We all have mutations

Han G. Brunner

Han.Brunner@RadboudUMC.nl

Maastricht UMC+

azM | Maastricht University

Human Genetics Nijmegen

Radboudumc

university medical center

Exome sequencing

Radboudumc

- **~20,000 exonic variants**
  - Excluding known variants (dbSNP+ inhouse) **~200**
    - Silent ~ 60
    - Nonsense/ frameshift ~ 40
    - Missense ~ 95
    - Canonical Splice Site ~ 5
    - Coding *de novo* **~ 1**

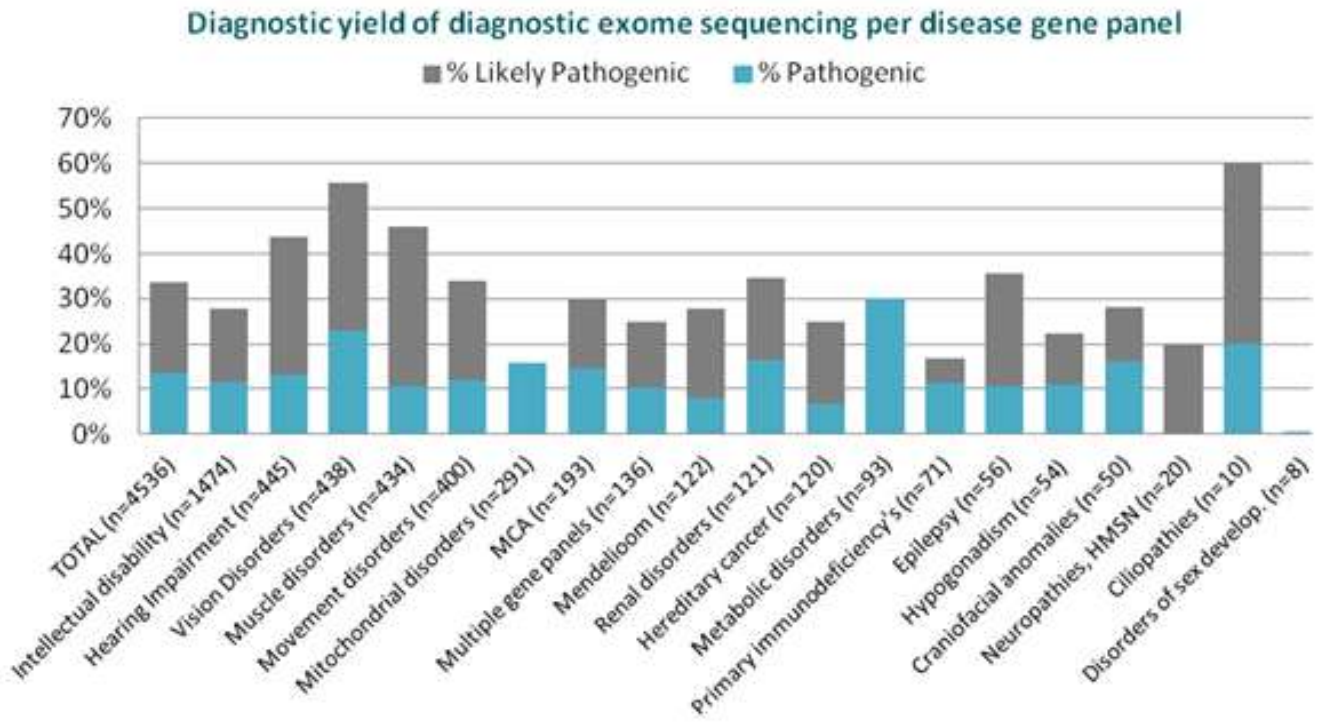
Lessons we learned

Doctors are good; Exomes are better

We all have a mutated gene

New mutations are the most important cause of severe intellectual disability

Genes do not respect nosology


Diagnostic yield of diagnostic exome sequencing per disease gene panel
% Likely Pathogenic
% Pathogenic
70%
60%
50%
40%
30%
20%
10%
0%
TOTAL (n=4536)
Intellectual disability (n=1474)
Hearing impairment (n=445)
Vision Disorders (n=438)
Muscle disorders (n=434)
Movement disorders (n=400)
Mitochondrial disorders (n=291)
MCA (n=193)
Multiple gene panels (n=136)
Mendelioom (n=122)
Renal disorders (n=121)
Hereditary cancer (n=120)
Metabolic disorders (n=93)
Primary immunodeficiency's (n=71)
Epilepsy (n=56)
Hypogonadism (n=54)
Craniofacial anomalies (n=50)
Neuropathies, HMSN (n=20)
Ciliopathies (n=10)
Disorders of sex develop. (n=8)

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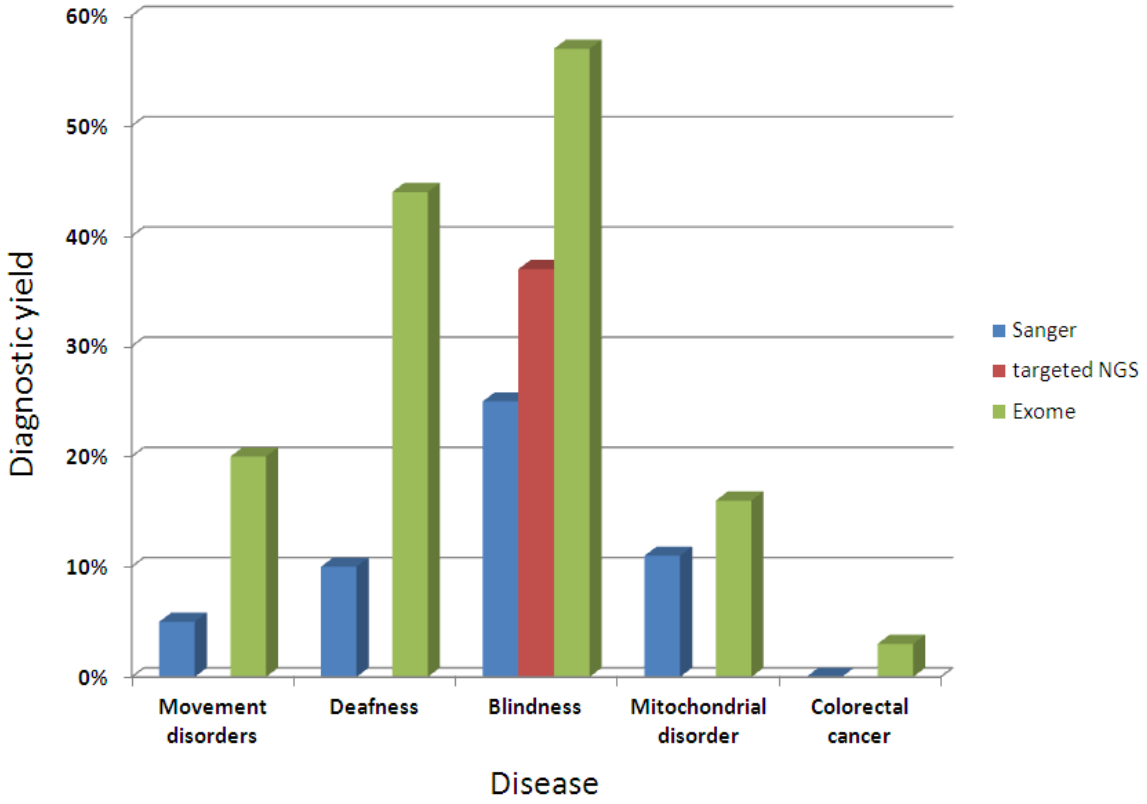
An inconvenient truth

The hit rate of diagnostic exome sequencing (including CNVs)

Clearly Exceeds

The current diagnostic standard of clinician driven investigation

Targeted analysis across 5 diagnostic groups



Compare with clinical diagnostic practice 2011

Neveling et al. Human Mutation 2013

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Lessons

Doctors are great; exomes are better

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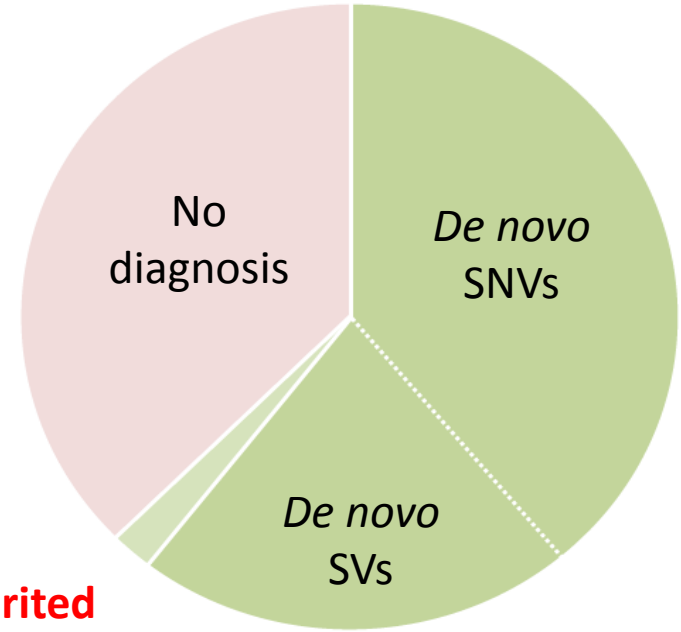
>60% of Intellectual disability is by *de novo* gene mutations

~1000 / 20.000 genes (5%) are ***crucial*** for the brain

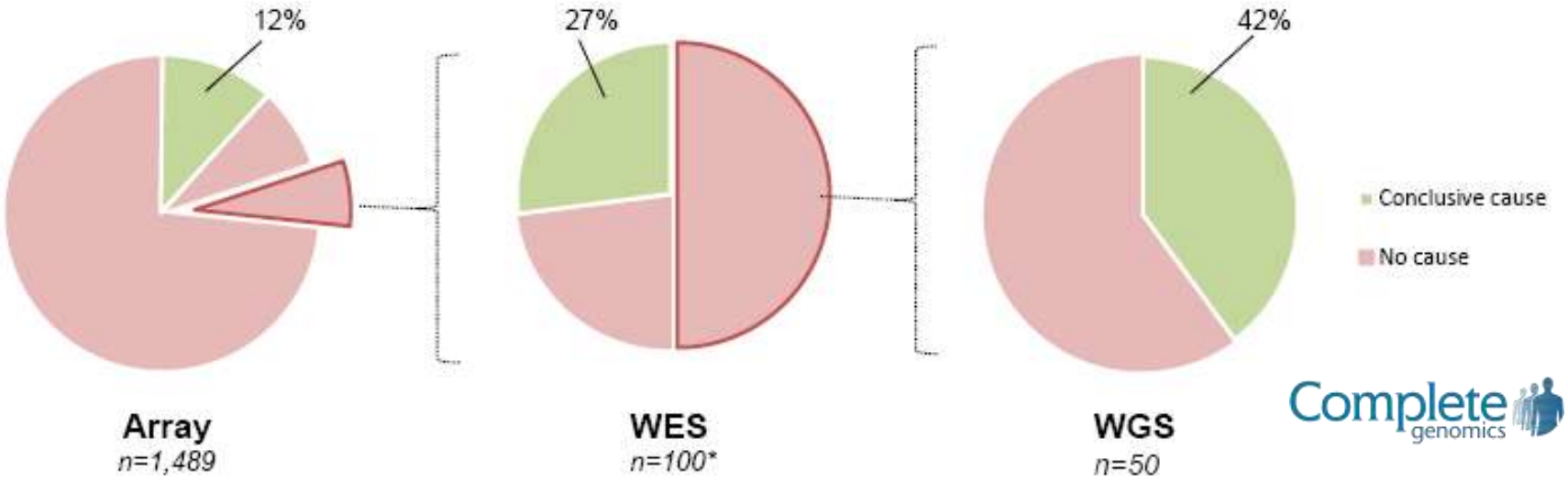
Gilissen *et al*. Nature, 17 July 2014



Inherited 2%

***De novo* 60%**

New GeneticTechnologies Elucidate Intellectual Disability



De Vries et al. American Journal Human Genetics 2006

De Ligt et al. New England Journal of Medicine 2012

Gilissen et al. Nature 2014

Why do things get better over time?

De Ligt et al NEJM 2012

- Trio exome sequencing in 100 patients with unexplained ID
  * 16% Diagnosis

- Reanalysis of data 2012-2014

  Better mapping algorithms

  Candidate genes confirmed

  Better variant interpretation

  * 27% Diagnosis by 2014

- Whole Genome sequencing

  Gilissen et al. Nature 2014

  * 40% Diagnosis mostly coding and structural variation

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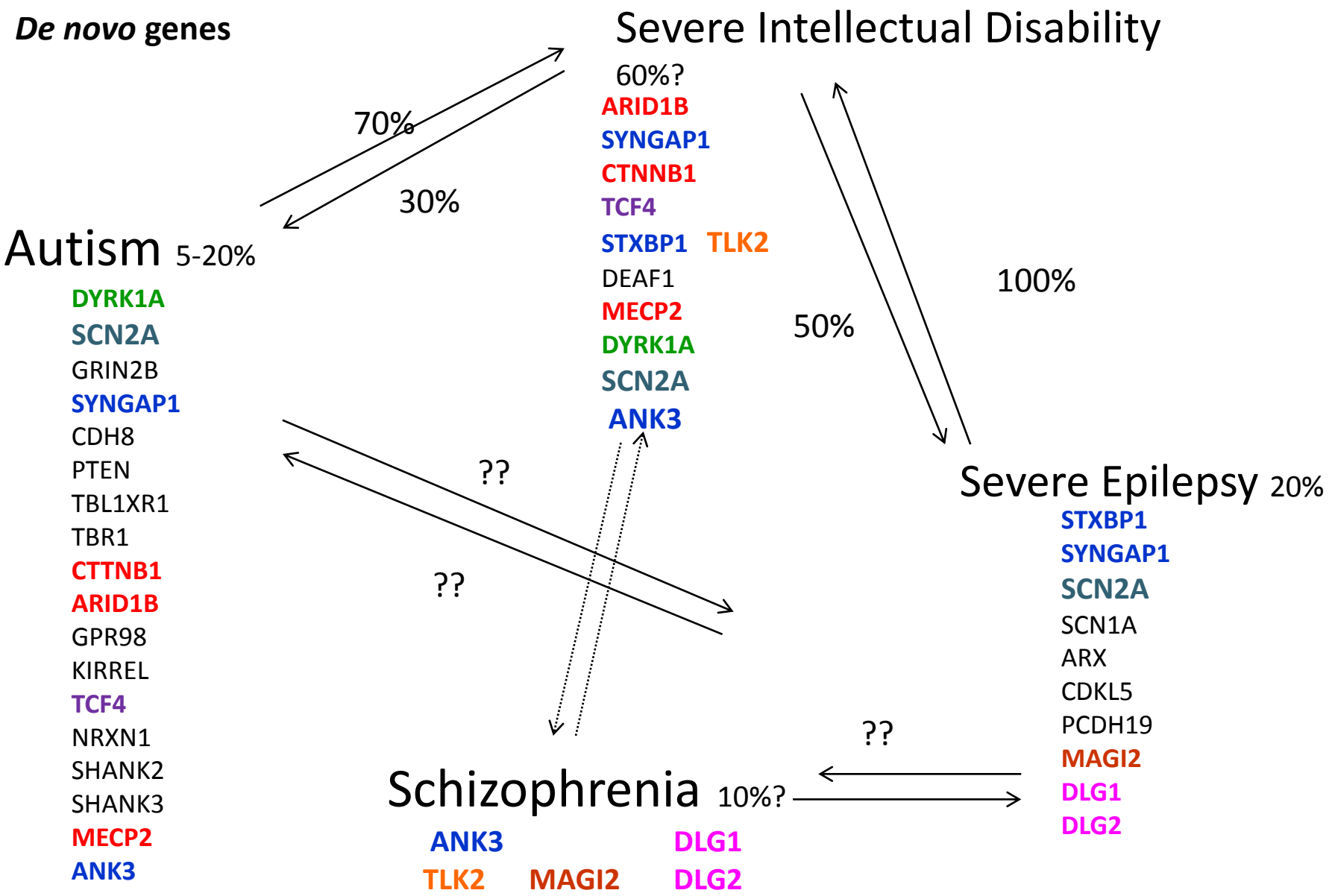
Nothing non-coding that we understand!

Majority of *new candidate* ID genes already confirmed

Additional mutations	No additional mutations
YY1	***ZMYM6***
DYNC1H1	***GRIA1***
DEAF1	***PHIP***
CIC	***WAC***
TANC2	***MIB1***
TNPO2	***PPP2R5D***
PHACTR	***KIF5C***
MTF1	***COL4A3BP***
GATAD2B	***EEF1A2***
CTNNB1	***MYTL1***
PROX2	***CAMIIKG***
LRP1	***ASH1L***
RAPGEF1	***PSMA7***
DDX3X	

An inconvenient truth:

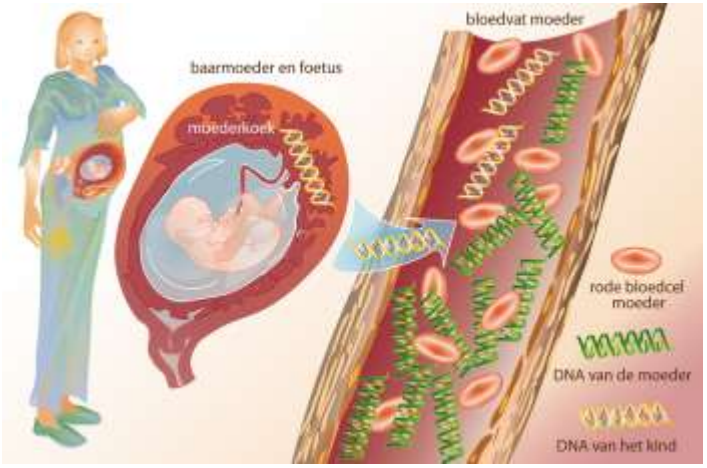
Genes do not respect diagnostic boundaries



An inconvenient truth

We cannot prevent *de novo* mutations

So should we offer prenatal testing to everyone?



Non invasive prenatal testing NIPT

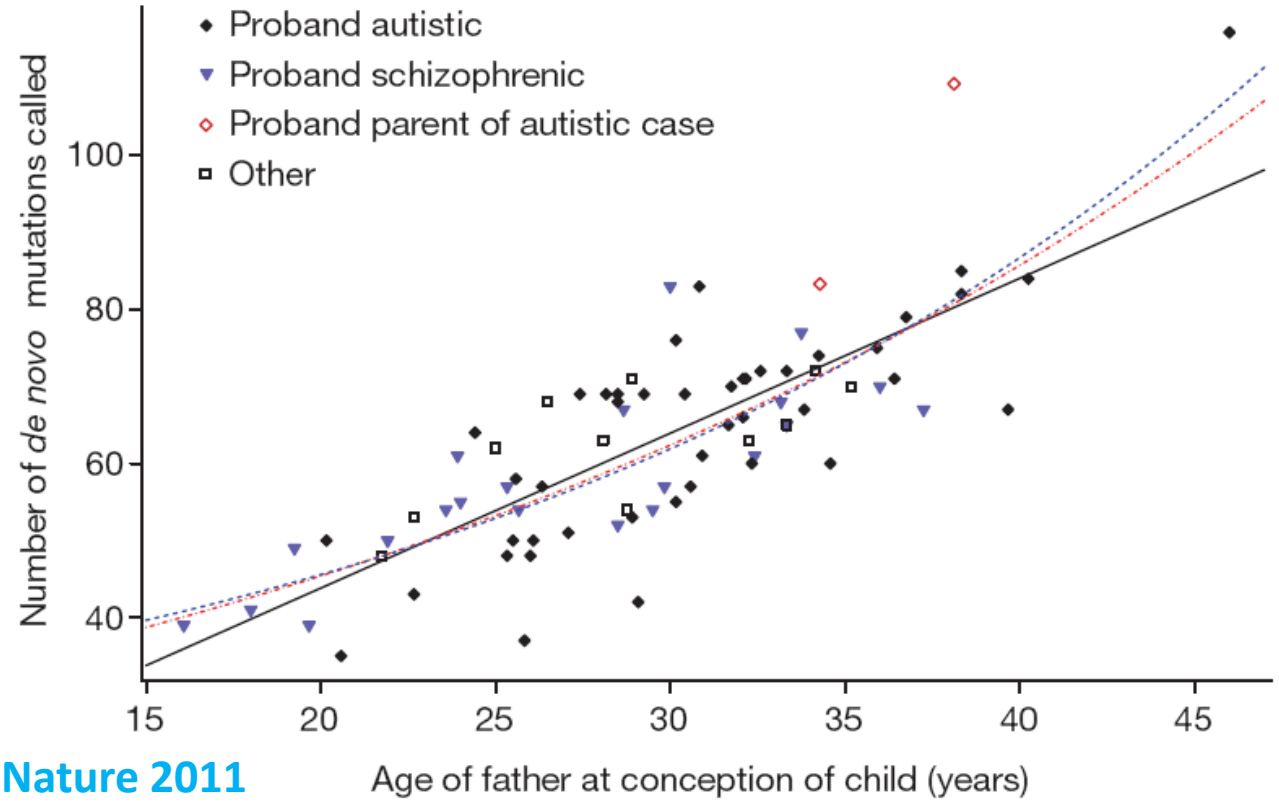
Why offer this for Down syndrome (risk 1/1000) and not for other forms of ID (risk 5/1000)?

Another inconvenient truth

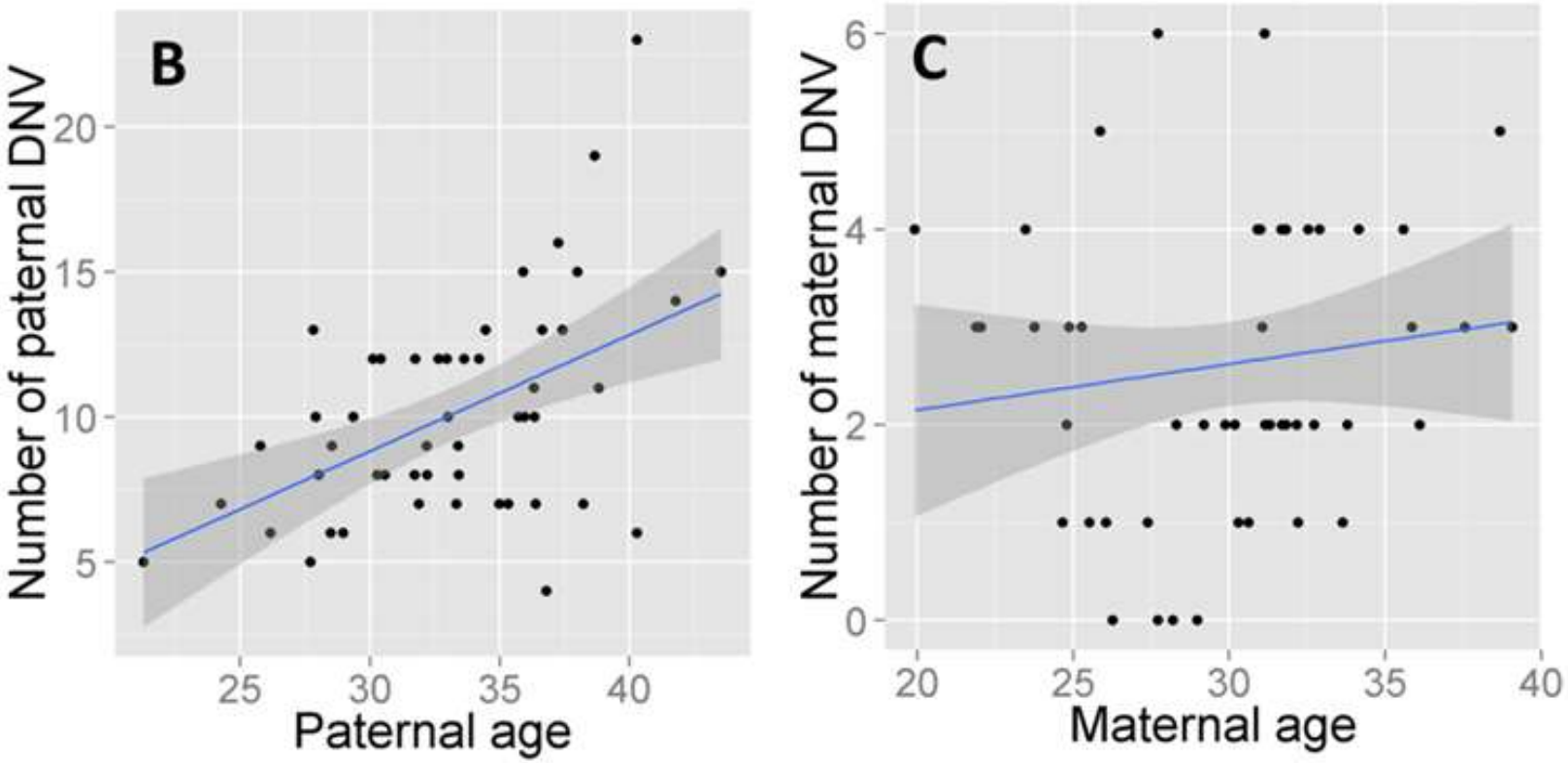
There is one known risk factor for *de novo* mutations

Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1],



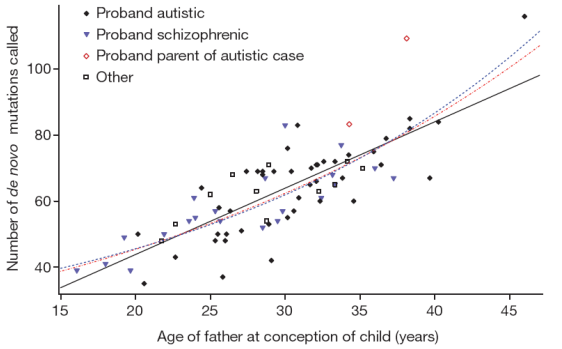
Kong et al. Nature 2011



Gilissen *et al*. Nature, 17 July 2014

A question to ponder

- Should we offer prenatal diagnosis to everyone?
- Should boys freeze their sperm at 17?



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Acknowledgements

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Maastricht UMC+

azM | Maastricht University

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