Genomes in the clinic

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Amersfoort, March 6th 2015

Maastricht UMC+ azM Maastricht University

Human Genetics Nijmegen

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Questions encountered in medical genetics

Exome sequencing could help to identify the causes of intellectual disability in children such as Siebe.

MEDICAL GENETICS

Gene hunt is on for mental disability

Pioneering clinical genome-sequencing projects focus on patients with developmental delay.

What is happening in our child?
What is cause (am I to blame)?
Who is expert in our child's disease?
What can be done about it?
What kind of complications can we expect and if possible prevent?
Is it hereditary, can we get a healthy next child?
Are there other children with similar disorders from which we can learn?

Finding the answer in the genome

6 billion nucleotides
46 chromosomes

2 people vary
at 4 million positions

1 variation (mutation)
can result in disease

Genome sequencing: All variation in one experiment!

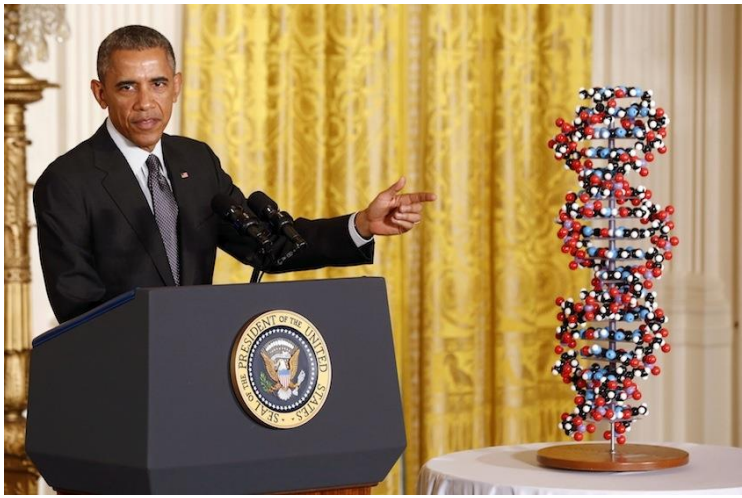
DNA from
blood/saliva

Genome
with all variation

Important:
- Accuracy
- Speed
- Price

Genome sequencing centers are being established around the world

Transformative Genomics: England Begins Daunting Task of Sequencing 100,000 Genomes by 2017



Genomics england

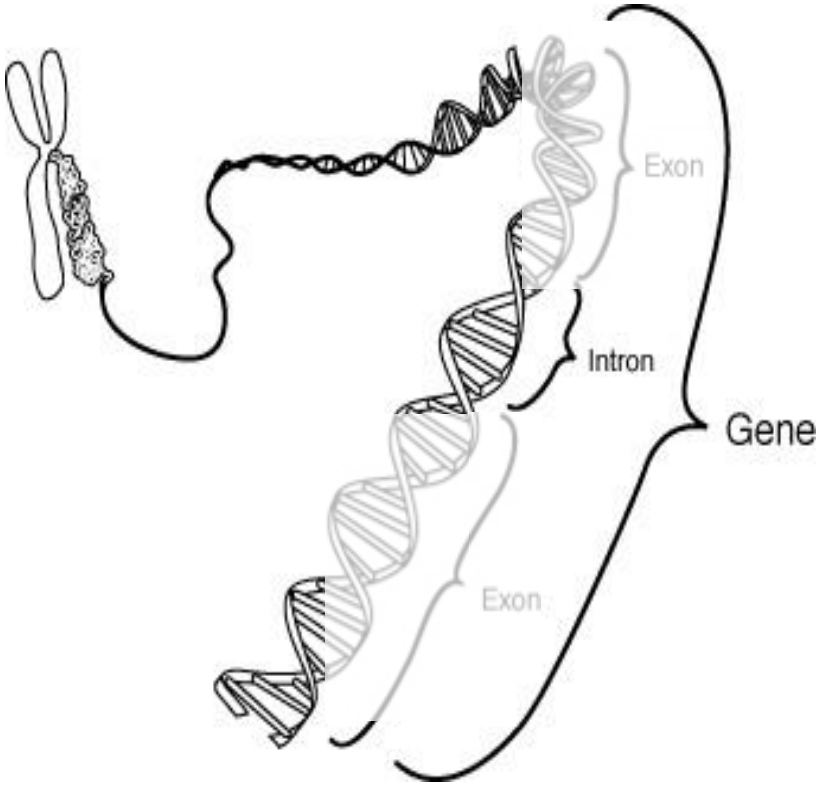
"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

— President Barack Obama, State of the Union Address, January 20, 2015

Exome sequencing; Practicing for genomes

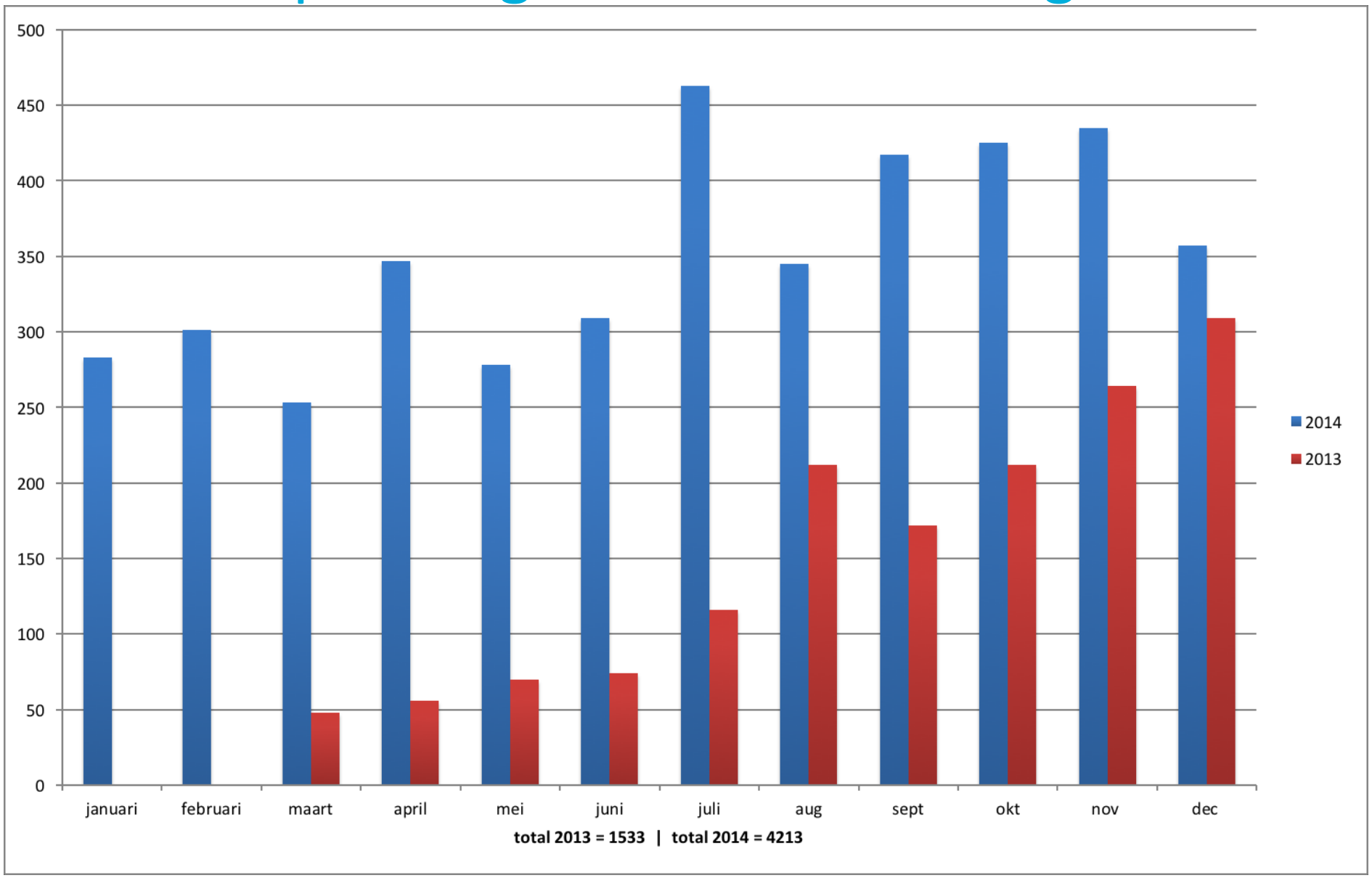
‘Exome’ (all exons of a genome)

~1% of the human genome

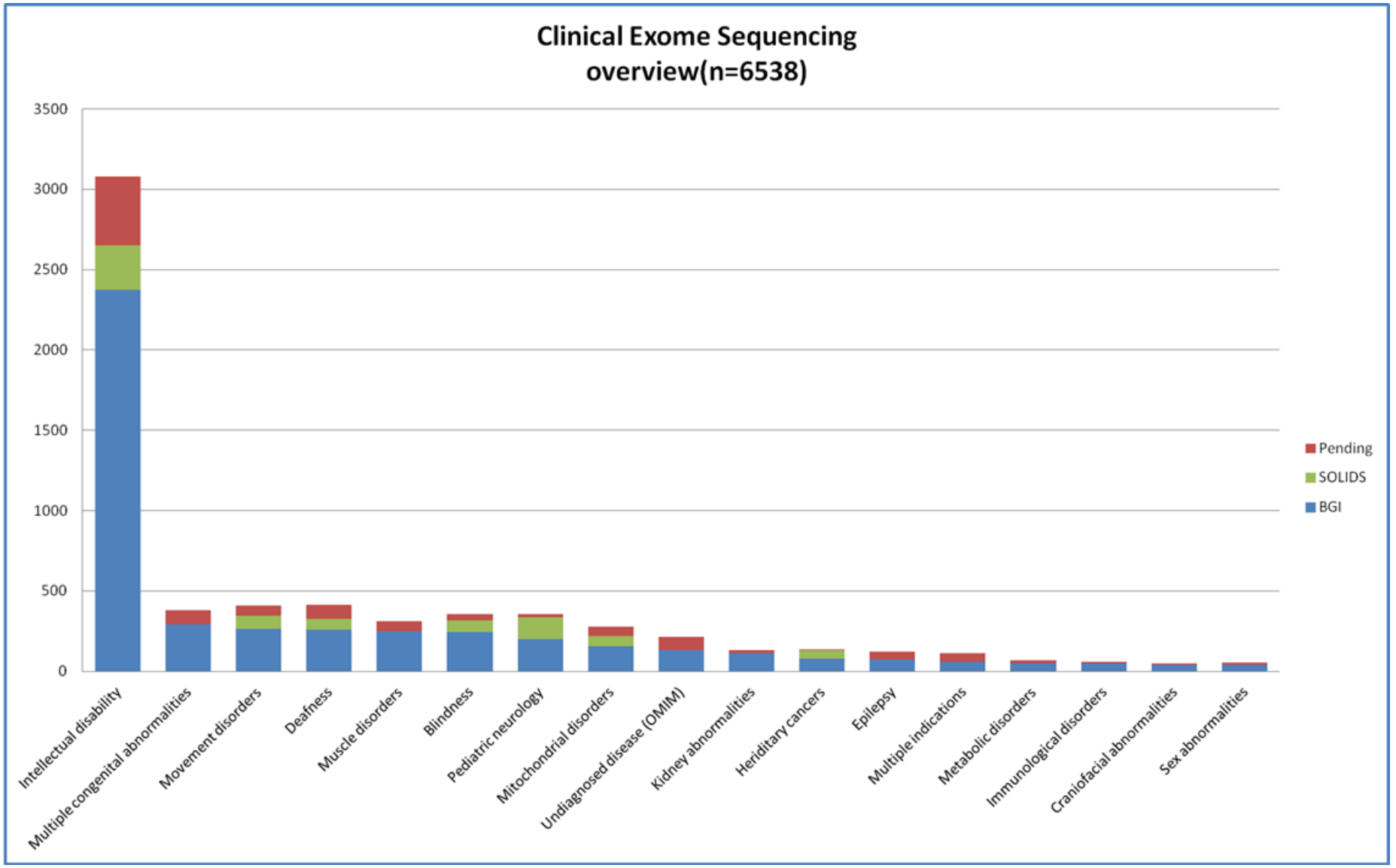


‘All’ coding sequences of a human genome (>180,000 exons), sequenced and analyzed in **one** experiment

Exome sequencing now a routine diagnostic test



Exome sequencing used for 17 diseases



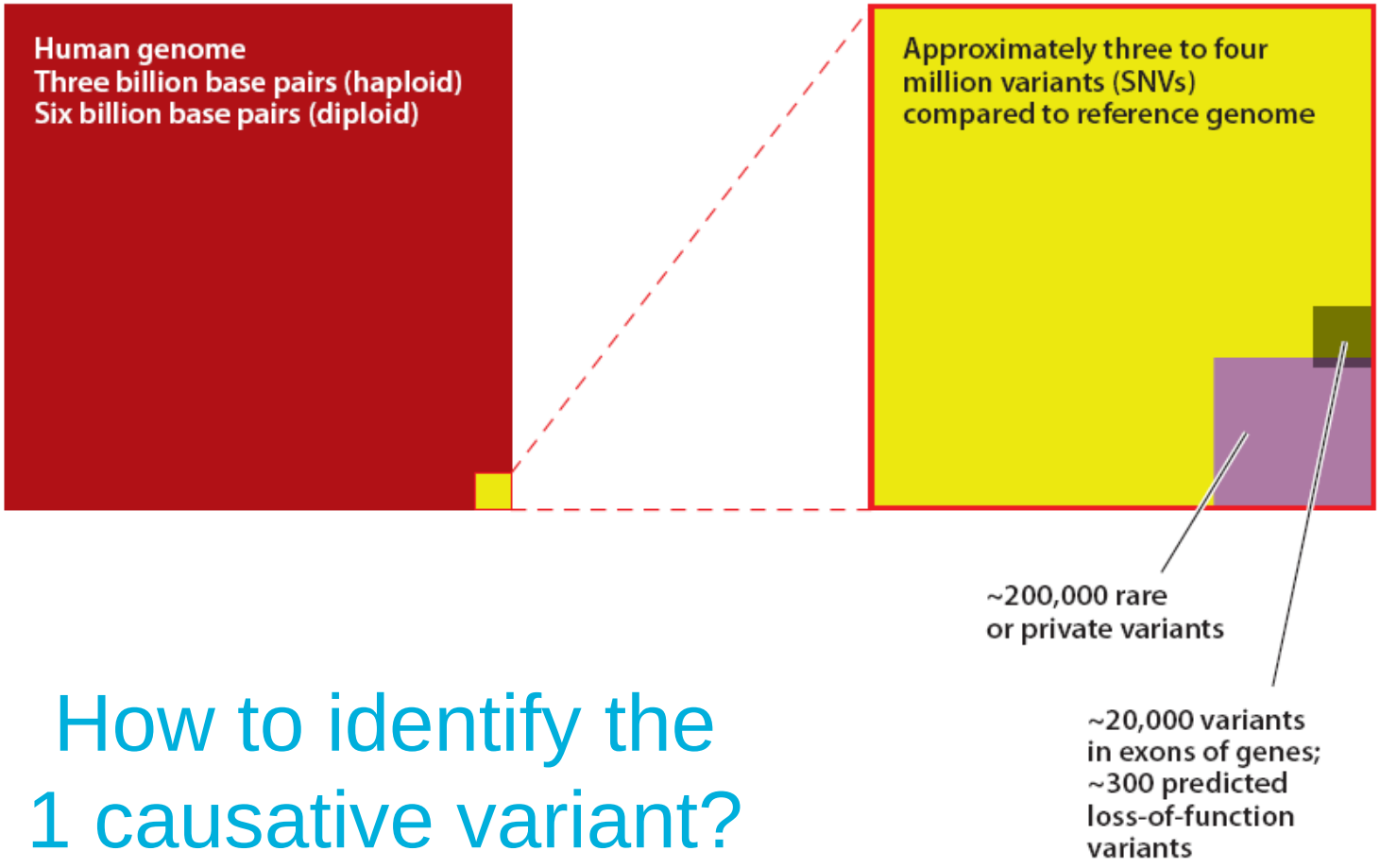
New challenges

- Variant identification has become easy:
  All variation is present in genome sequence

- Variant interpretation remains difficult:
  Which variant causes disease?

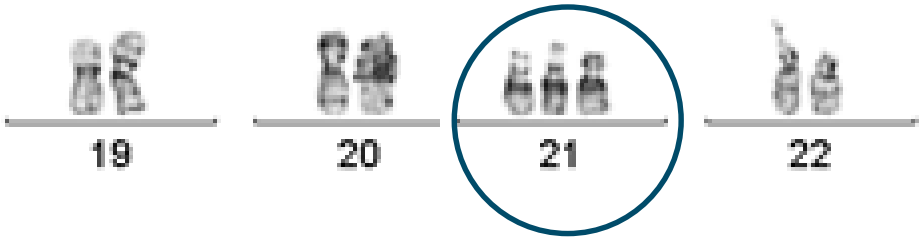
- Learn about normal variation
- Start with severe genetic diseases
- Try to prioritize pathogenic variants

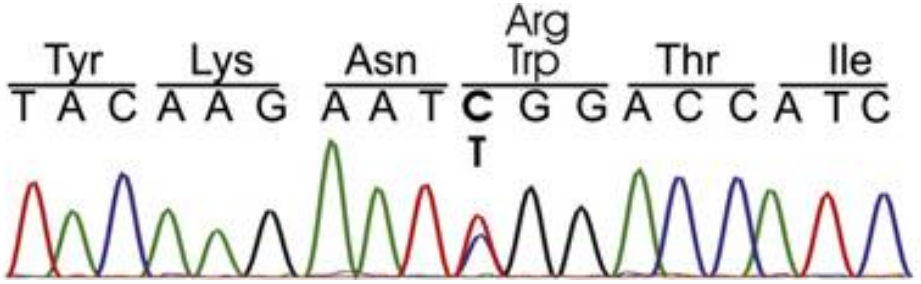
Prioritization of variants causing genetic disease



How to identify the 1 causative variant?

Boyd SD. Annu Rev Pathol Mech. Dis. 2013



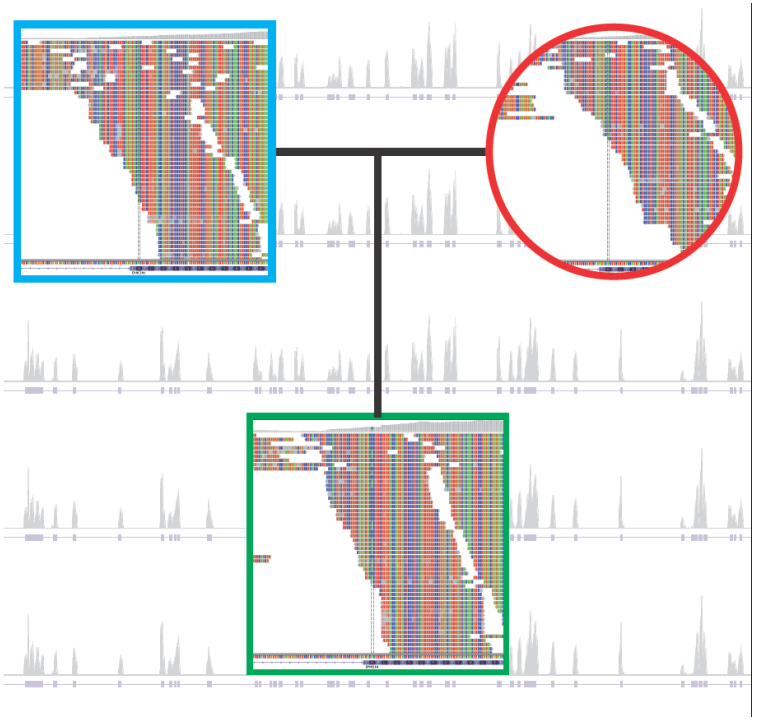


PACS1 gene

Unbiased detection of *de novo* mutations is now possible!

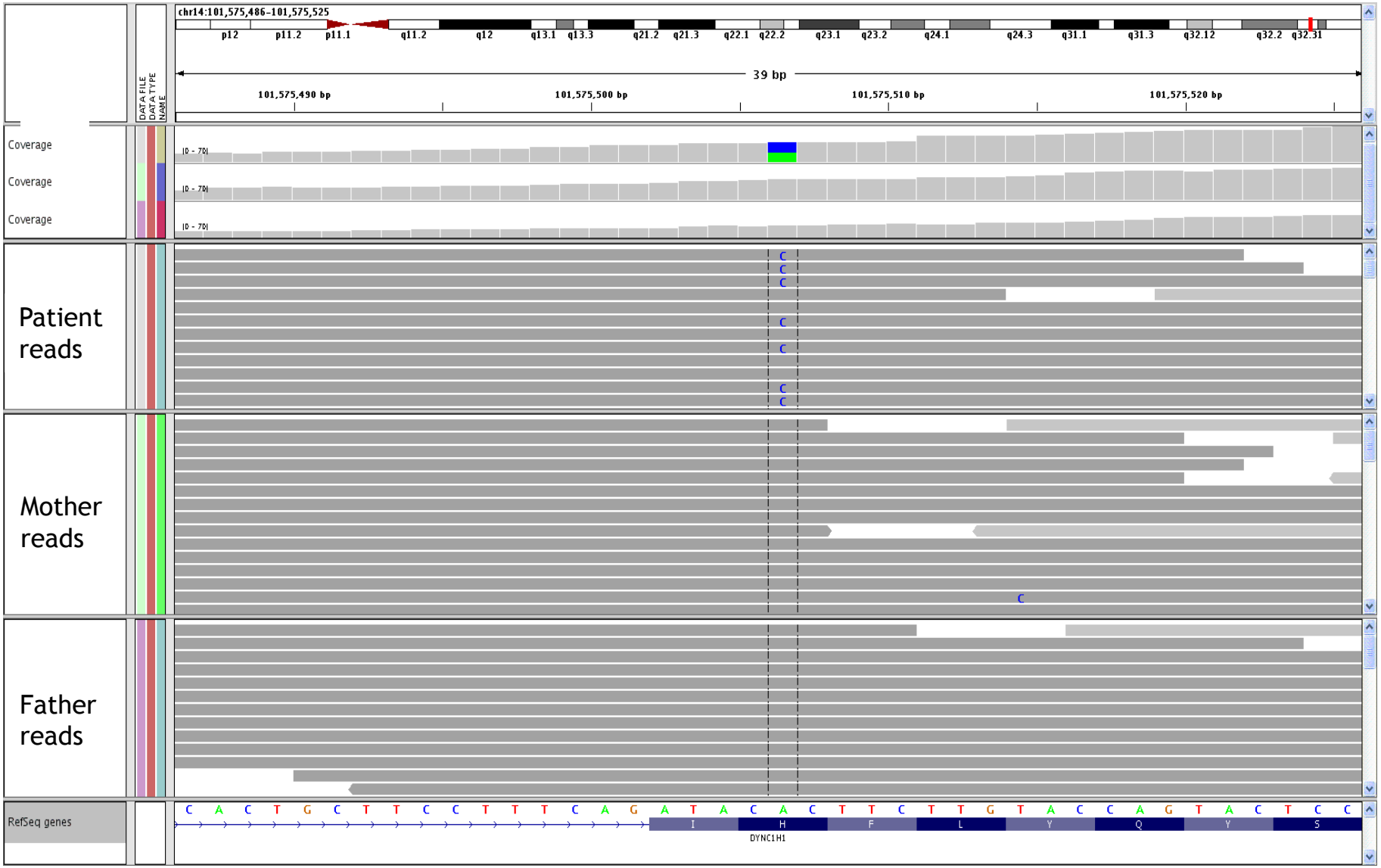
Genome/exome sequencing of patient-parent trios

All genomic variants
robust, fast & inexpensive



Use trio-approach to filter
for *de novo* mutations

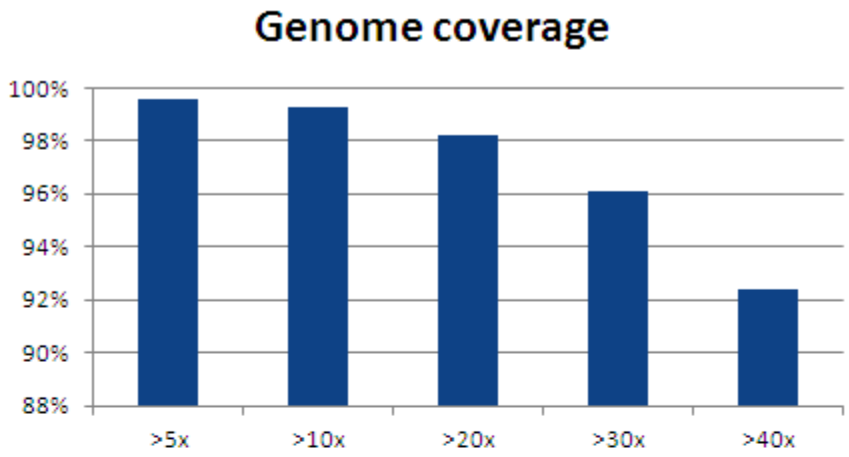
Visualization of *de novo* mutations

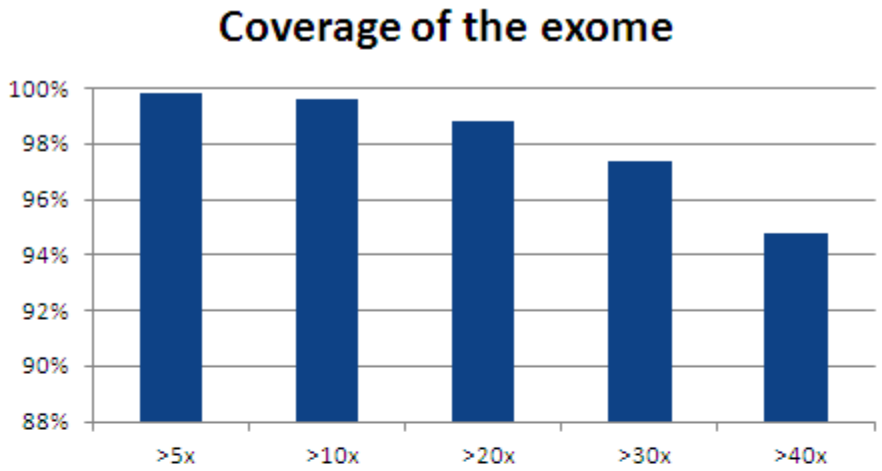


Whole Genome Sequencing in 50 ID trios

- Collaborative research project with Complete Genomics (sequencing outsourced)
- 50 patients/parent trios “negative” after Sanger sequencing, diagnostic microarrays and exome sequencing
- High quality WGS: >80 fold coverage

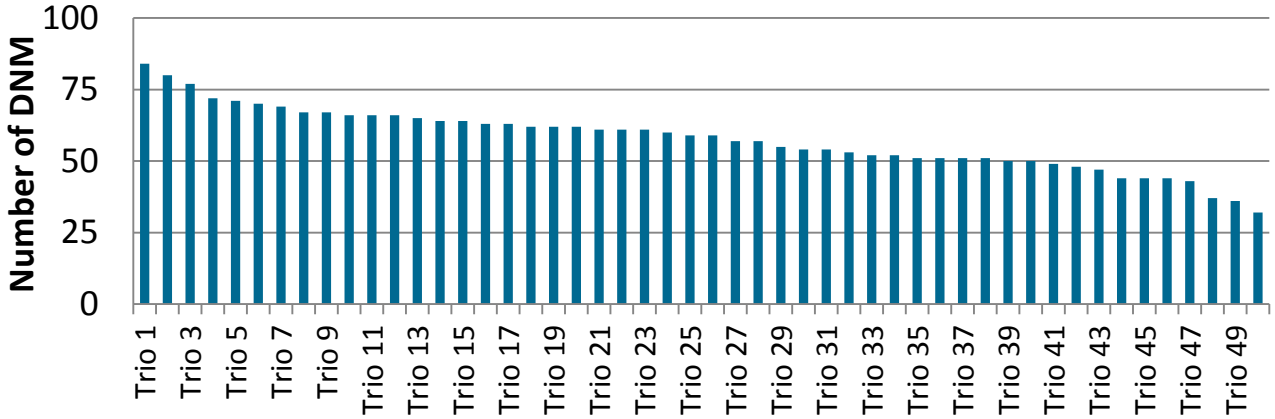
Sequencing statistics: High coverage of genome





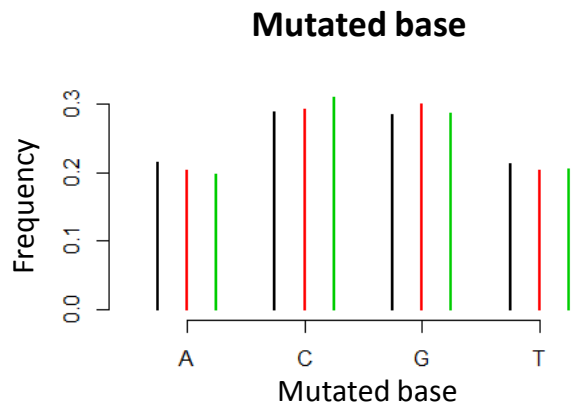
Variant type	Genome (StDev)	Exome (StDev)
SNV	3,440,782 (22,938)	21,575 (185)
Insertion	263,282 (9,509)	272 (15)
Deletion	272,266 (8,686)	242 (10)
Deletion/Insertion	90,263 (1,798)	380 (18)
CNVs	270 (35)	45 (4)
Possible *de novo* (high QC)	77 (range 45-105)	1-2 (range 0-4)

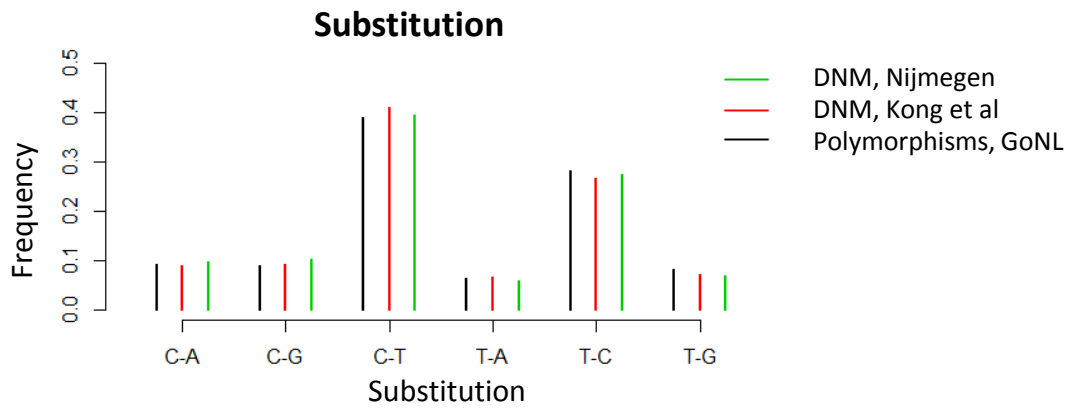
De novo mutations identified by genome sequencing



- Single Nucleotide
- Autosomes
- Private

- Average = 56 per person
- Range: 32 – 84
- Mut Freq: 10^{-8} - $3 \cdot 10^{-8}$





Kong *et al.* Nature 2012; Boomsma *et al.* EJHG 2014

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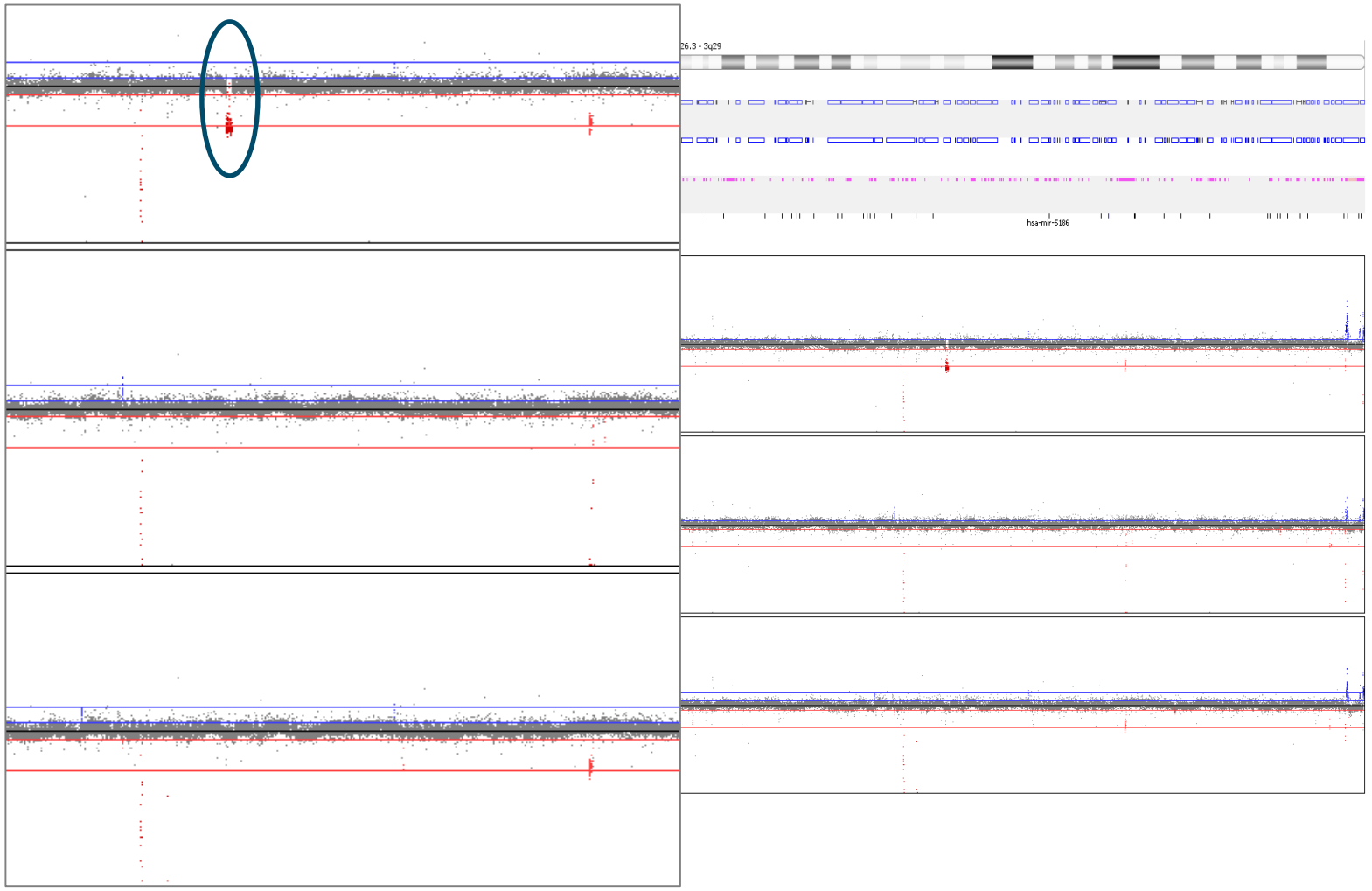
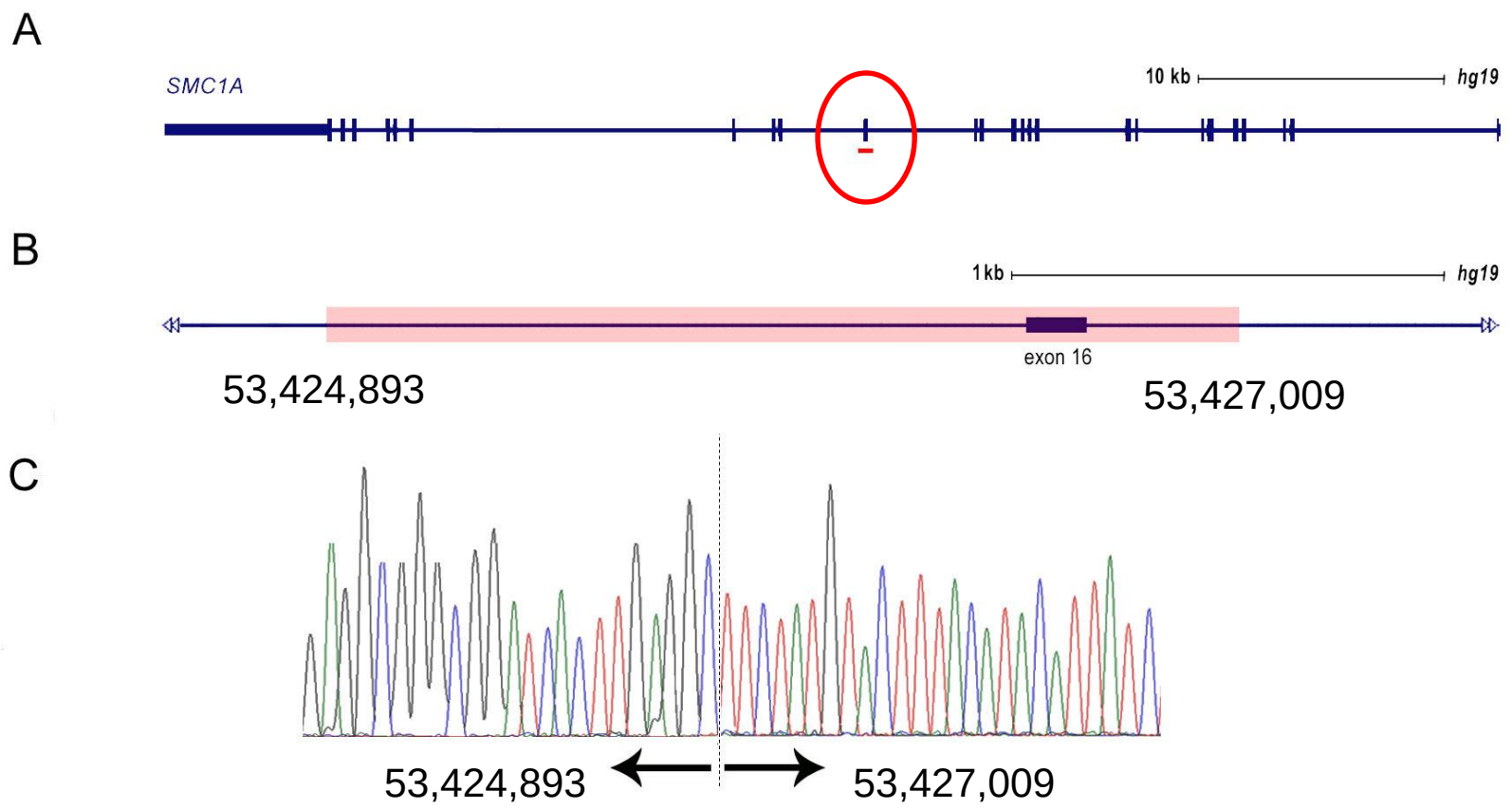
Genome sequencing detects many *de novo* mutations in known ID genes!

Trio	Gene	Protein effect	Mutation type	PhyloP	Gene Classification†
9	*WDR45*	p.(Cys344Alafs*67)	Frameshift	-	Known
13	*SMC1A*	p.(Asn788Lysfs*10)	Frameshift	-	Known
25	*SATB2*	p.(Gln310delinsHisCysLysAlaThr)	Insertion	-	Known
46	*TBR1*	p.Thr532Argfs*144	Frameshift		Known
1	*NGFR*	p.(Cys122Arg)	Missense	4.97	-
2	*GFPT2*	p.(Thr680Ser)	Missense	6.02	-
7	*TBR1*	p.(Gln373Arg)	Missense	3.51	Known
15	*SPTAN1*	p.(Glu91Lys)	Missense	5.69	Known
22	*MED13L*	p.(Asp860Gly)	Missense	4.75	Candidate
24	*BRD3*	p.(Phe334Ser)	Missense	4.48	-
26	*PPP2R5D*	p.(Trp207Arg)	Missense	5.13	Candidate
27	*KCNA1*	p.(Thr371Ile)	Missense	5.69	Known
30	*MAST1*	p.(Pro1177Arg)	Missense	5.28	-
41	*NACC1*	p.(Arg468Cys)	Missense	3.51	-
21	*ALG13*	p.(Asn107Ser)	Missense	1.34	Known*
17	*ASUN*	p.(Gln99*)	Nonsense	-	-
21	*RAI1*	p.(Gln88*)	Nonsense	-	Known
28	*SCN2A*	p.(Gln1521*)	Nonsense	-	Known
34	*APPL2*	p.(Ser329*)	Nonsense	-	-
43	*POGZ*	p.(Arg1001*)	Nonsense	-	Candidate

Power of high quality WGS: Detection of 8 clinically relevant CNVs missed by microarrays



2 kb *de novo* single exon deletion SMC1A



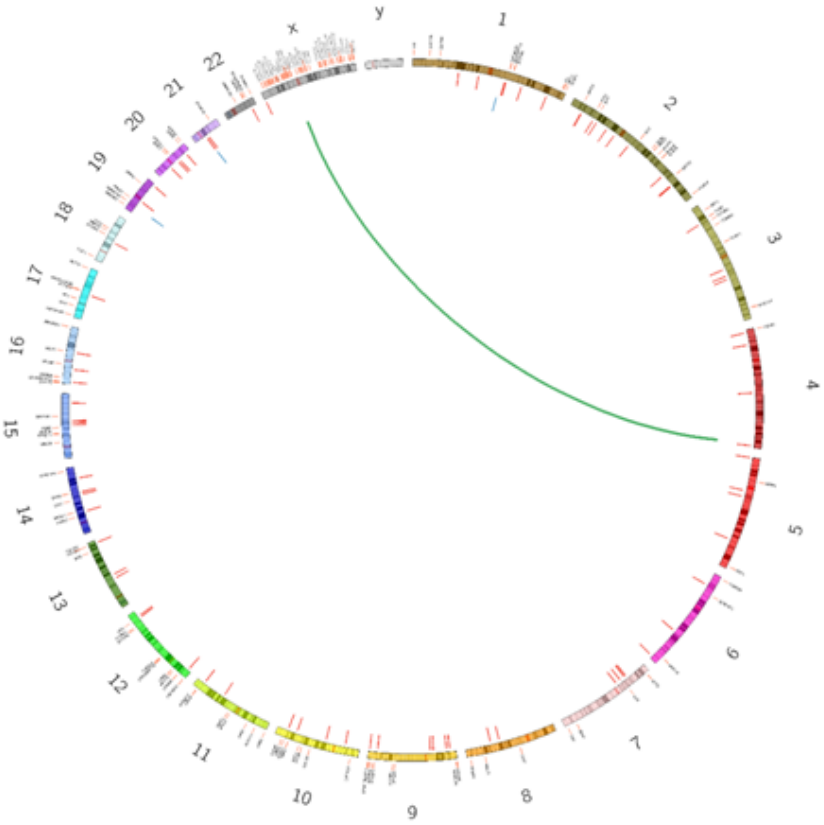
Breakpoint resolution WGS data, detected with SV annotator!

Patient

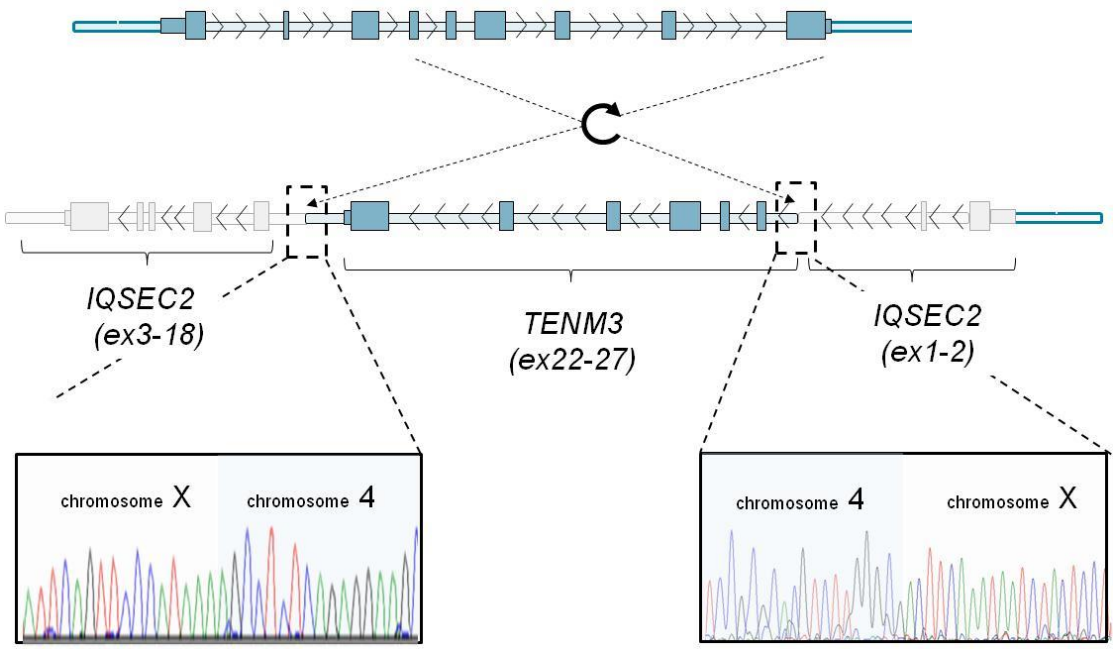
De novo duplication on chr 4

Mother

Father



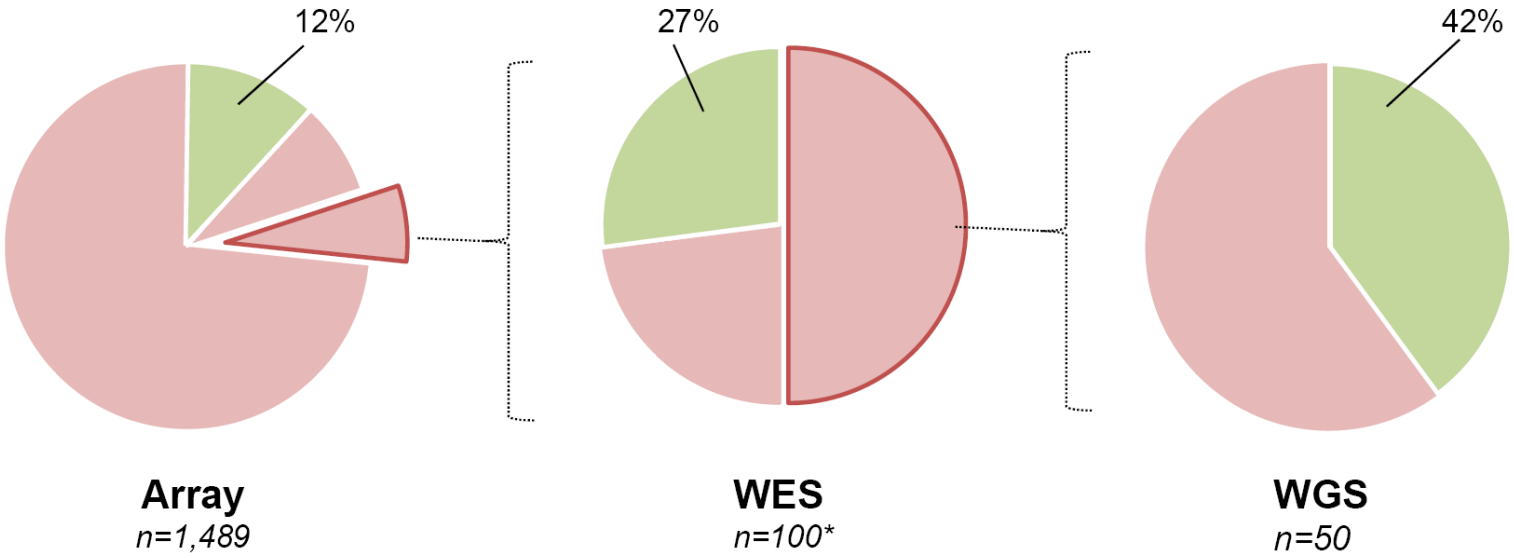
Duplication in chr X



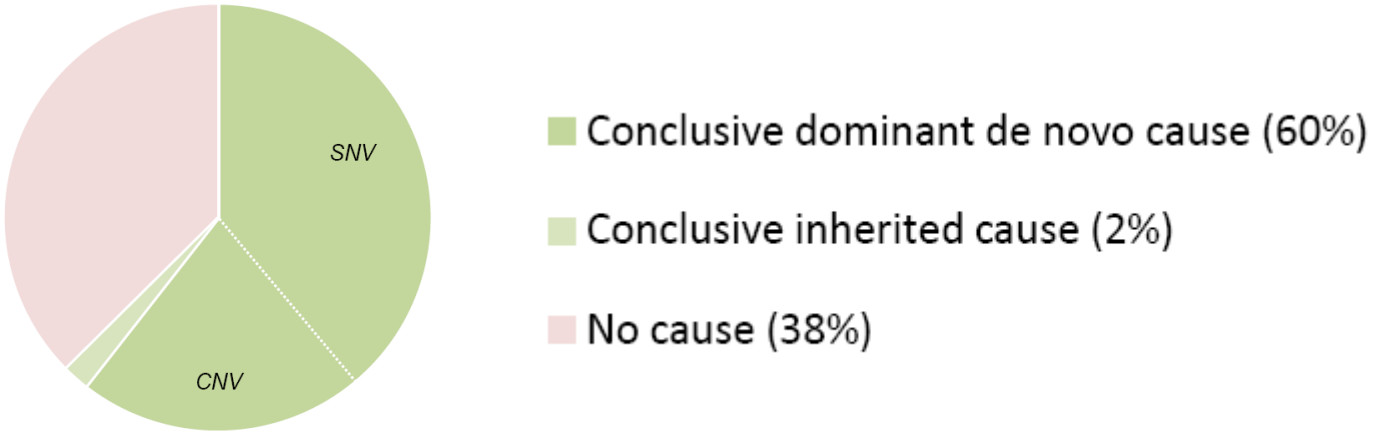
Duplication disturbs IQSEC2 gene

Diagnostic yield WGS this study and unbiased cohort

This study



Unbiased cohort



Gilissen *et al.* Nature 2014

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DIAGNOSTICS

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5]* Neil Andrew Miller,[1,2,4]* Sarah Elizabeth Soden,[1,2,4]* Darrell Lee Dinwiddie,[1,2,3,4,5]* Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3] Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6] Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6] Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4] Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5]†

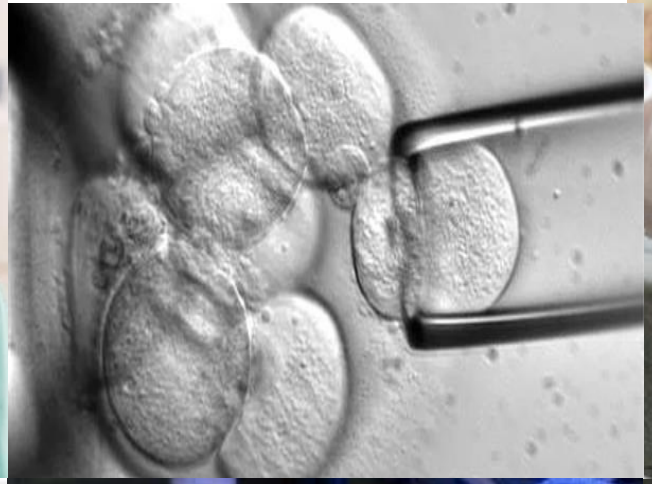
Preconceptional genetic carrier testing and the commercial offer directly-to-consumers

Pascal Borry[1,2,3,*], Lidewij Henneman[2], Phillis Lakeman[2], Leo P. ten Kate[2], Martina C. Cornel[2], and Heidi C. Howard[1]

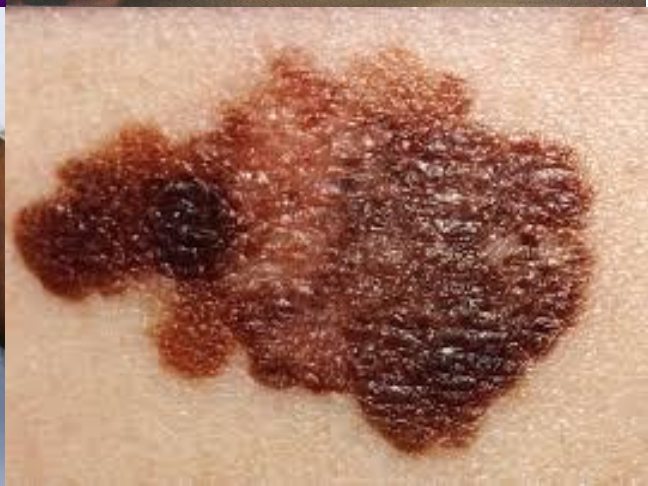
Diagnostic Accuracy of Noninvasive Detection of Fetal Trisomy 21 in Maternal Blood: A Systematic Review

Non-invasive prenatal measurement of the fetal genome

H. Christina Fan[1]†*, Wei Gu[1]*, Jianbin Wang[1], Yair J. Blumenfeld[2], Yasser Y. El-Sayed[2] & Stephen R. Quake[1,3,4]

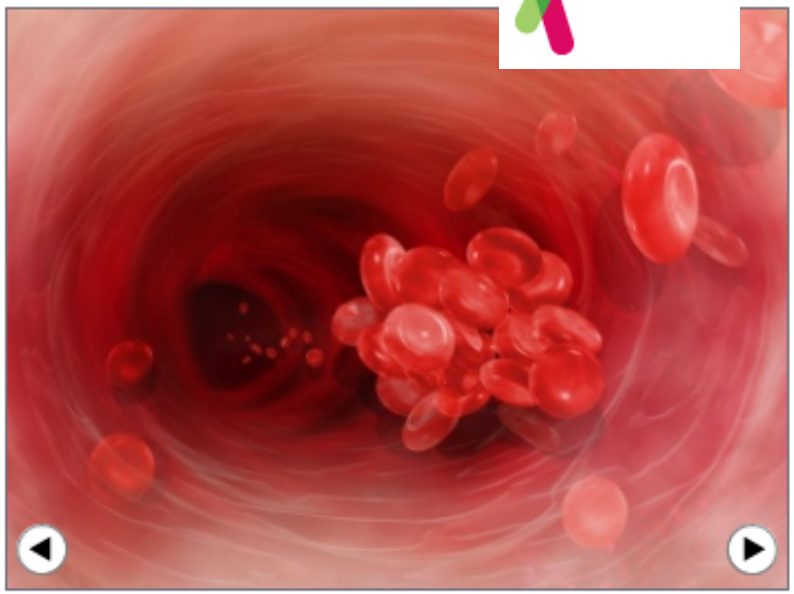



"My doctors estimated that I had an 87% risk of breast cancer and a 50% risk of ovarian cancer."
CTV



About Warfarin Sensitivity

Each time a doctor writes a prescription for warfarin (Coumadin ®), a blood thinner given to about two million people each year in the United States, it's a guessing game. There is no "right" dose of the drug. Everyone is different and it can take weeks of adjustment to find a patient's optimal amount of the medication. Too much puts the patient at risk for bleeding. Too little can lead to clots and in turn, heart attack, stroke or even death. A patient's optimal dose depends not only on age, size, other medications and even diet, but also to a large extent on genetics.



1 of 3. Warfarin is a drug that can help prevent blood clots.

SNP	Genotype	Combination
rs1799853	CC	CYP2C9 *1/*1, VKORC1 -1639/3673 AG
rs1057910	AA	
rs9923231	CT	

Your Genetic Data

Show results for all profiles

Who	What It Means
	Substantially increased warfarin sensitivity. May require greatly decreased warfarin dose.
	Increased warfarin sensitivity. May require decreased warfarin dose.
Joris Veltman	Slightly increased warfarin sensitivity. May require decreased warfarin dose.
	Typical warfarin sensitivity.

Genes vs. Environment

Only a medical professional can determine the right dosage of warfarin for a particular patient. Clinical information such as age, size and other medications the patient is taking can affect a person's optimal dose. The amount of vitamin K in the diet is also a factor. In addition to the genetic variations reported here, there may be other genetic factors that impact warfarin response. The information contained in this Clinical Report should not be used to independently establish or adjust an existing warfarin regimen.

Why perform whole genome sequencing?

If you consider genetics may play a role in your patient:

Why not read the entire book?
Why settle for studying what we now know?
We still live in the dark ages of genetics!

Key advantages of genome sequencing:

Completeness	All variation
Simplicity	One test