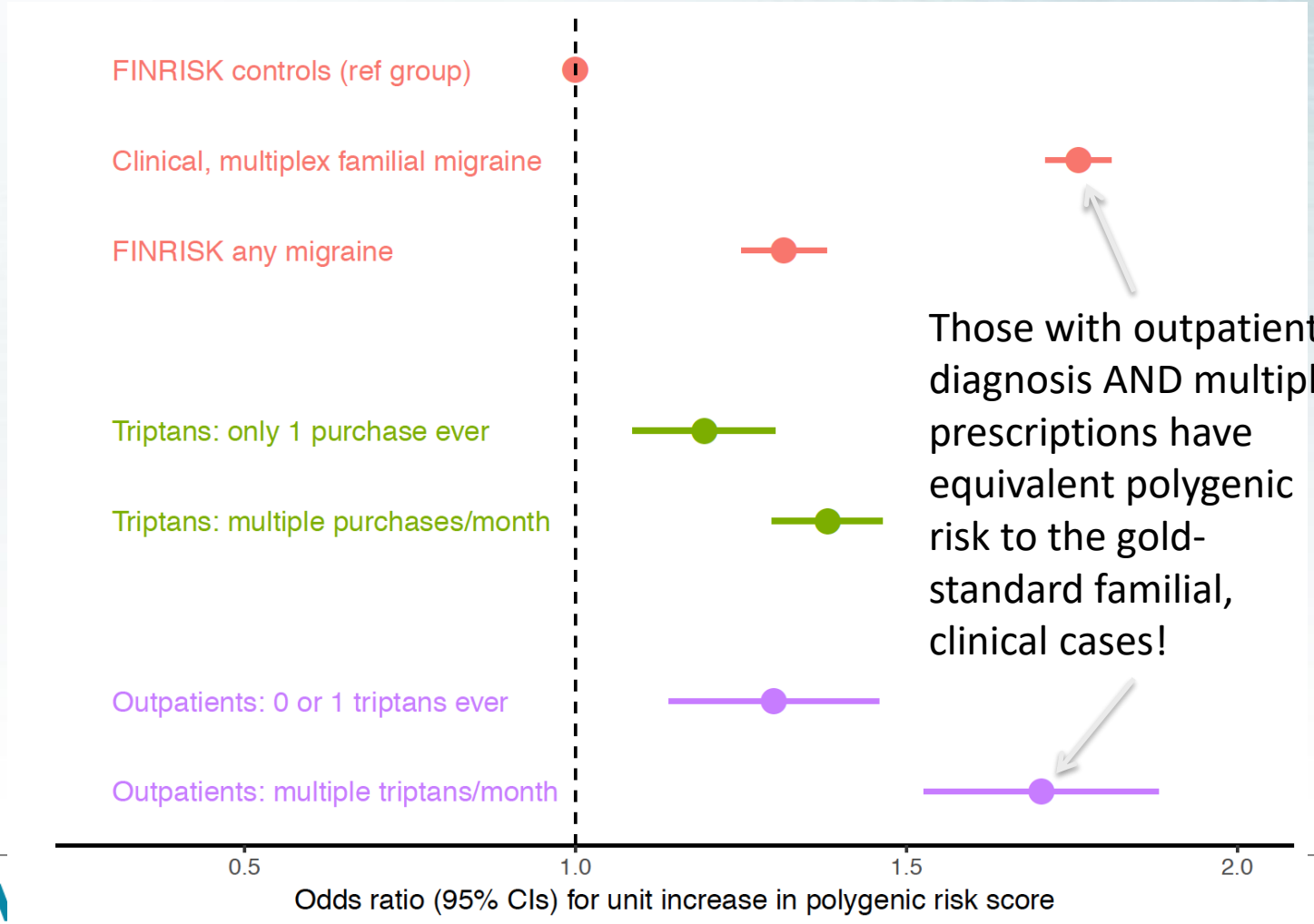

| | N | OR | *P*-value |
|---|---|---|---|
| FINRISK controls (ref. group) | 13,369 | NA | NA |
| FINRISK population cases | 1,101 | 1.32 | $7.2\times10^{-17}$ |
| Families: no migraine | 3,002 | 1.25 | $3.2\times10^{-15}$ |
| Families: any migraine | 5,317 | 1.76 | $1.7\times10^{-109}$ |
| Migraine without aura | 2,357 | 1.57 | $1.1\times10^{-48}$ |
| Migraine with typical aura | 2,420 | 1.85 | $1.4\times10^{-86}$ |
| Hemiplegic migraine | 540 | 1.96 | $8.7\times10^{-36}$ |

# Deeper-level subtypes –
# Typical aura without migraine headache has very low PRS




| | N | OR | *P*-value |
|---|---|---|---|
| i) Sporadic hemiplegic migraine | 343 | 1.98 | $3.2\times10^{-27}$ |
| ii) Familial hemiplegic migraine | 197 | 1.72 | $7.5\times10^{-10}$ |
| Hemiplegic migraine | 540 | 1.96 | $8.7\times10^{-36}$ |
| i) Typical aura with headache | 2,350 | 1.89 | $6.4\times10^{-90}$ |
| ii) Typical aura without headache | 70 | 0.85 | 0.20 |
| Migraine with typical aura | 2,420 | 1.85 | $1.4\times10^{-86}$ |

# Triptans use and purchase-frequency from registry data is associated with higher polygenic risk scores for migraine

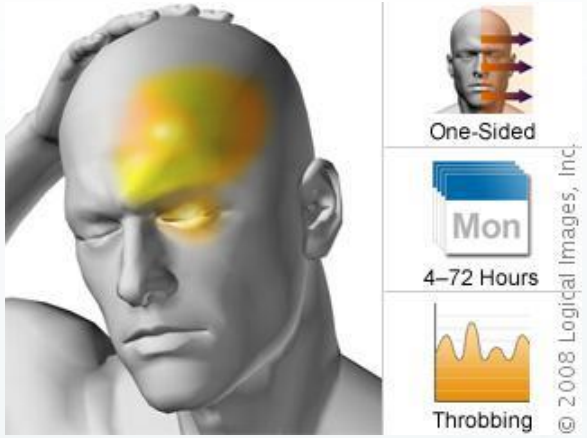



Those with outpatient diagnosis AND multiple prescriptions have equivalent polygenic risk to the gold-standard familial, clinical cases!

| | N (cases) | OR | P-value |
|---|---|---|---|
| FINRISK controls (ref group) | 13,359 | NA | NA |
| Clinical, multiplex familial migraine | 5,317 | 1.76 | 1.7E-109 |
| FINRISK any migraine | 1,101 | 1.32 | 6.8E-17 |
| Triptans: only 1 purchase ever | 359 | 1.19 | 0.001 |
| Triptans: multiple purchases/month | 625 | 1.38 | 3.8E-14 |
| Outpatients: 0 or 1 triptans ever | 158 | 1.30 | 0.001 |
| Outpatients: multiple triptans/month | 131 | 1.70 | 3.9E-09 |



Gormley et al. Neuron. 2018 May 16;98(4):743-753

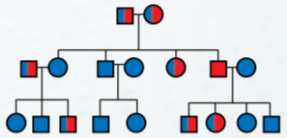



RARE ⟺ COMMON

# The Finnish migraine family collection

Padhraig Gormley

Maija Wessman
Mikko Kallela

1,589 ×  = 8,319 × 

Migraine families — Individuals

| Phenotypes | No. of individuals |
|---|---|
| No migraine | 3,002 |
| Any migraine (total) | 5,317 |
| • Migraine without aura (MA) | 2,357 |
| • Migraine with typical aura | 2,420 |
| • Hemiplegic migraine (HM) | 540 |

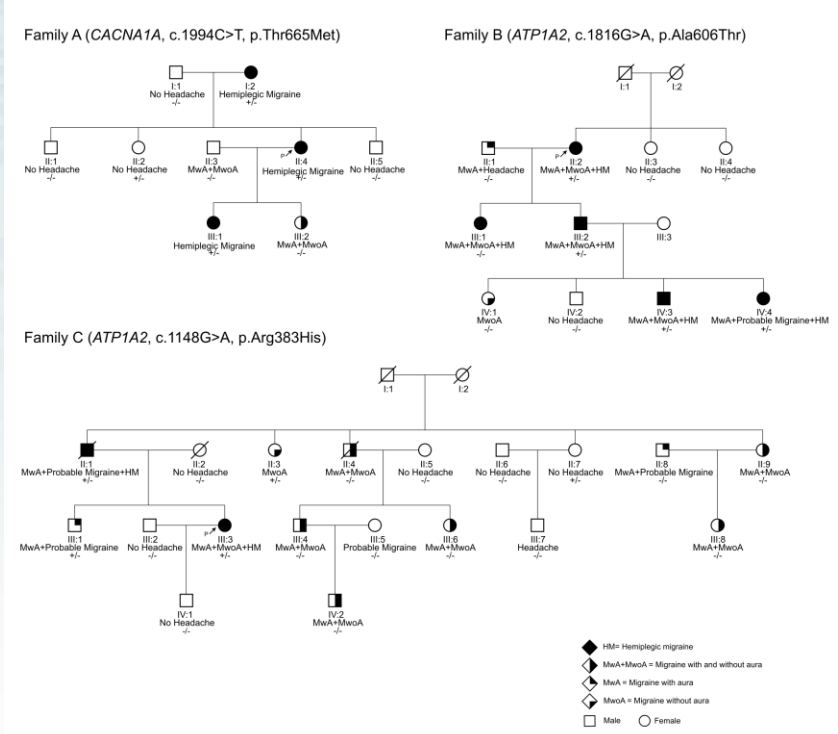
Families collected from Headache Clinics throughout Finland



Gormley et al, Neuron. 2018 May 16;98(4):743-753

# Searched for rare variants in known Hemiplegic Migraine genes - found very little

- Exome-sequenced 293 (of 540) HM cases
- Filtered variants for:
  - LoF/missense variants in 3 known genes (*CACNA1A, ATP1A2, SCN1A*)
  - rare in gnomAD (MAF < 0.01)
  - rare in Finland (SISu MAF < 0.01)
- Only found 3 pathogenic variants in 14 cases from 3 families



# Migraine: Polygenic Architecture

Neuron *98*, 1-11. May 2018.
Article

CellPress

## Common Variant Burden Contributes to the Familial Aggregation of Migraine in 1,589 Families

Padhraig Gormley,[1,2,3,26] Mitja I. Kurki,[1,2,3,26] Marjo Eveliina Hiekkala,[4,26] Kumar Veerapen,[1,2,3] Paavo Häppölä,[5] Adele A. Mitchell,[6,27] Dennis Lal,[1,2,3,7] Priit Palta,[5] Ida Surakka,[5] Mari Anneli Kaunisto,[5] Eija Hämäläinen,[5] Salli Vepsäläinen,[8] Hannele Havanka,[9] Hanna Harno,[8,10] Matti Ilmavirta,[11] Markku Nissilä,[12] Erkki Säkö,[13] Marja-Liisa Sumelahti,[14] Jarmo Liukkonen,[15] Matti Sillanpää,[16] Liisa Metsähonkala,[17] Seppo Koskinen,[18] Terho Lehtimäki,[19] Olli Raitakari,[20,21] Minna Männikkö,[22] Caroline Ran,[23] Andrea Carmine Belin,[23] Pekka Jousilahti,[18] Verneri Anttila,[1,2,3,5] Veikko Salomaa,[18] Ville Artto,[8] Markus Färkkilä,[8] 23andMe Research Team,[24], International Headache Genetics Consortium (IHGC), Heiko Runz,[6,28] Mark J. Daly,[1,2,3,5] Benjamin M. Neale,[1,2,3] Samuli Ripatti,[5,25] Mikko Kallela,[8] Maija Wessman,[4,5] and Aarno Palotie[1,2,3,5,29,*]

*Padhraig Gormley*

*"…a significant contribution of common polygenic variation to the familial aggregation of migraine"*

BROAD INSTITUTE


FINNGEN