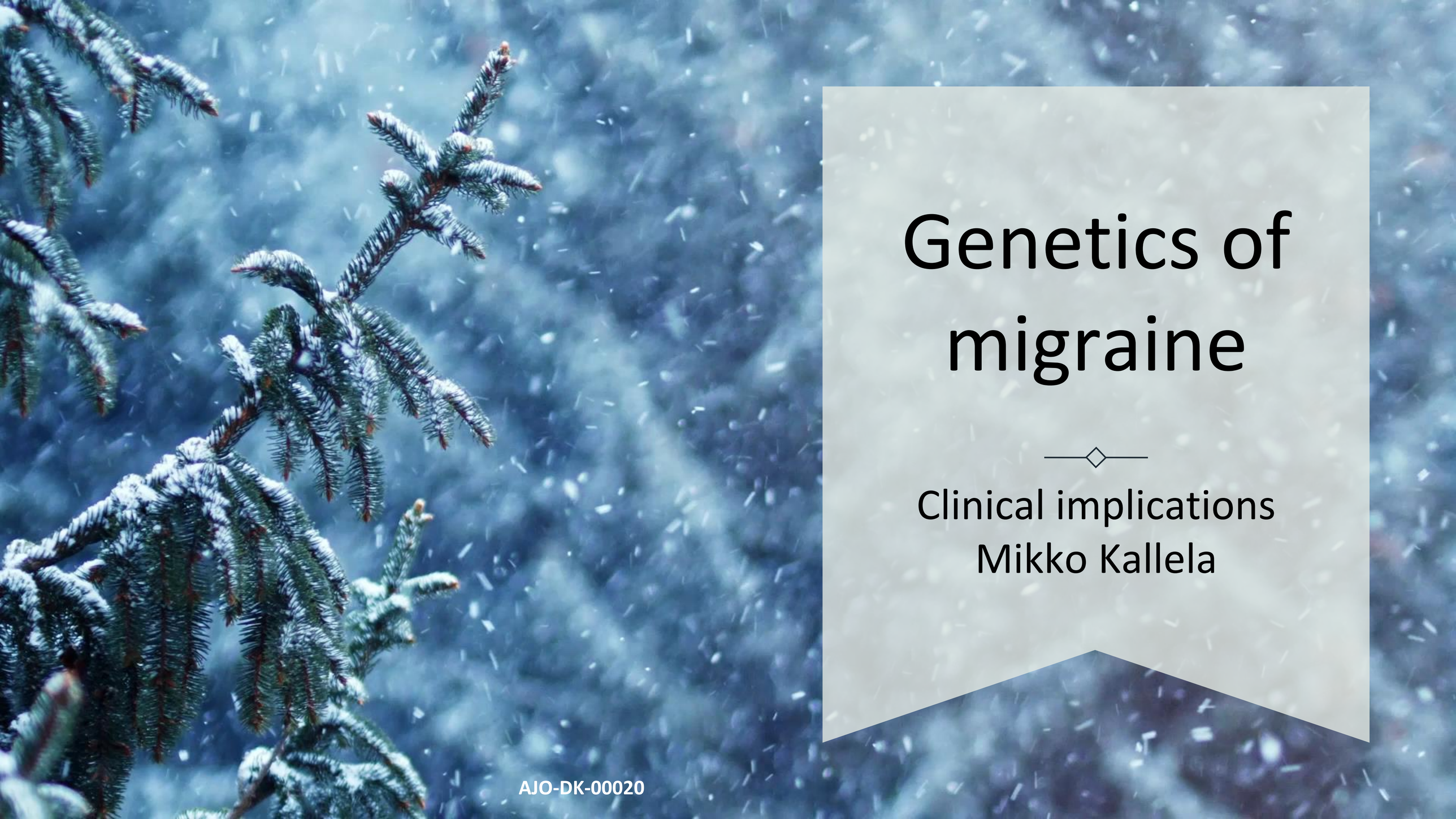


Genetics of migraine

Clinical implications

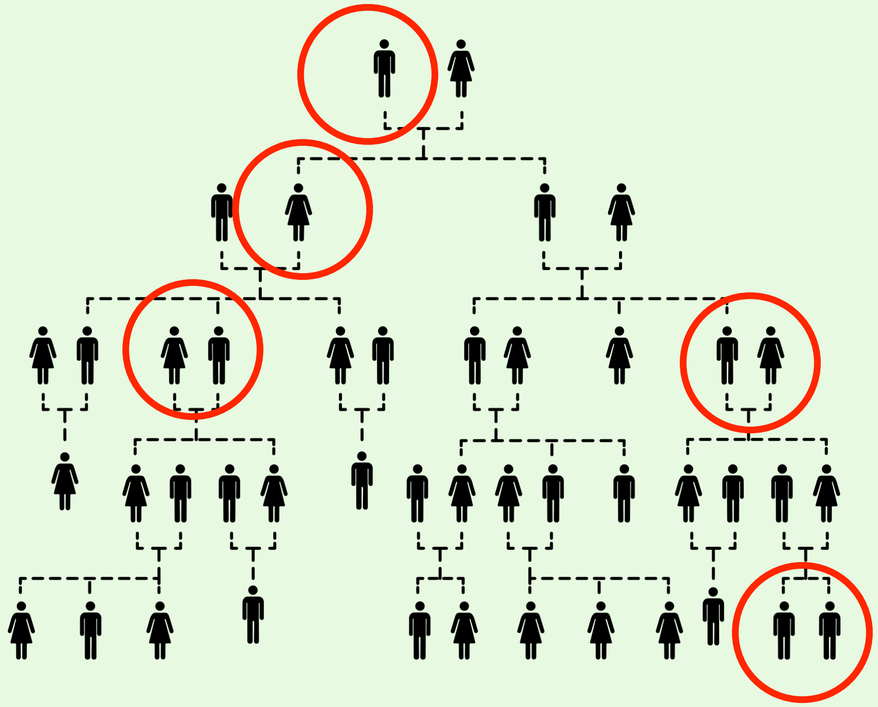
Mikko Kallela

AJO-DK-00020

Mikko Kallela - disclosures

Mikko Kallela has served on Advisory Boards for MSD, Allergan, TEVA, Lilly and Lundbeck; has received funding for travel and/or speaker honoraria from MSD, Allergan, TEVA, Novartis, Genzyme and Lundbeck; has received compensation for producing educational material from TEVA and Allergan; has received research support from Helsinki University Central Hospital; and holds stock/stock options and/or has received Board of Directors compensation from Helsinki Headache Center.

Linkage - analysis



Affected and non-affected family members

Rare causal genes such as CACNA1A (calcium channel), ATP1A2 (ion pump), SCN1A (sodium channel)

Genomwide association studies (GWAS)

Cases and controls

Common variants - increase the risk to have the disorder, such as TPRM8

Stam AH, van den Maagdenberg AM, Haan J, Terwindt GM, Ferrari MD. Genetics of migraine: an update with special attention to genetic comorbidity. Curr Opin Neurol. 2008;21(3):288-93.

Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 2016;48(8):856-66.

Linkage studies

Genomwide association studies

Rare phenotypes
like FHM

MwA = migraine with aura
MwoA = migraine without aura
FHM = familial hemiplegic migraine

Common phenotypes
like MwoA and MwoA

FHM, sporadic HM

Molecular genetic diagnosis

Strange symptoms, no diagnosis, no treatment, no hope, live with it

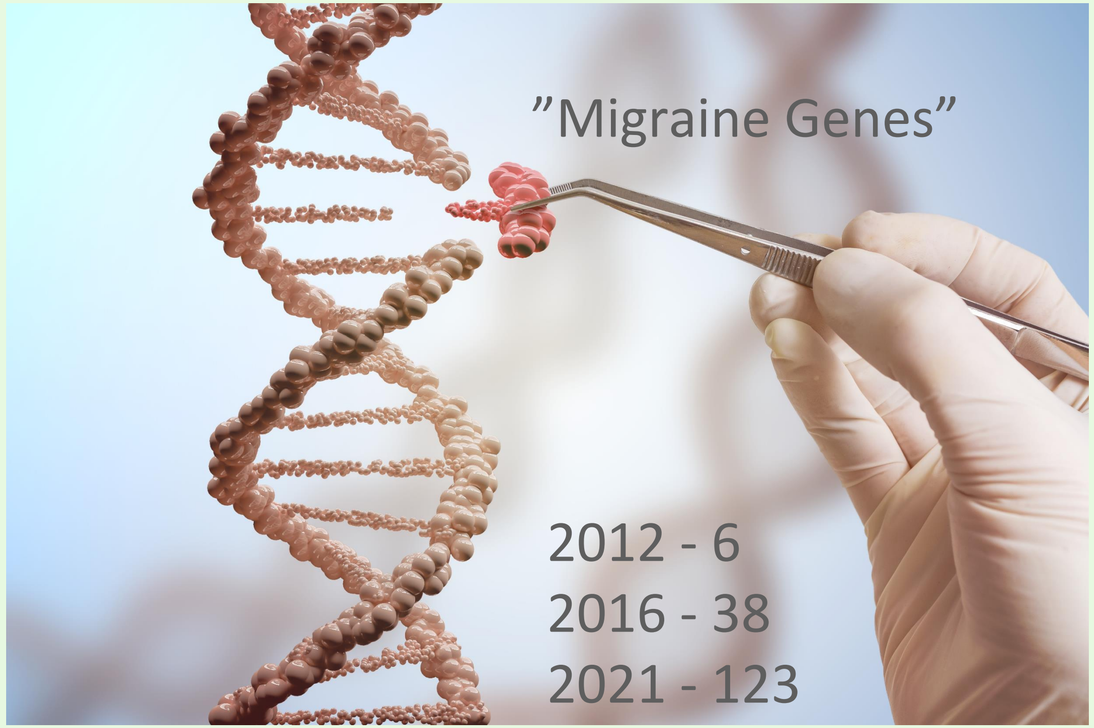
Strange symptoms, proper diagnosis, treatment and prognosis

1.2.3.1.1 CACNA1A (calcium channel)
1.2.3.1.2 ATP1A2 (ion pump)
1.2.3.1.3 SCN1A (sodium channel)

Part of migraine is a chanellopathy

Carrera P, Stenirri S, Ferrari M, Battistini S. Familial hemiplegic migraine: a ion channel disorder. Brain Res Bull. 2001;56(3-4):239-41.

Genomwide association studies (GWAS)



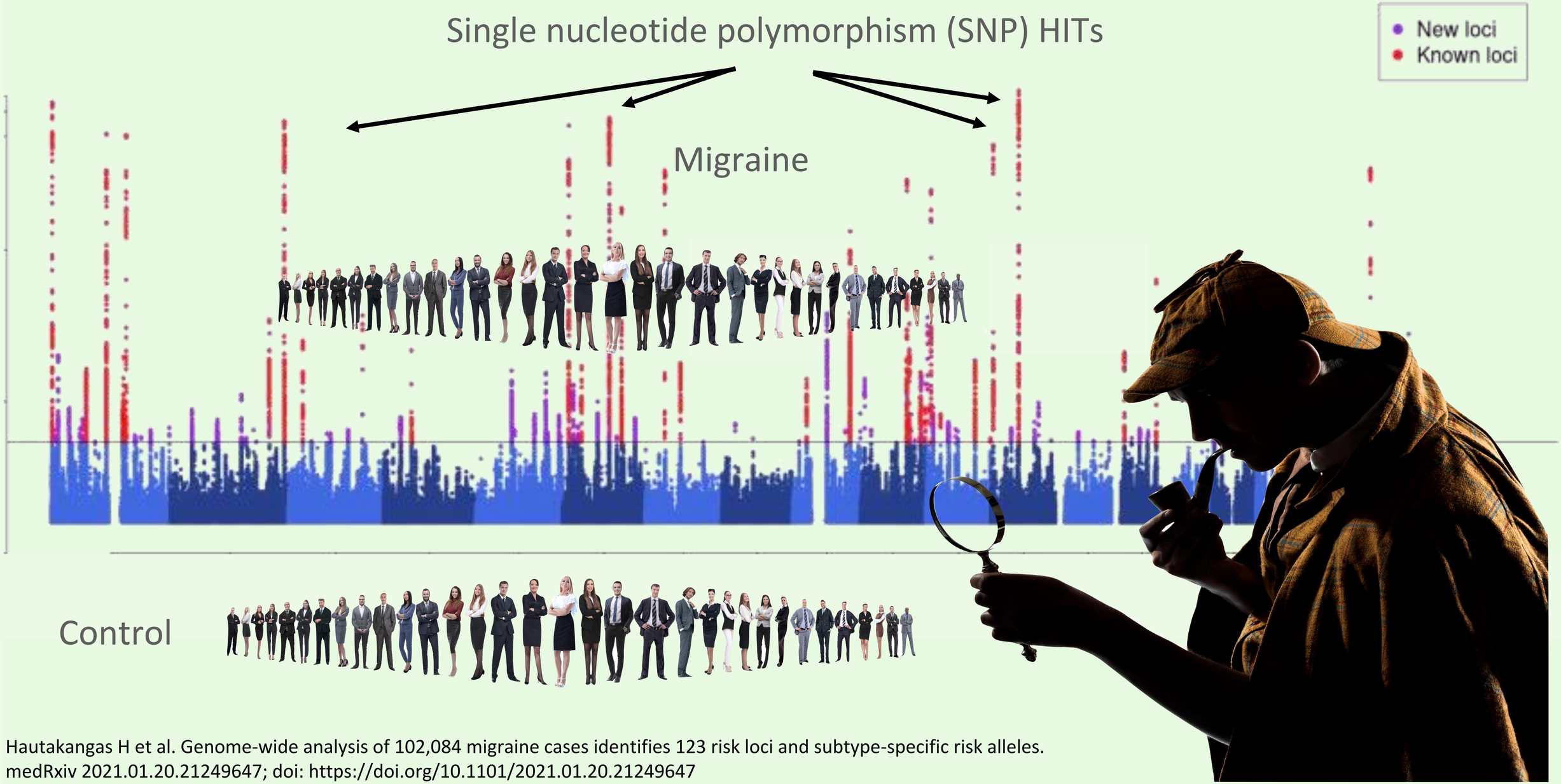
Cases and controls

Common variants - increase the risk to have the disorder, such as MEF2D, TGFBR2, PHACTR1, ASTN2, LRP1, TPRM8

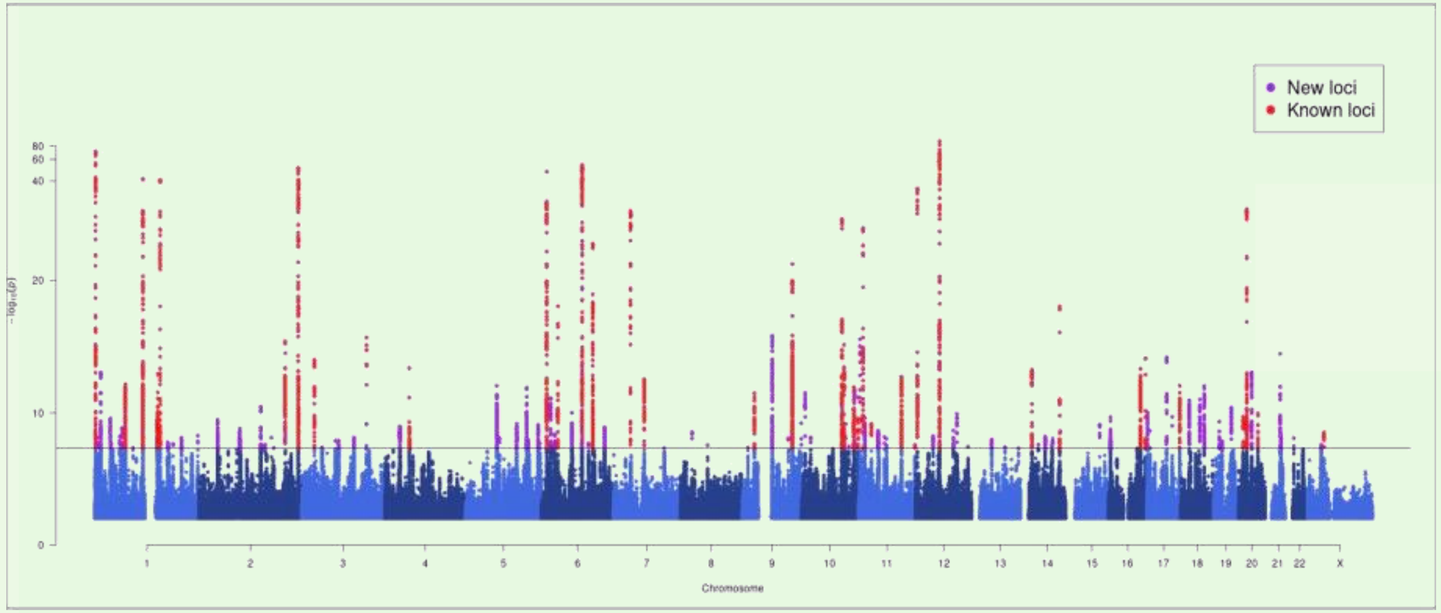
Rare causal genes such as CACNA1A (calcium channel), ATP1A2 (ion pump), SCN1A (sodium channel) can (and will be) be missed

Freilinger T, Anttila V, de Vries B, Malik R, Kallela M, Terwindt GM, et al. Genome-wide association analysis identifies susceptibility loci for migraine without aura. Nat Genet. 2012;44(7):777-82; Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 2016;48(8):856-66; Hautakangas et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles 2021.

100 000 migraine cases - 500 000 controls - 123 SNP hits



Hautakangas H et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. medRxiv 2021.01.20.21249647; doi: https://doi.org/10.1101/2021.01.20.21249647

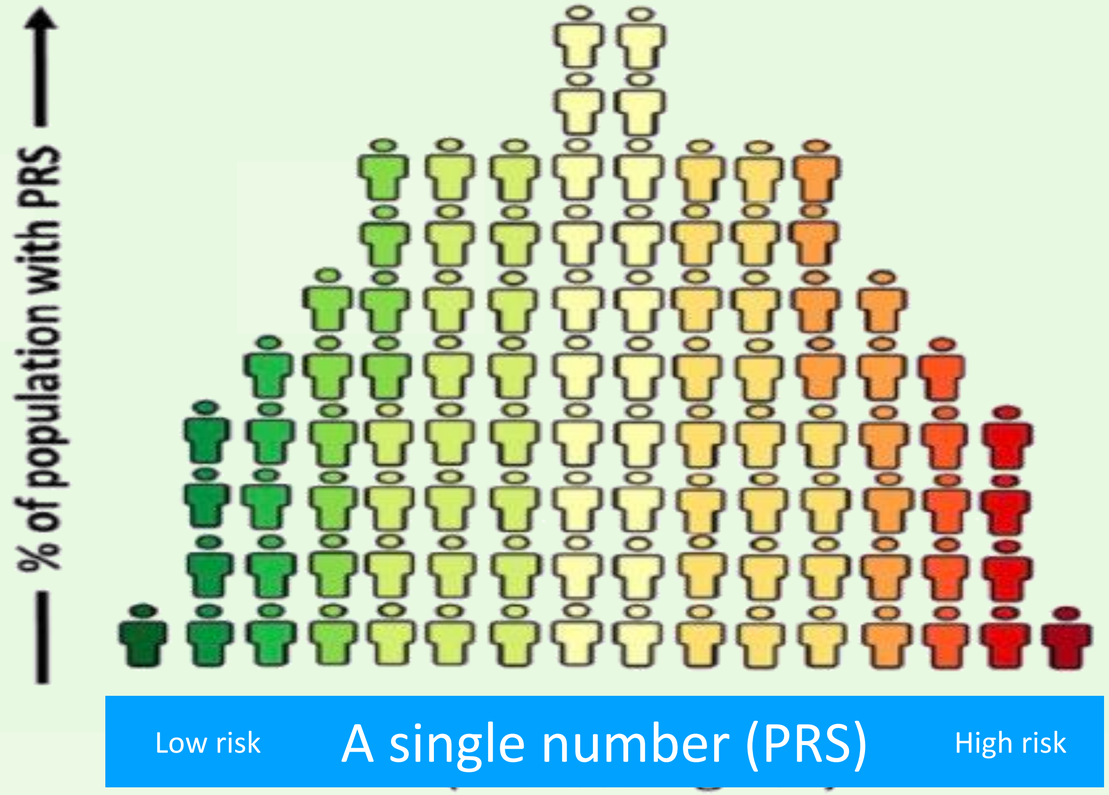


How to use the GWAS - data?

Hautakangas H et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. medRxiv 2021.01.20.21249647; doi: https://doi.org/10.1101/2021.01.20.21249647

Common variants contribution to a disease in a single number = 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

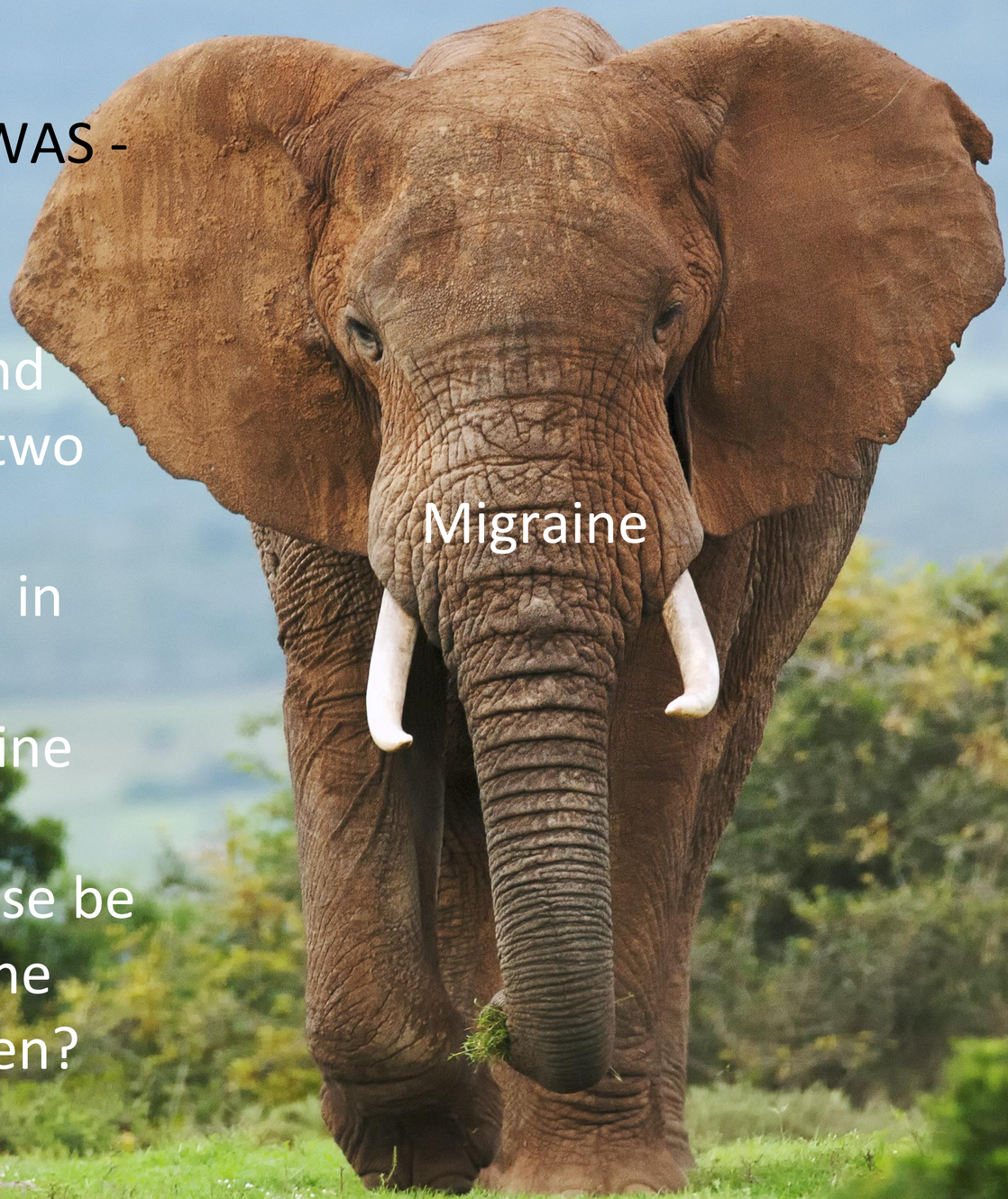


Source: RGA

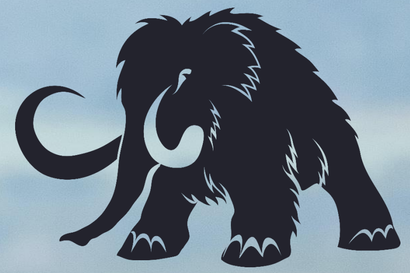
Polygenic Risk Scores = Statistical geneticists have developed the ‘polygenic risk score’ (PRS), identifying hundreds, thousands and even millions of SNPs (variants) that can be included in a single score that measures the individual’s genetic predisposition to specific diseases or traits. Source: RGA = Reinsurance Group of America

Based on the current GWAS - data:

1. Is migraine with and without aura - one or two disorders?
2. Where is the lesion in migraine?
3. Is hemiplegic migraine migraine?
4. Can treatment response be predicted based on the common variant burden?



Migraine



Hemiplegic migrain

1. Is migraine with and without aura - one or two disorders?

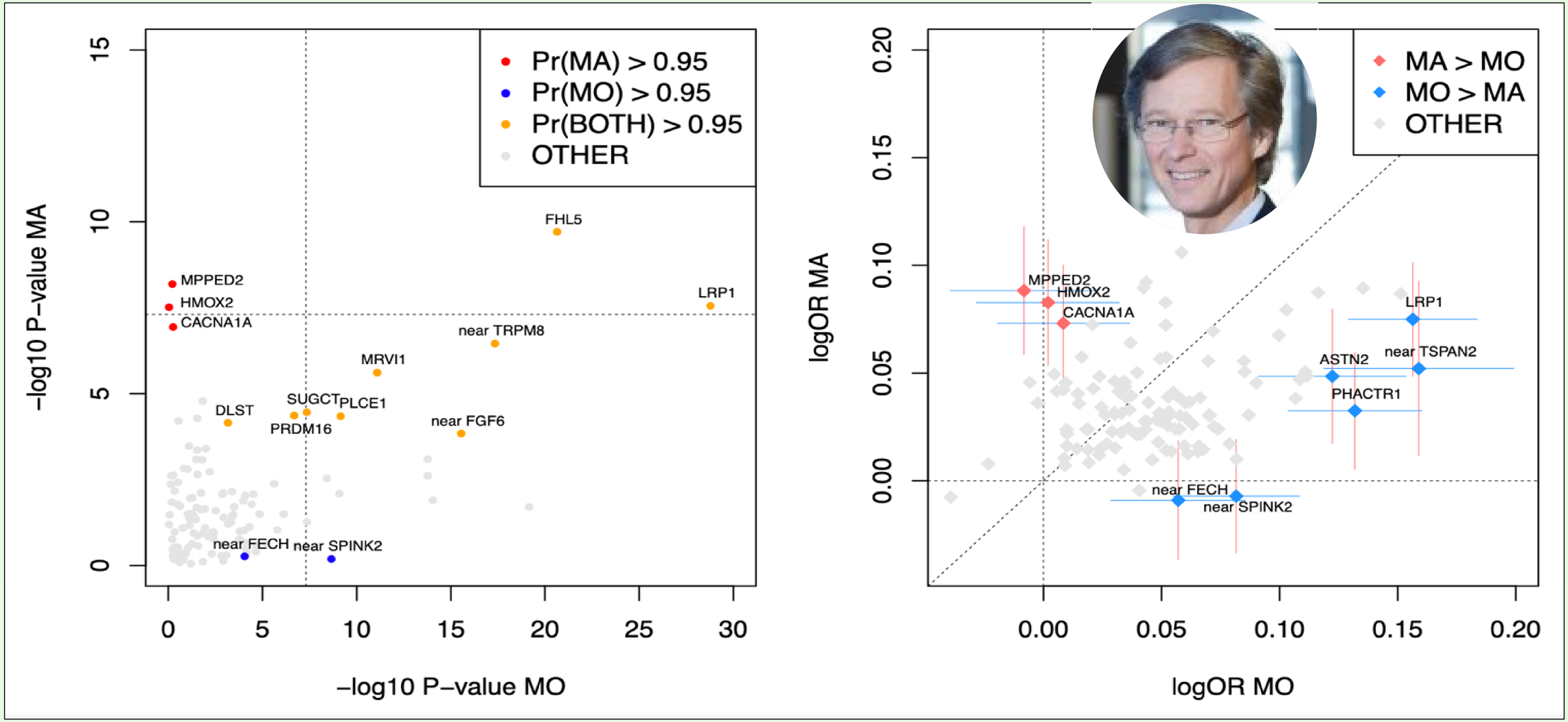
MwA

MwA + MwoA

MwoA

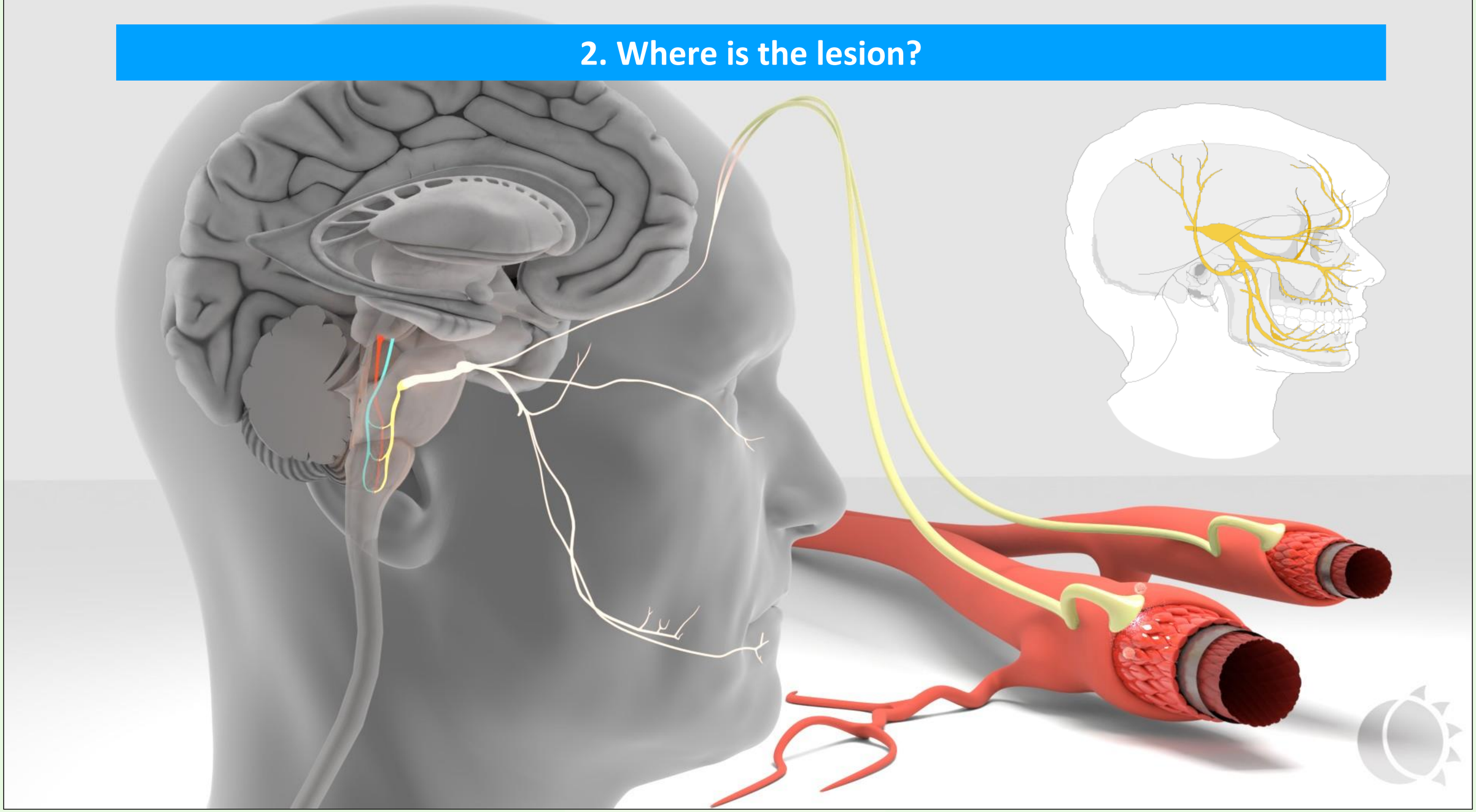
MwA = migraine with aura, MwoA = migraine without aura.

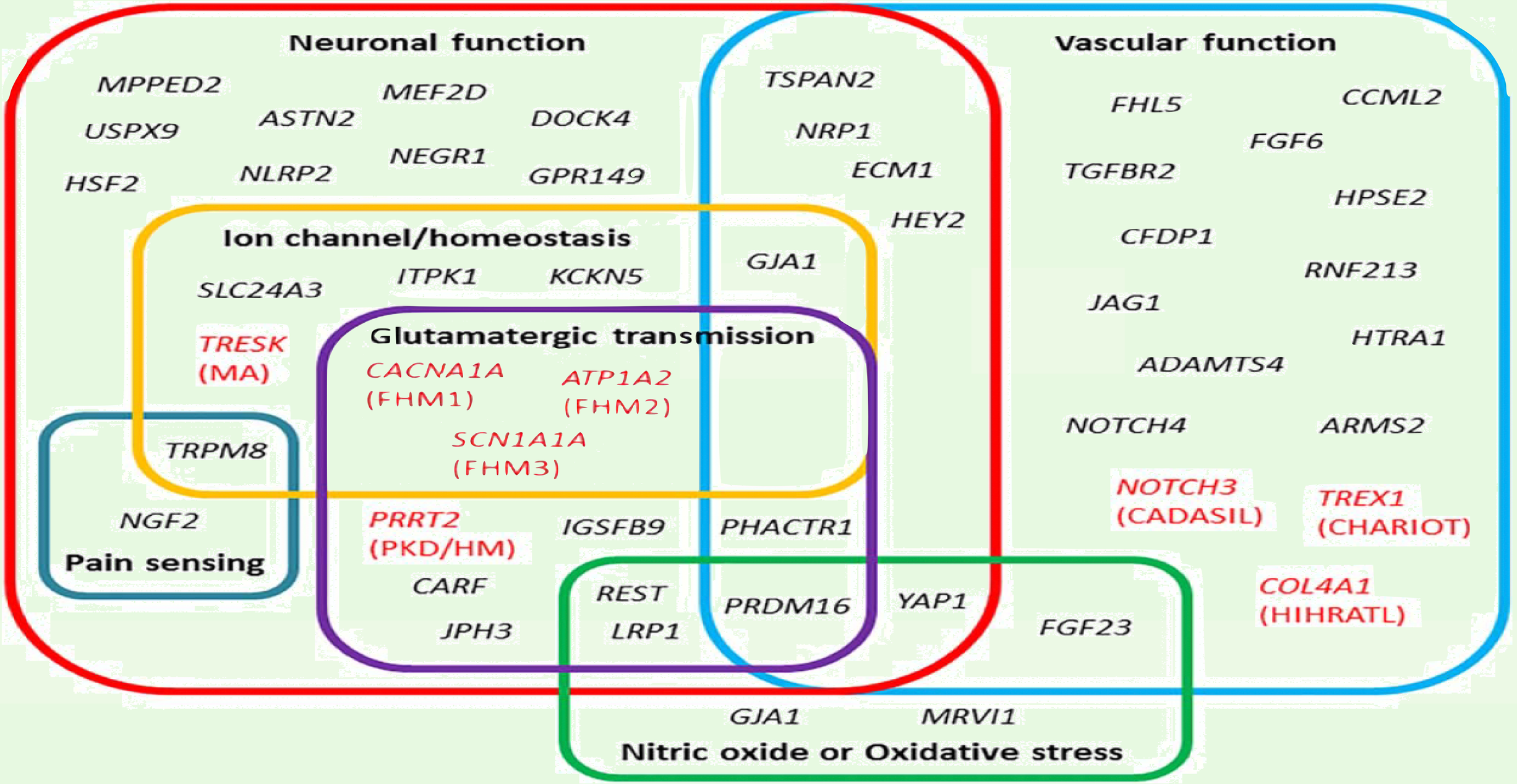
Maybe three - there are aura variants, headache variants, aura and headache variants



Hautakangas H et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. medRxiv 2021.01.20.21249647; doi: https://doi.org/10.1101/2021.01.20.21249647

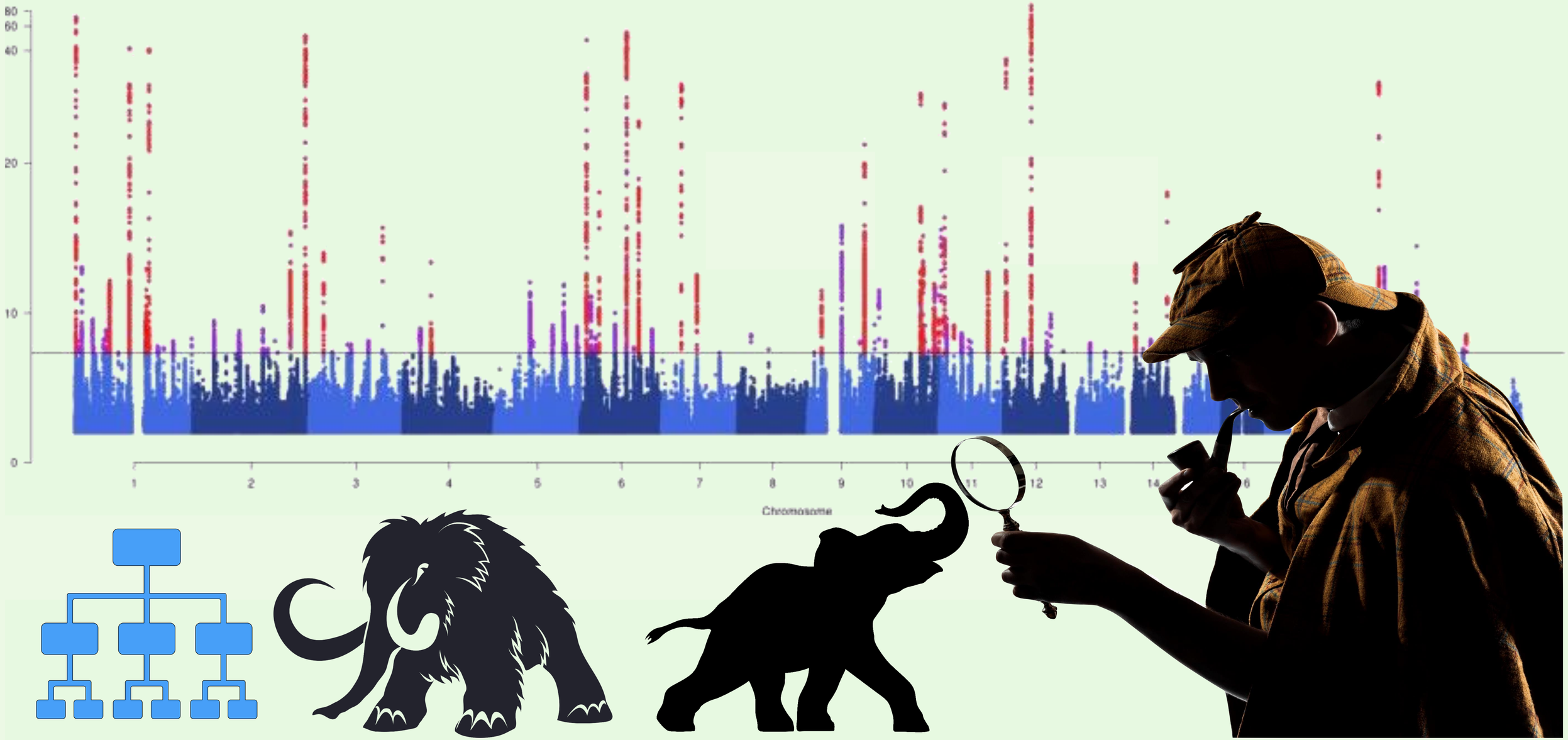
2. Where is the lesion?

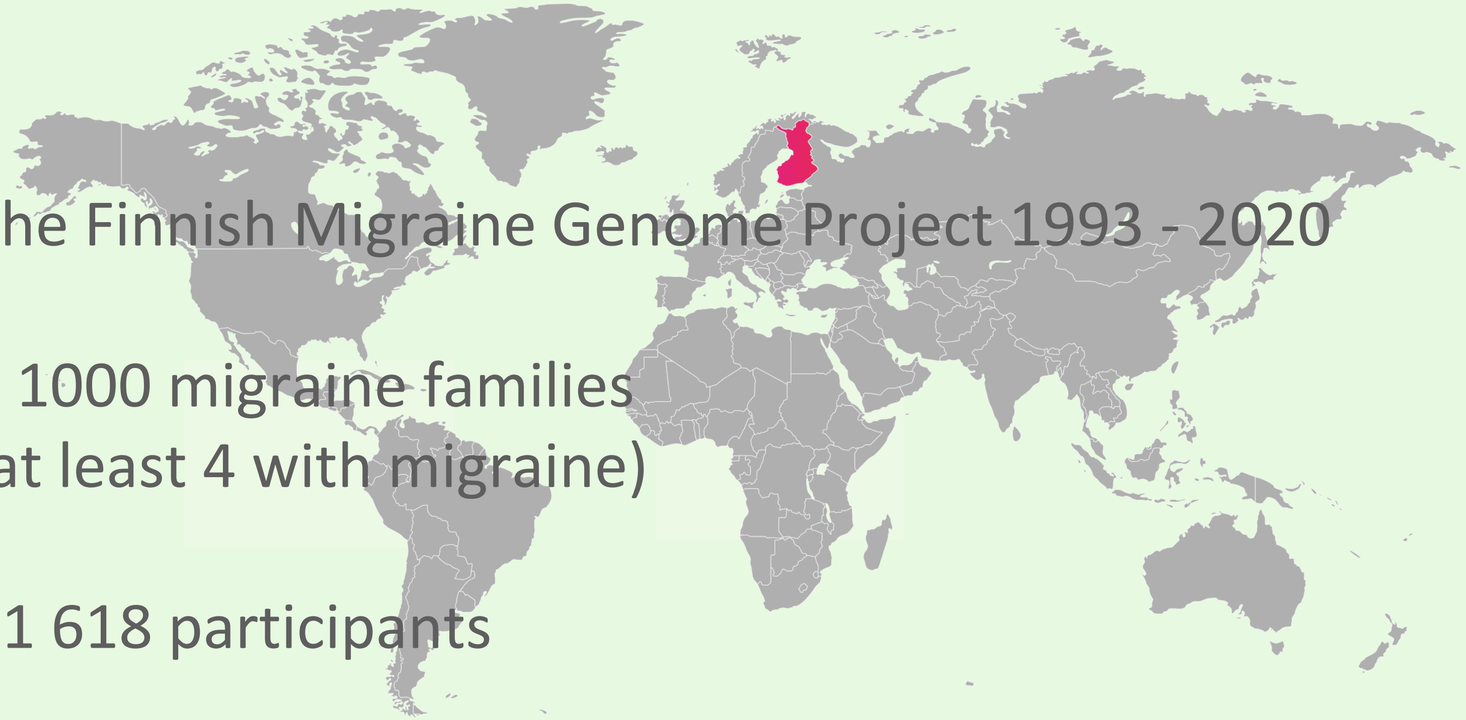




Sutherland HG, Griffiths LR. Genetics of Migraine: Insights into the Molecular Basis of Migraine Disorders. Headache. 2017;57(4):537-69.

3. Is hemiplegic migraine (HM) migraine?





The Finnish Migraine Genome Project 1993 - 2020

> 1000 migraine families
(at least 4 with migraine)

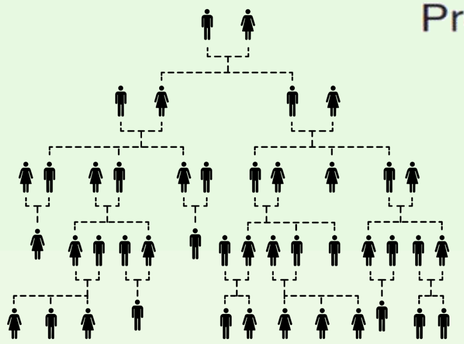
11 618 participants

8 602 analysed

3920 MwoA, 3138 MwA, 578 HM, 3542 no migraine
According to the ICHD-3 criteria

MwoA = migraine without aura, MwA = migraine with aura, HM = hemiplegic migraine

Hemiplegic migraine belongs to the migraine spectrum

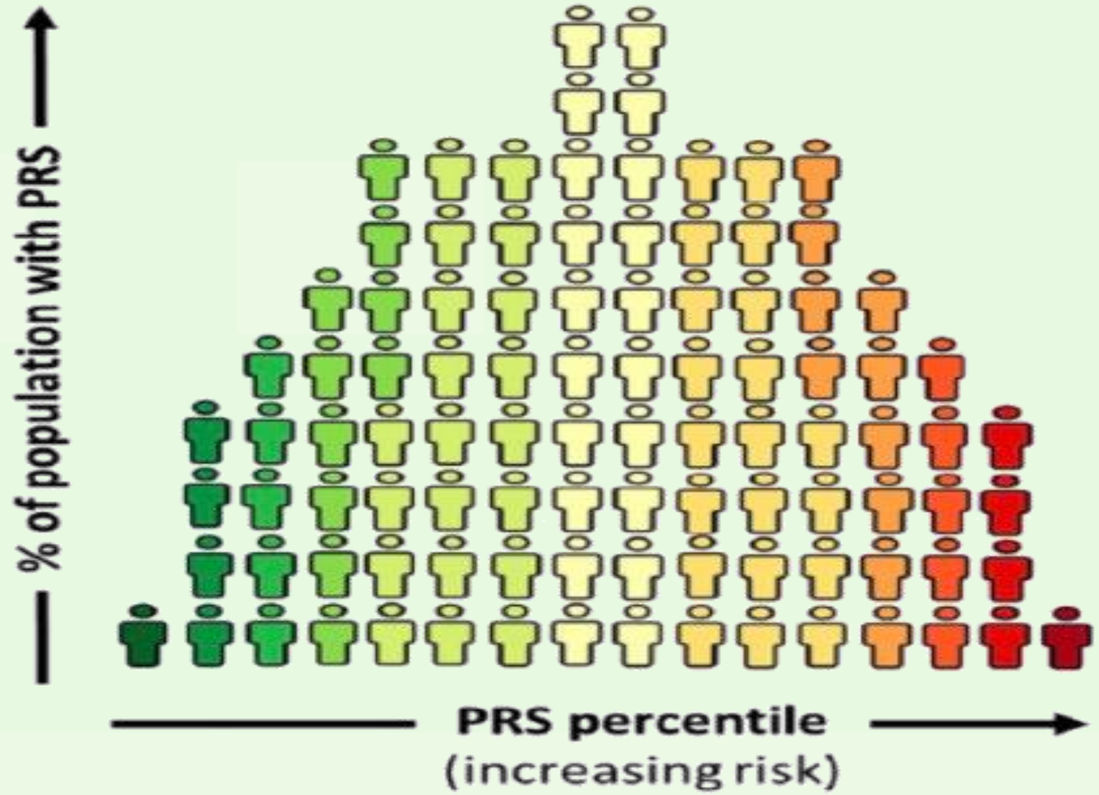


Migraine complexity continuum and mean PRS. Categories illustrated are mutually exclusive and all p-values contrasted to the “No headache” category

Happola P, Gormley P, Nuottamo ME, Artto V, Sumelahti ML, Nissila M, et al. Polygenic risk provides biological validity for the ICHD-3 criteria among Finnish migraine families. Cephalalgia. 2021:3331024211045651.

4. Can treatment response predicted based on the common variant burden?

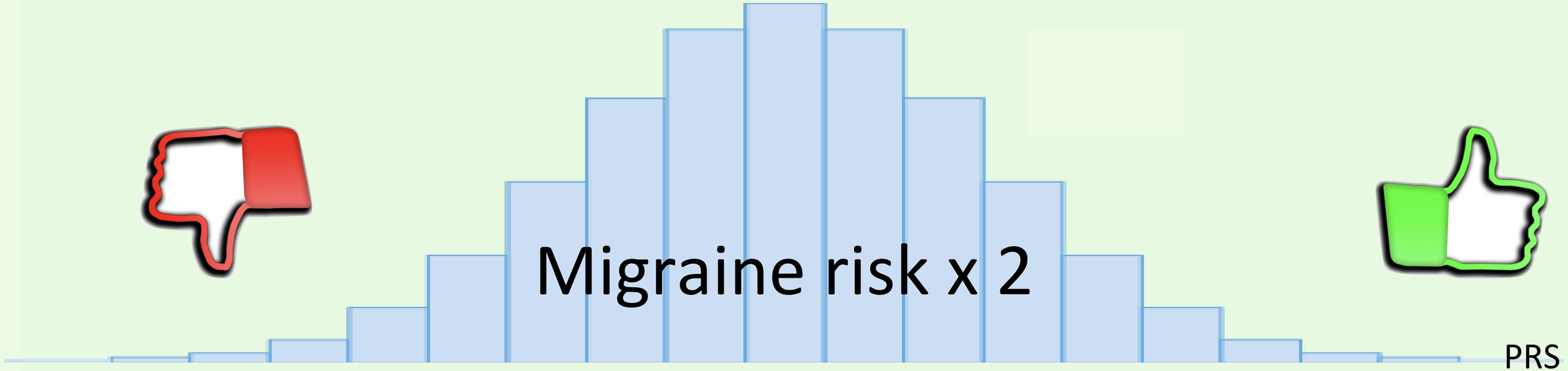
PRS percentile	Risk of disease vs. reference group
0-1	Lowest
1-5	
5-10	
10-20	
20-40	
40-60 (reference)	1
60-80	
80-90	
90-95	
95-99	
99-100	Highest



Source: RGA

Polygenic Risk Scores = Statistical geneticists have developed the 'polygenic risk score' (PRS), identifying hundreds, thousands and even millions of SNPs (variants) that can be included in a single score that measures the individual's genetic predisposition to specific diseases or traits. Source: RGA = Reinsurance Group of America

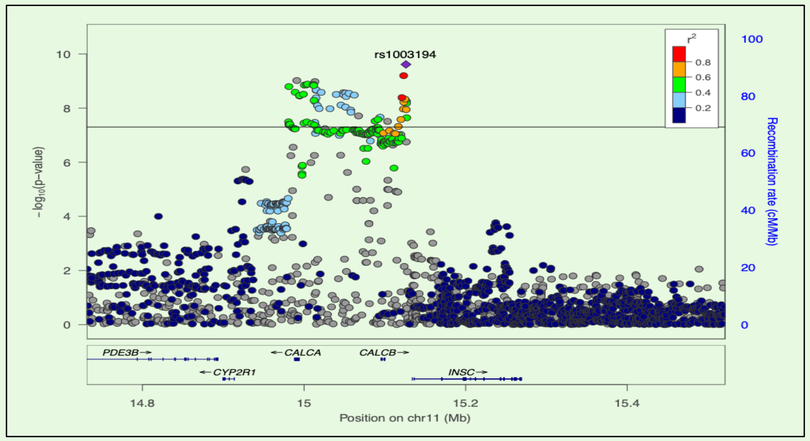
Response to triptans and genetics



A twofold increase in migraine risk associates with positive response to migraine-specific acute treatment (odds ratio [OR] = 1.25 [95% con!dence interval (CI) = 1.05–1.49]).

Kogelman LJA, Esserlind A-L, Francke Christensen A, Awasthi S, Ripke S, et al. Migraine polygenic risk score associates with efficacy of migraine-specific drugs. Neurol Genet. 2019

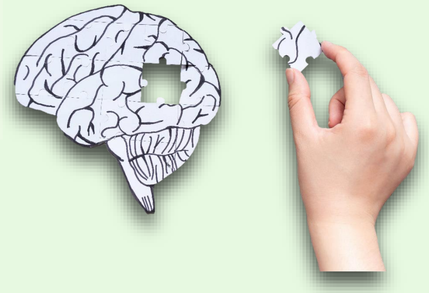
Hot Topic - genetics and migraine medications

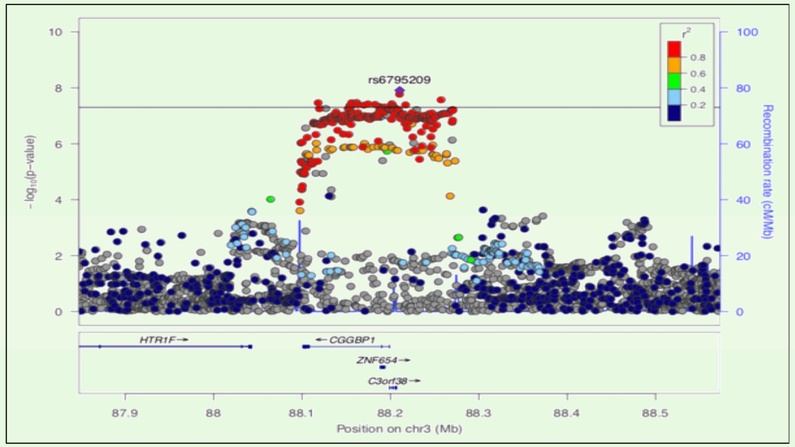


mAbs and gepants = CGRP-antagonists

CALCA
CALCB

Chromosome 11





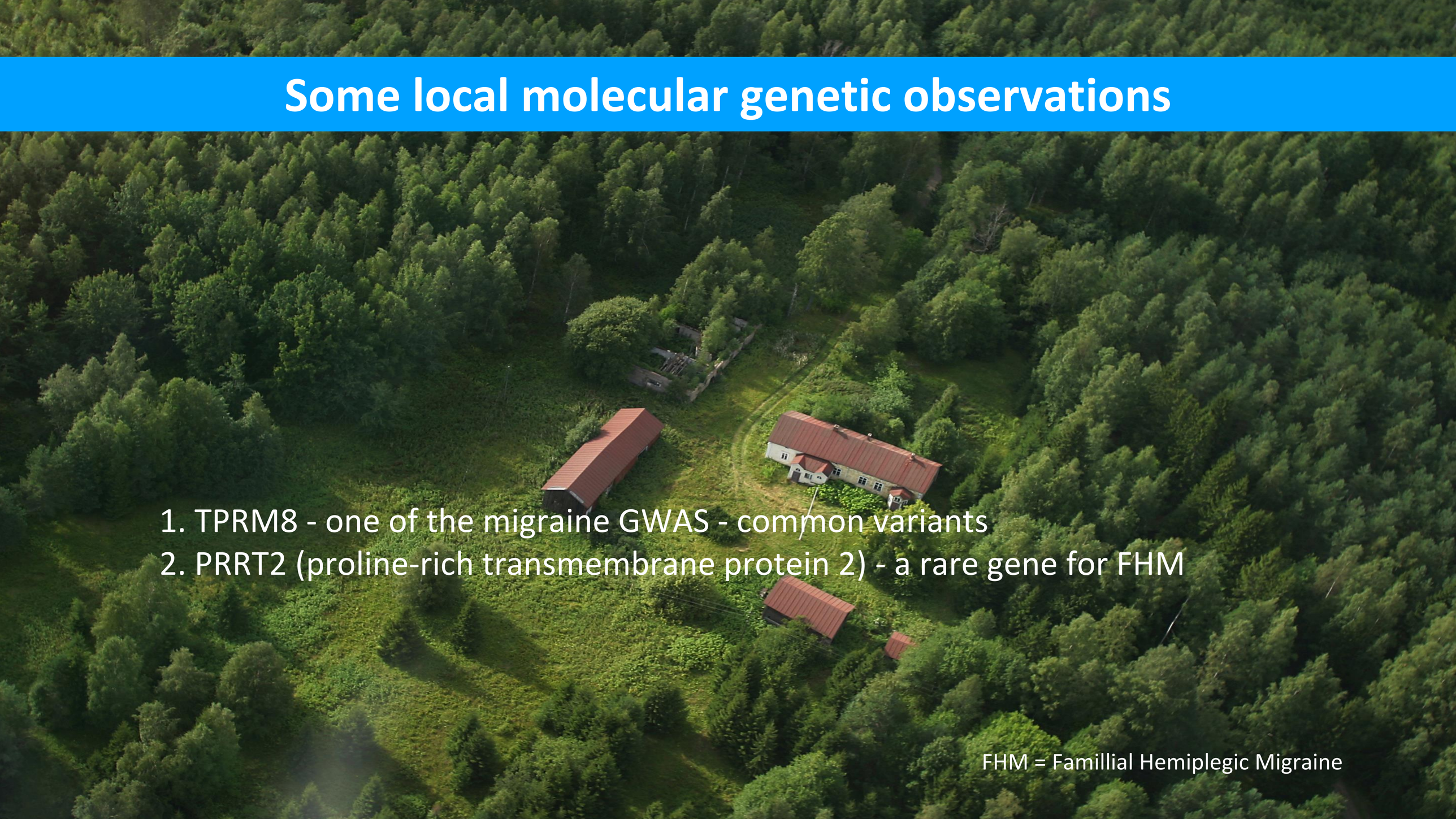
5-HT-1F Ditans (lasmiditan = 5-HT-1F agonist)

Chromosome 3

Chan C, Goadsby PJ. Recent Advances in Pharmacotherapy for Episodic Migraine. CNS Drugs. 2019

Hautakangas H et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. medRxiv 2021.01.20.21249647; doi: https://doi.org/10.1101/2021.01.20.21249647

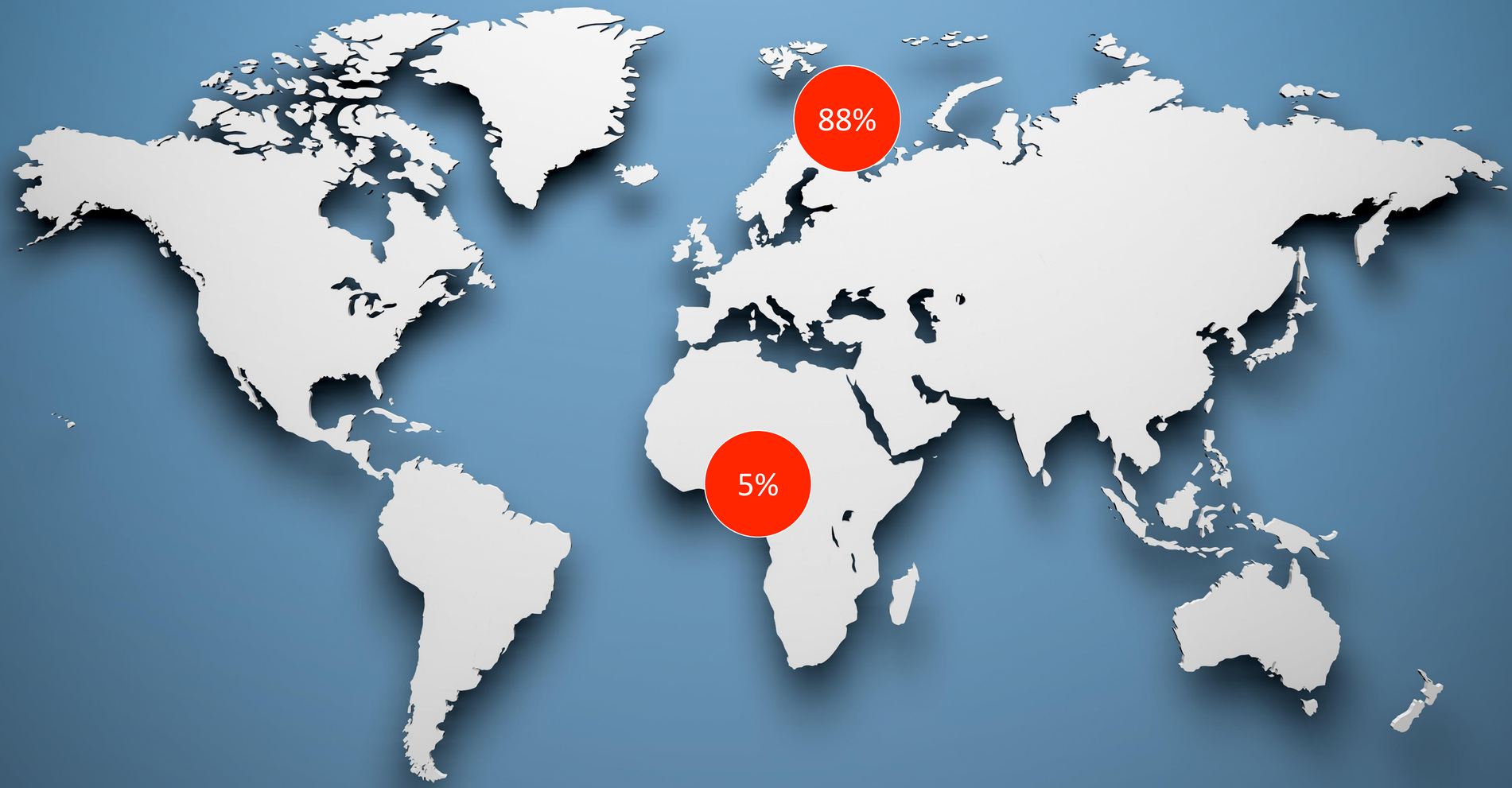
Some local molecular genetic observations



1. TPRM8 - one of the migraine GWAS - common variants
2. PRRT2 (proline-rich transmembrane protein 2) - a rare gene for FHM

FHM = Famillial Hemiplegic Migraine

1. TPRM8 The upstream variant rs10166942 shows extreme population differentiation, with frequencies that range from 5% in Nigeria to 88% in Finland



Key FM, Abdul-Aziz MA, Mundry R, Peter BM, Sekar A, D'Amato M, et al. Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. PLoS Genet. 2018;14(5):e1007298.

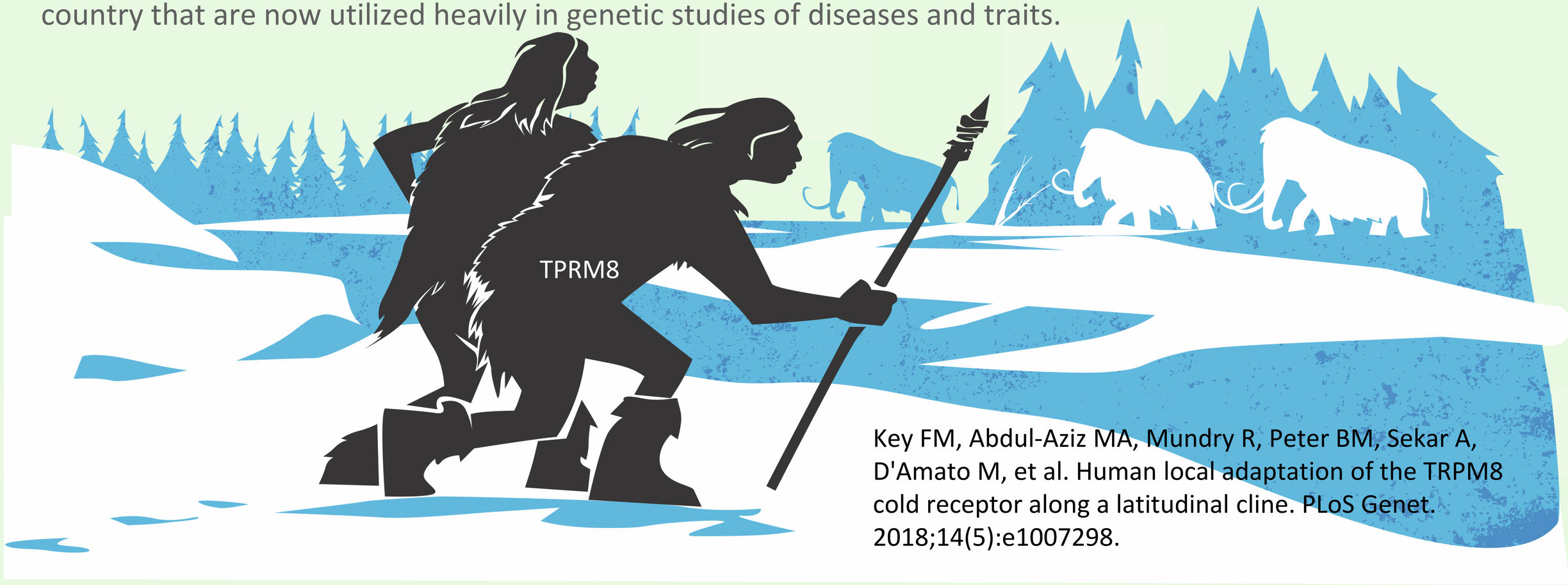
TPRM8 = Transient receptor potential cation channel subfamily M member 8

TPRM8 is a receptor for cold and menthol
and also one of the migraine variants

Key FM, Abdul-Aziz MA, Mundry R, Peter BM, Sekar A, D'Amato M, et al. Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. PLoS Genet. 2018;14(5):e1007298.

Two Finns going to the market anno 2021

The Finnish population is one of the most genetically studied in the world. A relatively small number of founder individuals and strong genetic isolation over centuries have shaped the unique genetic makeup across the country that are now utilized heavily in genetic studies of diseases and traits.



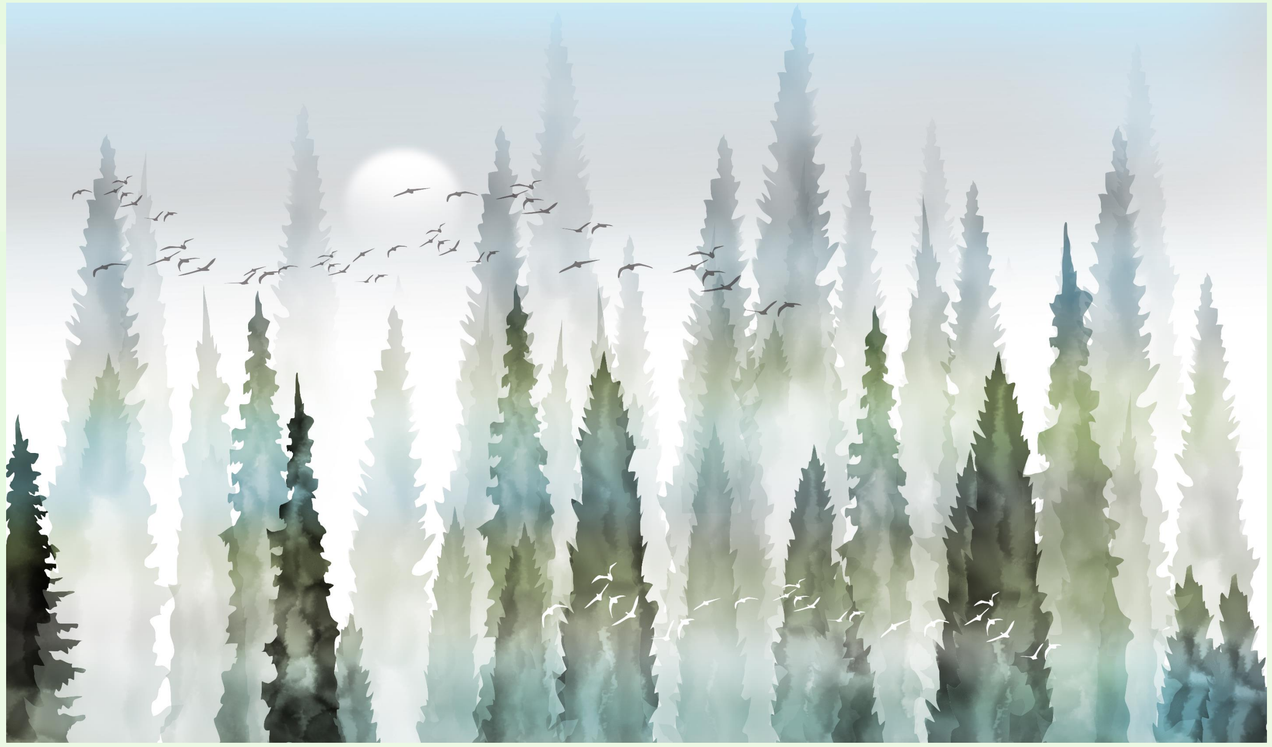
Key FM, Abdul-Aziz MA, Mundry R, Peter BM, Sekar A, D'Amato M, et al. Human local adaptation of the TRPM8 cold receptor along a latitudinal cline. PLoS Genet. 2018;14(5):e1007298.

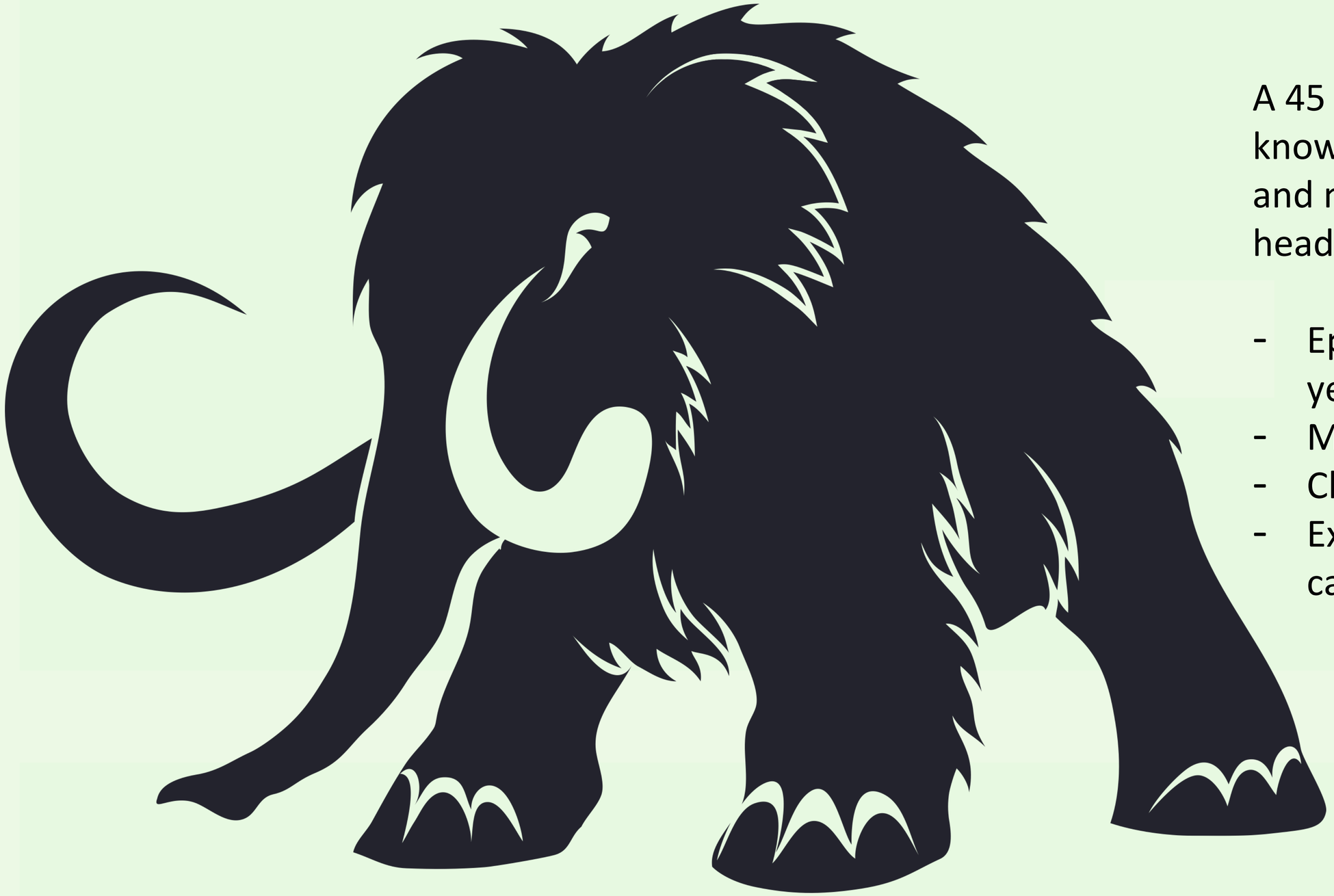
www.fimm.fi/en/research/projects/finnpopgen

TPRM8 = Transient receptor potential cation channel subfamily M member 8

The 2021 Nobel Prize in Physiology or Medicine was awarded to David Julius and Ardem Patapoutian for their discoveries of thermal and mechanical transducers including TRPV1 (receptor for capsaicin) and TPRM8 (receptor for cold and menthol)

https://www.nobelprize.org/prizes/medicine/2021/summary/

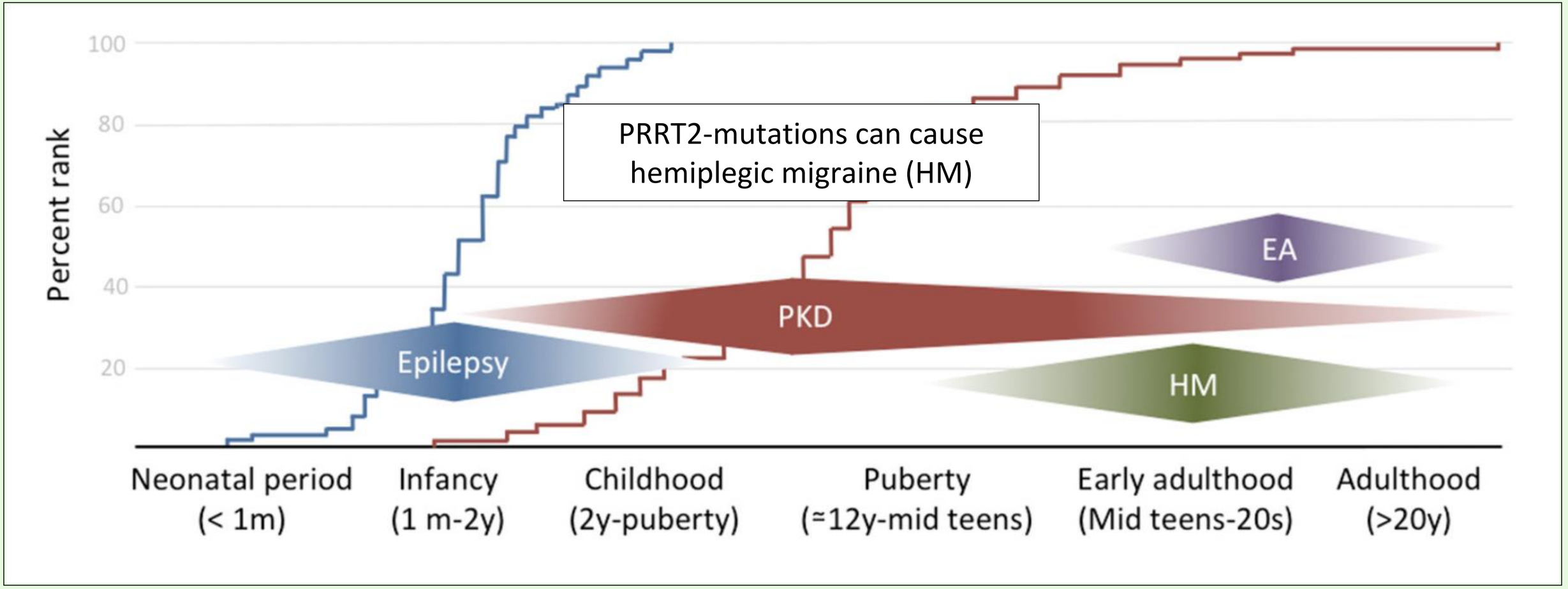




A 45 year old lady with known PRRT-mutation and migraine and cluster headache

- Epilepsy during first years of life
- Migraine
- Cluster headache
- Excellent response to carbamazepine

Hemiplegic migraine with excellent response to Na-channel blocker carbamazepine



Hemiplegic migraine (HM), epilepsy, paroxysmal kinesigenic dyskinesia (PKD) , episodic ataxia (EA), excellent response to Na-channel blocker carbamazepine

PRRT2 = proline-rich transmembrane protein 2 (PRRT2)

Landolfi A, Barone P, Erro R. The Spectrum of PRRT2-Associated Disorders: Update on Clinical Features and Pathophysiology. Front Neurol. 2021;12:629747.

What does future look like in migraine genetics?

Aarno Palotie - to make individual decisions it takes larger data sets

Jogi Berra - future is not what its used to be

Migraine - multiple mechanisms - multiple chances for progress

Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol. 2018;14(6):338-50.

Detailed clinical and genetic phenotyping - better migraine spesific tretments

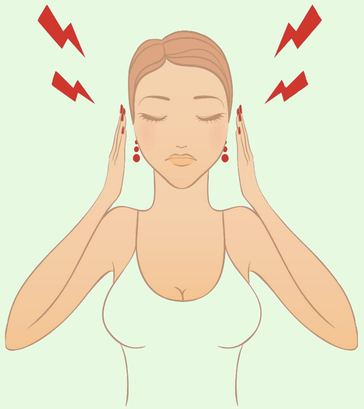
Triptans (serotonin - IB/D - agonists), Gepants (CGRP - antagonists), Ditans (serotonin - !F - agonists), mAbs (monoclonal antibodies agains CGRP or it’s receptor))

Tfelt-Hansen PC, Koehler PJ. One hundred years of migraine research: major clinical and scientific observations from 1910 to 2010. Headache. 2011;51(5):752-78.

Clinical problem

Randomised placebo controlled trial (RCT)

Treatment versus placebo



Clinical diagnostic criteria

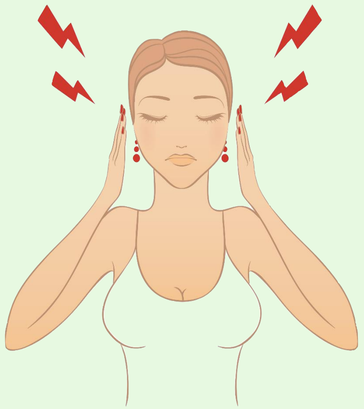
Treatment superior to placebo in Phase 3 study

Patients with hemiplegic and brainstem aura excluded

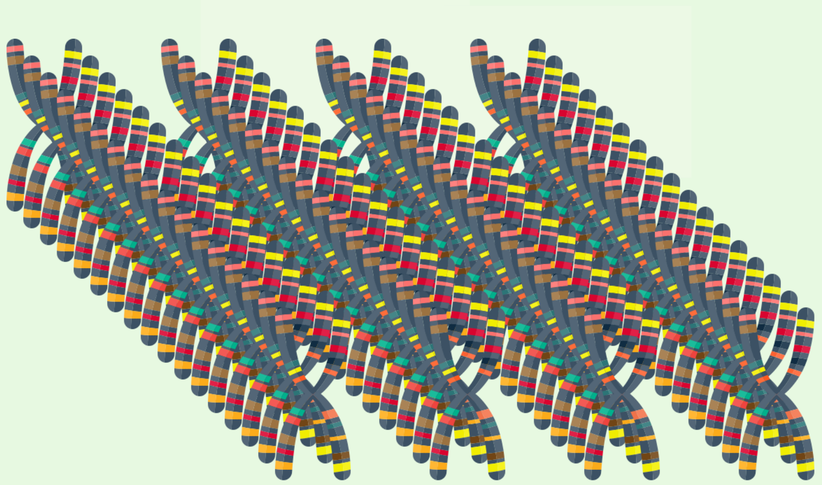
Clinical problem

Randomised placebo controlled trial (RCT) including PRS - data

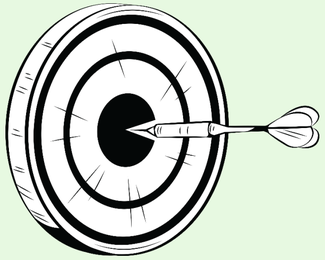
Clinical trial - data and PRS) of the patient



Clinical diagnostic criteria



Treatment based on clinical trials and the PRS of the patient

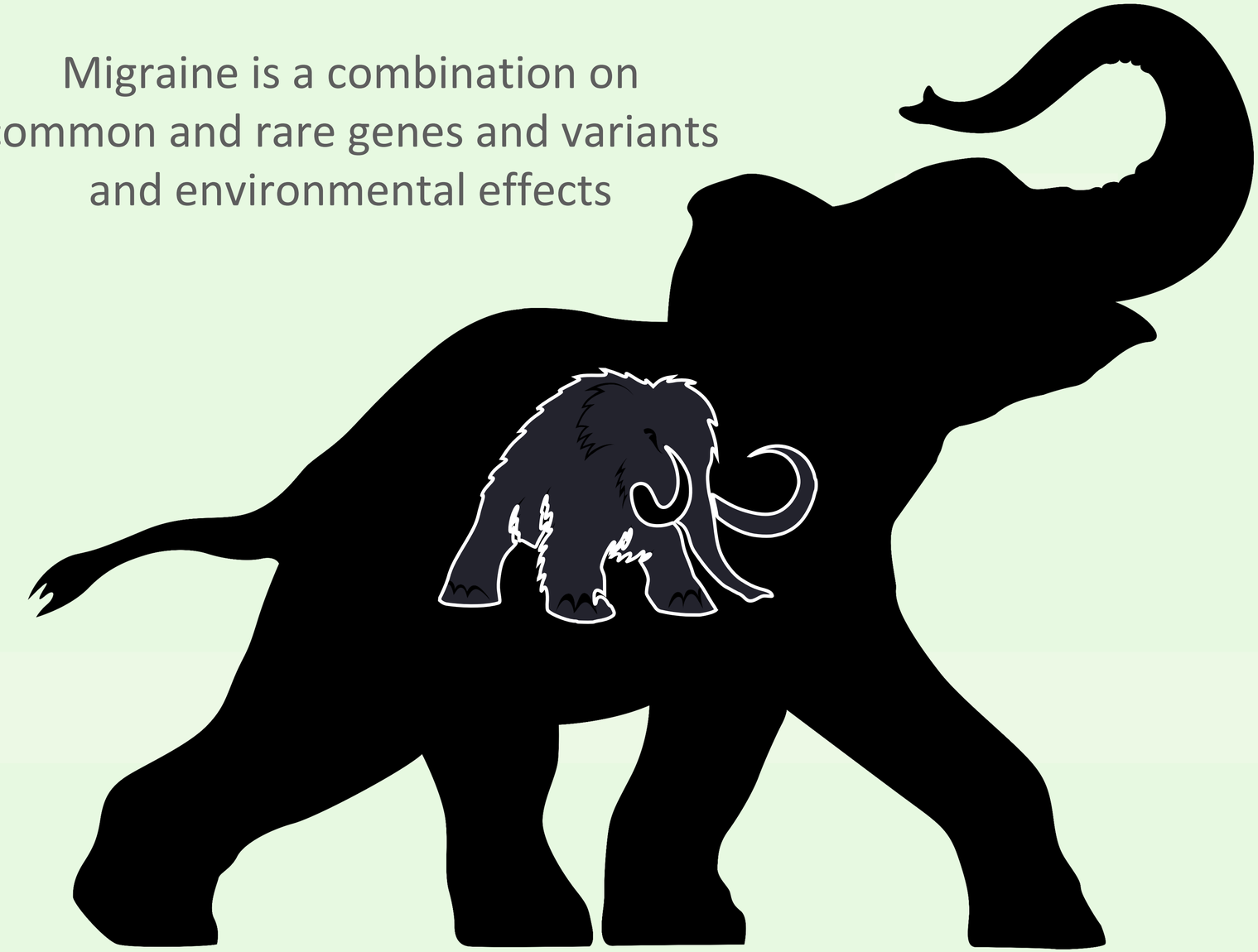


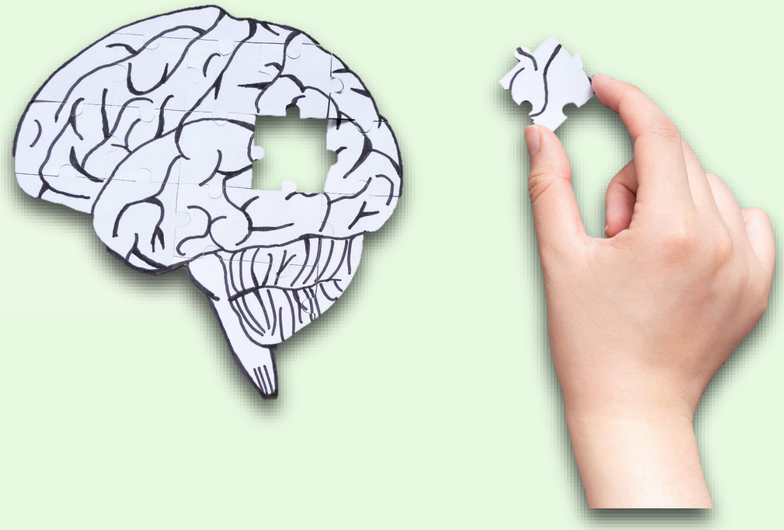
PRS based on >> 100 000 genotypes


Clinical and genomic big data - registries, biobanks, national records, etc.
Super responder
In personalized medicine to treat one it takes many”
Super responder
A rare complication
A rare complication

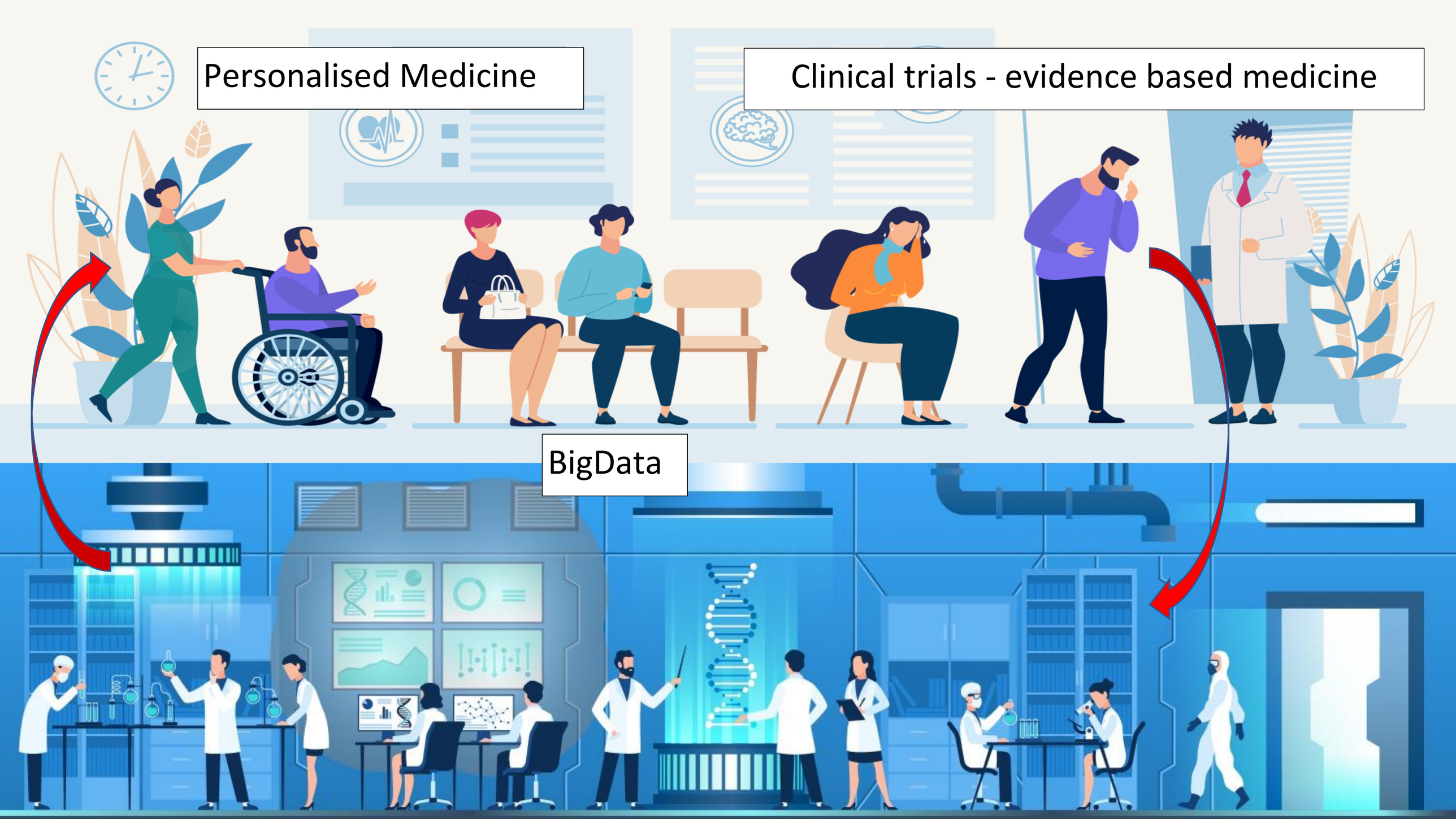
Migraine is common and rare

Migraine is a combination on common and rare genes and variants and environmental effects





Migraine specific medications open unforeseen opportunities to study migraine pathophysiology in molecular level


Personalised Medicine
Clinical trials - evidence based medicine
BigData