Leiden University Medical Center

Why do people get Migraine: The role of genetics

HCOP meeting
Ojai, 25th January 2020

LUMINA
Leiden University Medical Centre Migraine Neuro Analysis Programme

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LEIDEN, THE NETHERLANDS

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Disclosures

- Consultant: Novartis, Eli Lilly, Teva

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ARS

To answer the pre-test questions:

Log into www.slido.com

Enter Event Code #Z410

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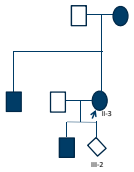
Pre-Test Question #1

A 32 year old woman (II-3) suffers from attacks of one-sided pulsating headache worsening with physical activity, nausea and vomiting. Prior to the headache, she suffers from visual disturbances followed by vertigo, dysarthria and one-sided weakness of the arm and leg. Several of her family members suffer from the same complaints (see pedigree below). She is pregnant and has come to you for counseling.

What is the mode of inheritance of her disease?

A. Autosomal recessive
B. Autosomal dominant
C. X-linked dominant
D. X-linked recessive



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Pre-Test Question #2

What is the name of the disease?

A. Migraine with aura
B. Hemiplegic migraine
C. Familial hemiplegic migraine
D. Migraine with brainstem aura

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Pre-Test Question #3

Another patient (unrelated to the first patient) visits the clinic. She suffers from migraine without aura. Her mother suffered from this type as migraine as well. She visits your clinic because she wants her children to be genetically tested for migraine.

Can a genetic test predict whether her children will get migraine?

A. Yes, it is likely that one gene will be responsible
B. Yes, but multiple genes will be responsible
C. No, migraine without aura is not genetic
D. At this moment there is no prediction model possible based on a genetic test

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Leiden University Medical Center
Why do people get Migraine?
The role of genetics
Let's talk about genetics!
What is the clinical use?

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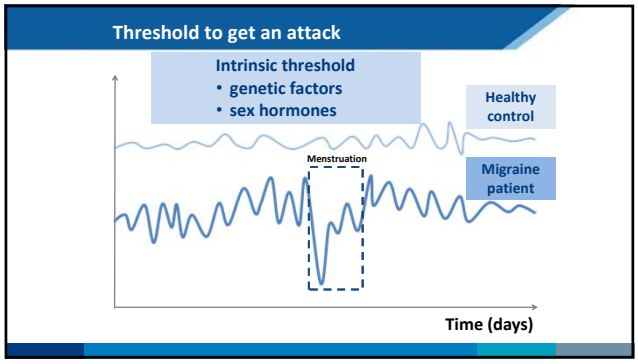
Threshold to get an attack
Intrinsic threshold
• genetic factors
• sex hormones
Healthy control
Menstruation
Migraine patient
Time (days)

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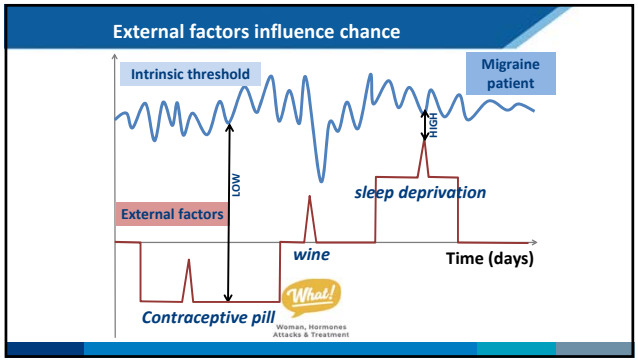
External factors influence chance
Intrinsic threshold
Migraine patient
LOW
High
sleep deprivation
External factors
wine
Time (days)
What!
Contraceptive pill
Woman, Hormones Attacks & Treatment

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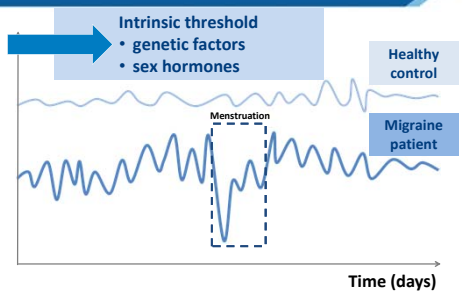
Vulnerability to migraine



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First aid: girl, 5 years

- Fever
- Vomiting and diarrhoea
- Confused
- Yelling
- Thrashing about

- Somnolence
- Reduced strength of limbs
- Bruises
- Falls asleep, largely recovered after a few hours

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First aid: girl, 5 years

Medical record:
- History of similar episodes after head trauma

Father: Is he drunk?
- Talks as if he is drunk
- Walking is imbalanced

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First aid: girl, 5 years

Conclusion:
- Possibly (repetitive) concussion
- Suspicion of child abuse
- Report to child protective service agency

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Father 43 years

- Since the age of 4, difficulty with balance, slurred speech
- Increased loss of coordination and balance

- **Migraine attacks with weakness and decreased consciousness**
- **Recovery takes months**

- Examination: balance disturbances

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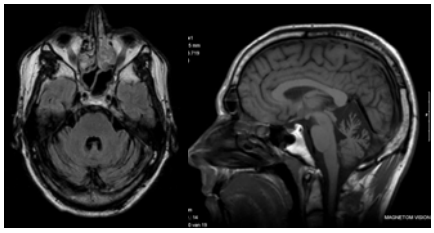
Father 43 years



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Grandmother 69 years

- Since infancy unbalanced gait, slurred speech, double vision
- Has walker and mobility scooter
- Possibly TIA/CVA's

SPINOCEREBELLAR ATAXIA

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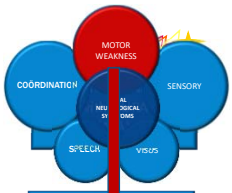
Migraine subtypes

MIGRAINE without AURA (MO)



HEMIPLEGIC MIGRAINE (HM)

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HM is part of the migraine spectrum

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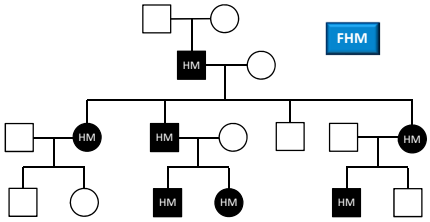
Familial hemiplegic migraine

AUTOSOMAL DOMINANT INHERITANCE



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Sporadic hemiplegic migraine

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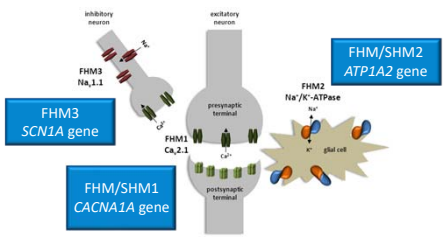
Genetics of HM: 3 known genes so far



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Genetic Testing: clinical practice!

Mutation in HM gene identified → Diagnosis FHM/SHM confirmed

No mutation in HM genes identified → Diagnosis FHM/SHM is **NOT** excluded

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Special Symptoms

DYSARTHRIA | VERTIGO | TINNITUS

DIPLOPIA | HYPOACUSIS | ATAXIA

DECREASED CONSCIOUSNESS | COMA

TUNNELVISION | BILATERAL AURA'S

→ Brainstem aura

EPILEPSY | CONFUSION | FEVER

CASE

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Special Symptoms

DYSARTHRIA | VERTIGO | TINNITUS

DIPLOPIA | HYPOACUSIS | ATAXIA

DECREASED CONSCIOUSNESS | COMA

TUNNELVISION | BILATERAL AURA'S

→ Brainstem aura

- TIA
- Cerebral hemorrhage
- Stroke
- Meningitis
- Brain-tumor
- Epilepsy

EPILEPSY | CONFUSION | FEVER

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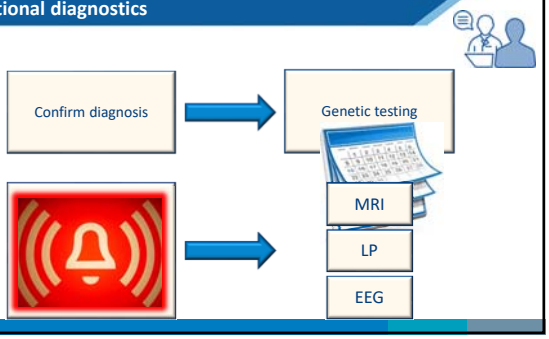
Additional diagnostics



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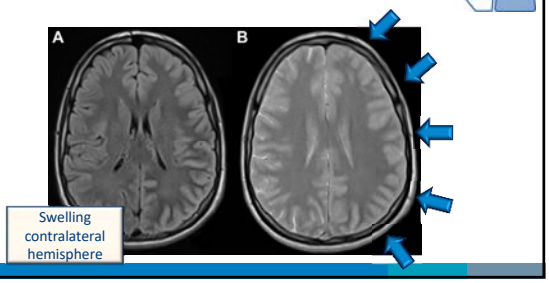
Imaging



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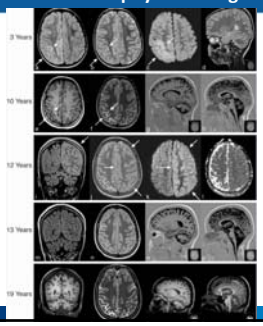
Brain atrophy following HM attacks



Brain atrofie following hemiplegic migraine attacks.
Pelzer, Hoogeveen, Ferrari, Poll-The, Kruit, Terwindt
Cephalalgia. 2018;38:1199-1202

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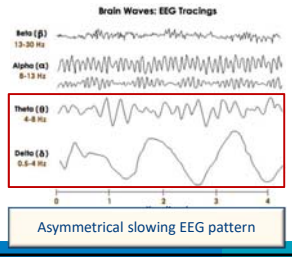
Electroencephalography (EEG)



Asymmetrical slowing EEG pattern

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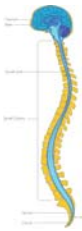
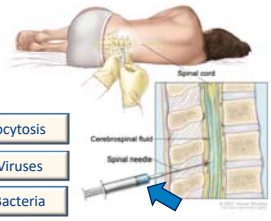
Lumbar punction





Pleiocytosis

No Viruses

No Bacteria

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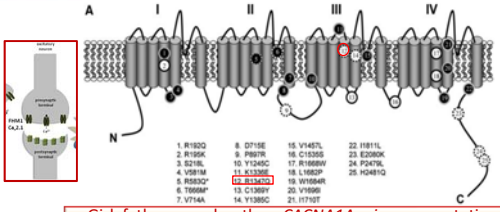
Case: FHM1 family



- Girl, father, grandmother: *CACNA1A missense* mutation
- Father/grandmother: chronic progressive balance/speech problems (ataxia): specific feature in FHM1

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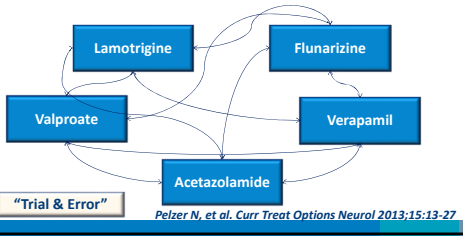
Prophylactic treatment

Other prophylactics than for common migraine



"Trial & Error"

Pelzer N, et al. Curr Treat Options Neurol 2013;15:13-27

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FHM-1 mouse model

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FHM1 KI mouse models to study migraine

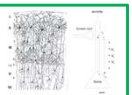
Disease aspects of mutated $Ca_v2.1$ Ca^{2+} channels

Cellular level

$Ca_v2.1$ channel characteristics

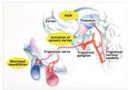
Neural networks

CNS $Ca_v2.1$ channel function



Cortical Spreading Depression

Aura mechanism



Trigeminovascular system

Pain mechanisms

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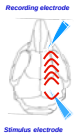
FHM 1 KI mouse models to study CSD



- Increased susceptibility for CSD
- CSD more severe in female mice
- Increased glutamatergic neurotransmission

Van den Maagdenberg et al Ann Neurol 2010
Eikermann-Haerter et al. J Clin Invest 2009; Ann Neurol 2010
Tottene et al. Neuron 2009

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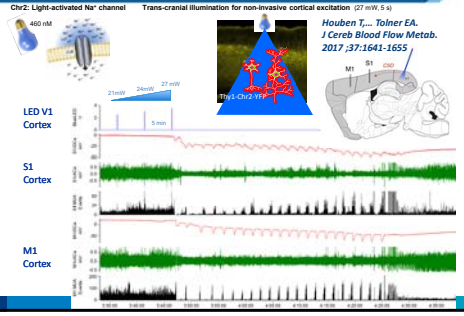
Repeated CSD: optogenetics FHM1 mice



Houben T,... Tolner EA.
J Cereb Blood Flow Metab.
2017 ;37:1641-1655

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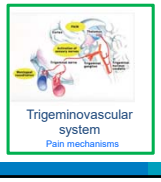
FHM1 KI mouse models to study migraine

- Evidence for (stress-induced) head pain
- CGRP-dependent activation of purinergic receptors & pro-inflammatory state in the trigeminal ganglion



Chanda et al. PAIN 2013
Ceruti et al. 2011 J Neurosci
Nair et al. Mol Pain; Gnanasekaran et al. Mol Pain 2013

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The 4e HM gene?

Pelzer et al. Neurology 2018

~~*CACNA1A* mutation~~

~~*ATP1A2* mutation~~

~~*SCN1A* mutation~~

FHM4?

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Implications for clinical practice

1. **Major FHM4 gene** seems unlikely.
   Motor aura **not always** monogenic cause:
   not always 50% chance for offspring to get HM.

2. **Chance of finding a mutation in *CACNA1A*, *ATP1A2* or *SCN1A* *increased if*:**
   - Comorbidity with ataxia or epilepsy
   - Severe motor aura
   - Brainstem aura
   - Young age at onset
   - More affected relatives

Pelzer et al. Neurology 2018

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Common forms of Migraine

MIGRAINE without AURA (MO)

MIGRAINE with AURA (MA)

Complex genetics: not one gene causing the disease

Genetic SUSCEPTIBILITY for migraine (genetic risk variant)

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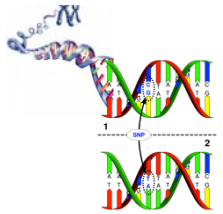
Genome-wide association studies

Single nucleotide polymorphism (SNP)
(500K - >>1M)



Cases (>>1K) Controls (>>1K)

Genetic risk variant
Carrier
Non-carrier

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Meta-analysis in 375,000 individuals
42 distinct genomic loci

Migraine meta-analysis
58,930 cases vs. 314,166 controls
Gormley et al. Nat Genet. 2016;48:856-66

Relates also to monogenic forms of migraine (HM) & vascular disorders (CADASIL and RVCL-S)

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Clinical use for common types of migraine?

- **Risk variants, not one causative gene for migraine**
- **A SNP/locus itself is not the same as the causative gene but a marker!**
- **Multiple risk variants together may increase the risk for migraine**
- **Can not be used as a test for migraine diagnosis**

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Familial occurrence associated with severity?

- Migraine with aura
- Lower age-at-onset
- Higher number of medication days
- Higher migraine frequency (migraine days/month)

Pelzer et al. Cephalalgia 2018
Linking migraine frequency with family history of migraine

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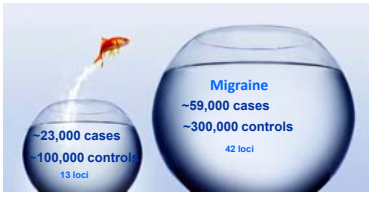
What's next? More loci



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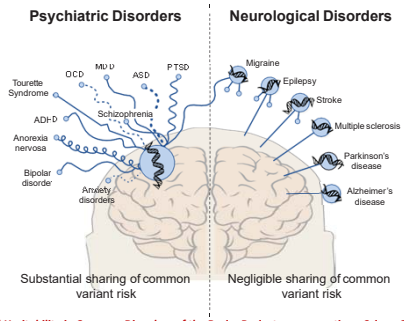

Analysis of Shared Heritability in Common Disorders of the Brain, Brainstorm consortium; Science2018; 22;360(6395)

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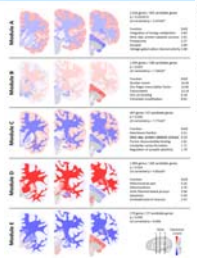
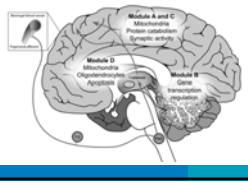
What's next: suggested pathways



Gene co-expression analysis identifies brain regions and cell types involved in migraine pathophysiology: a GWAS-based study using the Allen Human Brain Atlas



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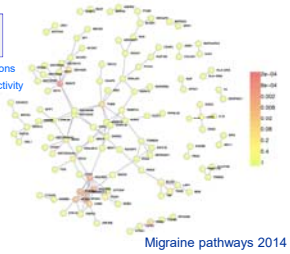
What's next: linking GWAS to proteins

Protein-protein interactions among all genes near 184 suggestive loci ($P < 1x10^{-5}$)

119 proteins with 157 direct interactions

12 proteins show significant connectivity



Migraine pathways 2014

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What's next: identification causal variants

Next generation sequencing

- identify rare *true* causal variants with best evidence for association -

1000 Genome project

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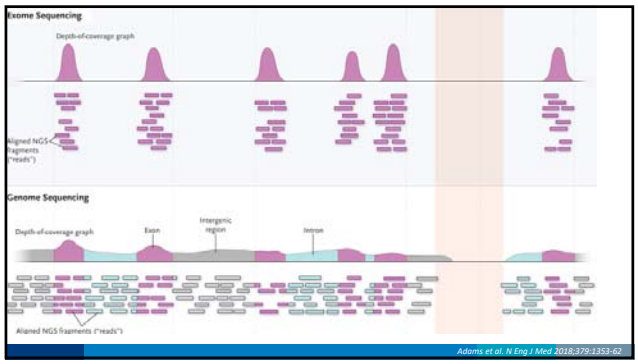

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What's next: iPSC and animal models

Functional analysis of causal variants?

Patient-derived Induced pluripotent stem cells **Genetically modified animal models**

How to best capture *combined* effect of GWAS-based gene variants?

Yang et al. Hum Mol Genet 2014

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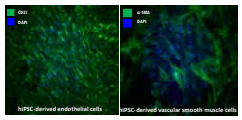
VASCULATURE-ON-A-CHIP FOR MIGRAINE

Valeria Orlova Dhanesh Kasi Arn van den Maagdenberg

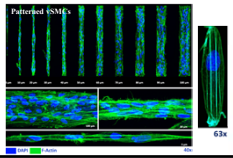
noci

Differentiation of hiPSC-derived vessel components

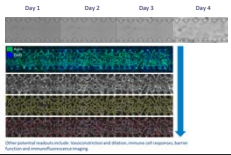


Human iPSCs of RVCL-S, CADASIL & migraine patients

Study shear stress & vascular tone in vascular cells in an anistropic manner (on stretched single vSMCs & ECs)



Study migraine relevant vascular parameters (incl. cell aggregation) in vascular cells seeded on a vessel chip



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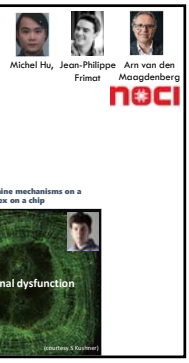
CORTEX-ON-A CHIP FOR MIGRAINE



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ARS

To answer the post-test questions:

Log into www.slido.com

Enter Event Code #Z410

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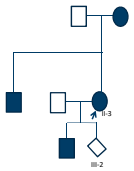
Post-Test Question #1

A 32 year old woman (II-3) suffers from attacks of one-sided pulsating headache worsening with physical activity, nausea and vomiting. Prior to the headache, she suffers from visual disturbances followed by vertigo, dysarthria and one-sided weakness of the arm and leg. Several of her family members suffer from the same complaints (see pedigree below). She is pregnant and has come to you for counseling.

What is the mode of inheritance of her disease?

A. Autosomal recessive
B. Autosomal dominant
C. X-linked dominant
D. X-linked recessive



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Post-Test Question #2

What is the name of the disease?

A. Migraine with aura
B. Hemiplegic migraine
C. Familial hemiplegic migraine
D. Migraine with brainstem aura

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Post-Test Question #3

Another patient (unrelated to the first patient) visits the clinic. She suffers from migraine without aura. Her mother suffered from this type as migraine as well. She visits your clinic because she wants her children to be genetically tested for migraine.

Can a genetic test predict whether her children will get migraine?

A. Yes, it is likely that one gene will be responsible
B. Yes, but multiple genes will be responsible
C. No, migraine without aura is not genetic
D. At this moment there is no prediction model possible based on a genetic test

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Take home messages

- **Multiple risk variants together may increase the risk for migraine**
- **SNPs can not be used as a test for migraine diagnosis**
- **GWAS can help to identify causal pathways for migraine**
- **A major FHM4 gene seems unlikely:**
  Motor aura not always monogenic cause
- **New developments:**
  - **Optogenetics in mice models**
  - **iPSC and Vessel- and Cortex-on-Chip -> Brain-on-Chip**

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Take home messages

- Multiple risk variants together may increase the risk for migraine 
- SNPs can not be used as a test for migraine diagnosis
- GWAS can help to identify causal pathways for migraine
- A major FHM4 gene seems unlikely:
  Motor aura not always monogenic cause 
- New developments:
  - Optogenetics in mice models 
  - iPSC and Vessel- and Cortex-on-Chip -> Brain-on-Chip