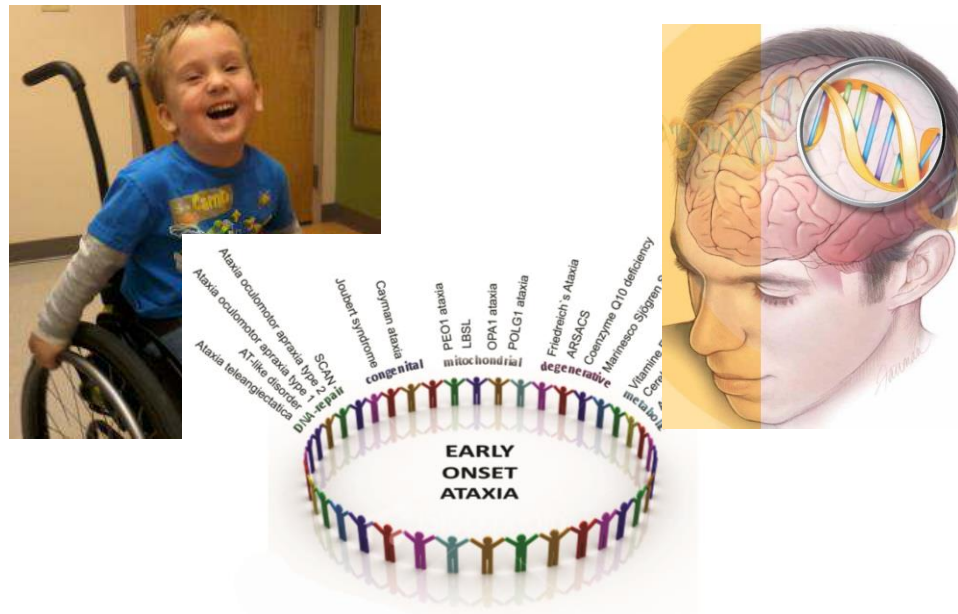


Recessive ataxias – novel genes, genetic mechanisms and diagnostic challenges



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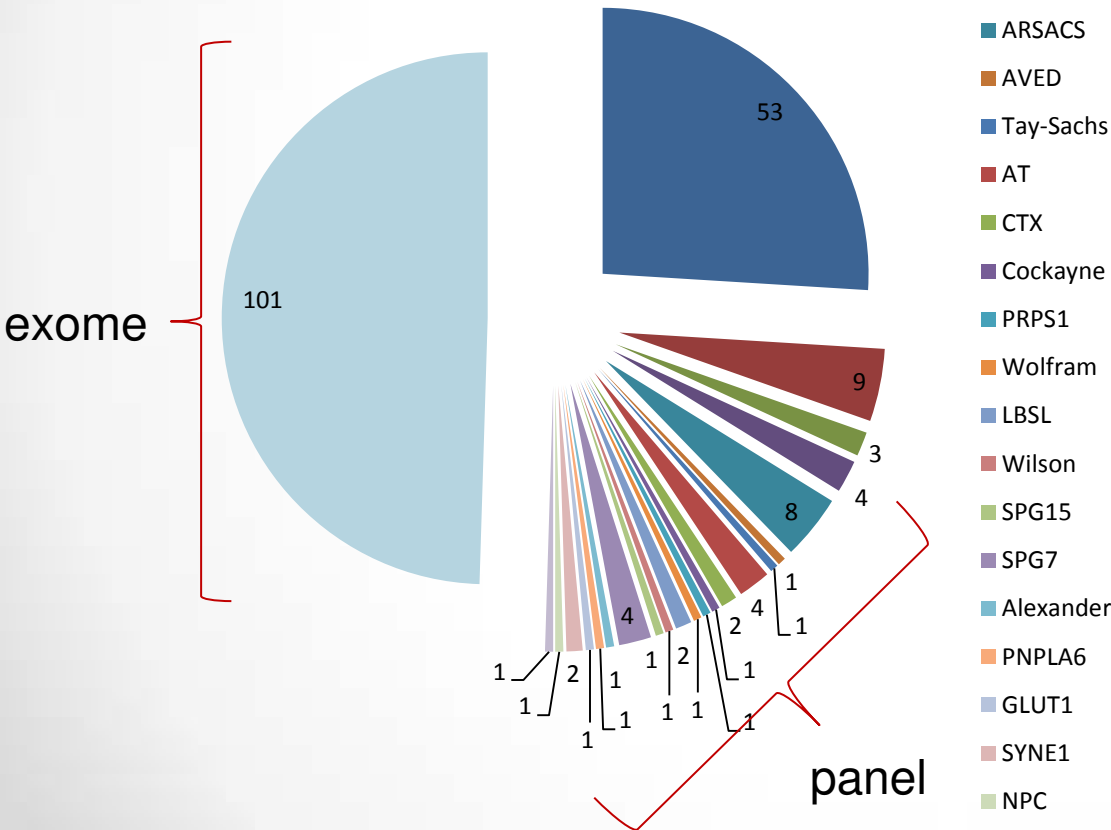
recessive ataxia: the problem of >120 ataxia genes...

EOAs age of onset <30 years

n=204

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

- FRDA
- POLG
- AOA1
- AOA2
- ARSACS
- AVED
- Tay-Sachs
- AT
- CTX
- Cockayne
- PRPS1
- Wolfram
- LBSL
- Wilson
- SPG15
- SPG7
- Alexander
- PNPLA6
- GLUT1
- SYNE1
- NPC



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 <i>57 genes</i> <i>195 kb</i>	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, MTPP, 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 <i>43 genes</i> <i>85 kb</i>	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 <i>19 genes</i> , <i>30 kb</i>	ADCK3, BTBD, 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

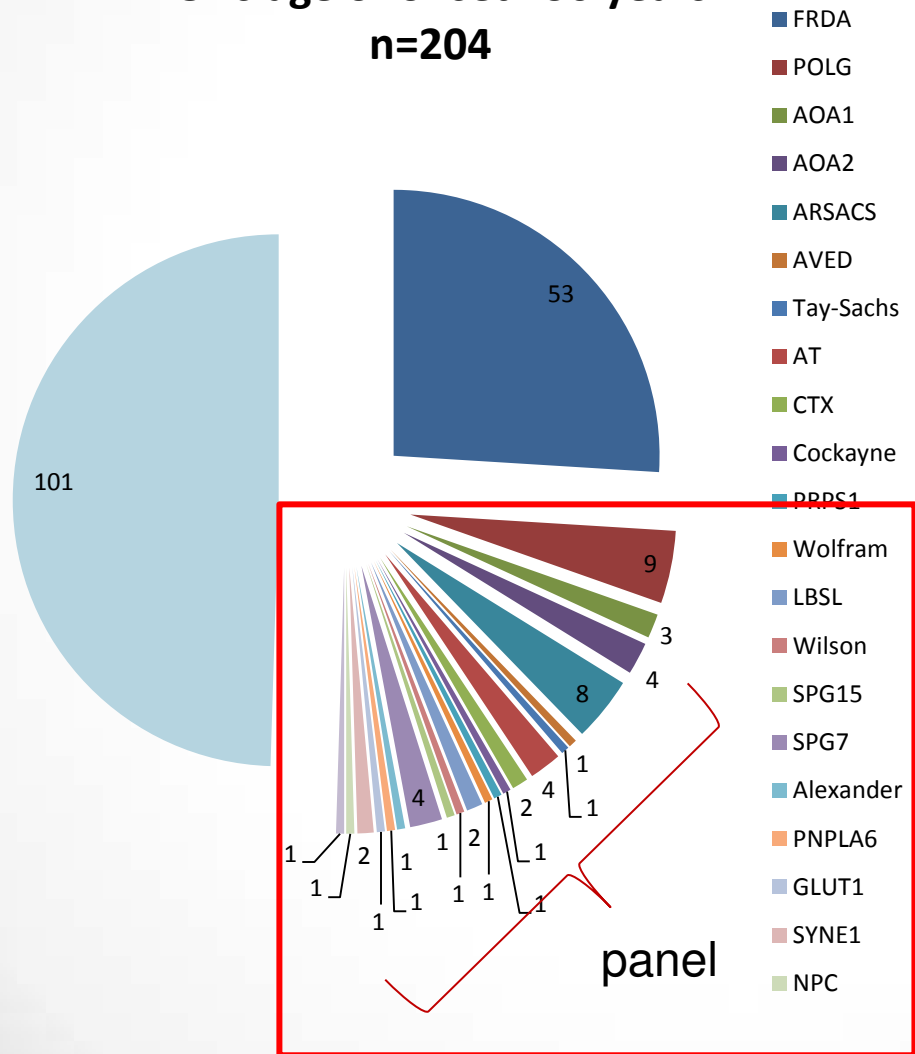
- > 25.000 genes

• for large families
• for complex phenotypes
• research

- ~1.200€
- 3 months

An example for PANEL sequencing

EOAs age of onset <30 years
n=204





slowly progressive cerebellar ataxia



ataxia
panel



> 50 genes!?!?



Focus	Gene list
Ataxia <i>57 genes</i> <i>195 kb</i>	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 <i>43 genes</i> <i>85 kb</i>	ABC7, 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 <i>19 genes, 30 kb</i>	ADCK3, BTD, C10orf2, COX9, CRAT, DARS2, DLAT, MTPAP, OPA1, OPA3, PDHX, PDSS1, PDSS2, POLG

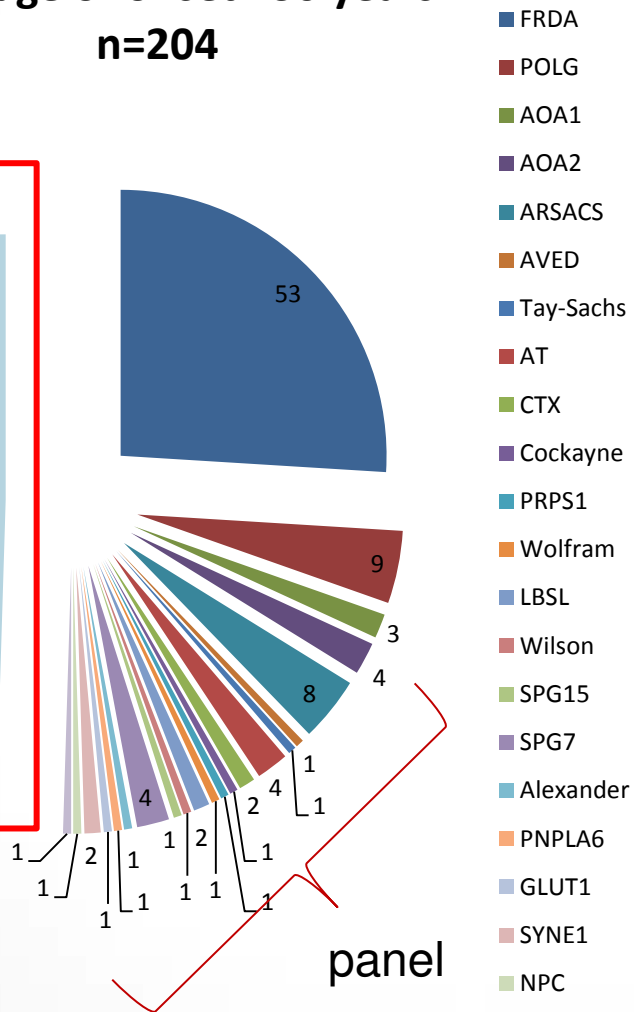
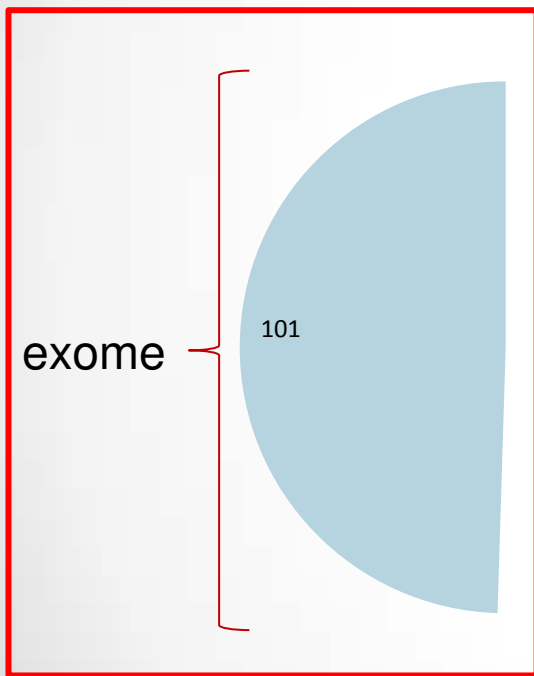


STUB1



An example for WHOLE EXOME sequencing

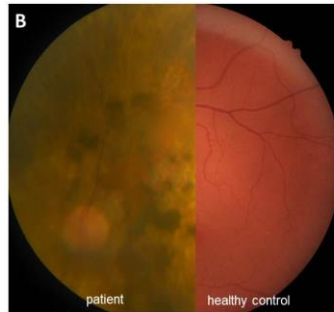
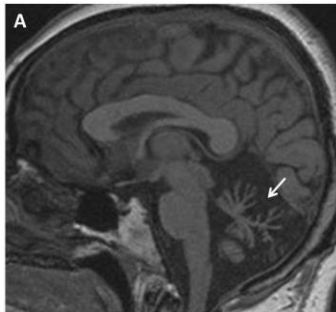
EOAs age of onset <30 years
n=204





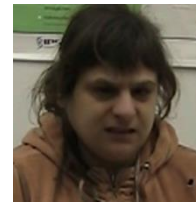
Ataxia, vision problems & reduced sex hormones- all due to ONE ataxia disease?

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)



whole exome sequencing
&
filtering

index family



x2

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

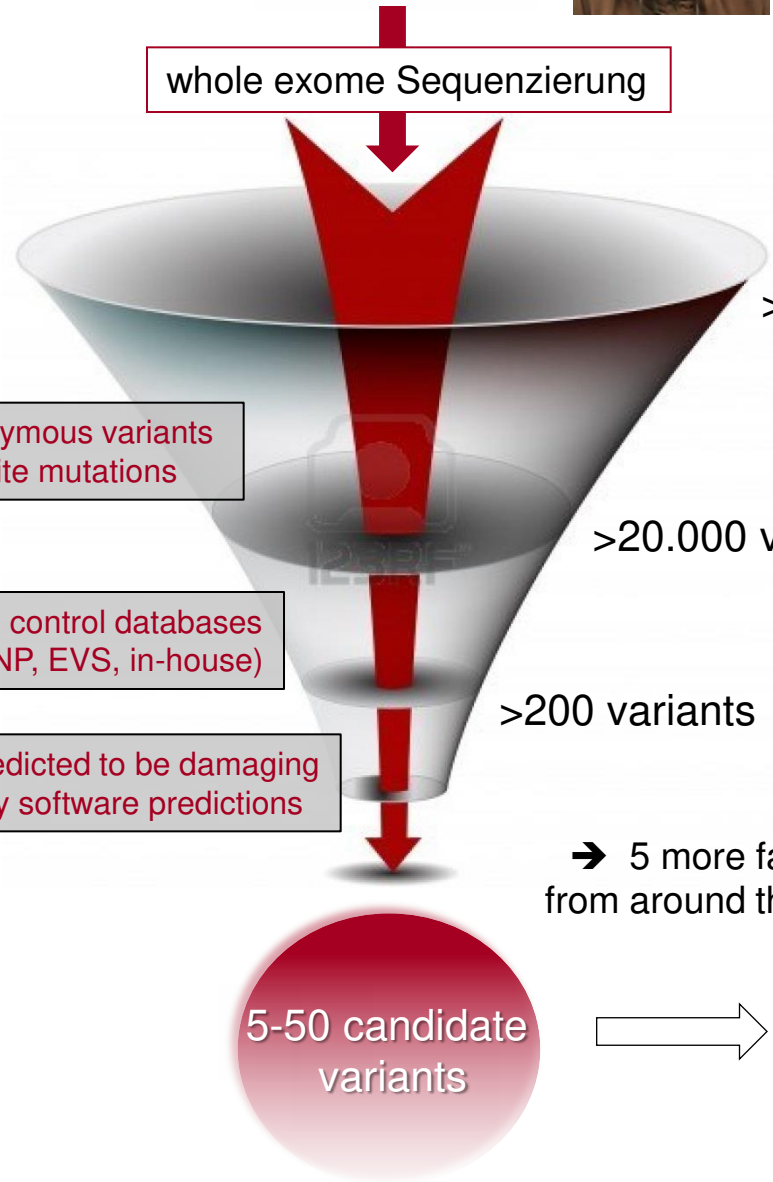
predicted to be damaging
by software predictions

→ 5 more families
from around the world

PNPLA6

5-50 candidate
variants

other families
with variants in this gene?



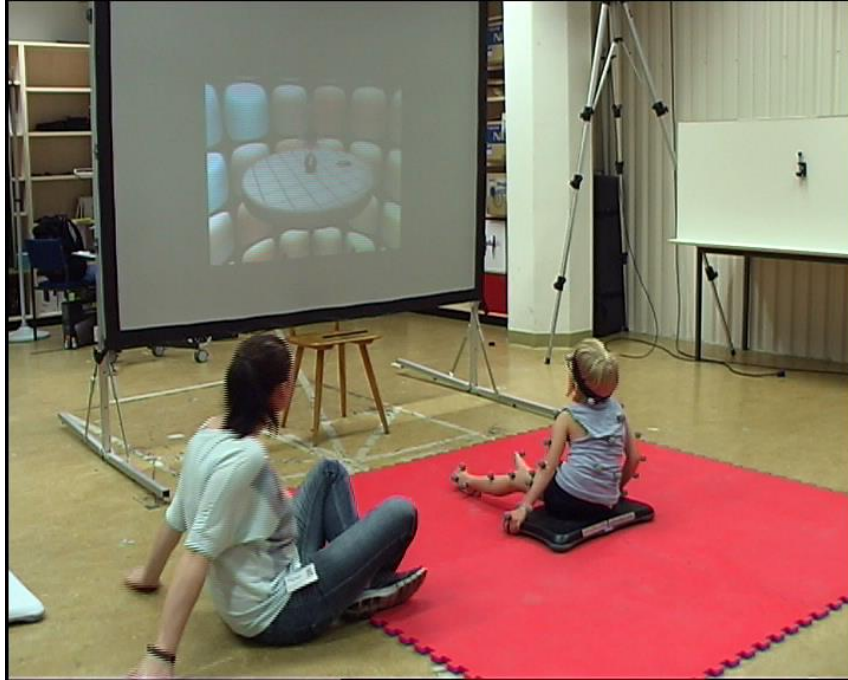


Study 1: exergames as a novel treatment for ataxias



ATAXIA
Ataxia UK

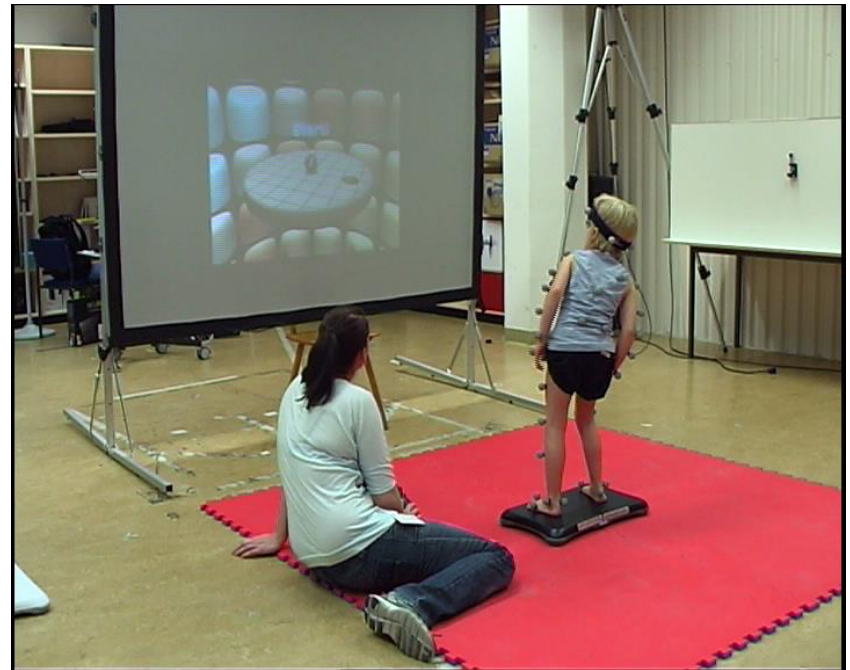
study 2: exergames in advanced ataxia (wheelchair-bound)



ATAXIA
Ataxia UK

→ *also upper limbs????*

ATAXIA
Ataxia UK





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 odyssey** 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 😊

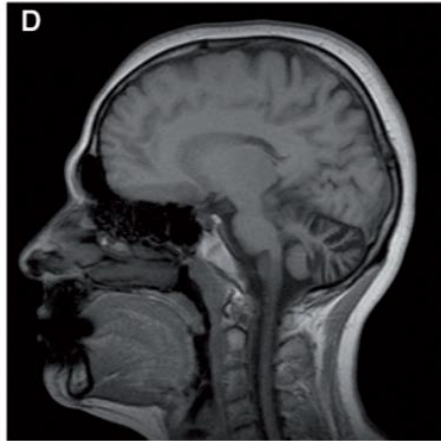
Thank you.



PNPLA6 defines many classic neurologic syndromes

Boucher Neuhäuser Syndrom

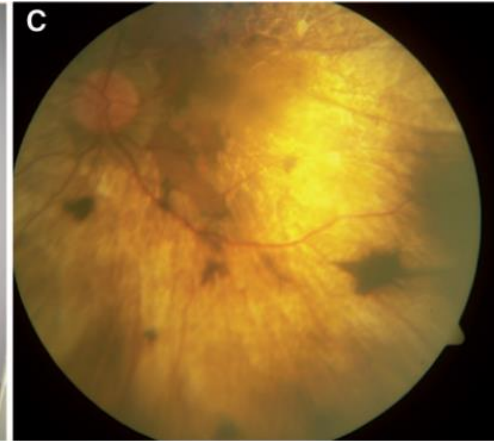
Gordon Holmes Syndrom



cerebellar atrophy



hypogonadism

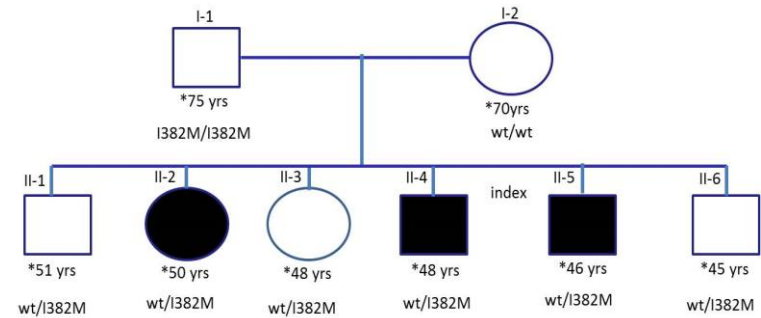
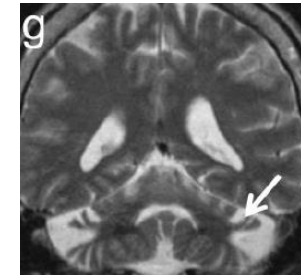


chorioretinal dystrophy

→ PNPLA6

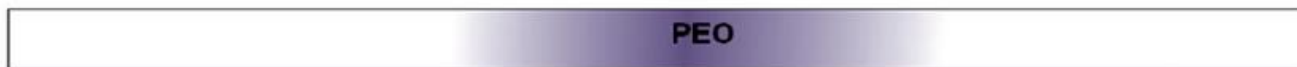


ataxia & optic atrophy



Age of onset (Yrs)

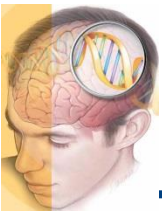
0 10 20 30 40 50 60 70 80



optic
atrophy plus-
syndrome

OPA1

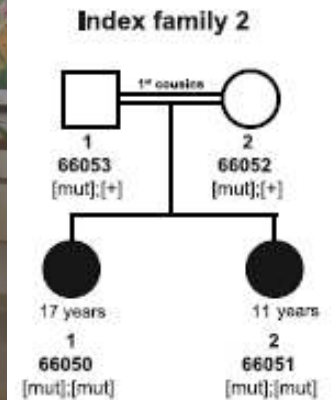
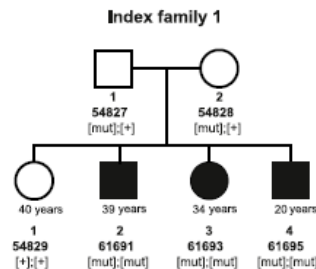
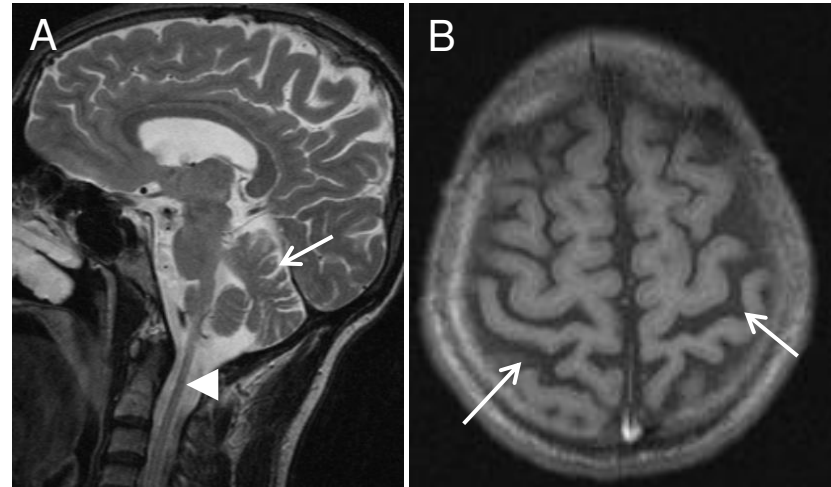
Yu-Wai-Man et al, 2010,
Brain



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