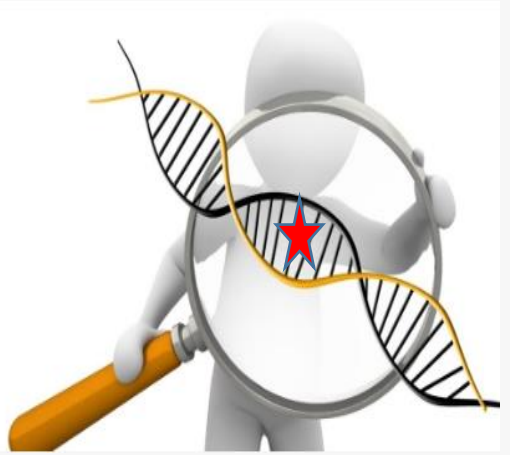
Genetic screening and counselling in ID/ASD/psychiatric diseases : benefits and limits

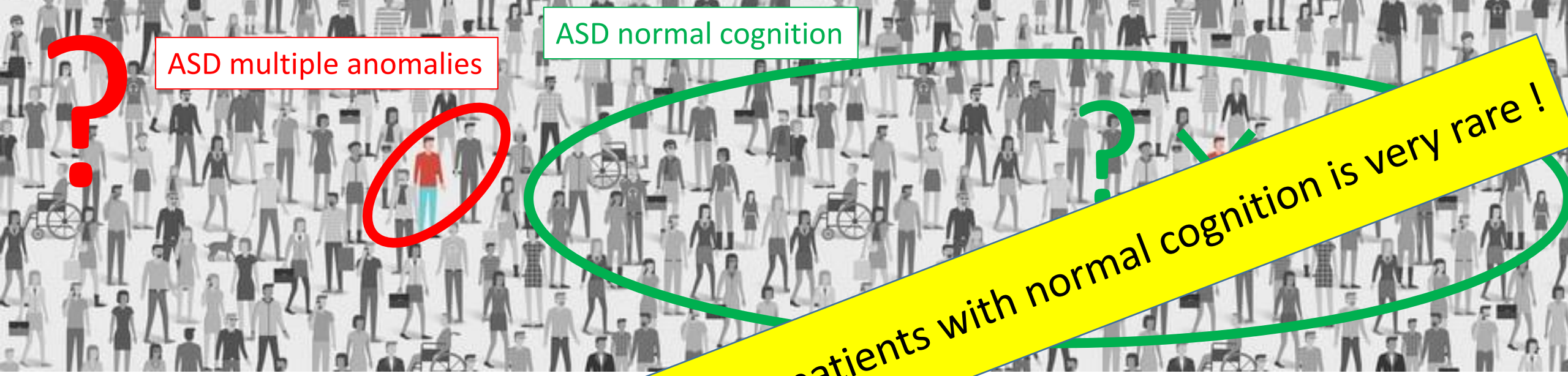
Hilde Peeters

Clinical diagnostics

Genetic test



MONOGENIC/CHROMOSOMAL disorder



Monogenic/single genetic causes of ASD in patients with normal cognition is very rare !

BUT ... **MONOGENIC/** disorders are rare

Most people with d abilities do NOT have a genetically detectable cause

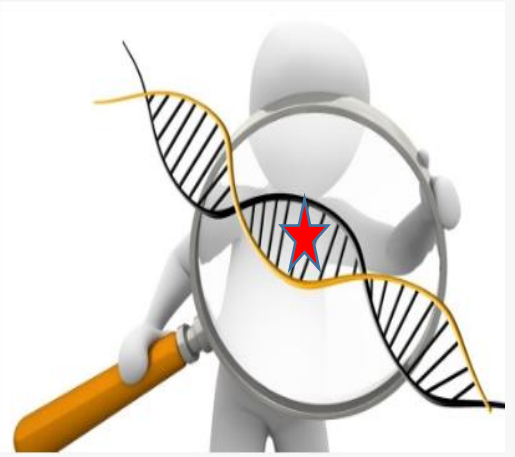
- disability
- xia
- ADHD
- ASD
- dyspraxia
- ...

Strong genetic component but often not monogenic

→ No DNA test ?

Clinical diagnostics

Genetic test



MONOGENIC/CHROMOSOMAL disorder

genetic cause

- mutation in 1 gene or a chromosomal aberration

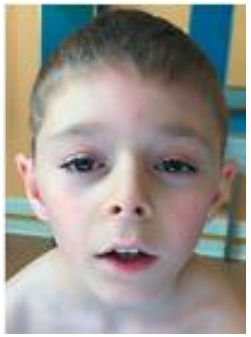
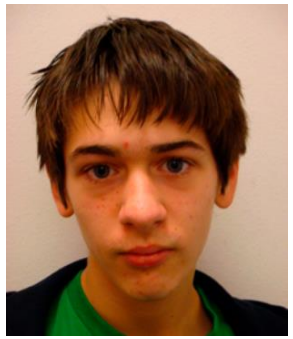
MONOGENIC CAUSE SINGLE GENETIC CAUSE

- the explanation why the condition occurs => genetic error
- a clinically observable impact on development
  => large effect, major gene effect

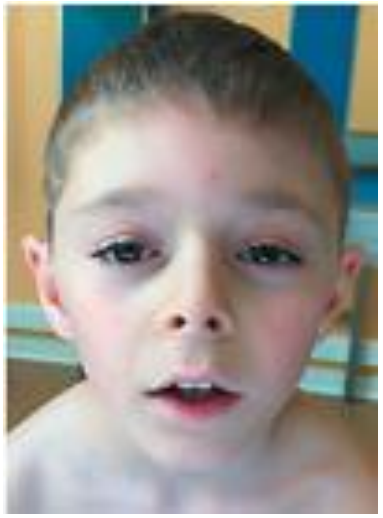
genetic risk variant

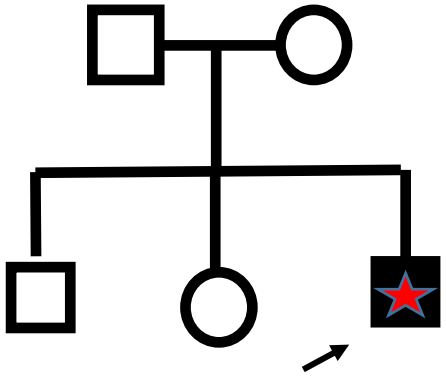
- variant in 1 gene or a chromosomal variant, copy number variant risk variant
- increases susceptibility to disease
- may be present without a clinically observable effect on development

IQ 67 and ASD in these 3 children

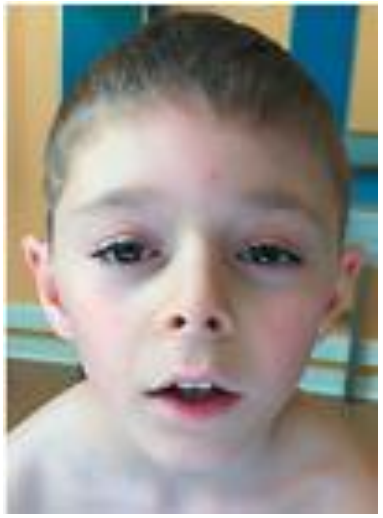

Cause of mild intellectual disability and ASD in the 3 children ?

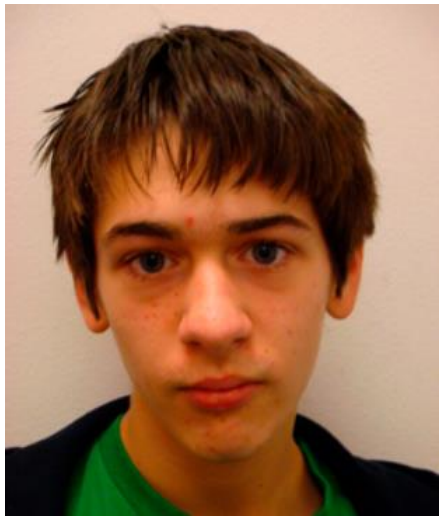


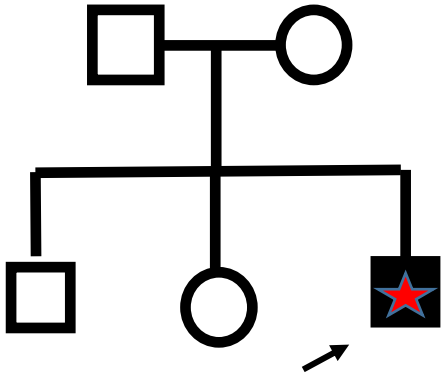


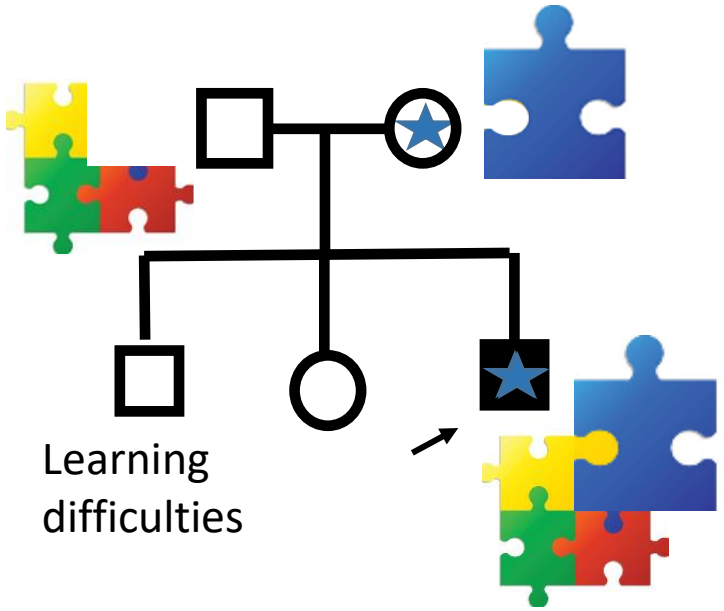
1 mutation in gene => KBG syndrome *ANKRD11* mutation

Cause of mild intellectual disability and ASD in the 3 children ?









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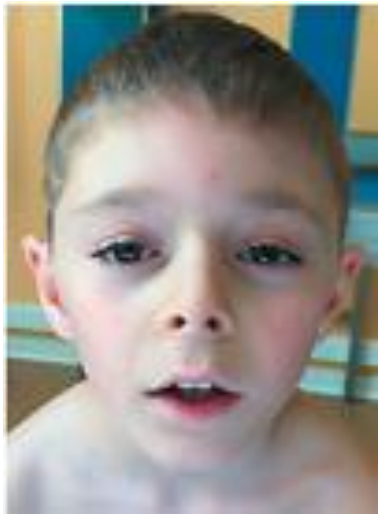
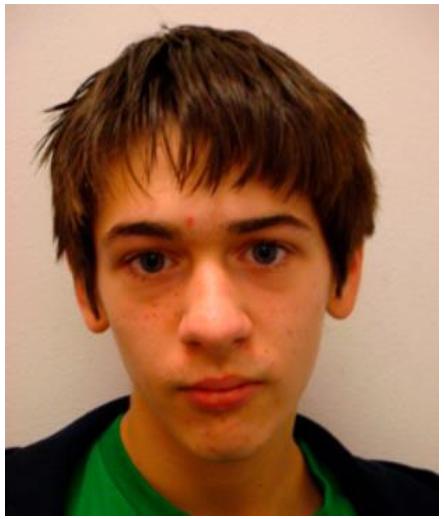
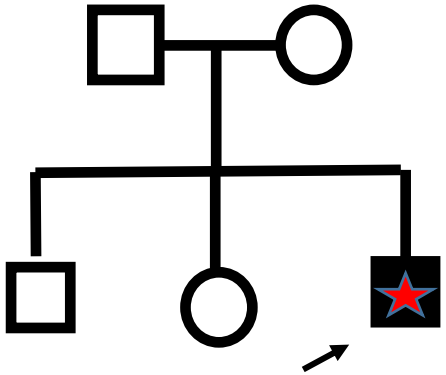
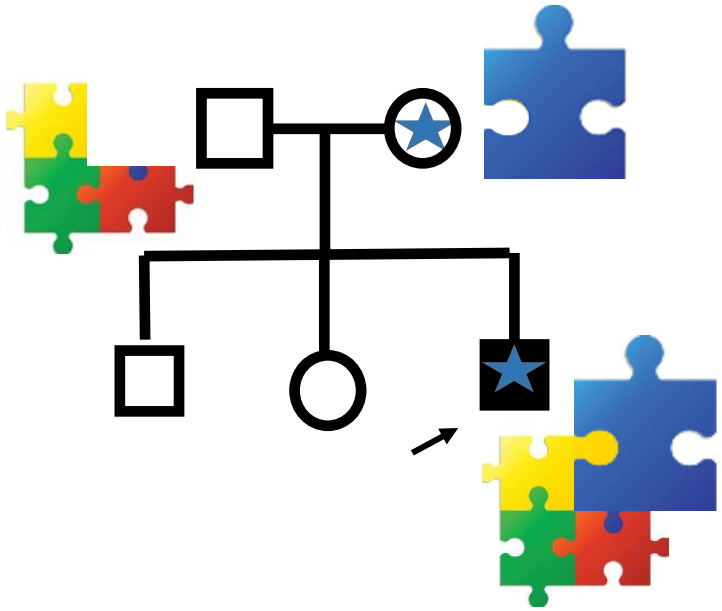
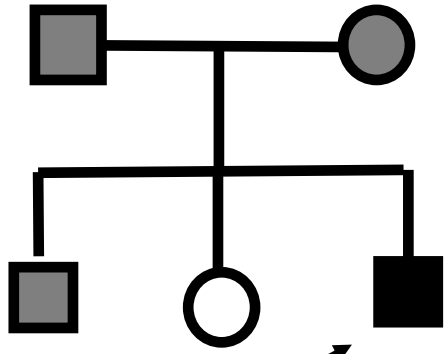








special education



special education

Special education

1 mutation in gene => KBG syndrome

1 CNV risk variant 16p11.2 deletion

normal test results

MONOGENEOUS/SINGLE

1 variant
major effect

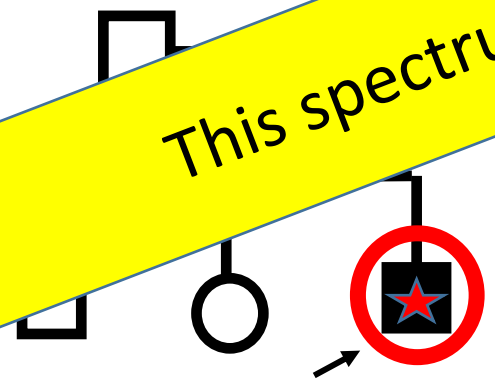
OLIGOGEEN

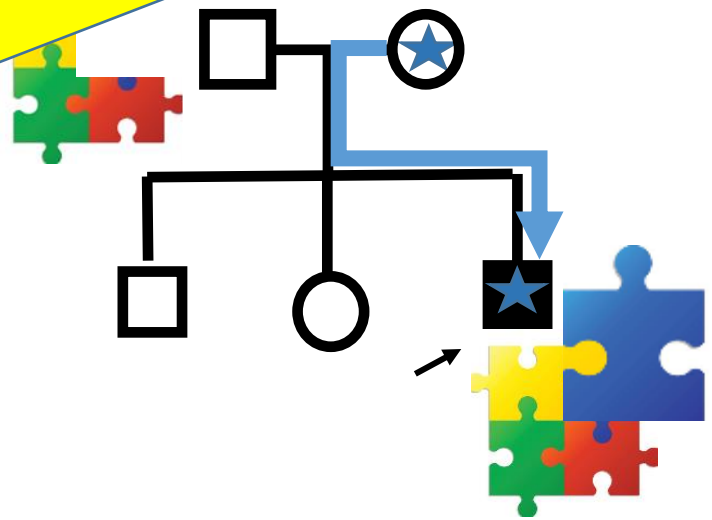
Some variants
moderate effect

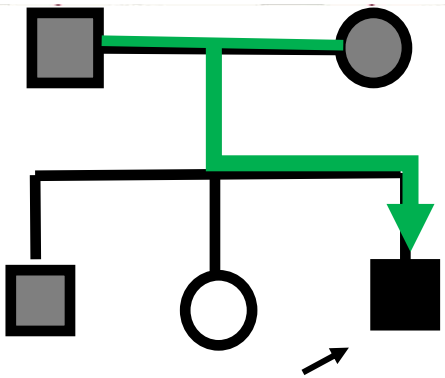
POLYGENIC/MU

ants
mall effect

This spectrum is the framewok of the clinical geneticist !







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normal test results

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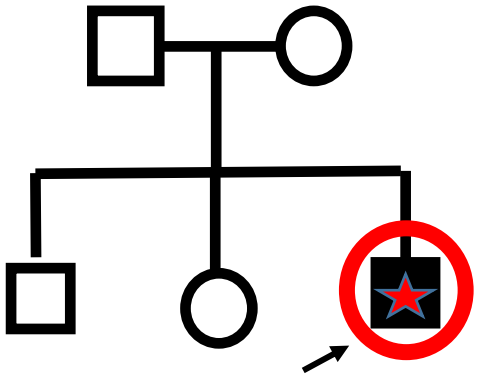
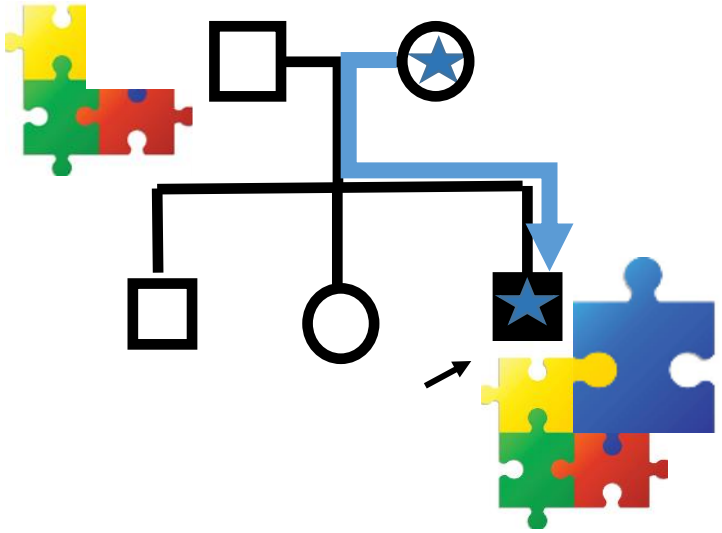
1 variant
major effect

High clinical utility, actionable!



OLIGOGEEN

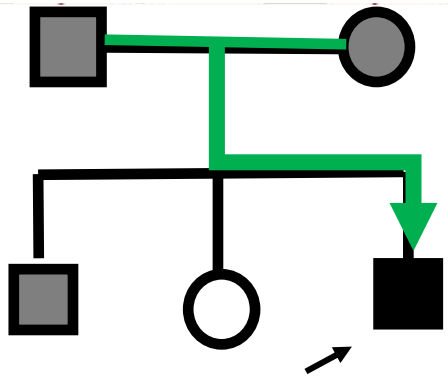
Some variants
moderate effect



1 CNV risk variant 16p11.2 deletion

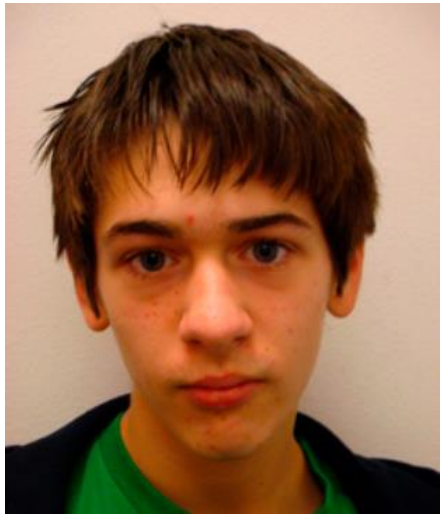
POLYGENIC/MULTIFACTORIAL

Many variants
small effect

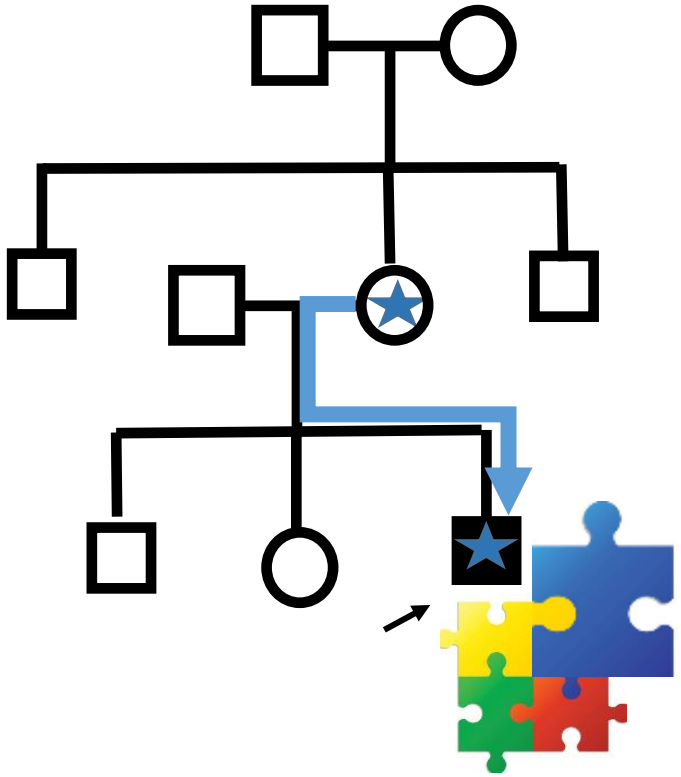


normal test results

OLIGOGENIC MODEL



mild intellectual disability and ASD



1 CNV risk variant 16p11.2 deletion

OPEN ACCESS

ORIGINAL ARTICLE

Estimating the effect size of the 15Q11.2 BP1–BP2 deletion and its contribution to neurodevelopmental symptoms: recommendations for practice

Aia Elise Jønch,[1,2] Elise Douard,[3,4] Clara Moreau,[3,4] Anke Van Dijck,[5,6] Marzia Passeggeri,[7] Frank Kooy,[5,6] Jacques Puechberty,[8] Carolyn Campbell,[9] Damien Sanlaville,[10,11] Henrietta Lefroy,[12] Sonia Richetin,[7] Aurelie Pain,[7,13] David Geneviève,[14,15] Usha Kini,[12,16] Cédric Le Caignec,[17] James Lespinasse,[18] Anne-Bine Skytte,[19,20] Bertrand Isidor,[17] Christiane Zweier,[21] Jean-Hubert Ca… Marie-Ange Delrue,[3,4] Rikke Steensbjerre Møller,[23] Anders Bojesen,[24] Charlotte Brasch-Andersen,[1,2] Emmanuelle Lemyre,[3,4] Lilia… Sébastien Jacquemont,[3,4] on behalf of 15q11.2 W…

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2018-105879).

For numbered affiliations see end of article.

Correspondenc… Dr Séba…

ABSTRACT

Background The 15q11.2 deletion is f… identified in the neurodevelop… studies have associate… neurodevelop… have … …(NDDs), …tion is observed …hrenia (OR 1.8),[2] devel- …OR 2.36),[3] epilepsy (OR 4.9)[4] …g disabilities (OR 4.4, dyslexia and …alculia combined).[5] The deletion has also been associated with congenital heart disease (CHD).[6–8] More than 200 15q11.2 deletion carriers have been reported in clinical series with mild, moderate …tion …elopmental

Results The deletion decreases IQ by 4.3 point… The estimated ORs and respective frequenci… on carriers for intellectual disabiliti… d epilepsy are 1.7 (3.4% … respectively. Th… malfor… …y referred …e of symptoms in …ent from those observed in …15q11.2 duplication suggesting that most …reported symptoms are due to ascertainment bias.

Conclusions We recommend that the deletion should be classified as 'pathogenic of mild effect size'. Since it explains only a small proportion of the phenotypic variance in carriers, it is not worth discussing in the developmental clinic or in a prenatal setting.

After >10 years, we decided NOT to report deletion 15q11.2 BP1-BP2 !

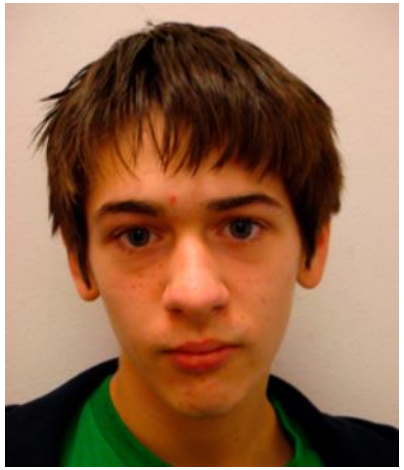
=> Moving forward!!!

… a microdeletion 15q11.2 between breakpoints 1 and 2 of the … critical region, possibly associated with behavioural disturbances

…anne Doornbos[a,c], Birgit Sikkema-Raddatz[b], Claudia A.L. Ruijvenkamp[d], Trijnie Dijkhuizen[b], Emilia K. Bijlsma[d], Antoinet C.J. Gijsbers[d], Yvonne Hilhorst-Hofstee[d], Roel Hordijk[b], Krijn T. Verbruggen[a], W.S. (Mieke) Kerstjens-Frederikse[b], Ton van Essen[b], Klaas Kok[b], Anneke T. van Silfhout[b], Martijn Breuning[d], Conny M.A. van Ravenswaaij-Arts[b,*]

[a] Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, The Netherlands
[b] Department of Genetics, University Medical Centre Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands
[c] Department of Paediatrics, Albert Schweitzer Hospital, Dordrecht, The Netherlands

OLIGOGENIC MODEL



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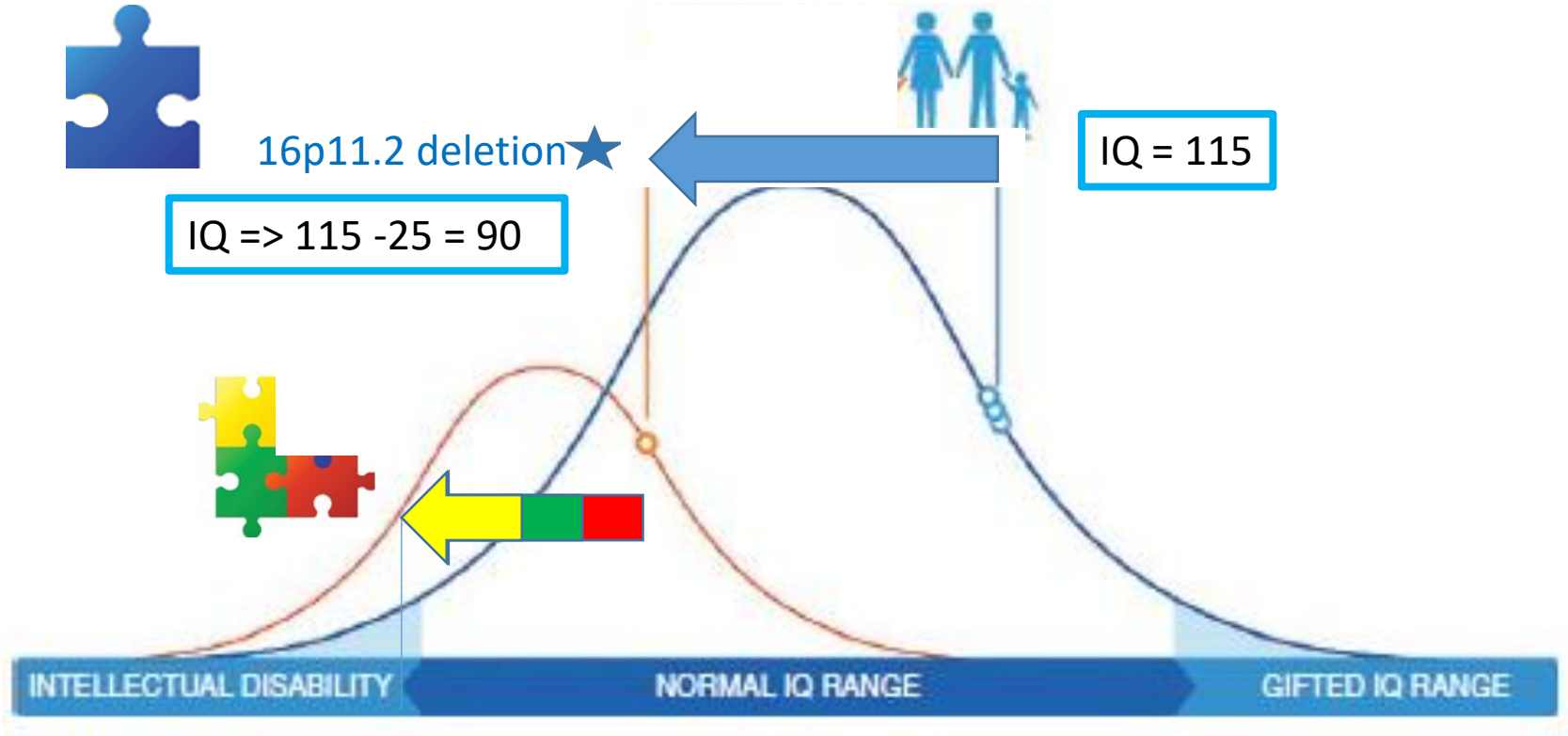
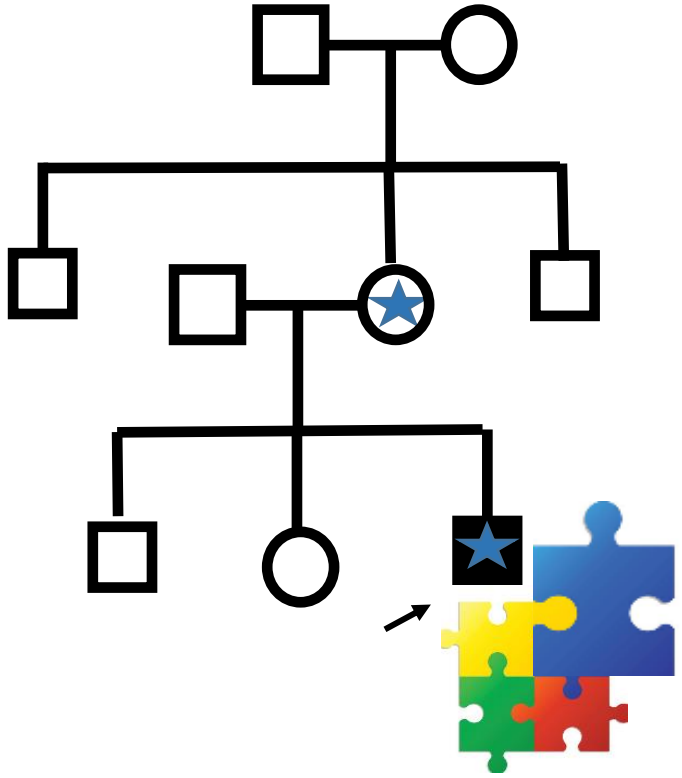




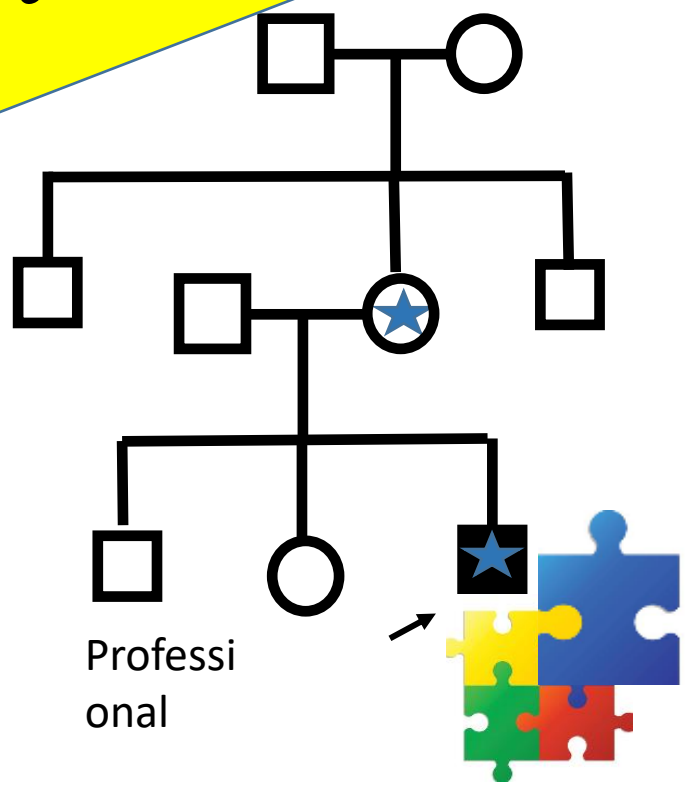
1 CNV risk variant 16p11.2 deletion

OLIGOGENIC MODEL

- Risk variants ≠ cause
- Often inherited from an unaffected parent
- Fairly recent event in family history: *de novo* at (grand)p
- Impact at the individual patient level?
- Difficult message for people / guilt
- In many situations, we no longer

For CNV risk variants, do not test the parents, refer them for counselling to the geneticist so that the decision can be made with them after counselling !

ctual and ASD



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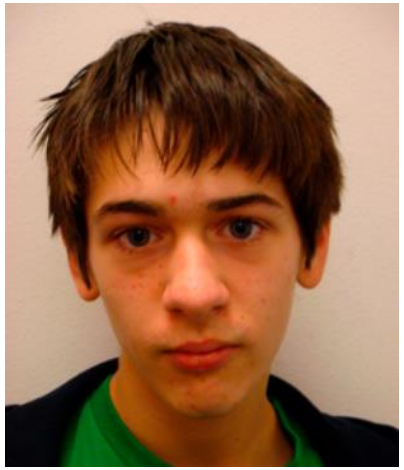
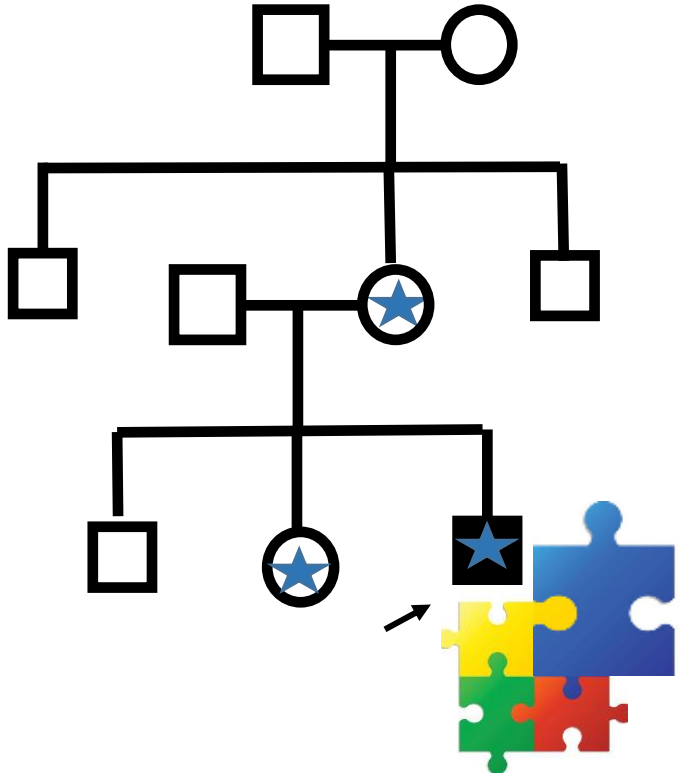


mild intellectual and ASD

- Risk variants = ~~cause~~
- Often inherited from an unaffected parent
- Fairly recent event in family history: *de novo* at (grand)parent?
- Impact at the individual patient level?
- Difficult message for people / guilt
- In many situations, we no longer check segregation among parents
- Does not always segregate with family problems
- Finding a risk variant sometimes requires searching for the true cause

- Difficulty counselling siblings
- PGD often cannot be offered
- We hope to be able to use this more specifically in the future to guide early and targeted therapy and intervention

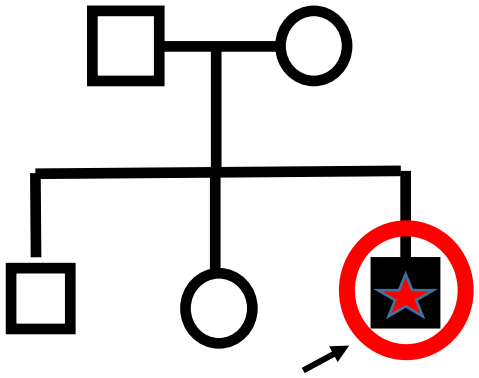


1 CNV risk variant 16p11.2 deletion

MONOGENEOUS/SINGLE

1 variant
major effect

High clinical utility, actionable!

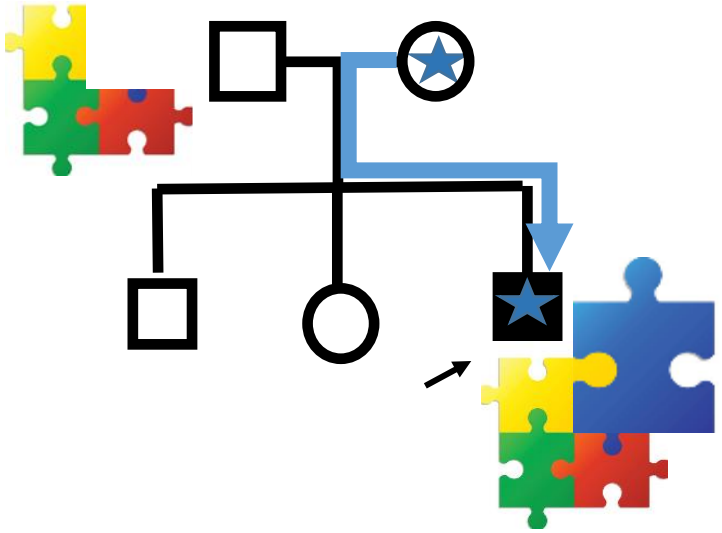


1 new mutation

OLIGOGEEN

Some variants
moderate effect

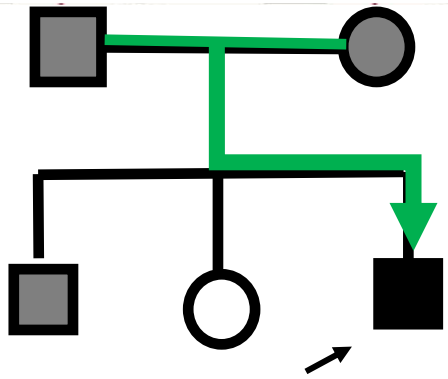
Limited clinical utility, questionable?
=> future!



1 CNV risk variant

POLYGENIC/MULTIFACTORIAL

Many variants
small effect



normal test results

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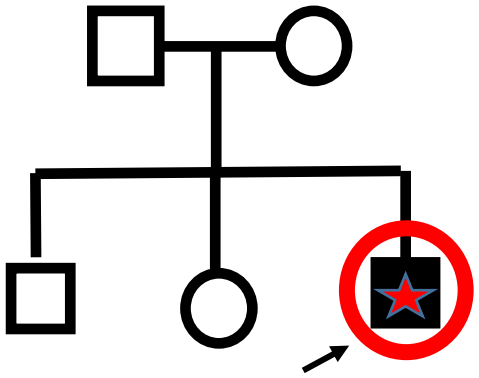

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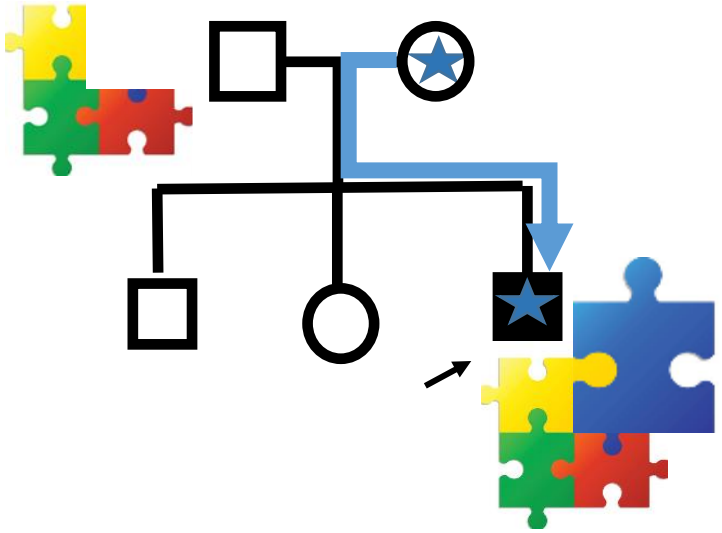

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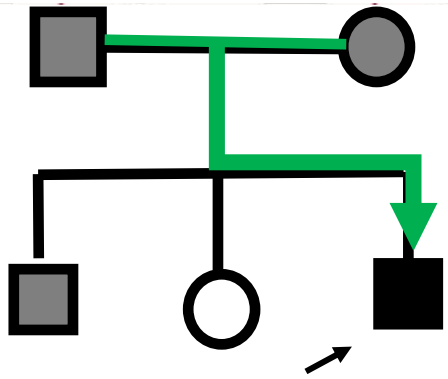
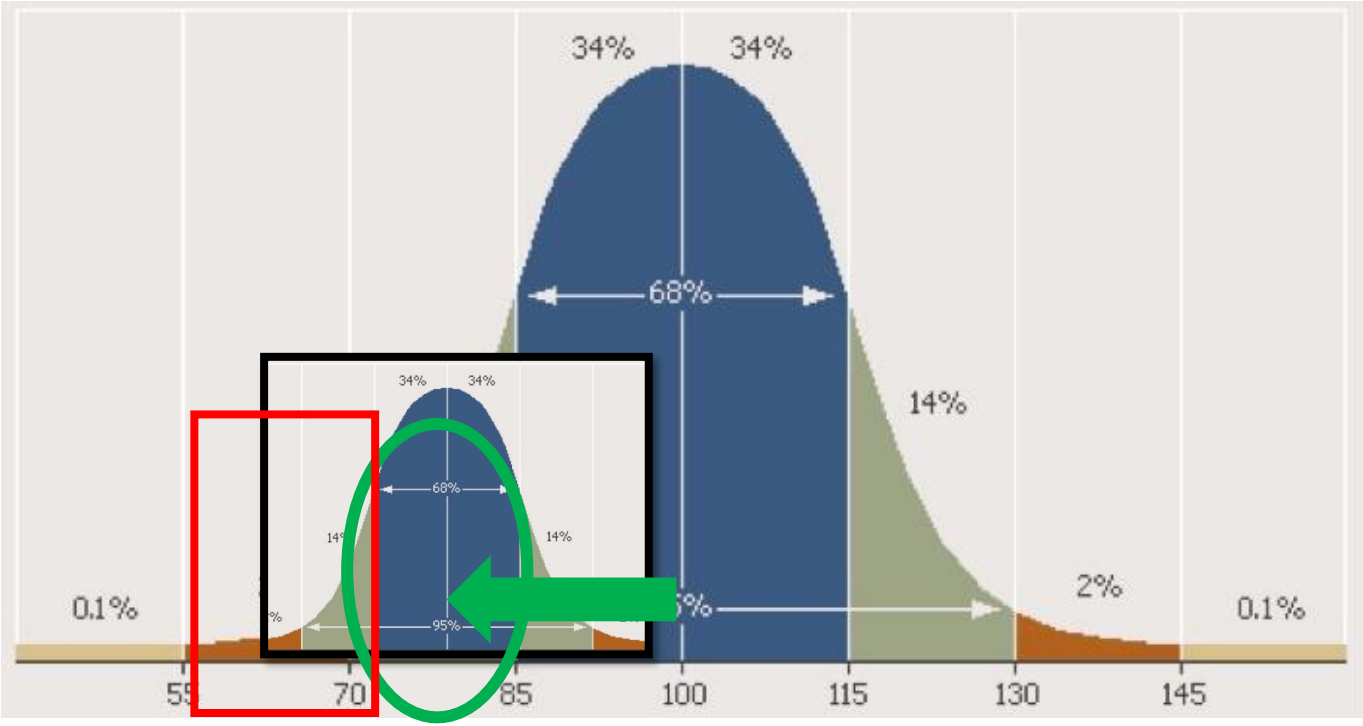
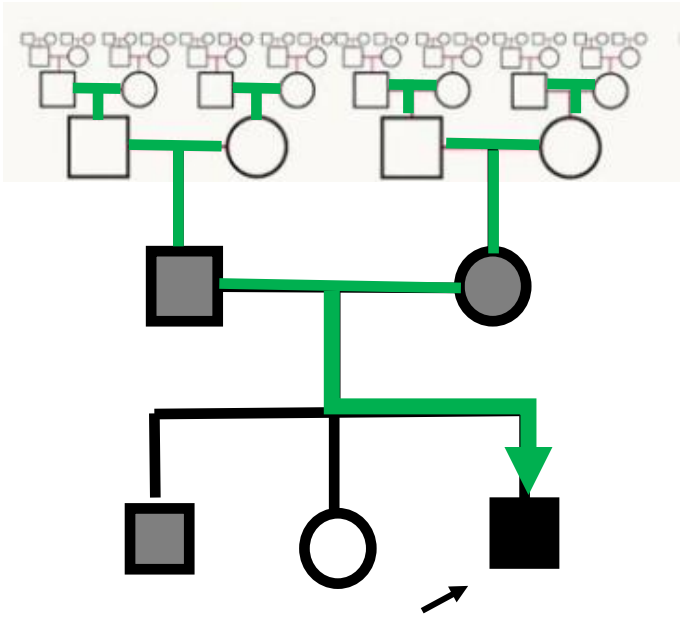


normal test results

POLYGENIC/MULTIFACTORIAL MODEL

Many variants
small effect





normal test results

POLYGENIC/MULTIFACTORIAL MODEL

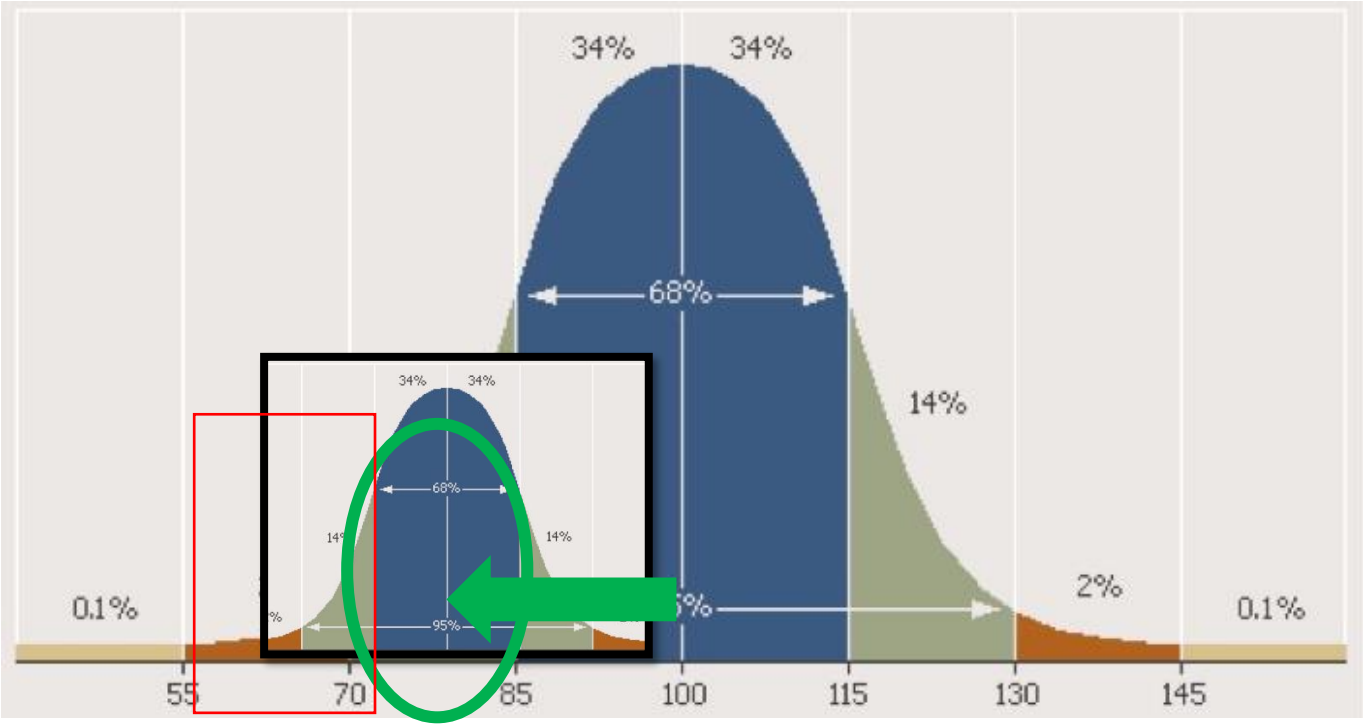
MONOGEEN/ENKELVOUDIG

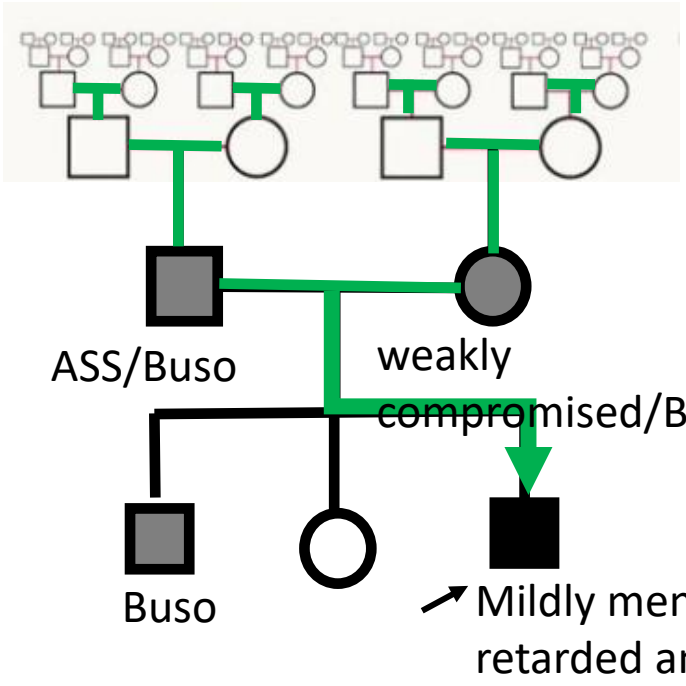
1 variant
groot effect

?

Hoge klinische utiliteit, actionable!

Many variants
small effect





normal test results

POLYGENIC/MULTIFACTORIAL MODEL

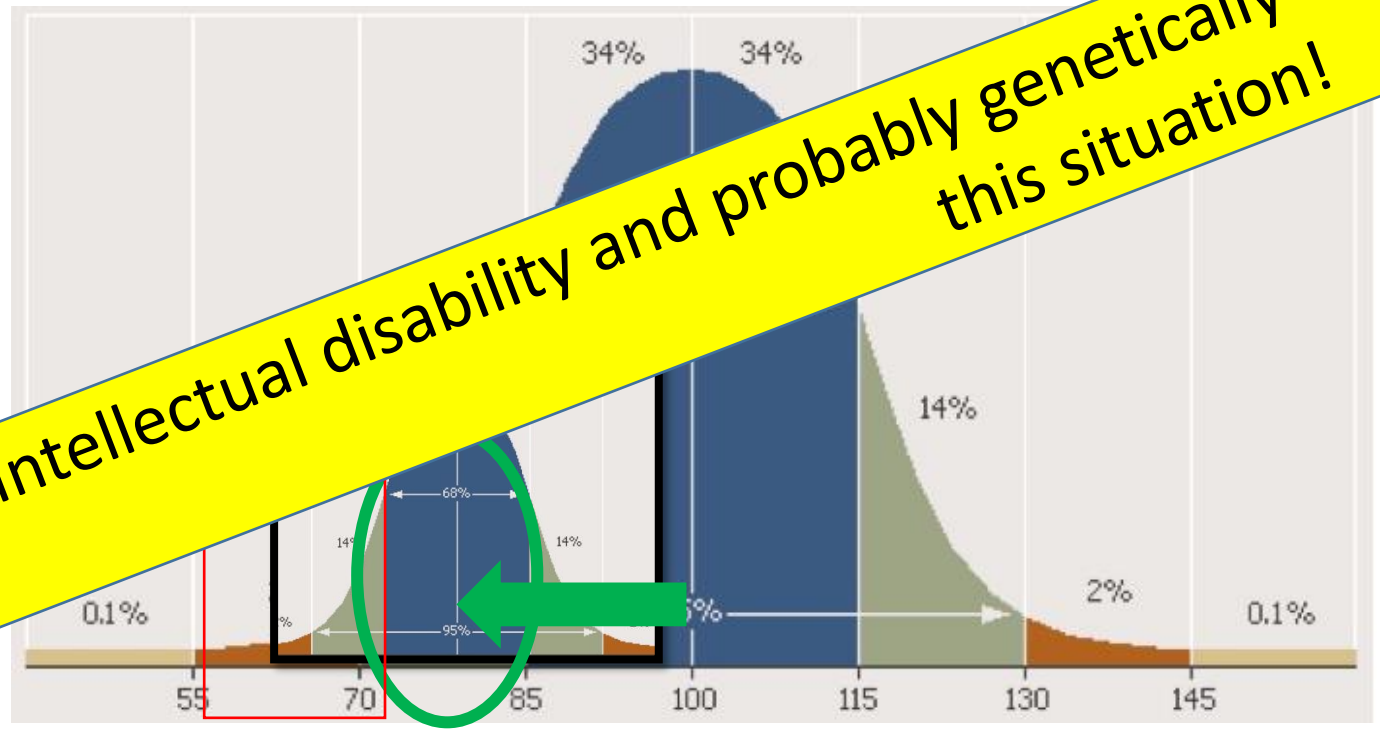
OLIGOGEEN

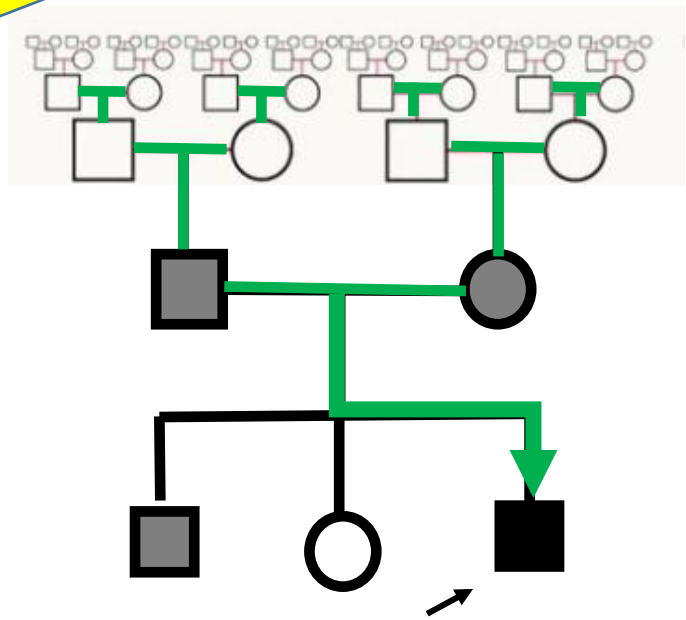
Enkele varianten matig effect ?

Many variants
small effect

Yes => micro array

Intellectual disability and probably genetically determined but still no exome in this situation!





normal test results

MONOGENEOUS/SINGLE

1 variant
major effect

OLIGOGEEN

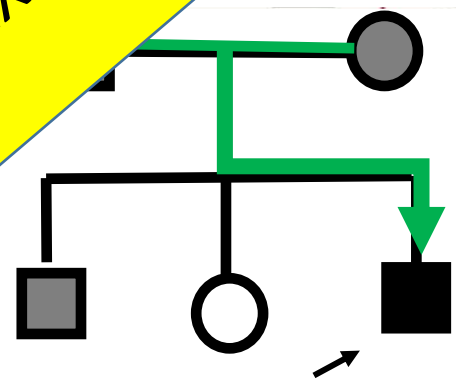
Some variants
moderate effect

POLYGENIC/MULTIFACTORIAL

Many varia
small

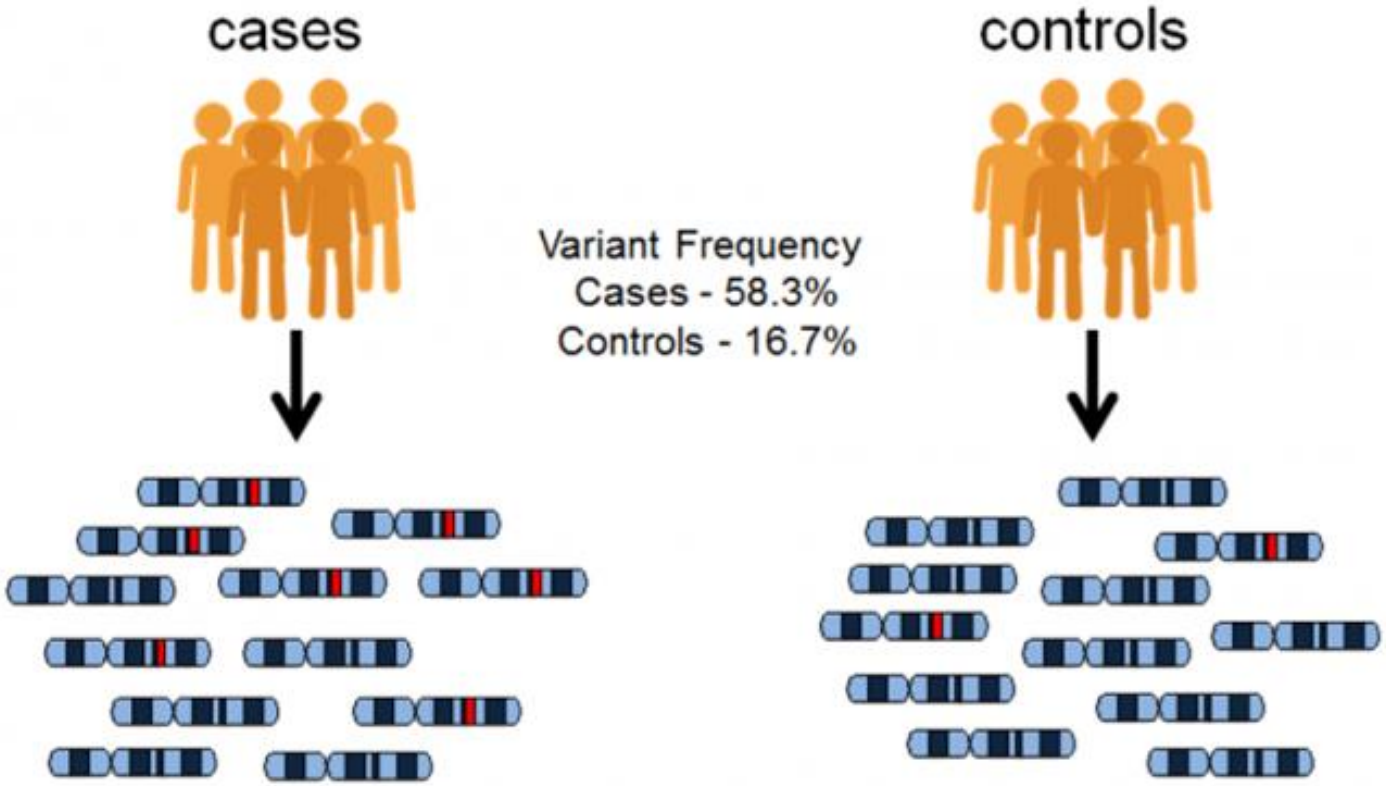
SPECTRUM

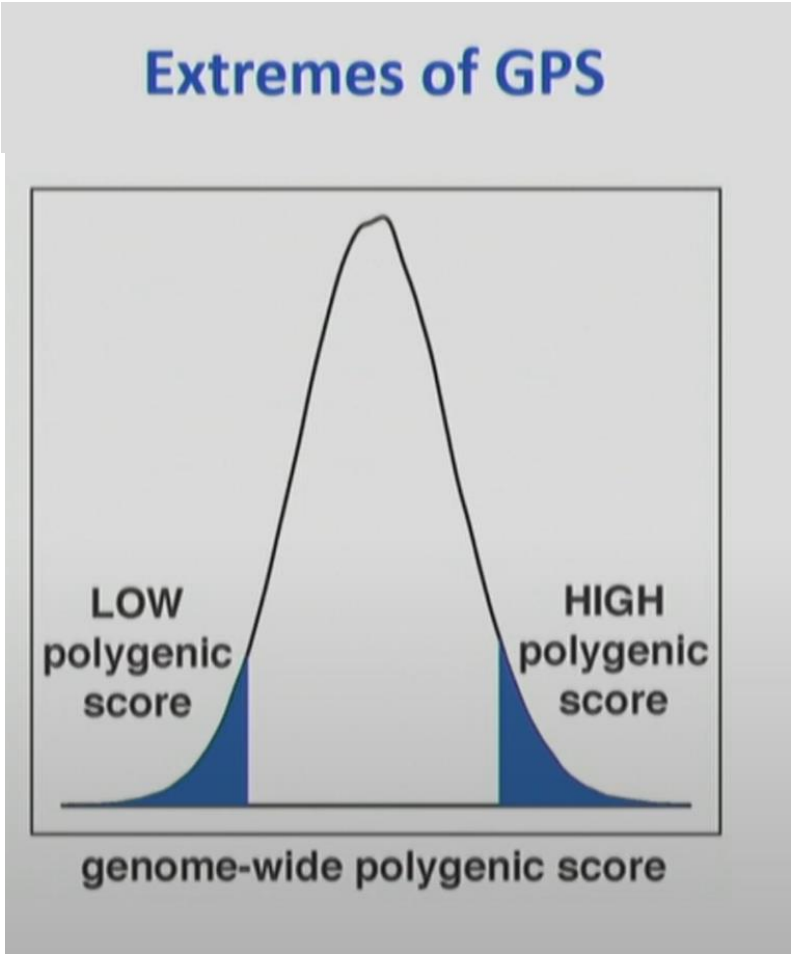
NO EXOOM !



POLYGENIC/MULTIFACTORIAL MODEL

Many variants
small effect





ICARE

Inherited Cancer Registry

WHOA!

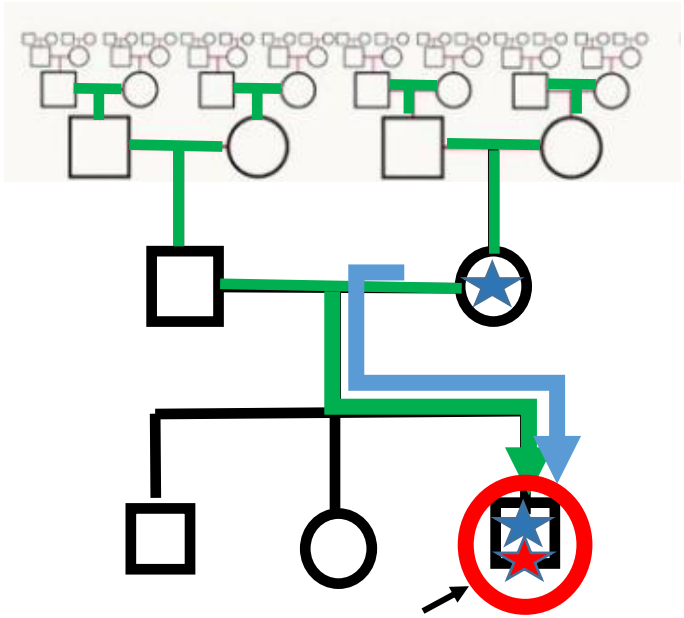
DID YOU KNOW?

Polygenic Risk Score helps estimate breast cancer risk

Genetic Markers + Clinical History + Family History = **Polygenic Risk Score**

Benefit of a **Polygenic Risk Score**?

Identify breast cancer risk among women and guide prevention

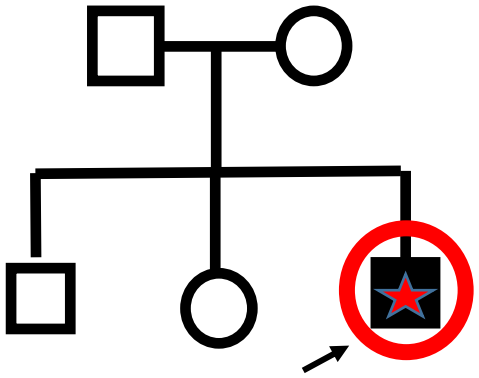



From birth:
Risk prediction
Early symptoms,
prodromal phase
To support
diagnosis
Treatment
decision-making
Prognosis:
prediction of
disease course
and outcome

MONOGENEOUS/SINGLE

1 variant
major effect

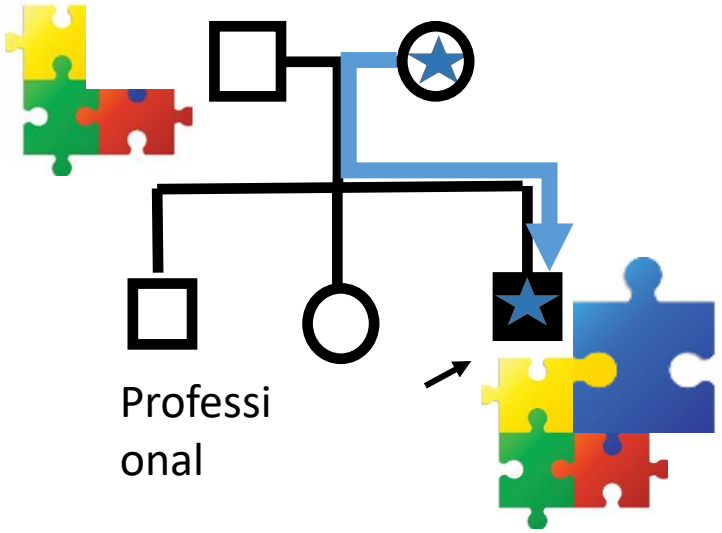
High clinical utility, actionable!



OLIGOGEEN

Some variants
moderate effect

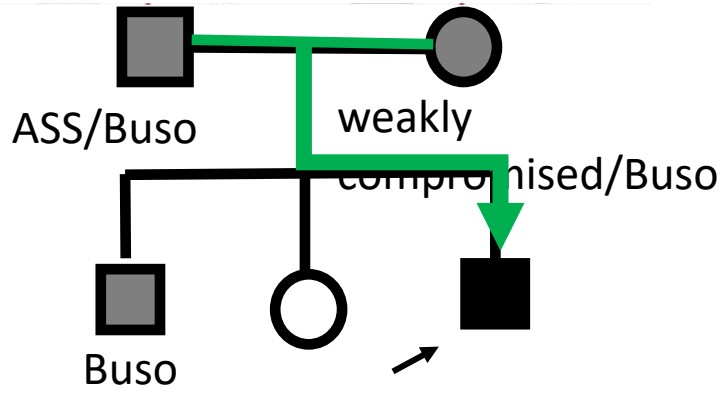
Limited clinical utility, questionable?
=> future!



POLYGENIC/MULTIFACTORIAL

Many variants
small effect

Future!!



MONOGENEOUS/SINGLE

1 variant

major effect

OLIGOGEEN

Some variants

moderate effect

POLYGENIC/MULTIFACTORIAL

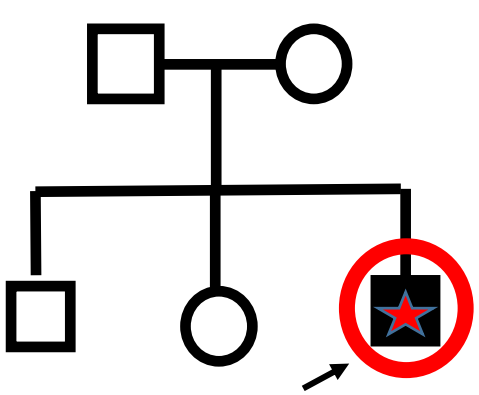
Many variants

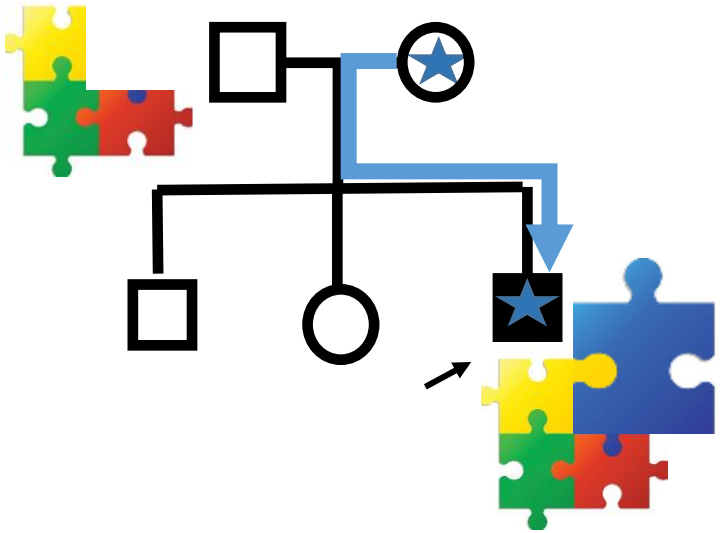
small effect

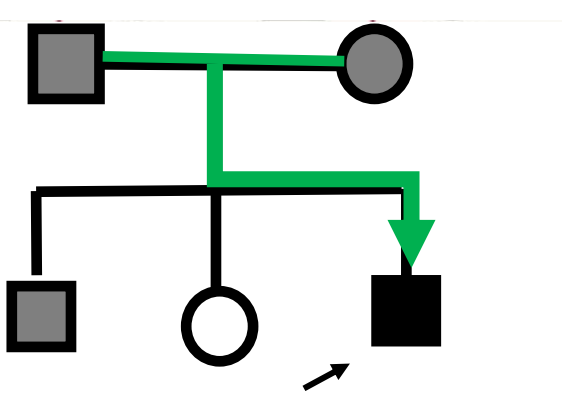
effect of the genetic variant

importance of environmental factors

usefulness of genetic diagnostics





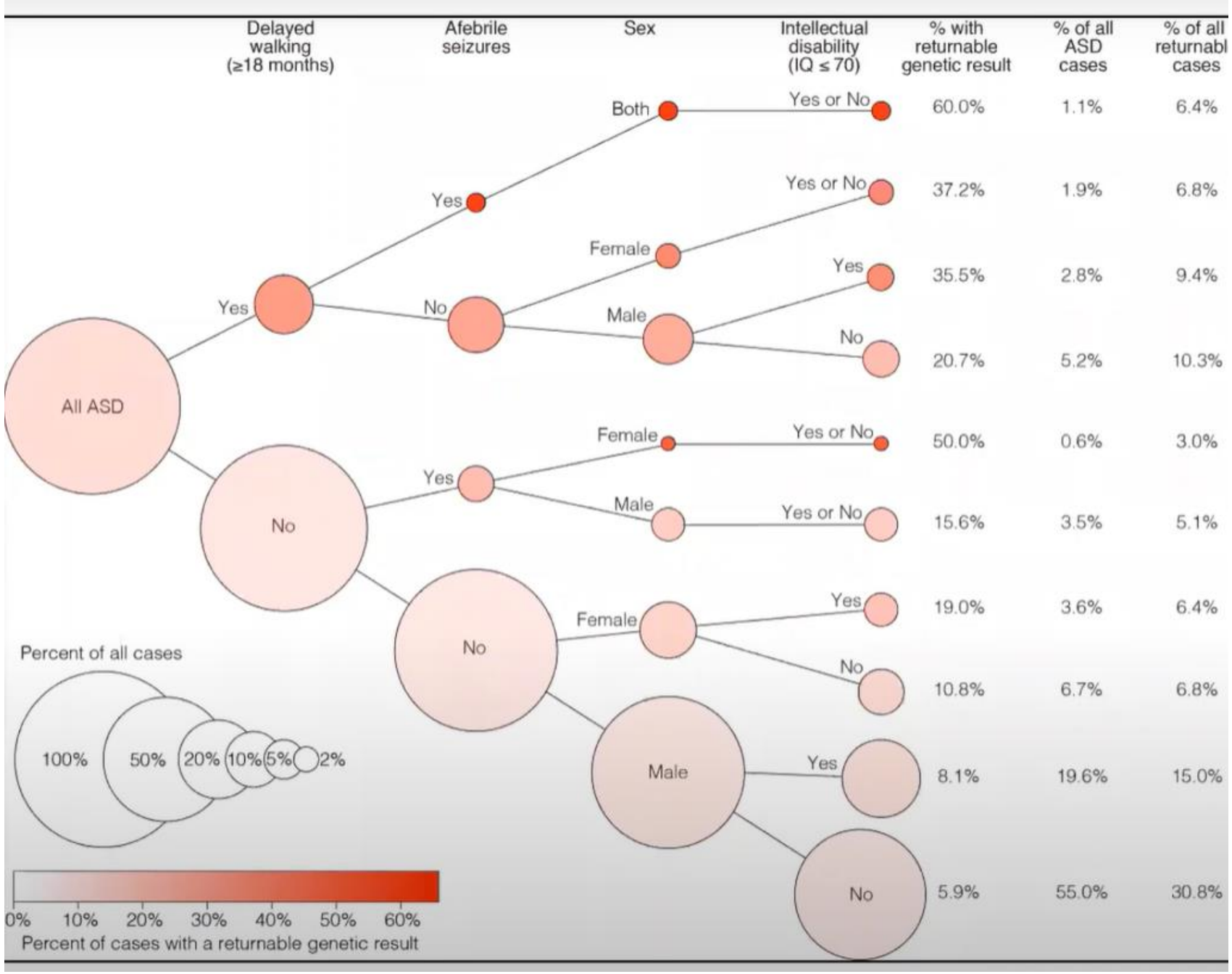


Challenges genetic testing for ID/neuropsychiatric disorder

Clinical assessment ! => monogenic versus multifactorial

- clinical presentation
- course of the disorder
- the parental phenotypes
- the family history

- What is the evidence for the actual contribution of the variant to the phenotype of the patient in this family?
- Phenocopy!!



Prevalence of Returnable Genetic Results Based on Recognizable Phenotypes among Children with Autism Spectrum Disorder

Somer L. Bishop, Audrey Thurm, Elise Robinson, Stephan J Sanders

ASD in practice who to refer to clinical genetics?

Do refer

- if the parents themselves request it
- moderate/serious intellectual disability
- Mild intellectual disability or borderline
  if an outlyer in the family !
- deviating biometrics
- epilepsy
- dysmorphia or organ dysfunction
- neuropsychiatric severe: regression, psychosis
- Abnormal neurological examination

Usually do not refer

- if the parents do not wish this
- Normal cognition 
- Familial presentation 

dyslexia ADHD dyspraxia ... in practice who to refer to clinical genetics?

Do not refer if this is isolated

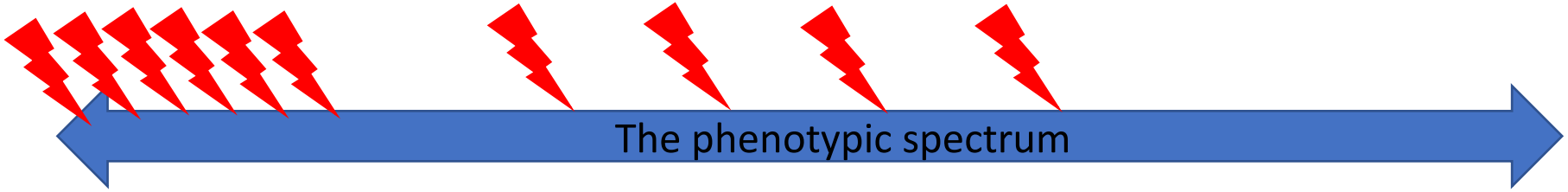
Future...

Do refer

- if the parents themselves ask for it
- moderate/serious intellectual disability
- Mild intellectual disability or retarded
  As an outlyer in the family !
- deviating biometrics
- epilepsy
- dysmorphia or organ dysfunction
- strikingly serious
- abnormal neurological examination

Monogenic autism also in patients with normal cognition

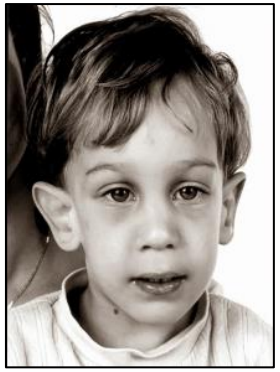
2015



Intellectual disability

Normal cognition

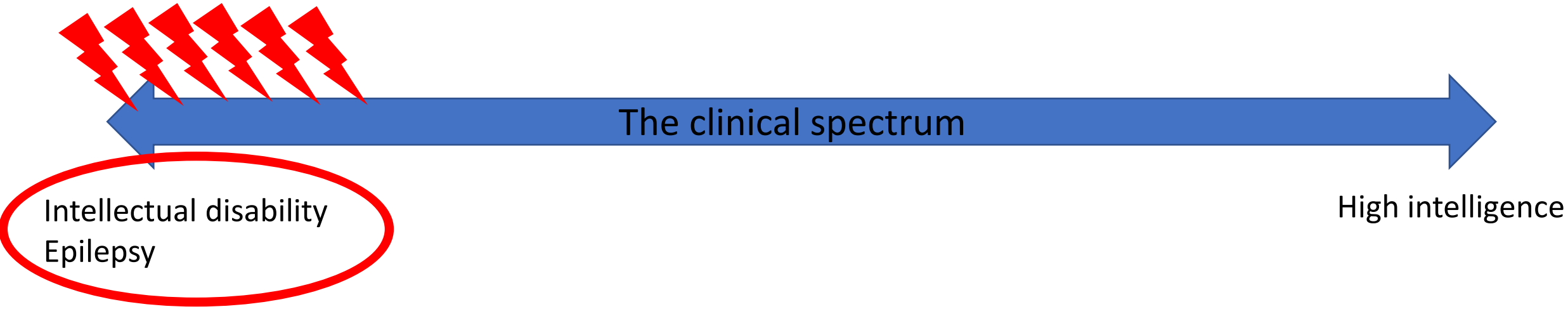
High intelligence



Author and professor Temple Grandin (Leonard Ortiz/Digital First Media/Orange County Register via Getty Images)

Interview with Temple Grandin: Autism, genetics and the steep price of being intelligent

Are our minds the product of genetics or development? Autism community icon Temple Grandin talks about new research

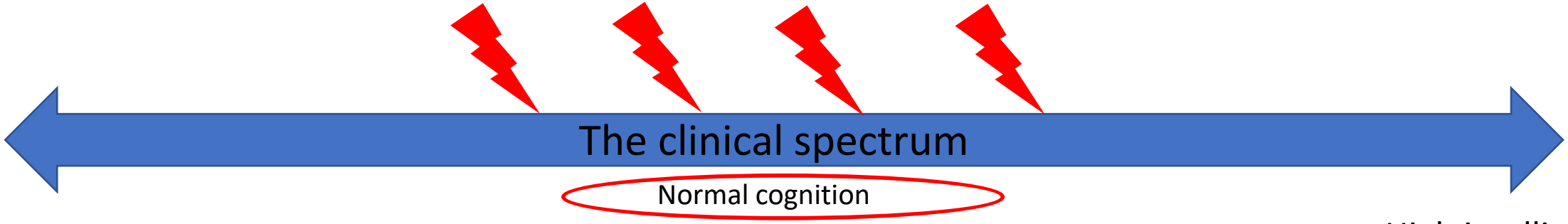


de novo splice-donor variant in *GRIN2B*

de novo stopgain variant in *ARID2*

de novo stopgain variant in *CSNK2A1*

de novo frameshift insertion in *HNRNPU*

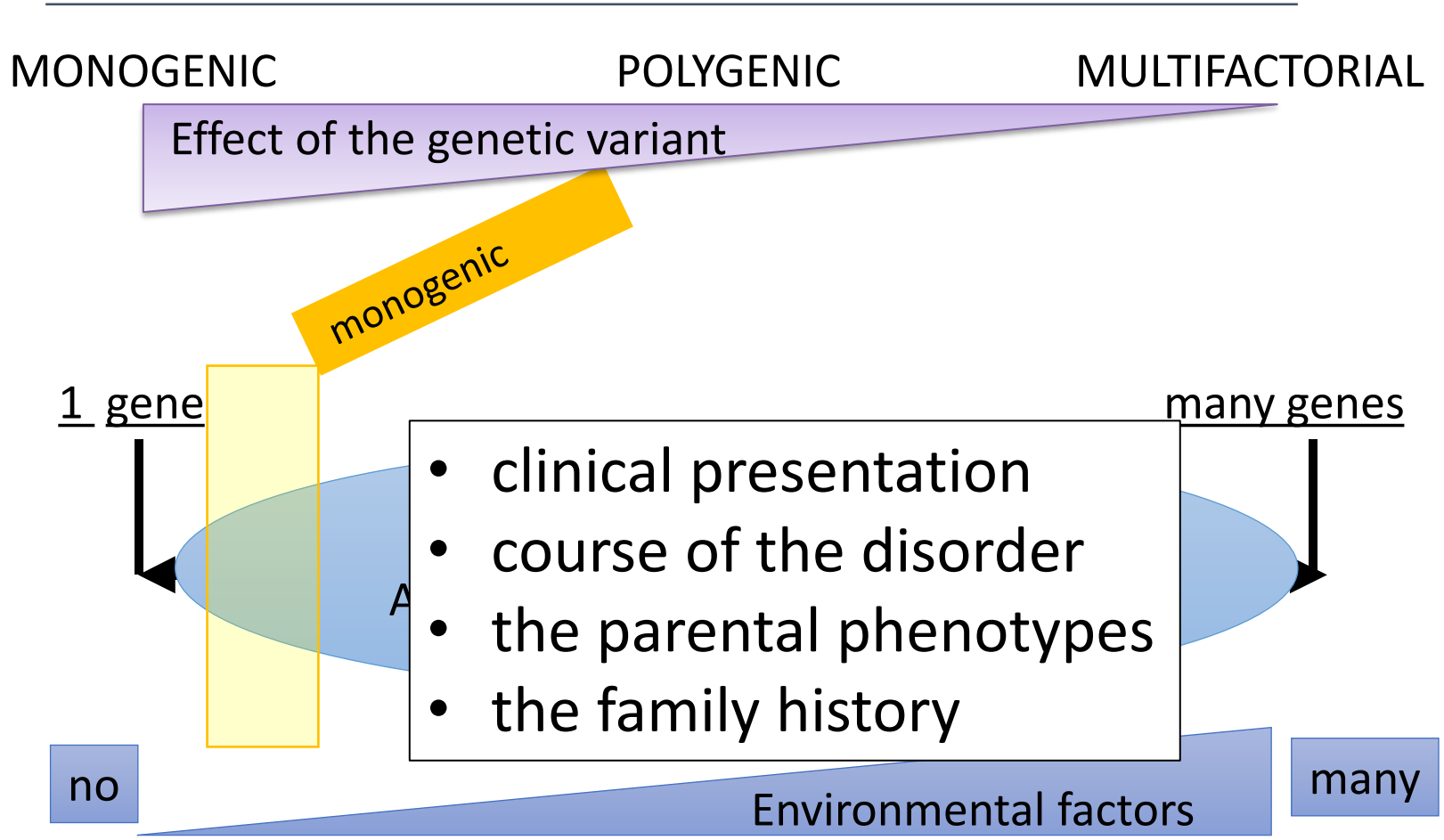


de novo missense variant in *SMAD4*

de novo frameshift deletion in *KMT5B*

de novo splice variant in *NFIA*

de novo frameshift deletion in *SETD2*

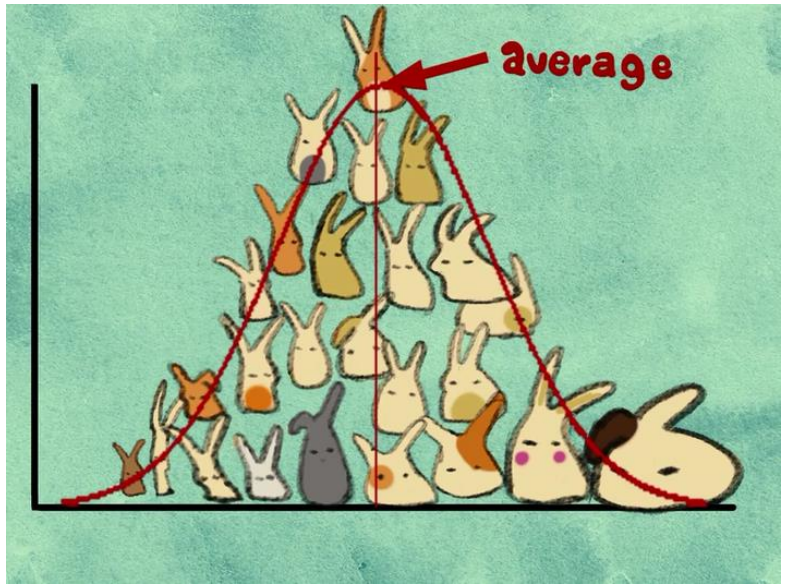


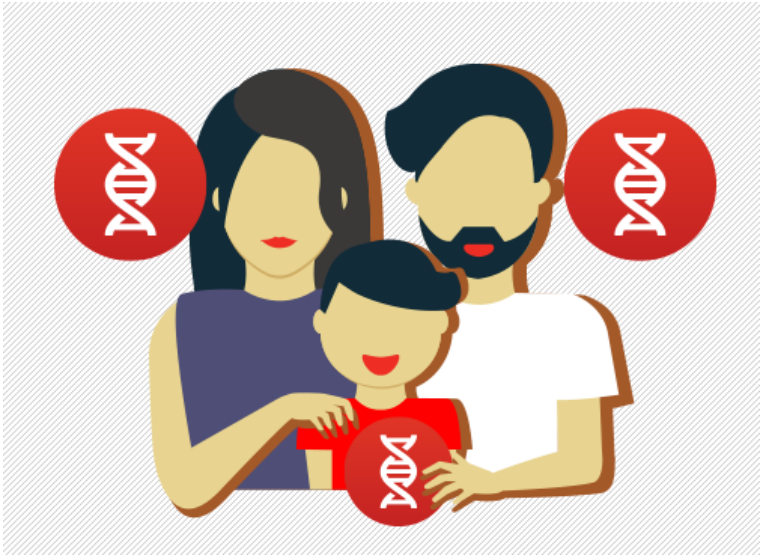
Mendelian inheritance

Complex inheritance

How to recognise monogenic ASD in the population

The outlyer phenotype !





5 years old

Early development

- Language
  - First words: 12-15 months
  - 2-4 word sentences: ± 3 years
- Motor
  - Sitting without support: 10 month
  - Walking independently: 18 months

Cognition (WPPSI-III-NL)

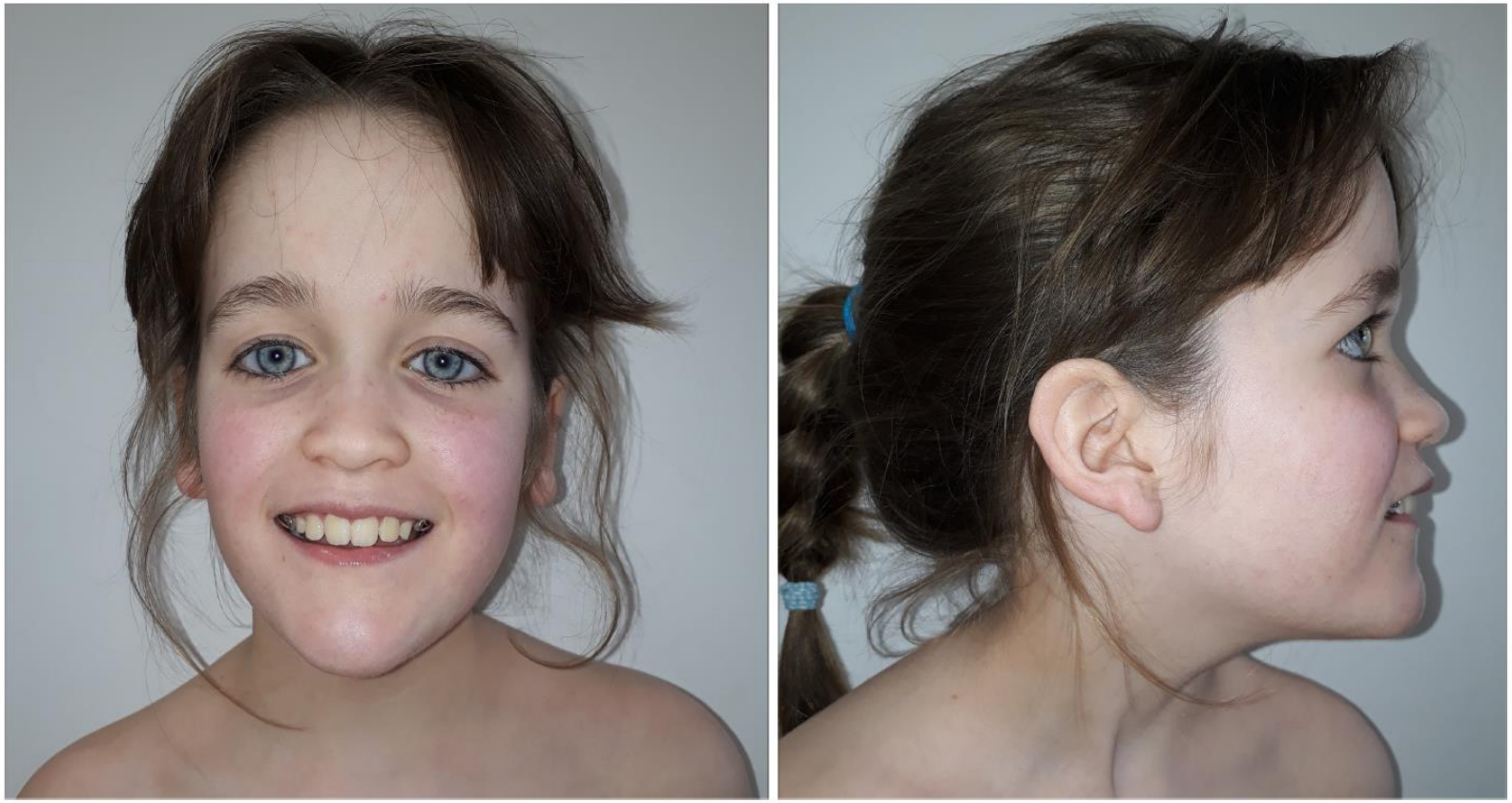
• Verbal IQ	= 84 (90% CI = 78-92)	Pc. 14,3
• Performance IQ	= 100 (90% CI = 92-108)	Pc. 50,0
• Total IQ	= 89 (90% CI = 83-96)	Pc. 23,2

Parents: “She does not resemble our 2 other girls”

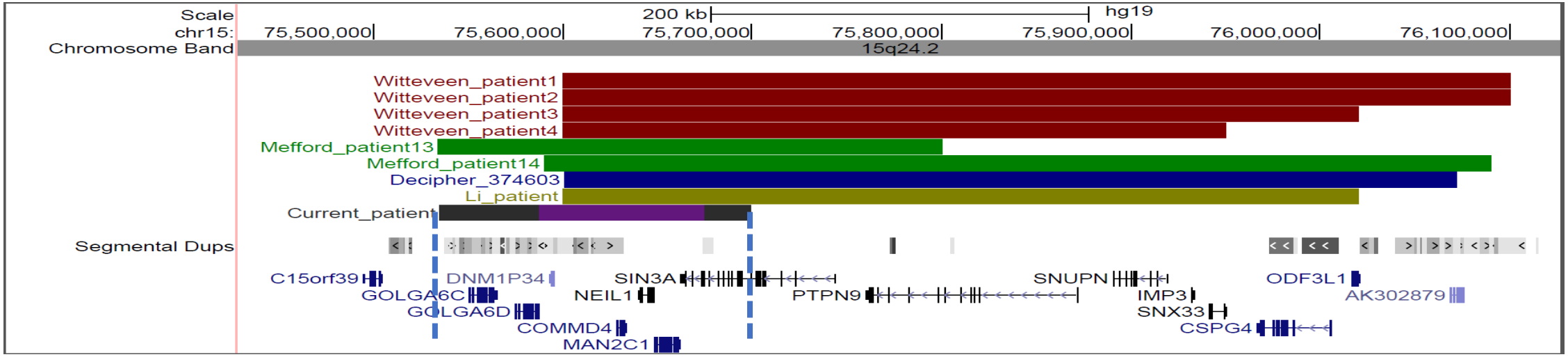
In the context of het family she has an outlyer phenotype !

Parents: “She does not resemble our 2 other girls”

- *De novo* deletion 1p36.22 (10,087,091 – 12,627,983)



de novo
15q24.2 atypical 84 kb deletion containing *SIN3A*



Interpretation of inherited monogenic conditions with subtle phenotype is challenging

Paternal splice donor variant in *CHD8*

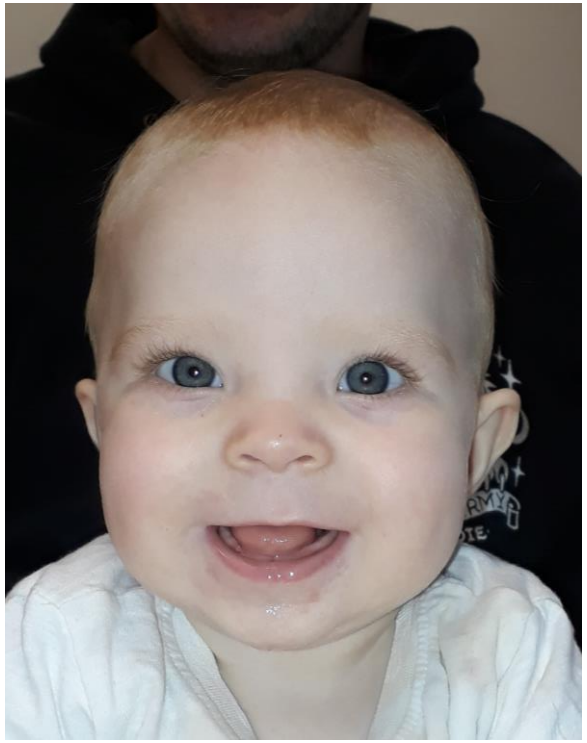
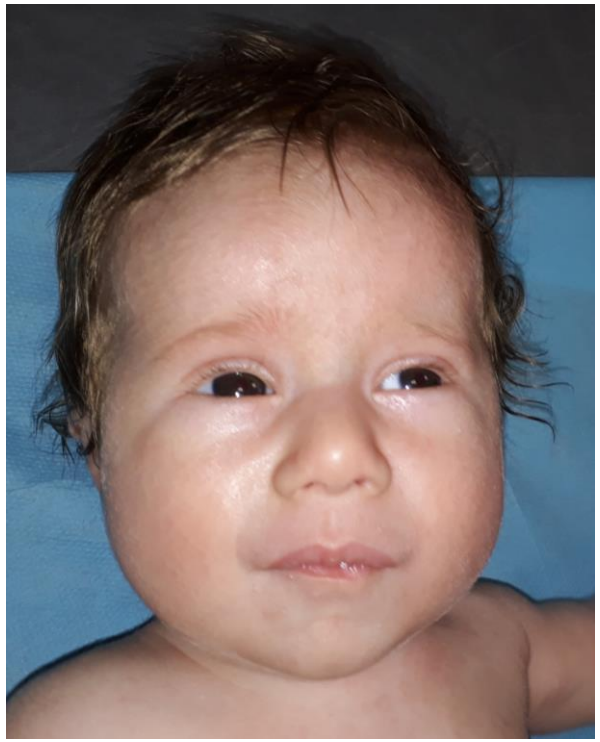
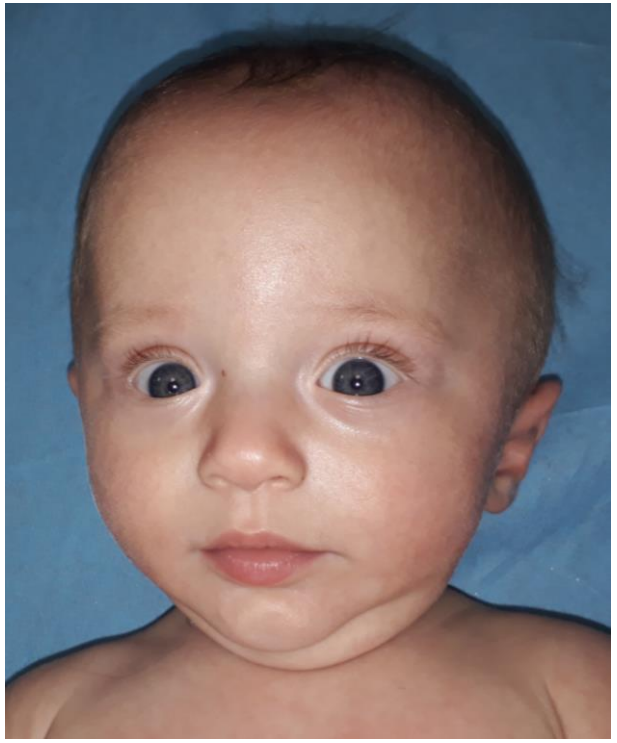
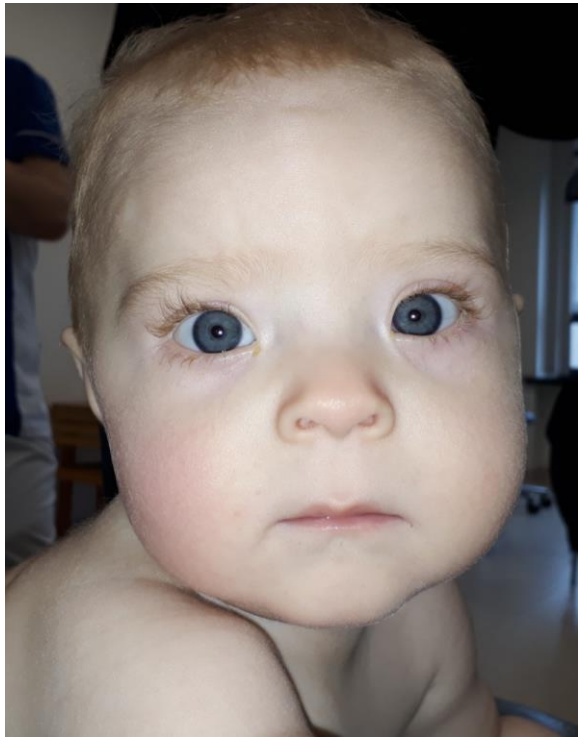
de novo in the father!

Benefit of a genetic diagnosis

- Clarifying a genetic cause and improving the psychosocial outcomes (e.g., improved knowledge and sense of empowerment) for patients and their families
- Providing prognosis or expected clinical course
- Evaluating recurrence risks and helping families in reproductive decision making
- Refining treatment options
- Avoiding unnecessary and redundant diagnostic tests
- Identifying associated medical risks to prevent morbidity
- Providing condition-specific family support
- Facilitating acquisition of needed services and improving access to treatment/support

Important elements in the consultation ID/ASD

- What is the question, who asks the question?

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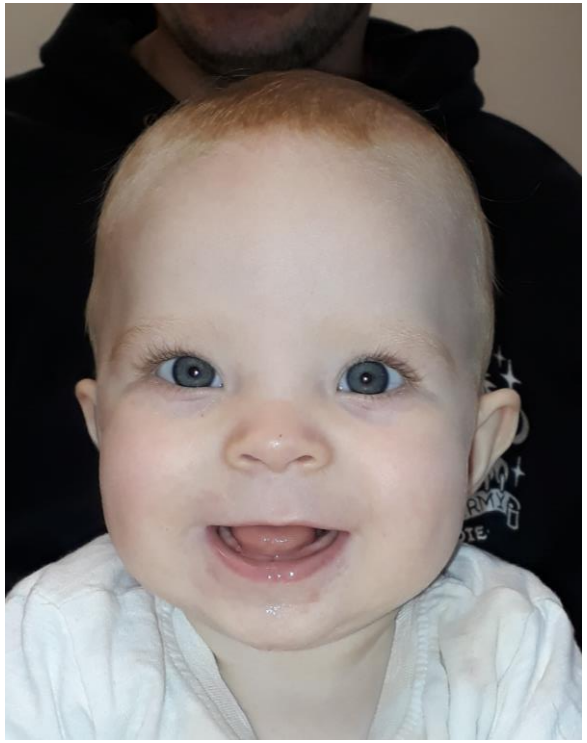
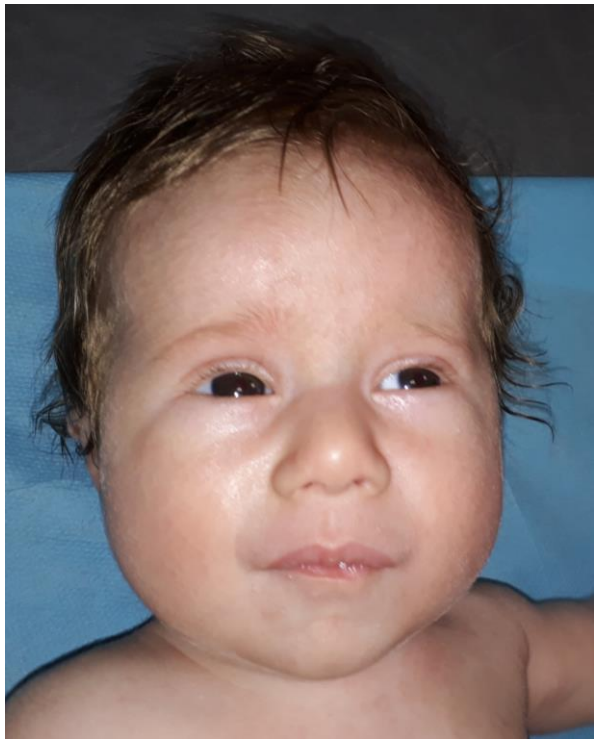
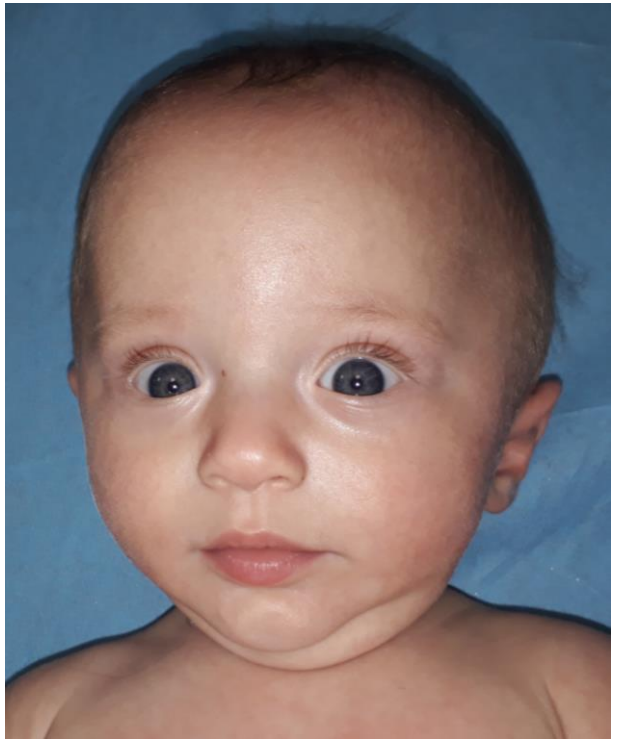
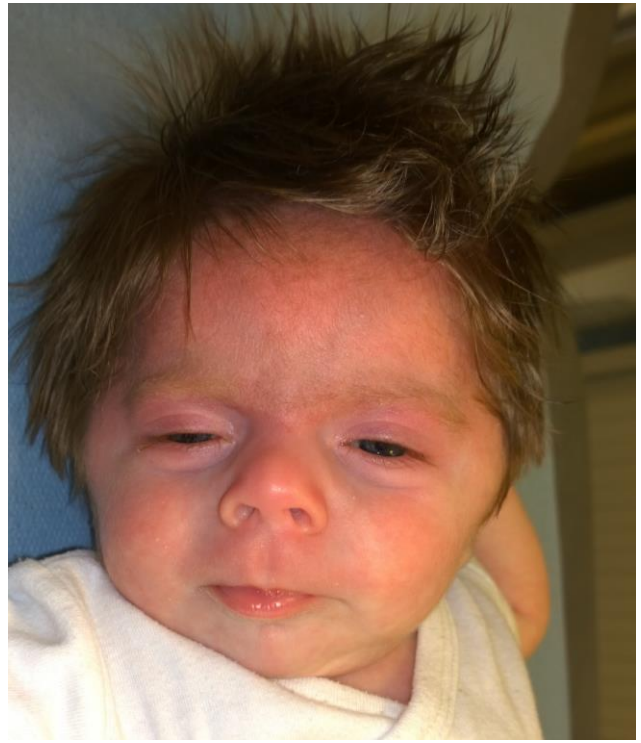

Important elements in the consultation ID/ASD

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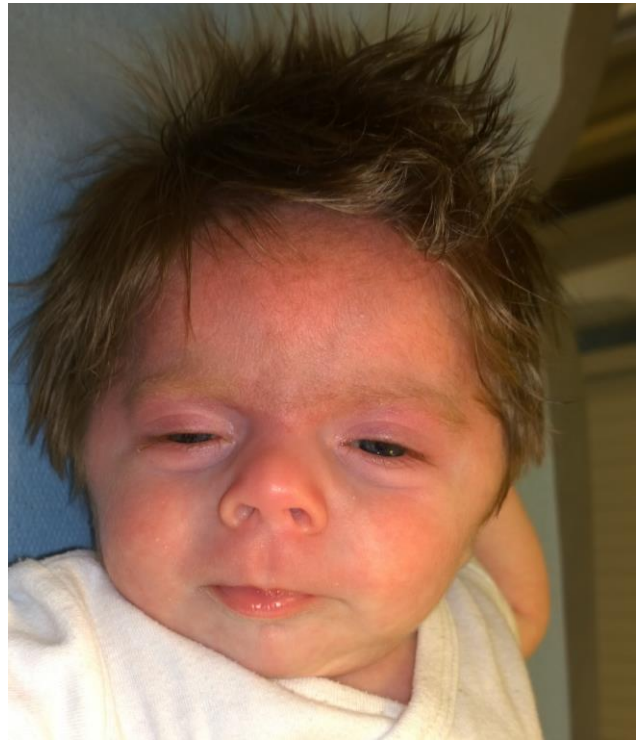

Important elements in the consultation ID/ASD

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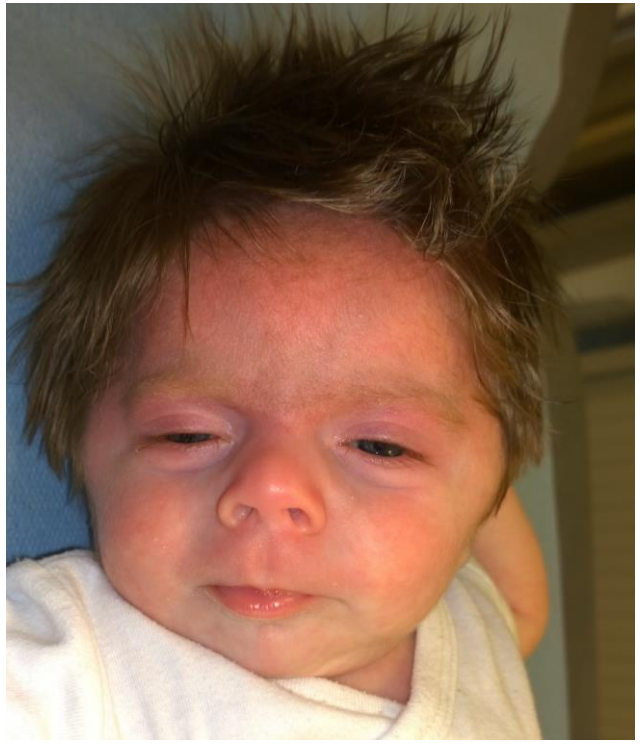


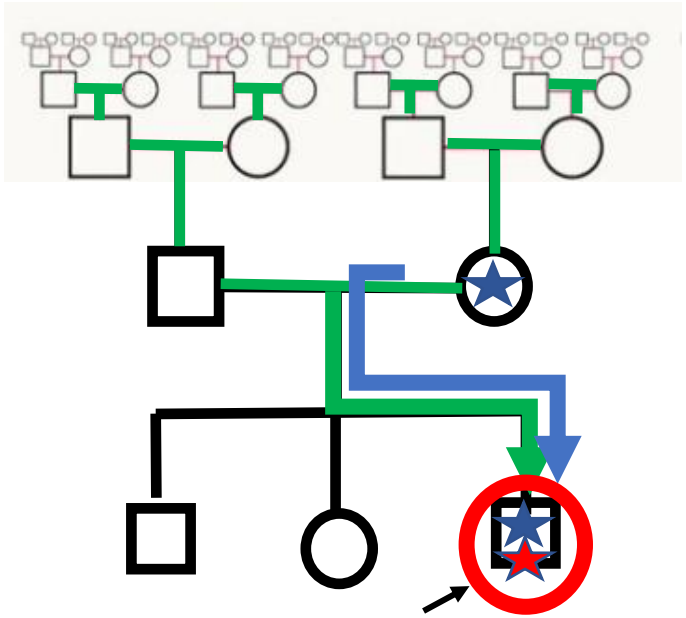
Important elements in the consultation ID/ASD

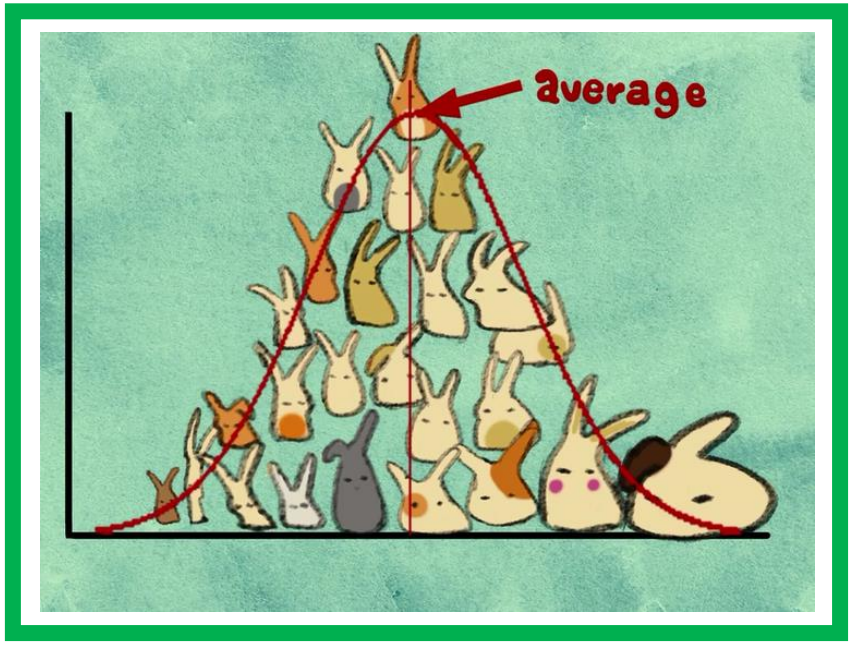
- Early signs of atypical development ?
  - Feeding difficulties
  - Delayed rolling over, sitting, or walking
  - Poor head and neck control
  - Muscle stiffness or floppiness
  - Speech delay
  - Swallowing difficulty
  - Body posture that is limp or awkward
  - Clumsiness
  - Muscle spasms
  - …

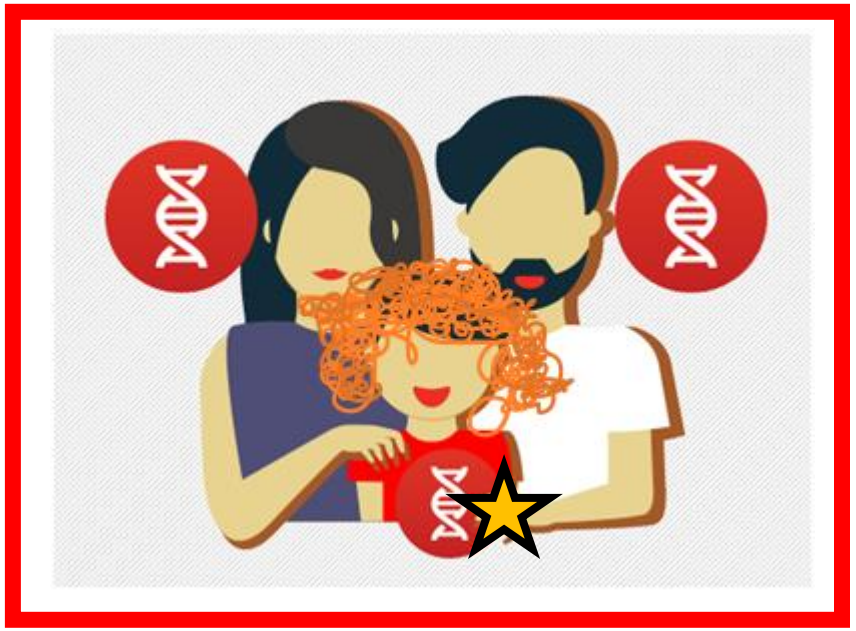
Olivia

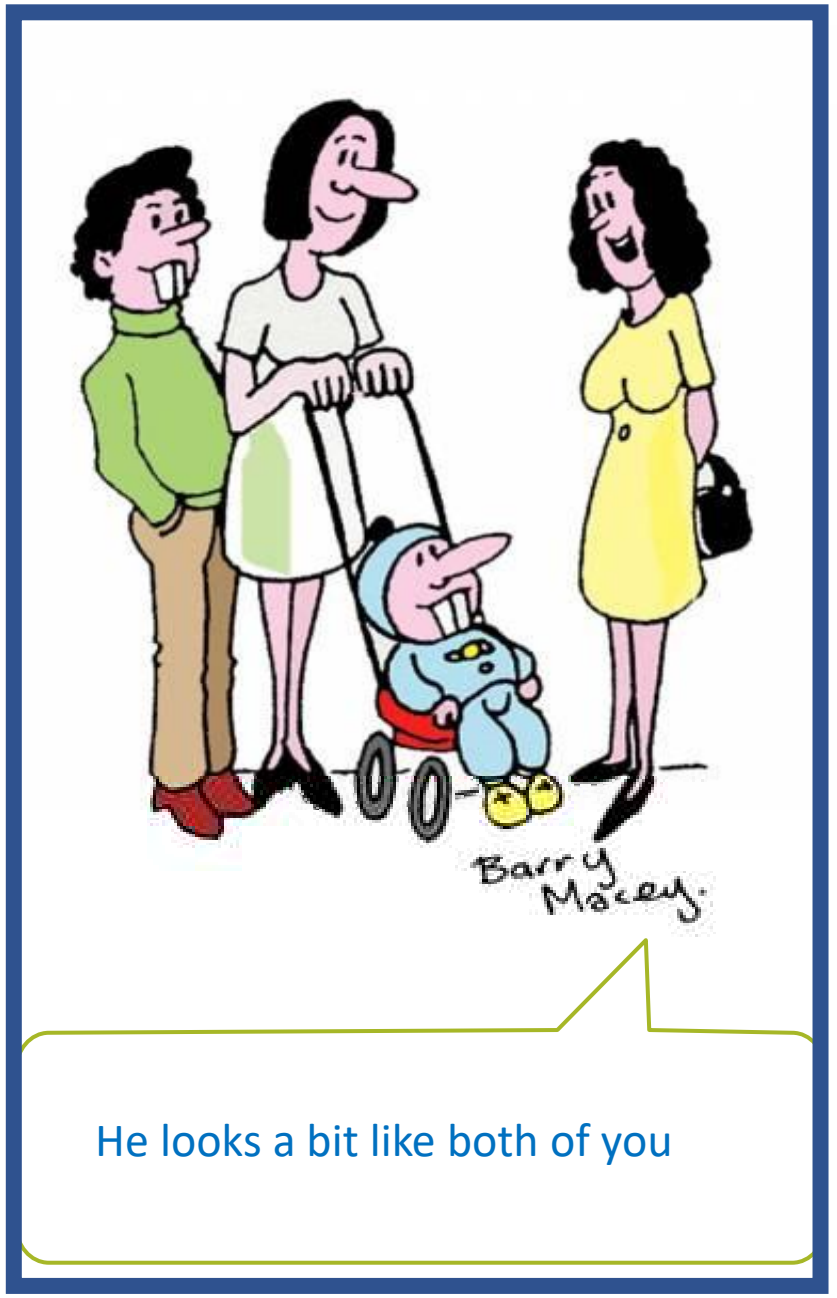
Kesha

Recent finding of SHANK3 de novo frameshift mutation




average




Barry Macey
He looks a bit like both of you