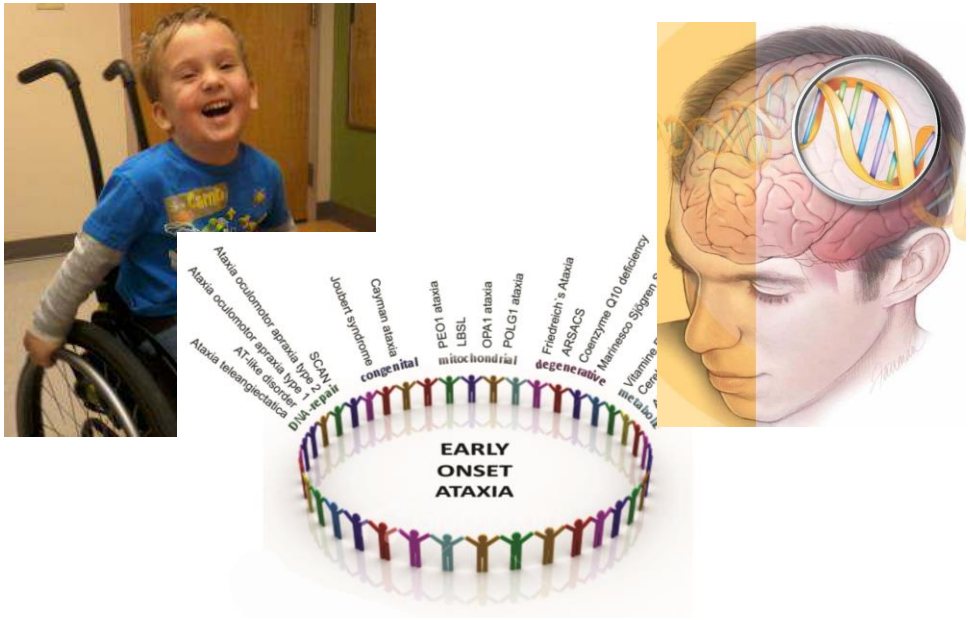
Hertie-Institut
für klinische Hirnforschung

Eberhard-Karls-Universität
UKT
Universitätsklinikum Tübingen

Recessive ataxias – novel genes, genetic mechanisms and diagnostic challenges



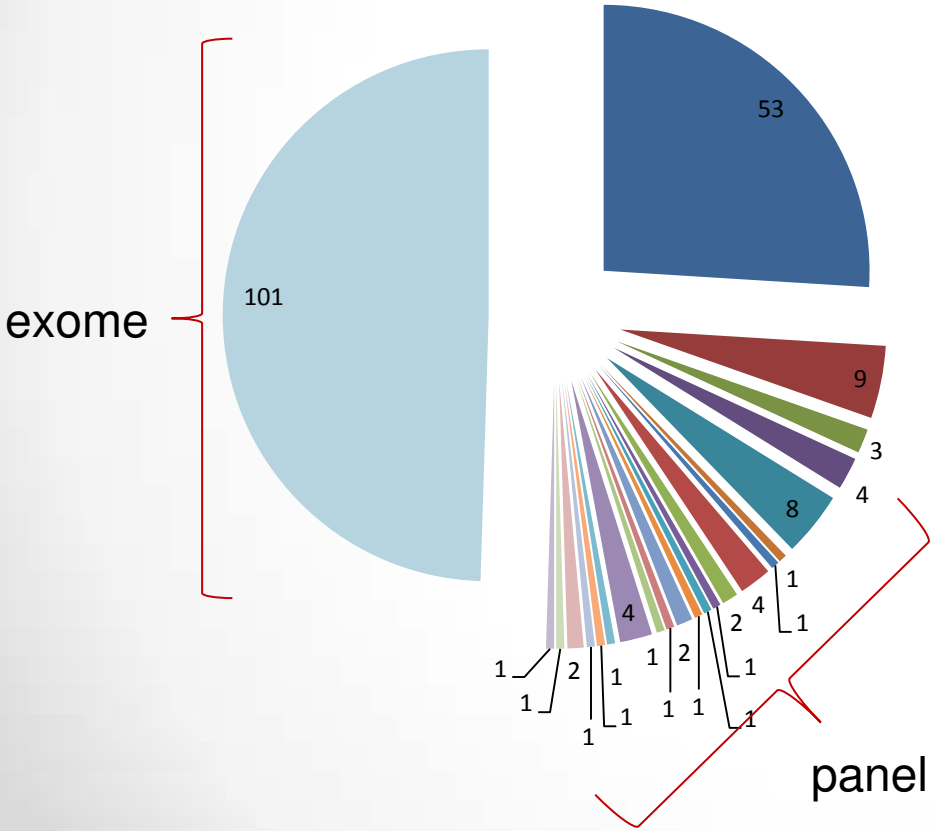
Matthis Synofzik

Dept. of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, Tübingen, Germany

recessive ataxia: the problem of >120 ataxia genes…

- no diagnosis
- no information about disease
- no access to disease specific therapies

EOAs age of onset <30 years
n=204



1. **very many rare genes**

2. **very many still unexplained patients**

the 3 genetic approaches

Sanger sequencing

- single gene(s)

FRDA

↓

Louis-Bar (AT)

↓

AOA2

↓

ARSACS

- **~10.000€**
- **>12 months**

targeted enrichment (panel)

- > 120 ataxia genes

Focus	Gene list
Ataxia *57 genes* *195 kb*	ABHD12, AFG3L2, AHI1, ALG6, ANO10, APTX, ARL13B, ATCAY, ATM, CA8, CACNA1A, CACNB4, CC2D2A, CEP290, DNAJC19, FGF14, FLVCR1, FXN, GPR56, INPP5E, ITPR1, KCNA1, KCNC3, KCNJ10, KIAA0226, MRE11A, MTTP, NPHP1, PAX6, PDYN, PLA2G6, PLEKHG4, PRICKLE1, PRKCG, RARS2, RELN, RPGRIP1L, SACS, SETX, SIL1, SLC1A3, SPTBN2, SYNE1, TDP1, TMEM216, TMEM67, TSEN2, TSEN34, TSEN54, TTBK2, TTPA, VLDLR, VRK1, WFS1, ZNF592,
Metabolic ataxia *43 genes* *85 kb*	ABCB7, ALAS2, ARSA, ATP7B, CLN5, CP, CSH1, CSH2, CSTB, CYP27A1, DDB2, DNAJC5, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EPM2A, ERCC2, ERCC3, ERCC4, ERCC5, GALC, GBA, GCDH, GLB1, GPR56, HEXA, HEXB, HPRT1, NEU1, NHLRC1, NPC1, NPC2, PEX10, PEX7, PHYH, PMM2, POLH, SLC17A5, VPS13A, XPA, XPC
Mitochondrial ataxia *19 genes, 30 kb*	ADCK3, BTD, C10orf2, COX9, CRAT, DARS2, DLAT, GCLC, L2HGDH, MT-CO2, MTPAP, OPA1, OPA3, PDHX, PDSS1, PDSS2, POLG, SLC5A2, SPR

- **~3.500€**
- **3-6 months**

the 3 genetic approaches

Sanger sequencing

- single gene(s)

only for single-shot

- **~10.000€**
- **>12 months**

targeted enrichment (panel)

- > 120 ataxia genes

for any „standard“ ataxia pat

- **~3.500€**
- **3-6 months**

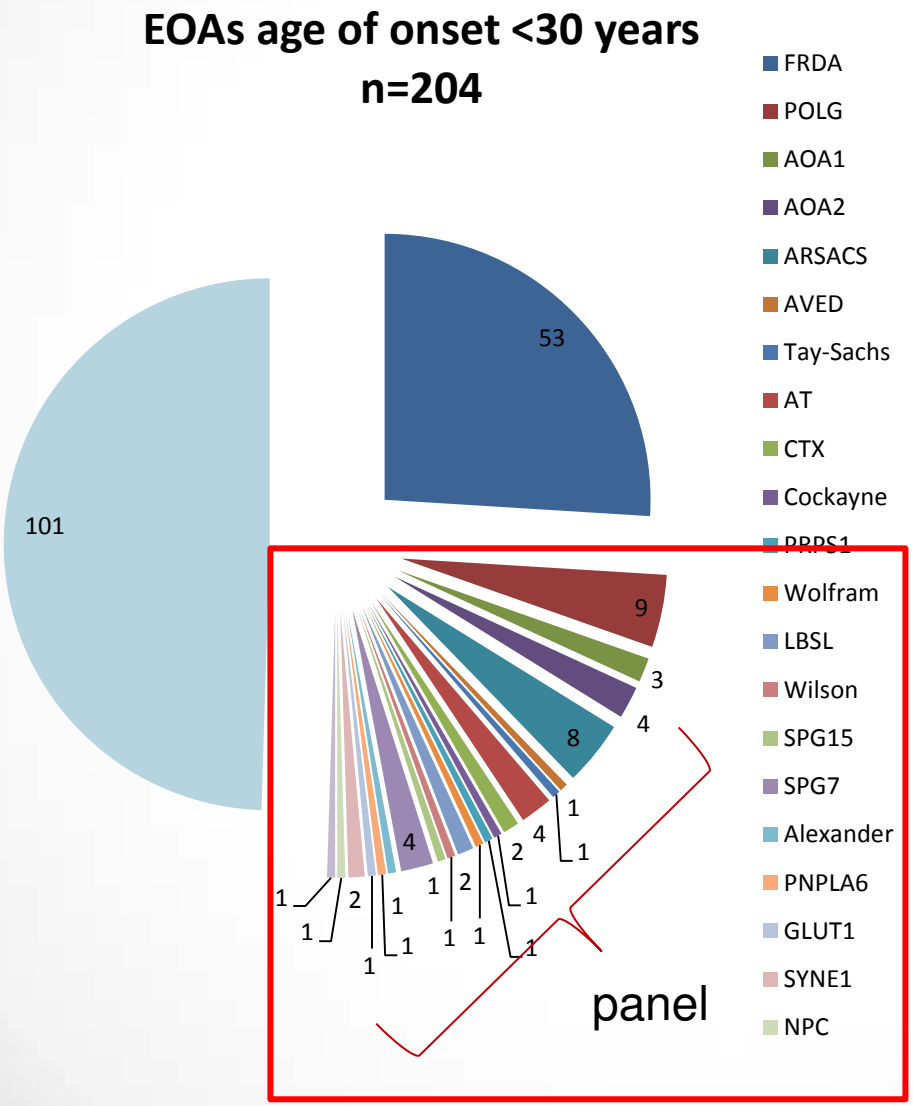
whole exome sequencing

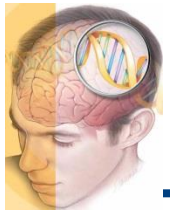
- > 25.000 genes

- **for large families**
- **for complex phenotypes**
- **research**

- **~1.200€**
- **3 months**

An example for PANEL sequencing



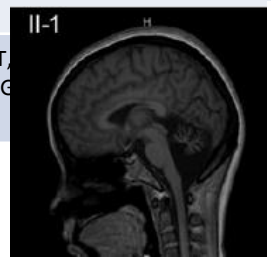


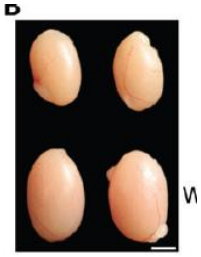
slowly progressive cerebellar ataxia

> 50 genes!?!?

ataxia panel

Focus	Gene list
Ataxia *57 genes* *195 kb*	ABHD12, AFG3L2, AHI1, ALG6, ANO10, APTX, ARL13B, ATCAY, ATM, CA8, CACNA1A, CACNB4, CC2D2A, CEP290, DNAJC19, FGF14, FLVCR1, FXN, GPR56, INPP5E, ITPR1, KCNA1, KCNC3, KCNJ10, KIAA0226, MRE11A, MTTP, NPHP1, PAX6, PDYN, PLA2G6, PLEKHG4, PRICKLE1, PRKCG, RARS2, RELN, RPGRIP1L, SACS, SETX, SIL1, SLC1A3, SPTBN2, SYNE1, TDP1, TMEM216, TMEM67, TSEN2, TSEN34, TSEN54, TTBK2, TTPA, VLDLR, VRK1, WFS1, ZNF592,
Metabolic ataxia *43 genes* *85 kb*	ABCB7, ALAS2, ARSA, ATP7B, CLN5, CP, CSH1, CSH2, CSTB, CYP27A1, DDB2, DNAJC5, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EPM2A, ERCC2, ERCC3, ERCC4, ERCC5, GALC, GBA, GCDH, GLB1, GPR56, HEXA, HEXB, HPRT1, NEU1, NHLRC1, NPC1, NPC2, PEX10, PEX7, PHYH, PMM2, POLH, SLC17A5, VPS13A, XPA, XPC
Mitochondrial ataxia *19 genes, 30 kb*	ADCK3, BTD, C10orf2, COX9, CRAT, DARS2, DLAT, MTPAP, OPA1, OPA3, PDHX, PDSS1, PDSS2, POLG

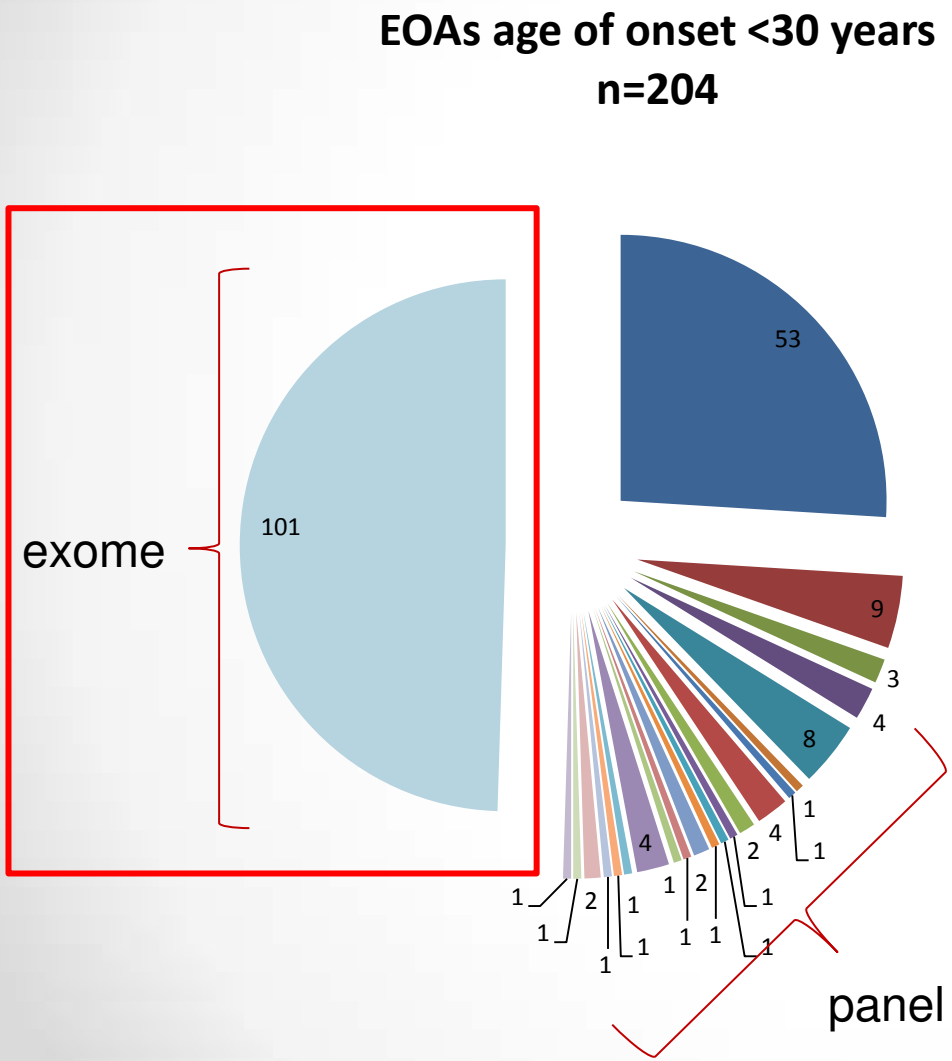


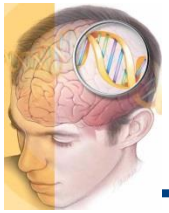


STUB1

Synofzik et al, 2014, OJRD

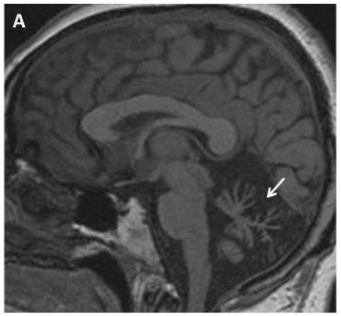
An example for WHOLE EXOME sequencing

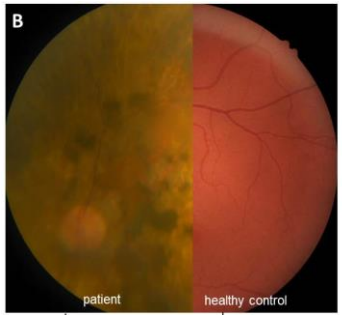




Ataxia, vision problems & reduced sex hormones- all due to ONE ataxia disease?

1. retinal dystrophy (since age 12)
2. no menstruation (since adolescence)
3. cerebellar ataxia (since age 27j)
4. spasticity legs (since age 27j)
5. cognitive deficits (since childhood)





Synofzik et al, 2014, *BRAIN*

whole exome sequencing
&
filtering

x2

index family

whole exome Sequenzierung

>25.000 genes

only non-synonymous variants
and splice site mutations

>20.000 variants

not in control databases
(dbSNP, EVS, in-house)

>200 variants

predicted to be damaging
by software predictions

➔ 5 more families
from around the world

PNPLA6

5-50 candidate
variants

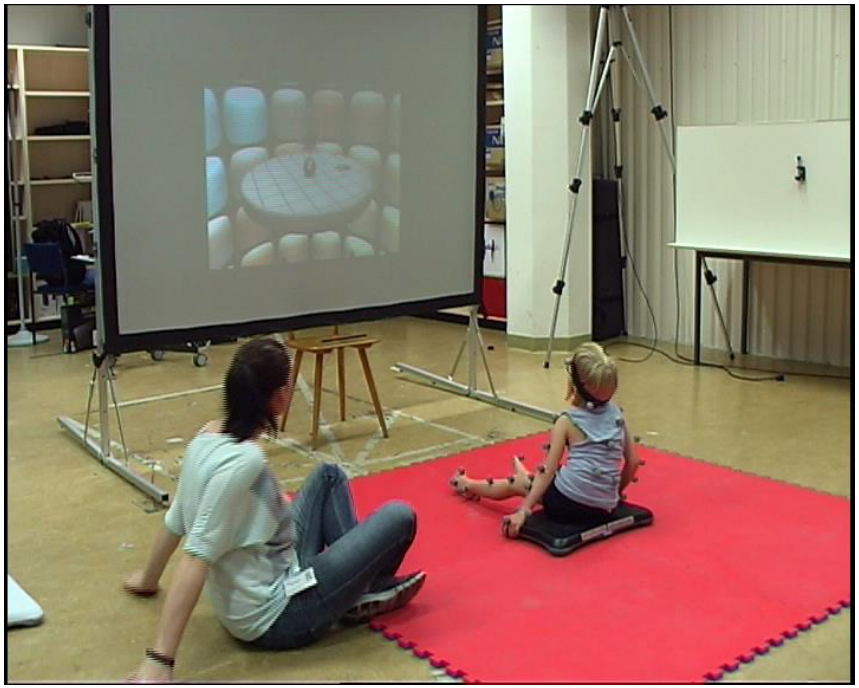
other families
with variants in this gene?

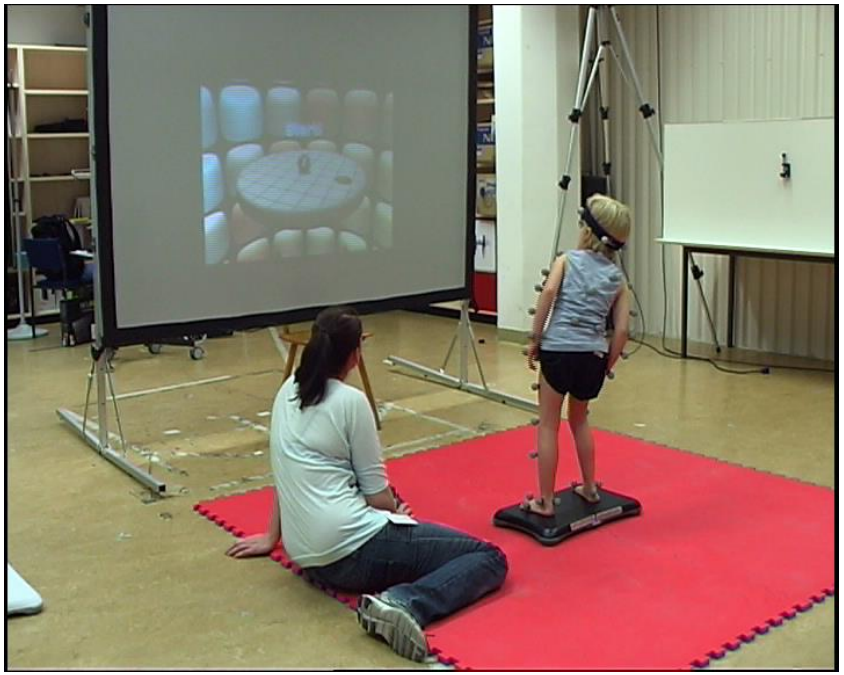
Study 1: exergames as a novel treatment for ataxias

Ataxia UK

Ilg et al., 2012

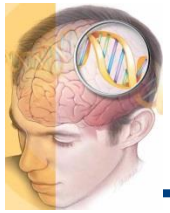
study 2: exergames in advanced ataxia (wheelchair-bound)





➔ ***also upper limbs????***

Ilg et al., in preparation



conclusions

1. **Friedreich is by far the most common recessive ataxia (25%)**
   – but there are >100 other recessive ataxias!

2. We can now screen patients for all of these ataxias *at once* and for (relatively) *low cost*! ➔ panel sequencing

➔ provide another ~25% patients with a diagnosis!

➔ should be new standard of care in the future!

3. We have now tools at hand to efficiently identify novel ataxias! ➔ exome

➔ provides several families with a diagnosis and clear cause of the disease

➔ allows to **stop the diagnostic odysee** for many patients

➔ makes them **accessible for disease-specific treatment studies**

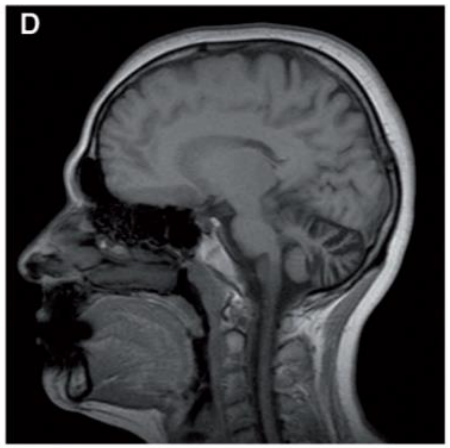
➔ We started a „PREPARE“ initiative to collect patients with rare recessive ataxias and to get ready for trials ☺

Thank you.

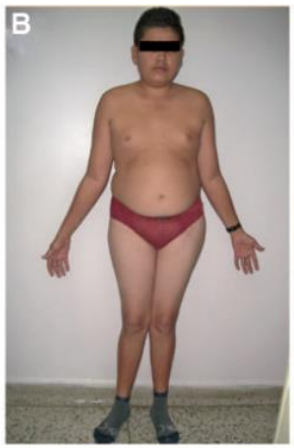
PNPLA6 defines many classic neurologic syndromes

Boucher Neuhäuser Syndrom

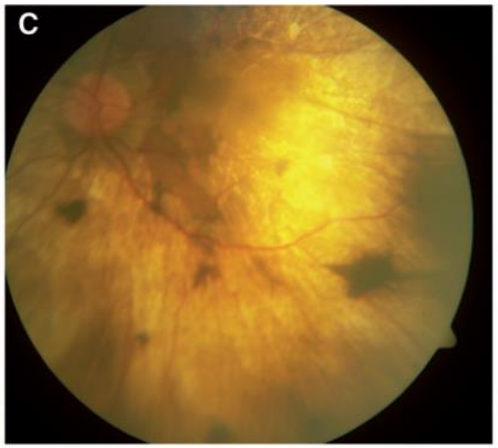
Gordon Holmes Syndrom



cerebellar atrophy



hypogonadism

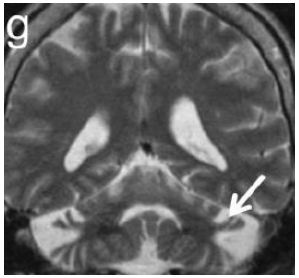


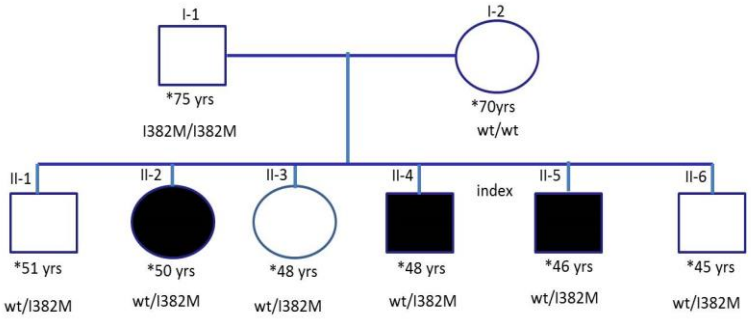
chorioretinal dystrophy

➔ PNPLA6

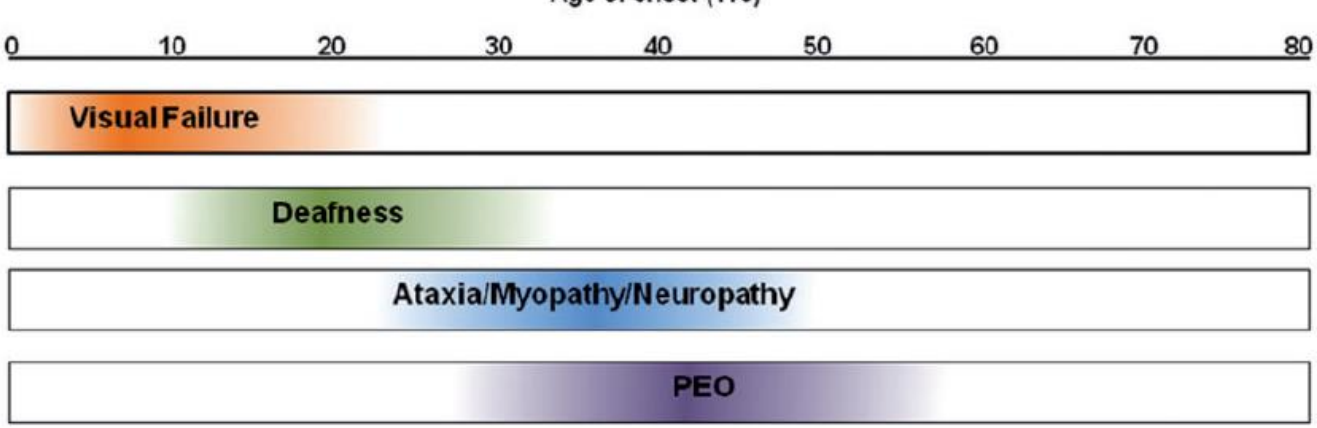
Synofzik et al, 2014, *BRAIN*

ataxia & optic atrophy





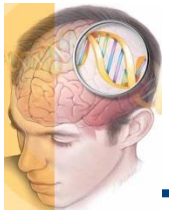
optic atrophy plus-syndrome



OPA1

Yu-Wai-Man et al, 2010, *Brain*

Bonifert, …. Synofzik, 2014, *Brain*

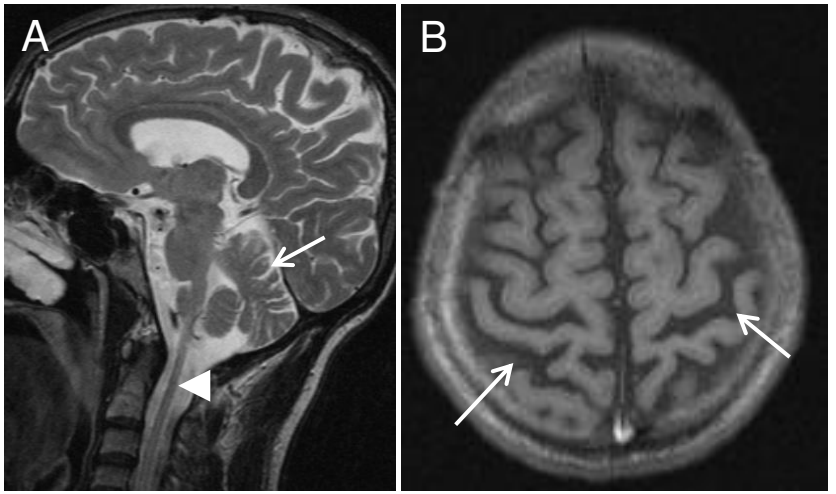


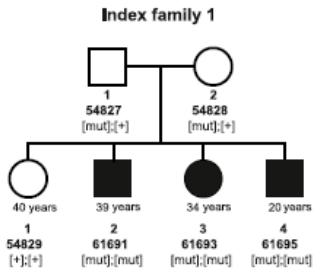
combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus (ACPHD)

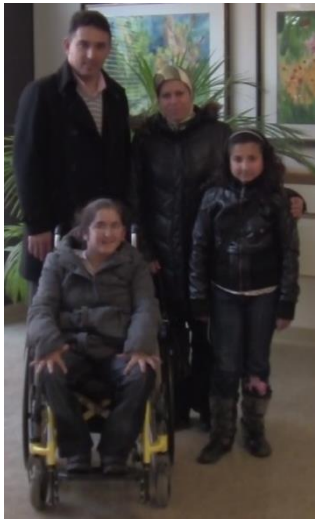
1. cerebellar+ afferent ataxia
2. hypoacusis
3. insulin-dependent diabetes
4. peripheral neuropathy

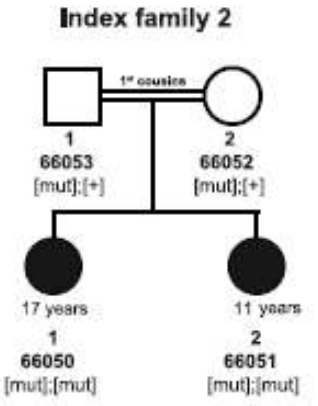
5. spastic paraparesis
6. cognitive deficits

➔ *mitochondriopathy ?*









➔ biallelic truncating mutations in ER protein ***DNJAC3***

Synofzik et al, 2014, *AJHG*