Preimplantation Genetic Testing by haplotyping

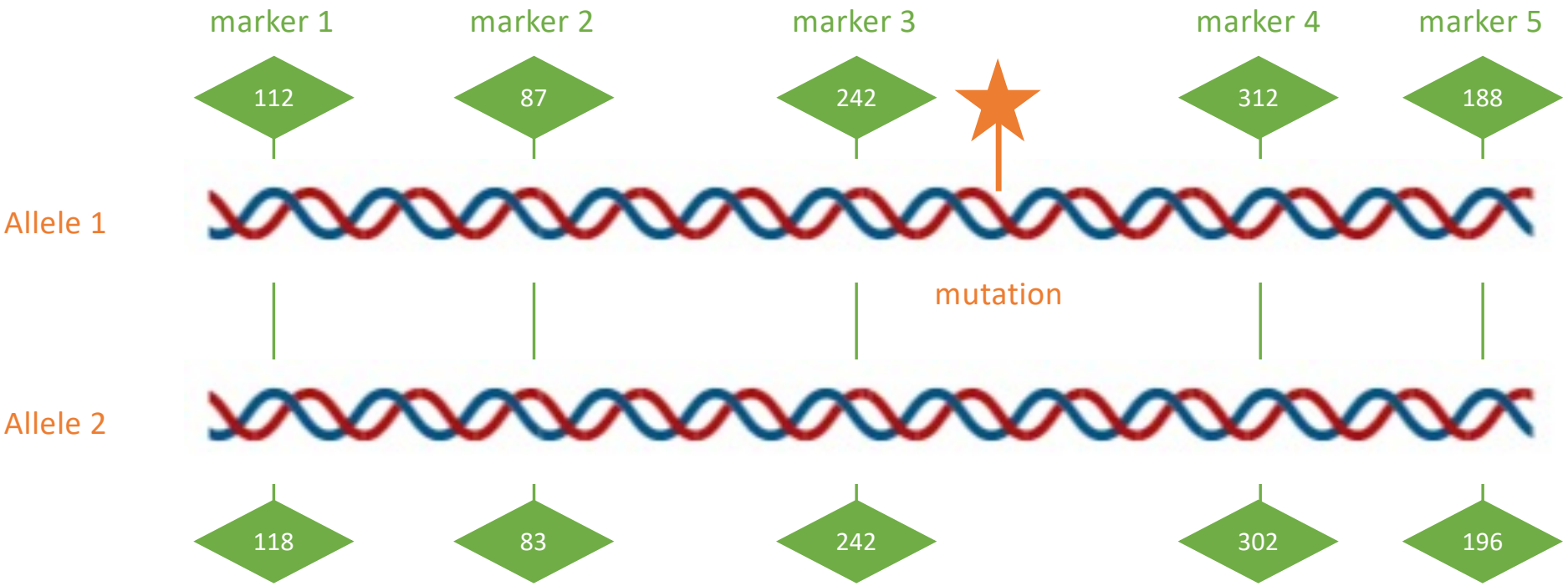
CENTRUM MEDISCHE GENETICA GENT

Björn Menten

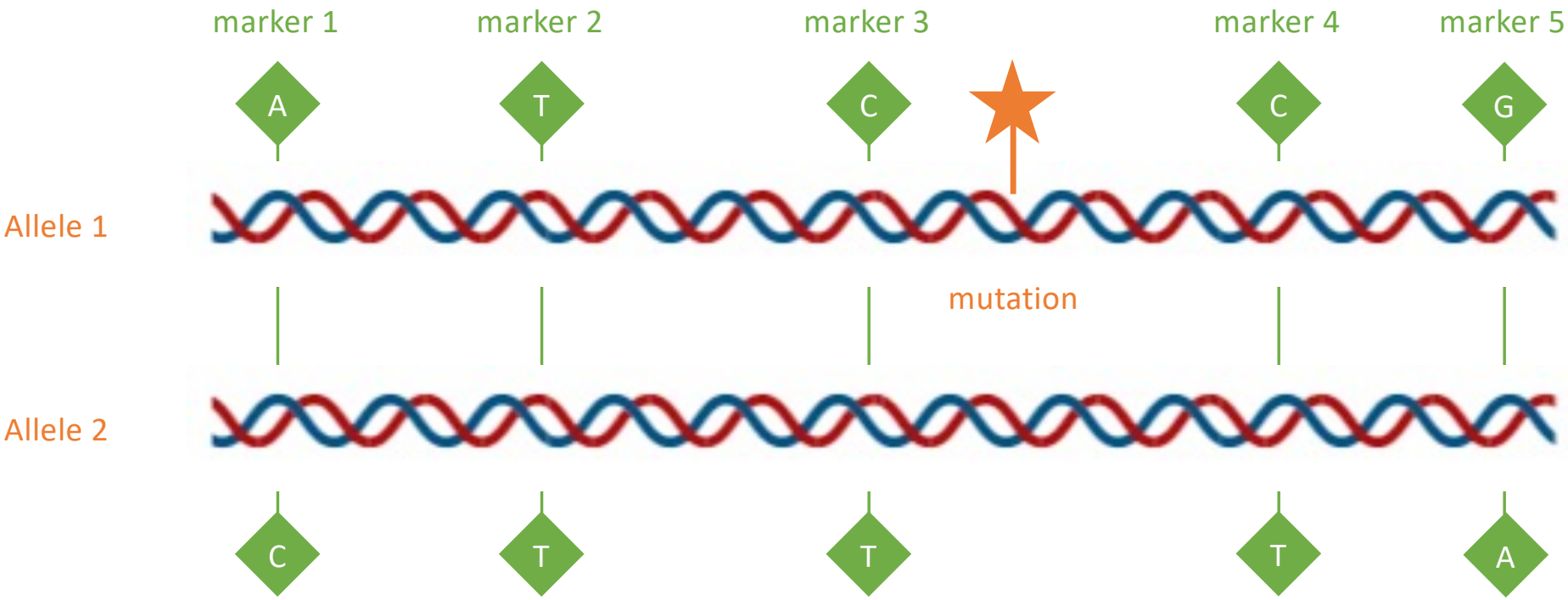
PGT-M by haplotype phasing

- The (familial) variant (locus) is known
- Only for class 4 or class 5 variants

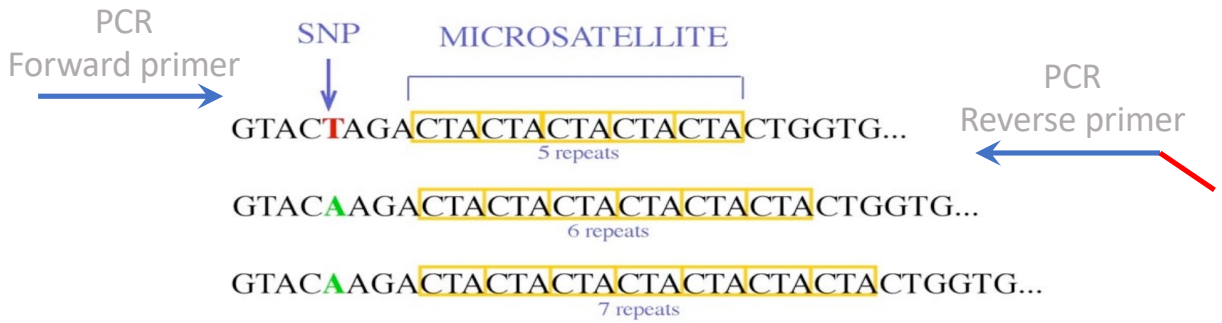
PGT-M by haplotype phasing – STR analysis

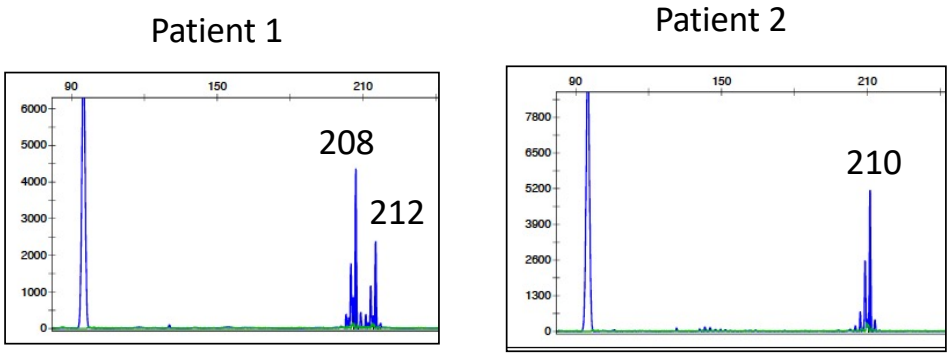


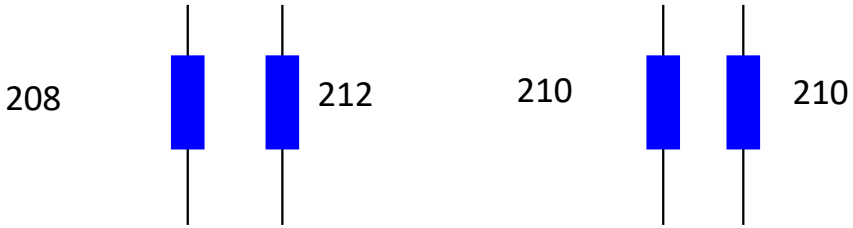
PGT-M by haplotype phasing – SNV analysis



Short Tandem Repeats

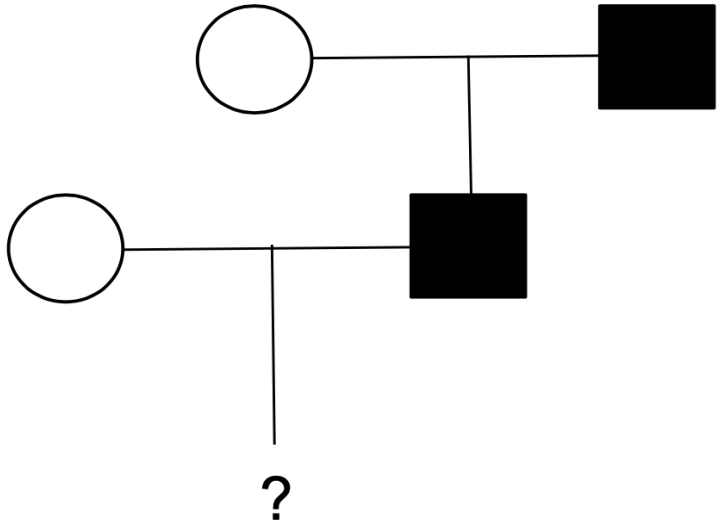






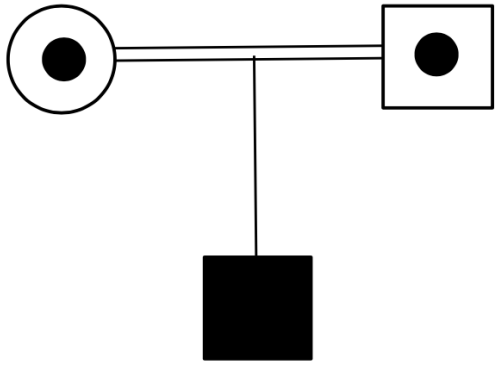
PGT-M by haplotype phasing

dominant inheritance



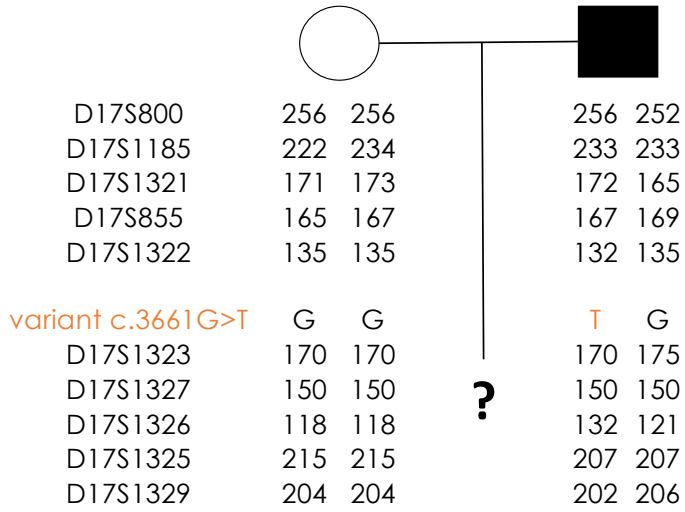
Sample from an additional affected family member needed for phasing of the haplotype

recessive inheritance

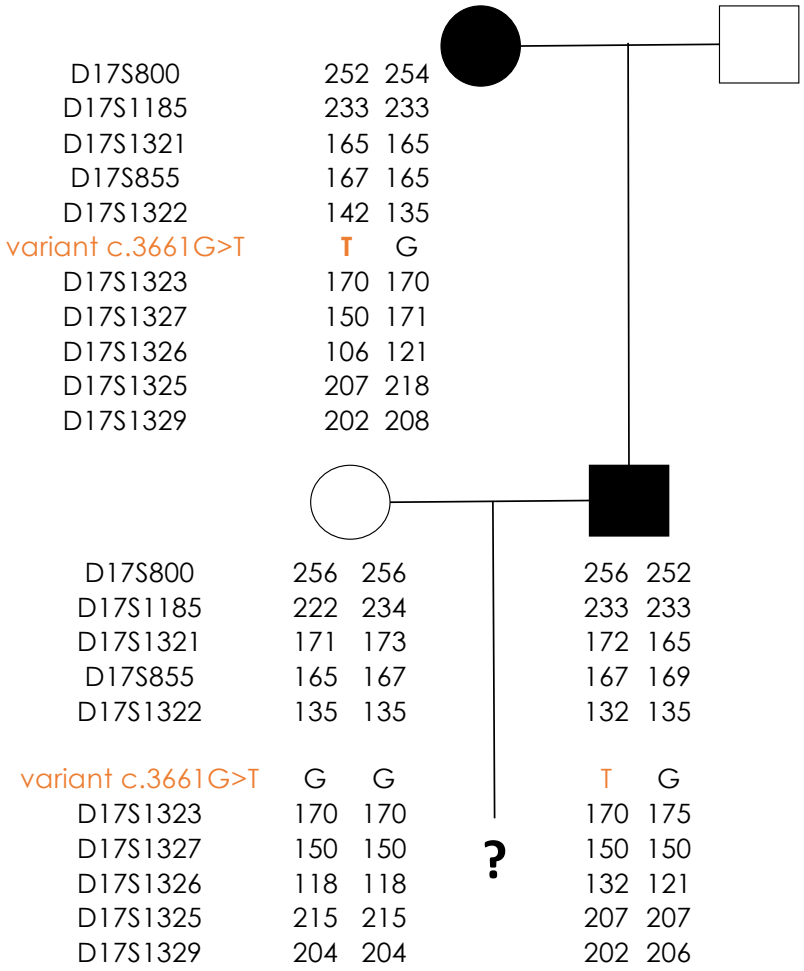


Sample from parents and affected child needed for phasing of the haplotype

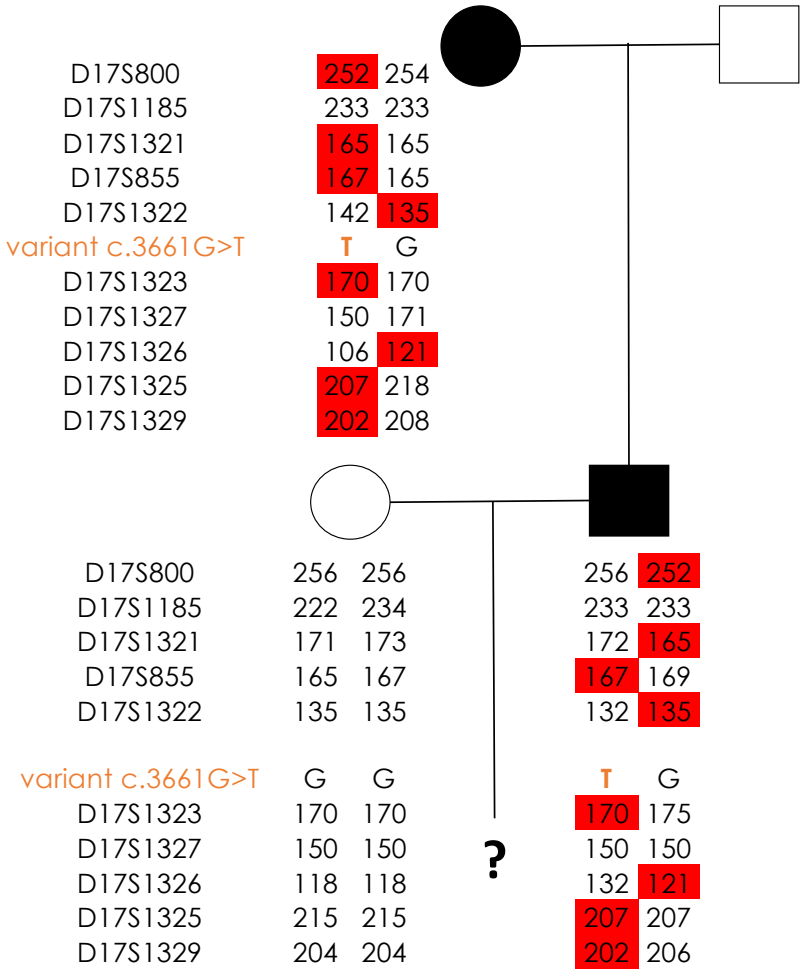
Haplotyping by STR analysis: genetic workup



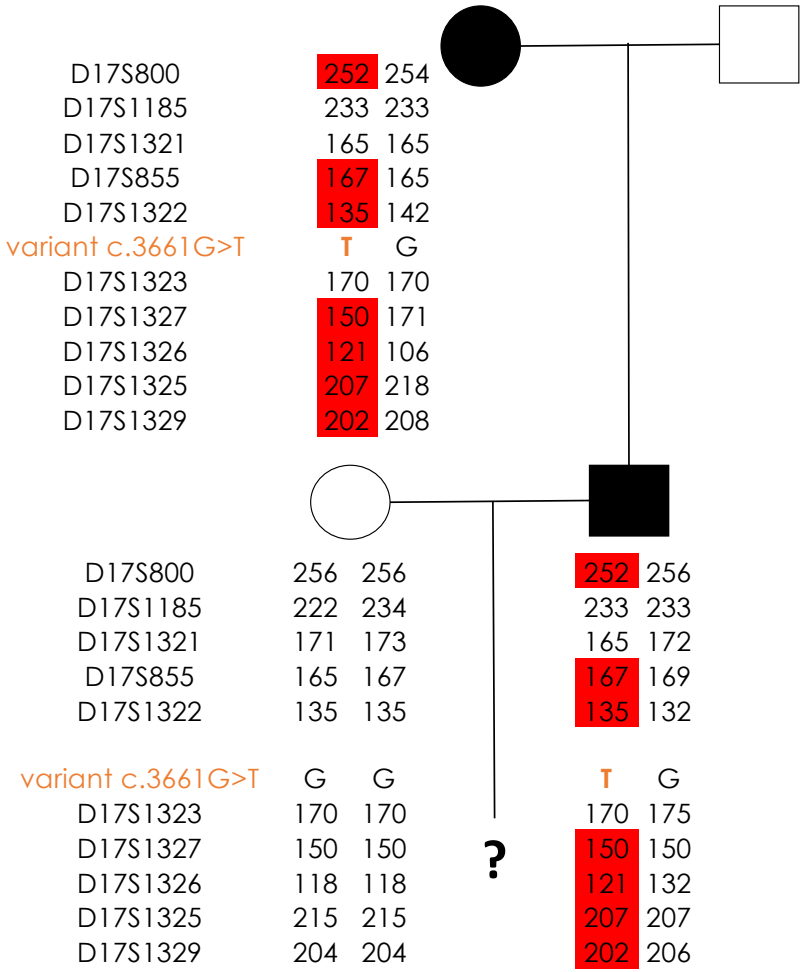
Haplotyping by STR analysis: genetic workup



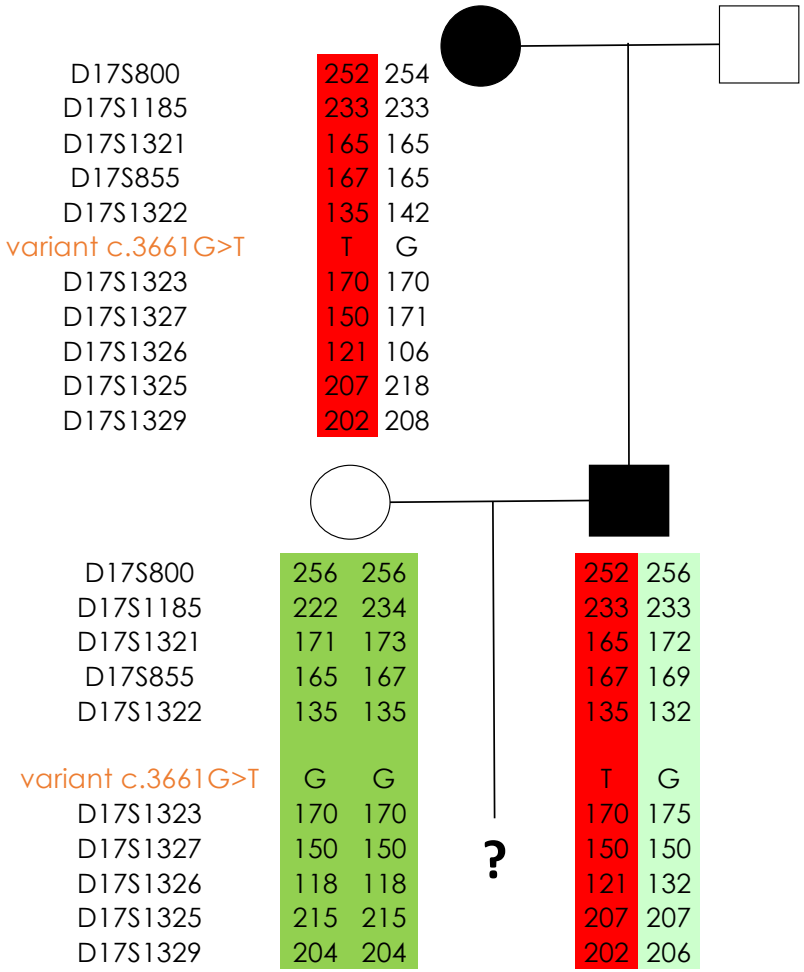
Haplotyping by STR analysis: genetic workup



Haplotyping by STR analysis: genetic workup



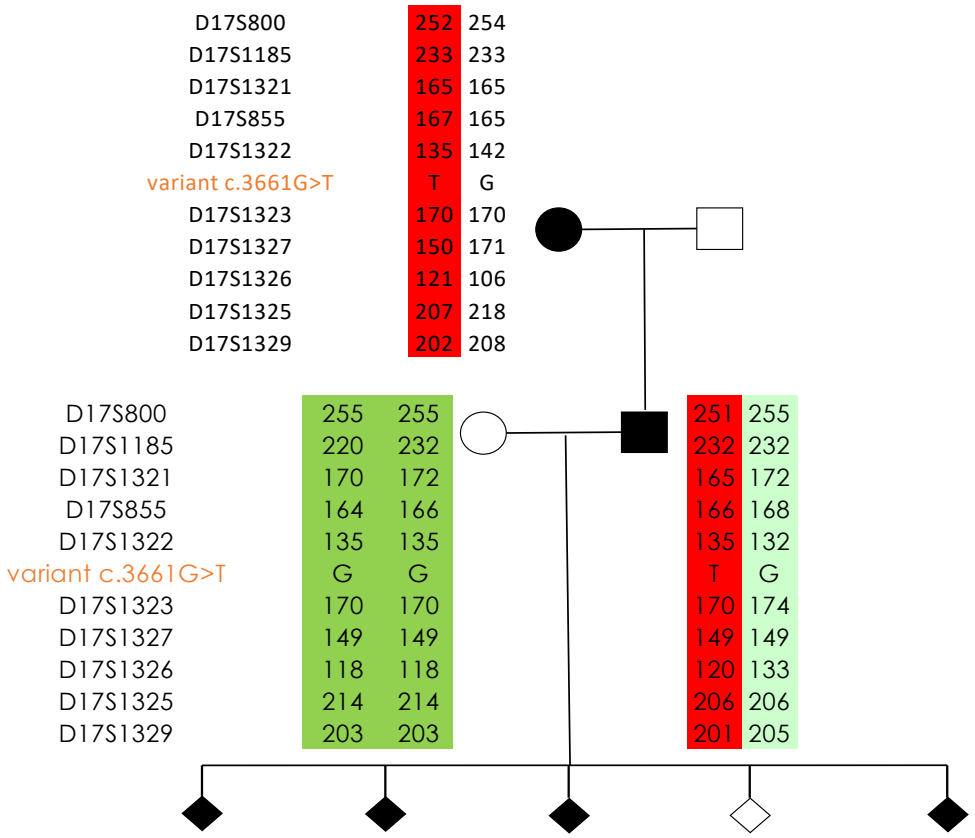
Haplotyping by STR analysis: genetic workup



Haplotyping by STRs

embryo analysis

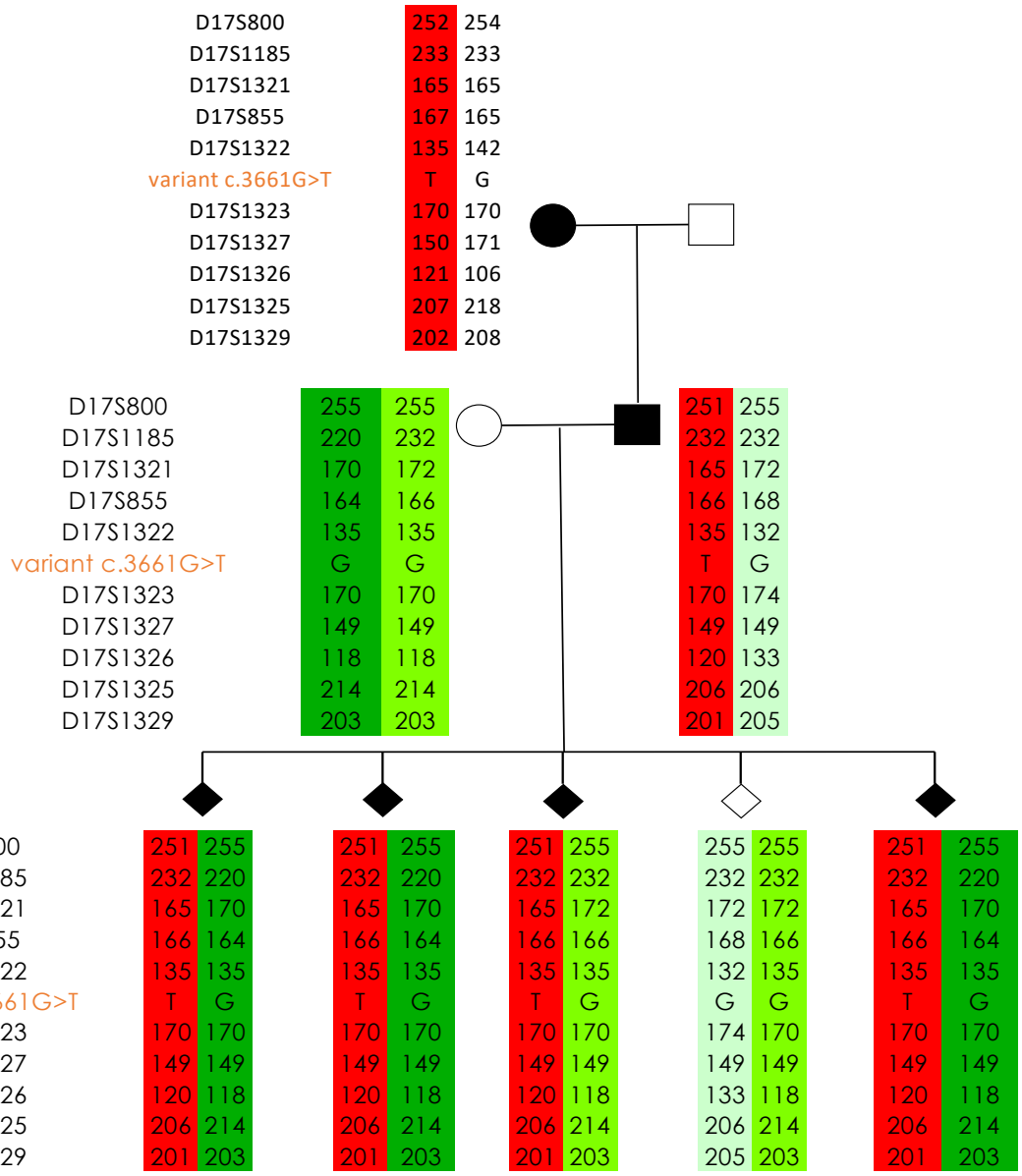
→ WGA



Haplotyping by STRs

embryo analysis

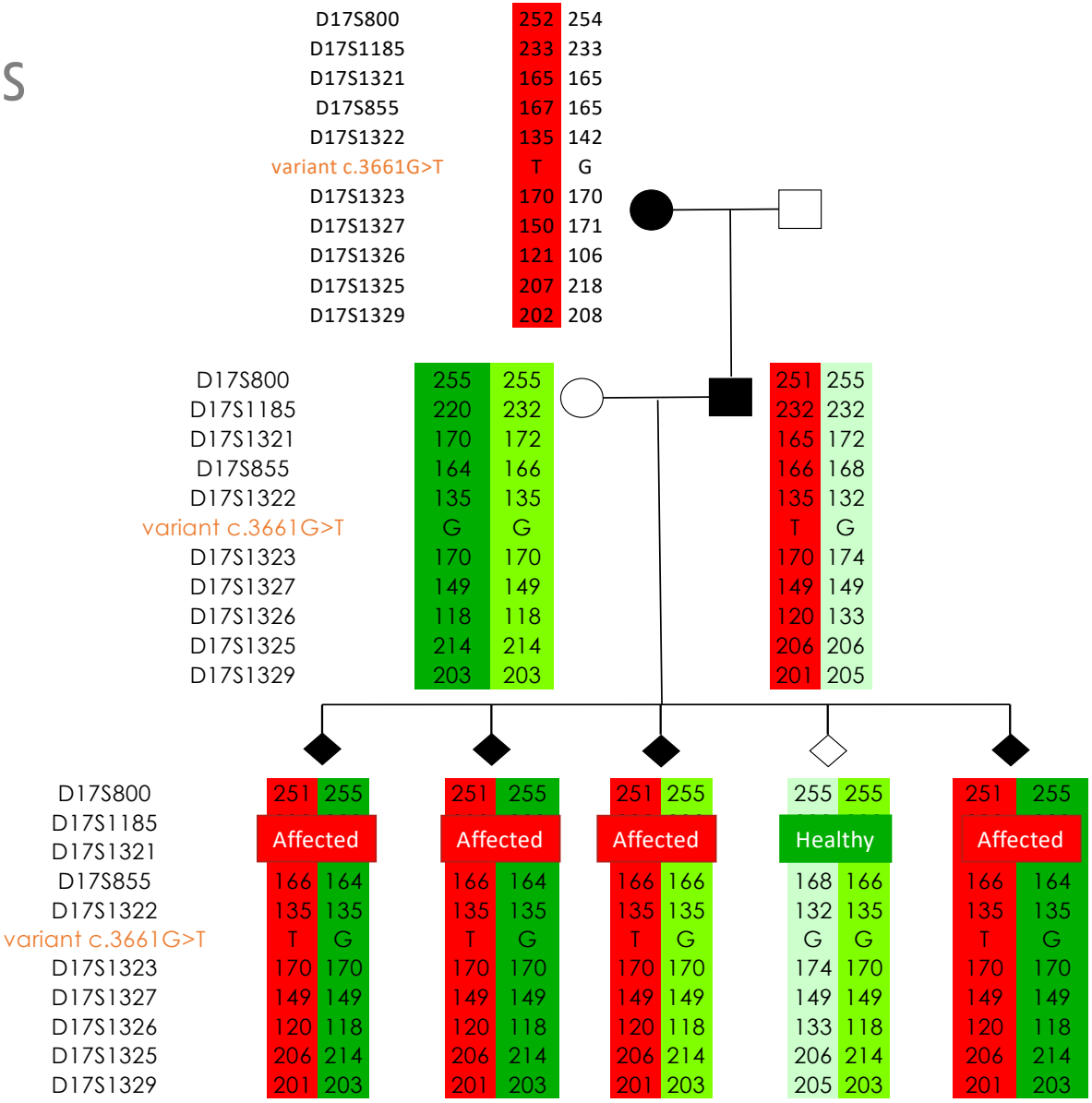
→ WGA



Haplotyping by STRs

embryo analysis

→ WGA

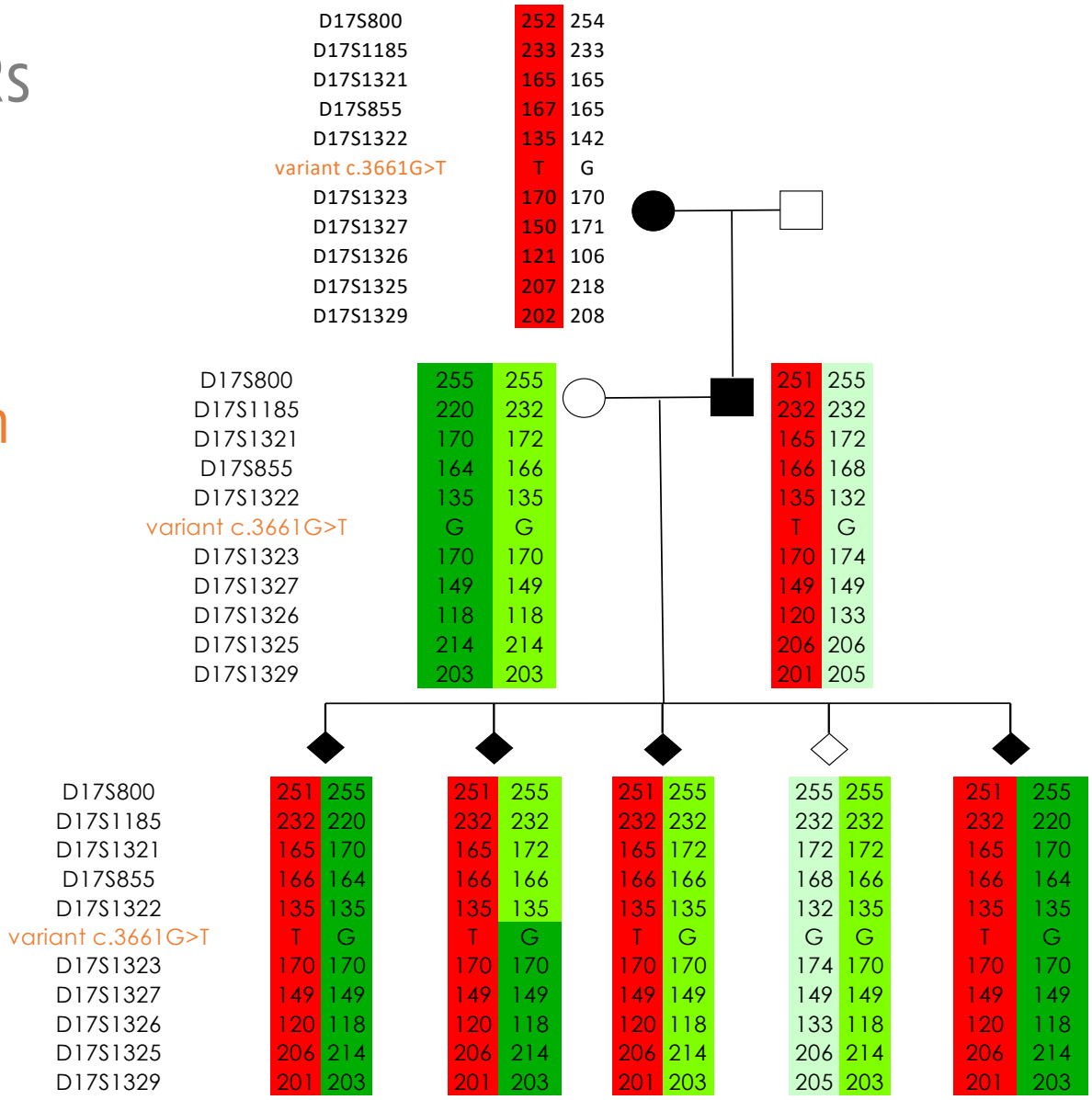


Haplotyping by STRs

embryo analysis

→ WGA

→ recombination

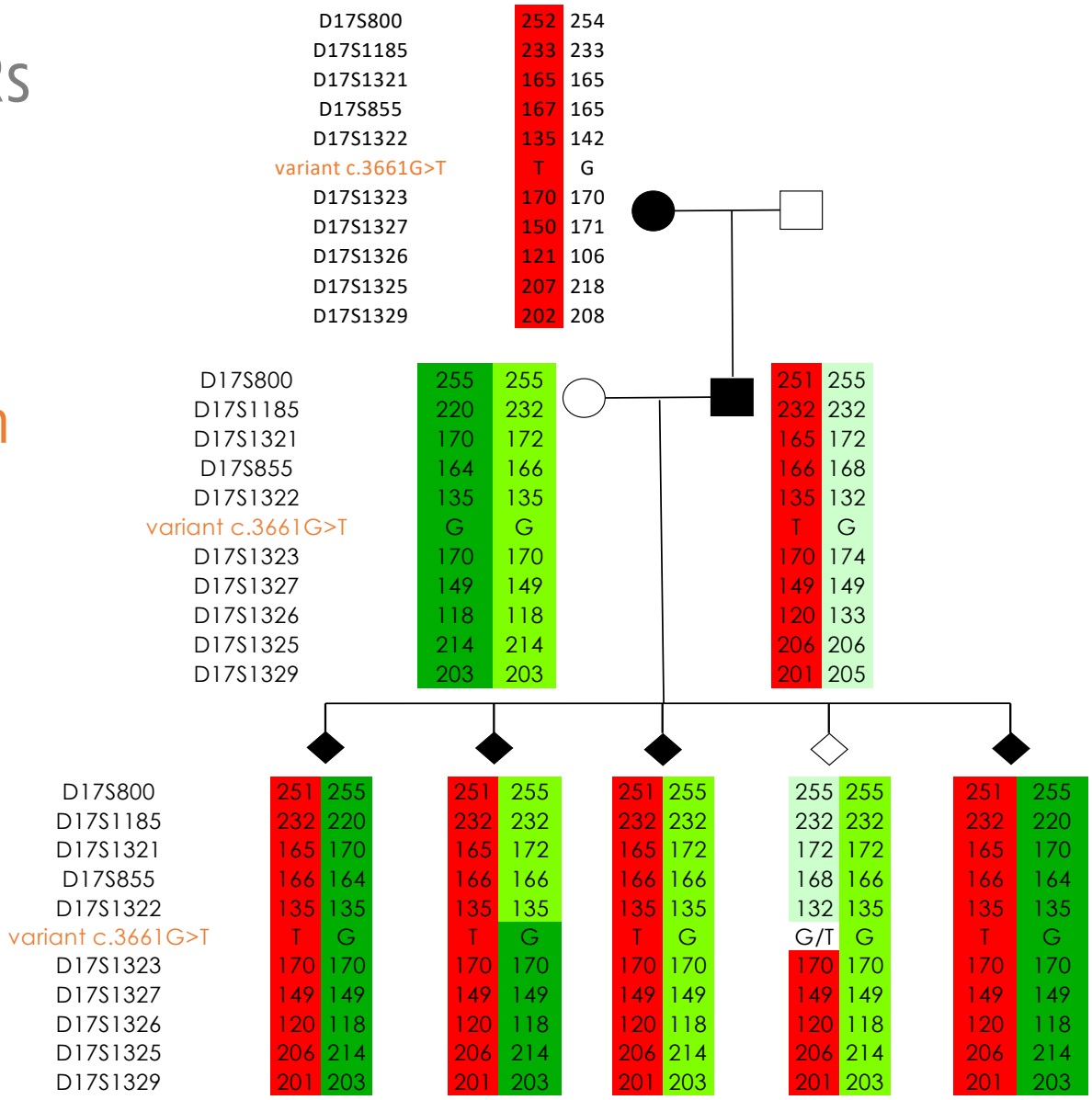


Haplotyping by STRs

embryo analysis

→ WGA

→ recombination

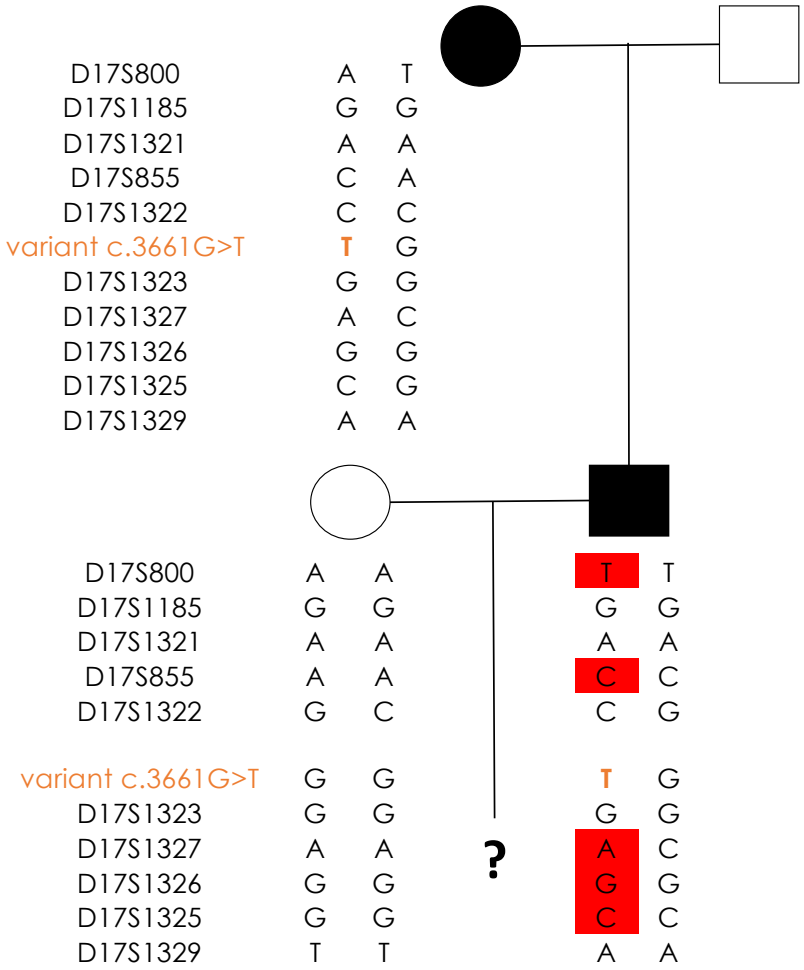


Haplotyping by STRs

- No chromosomal information
- Optimization per couple (disorder)
- Di-/tri-nucleotide repeats sometimes hard to interpret
- Allelic Drop Out

→ genomewide SNP analysis

Haplotype phasing by SNV analysis: genetic workup



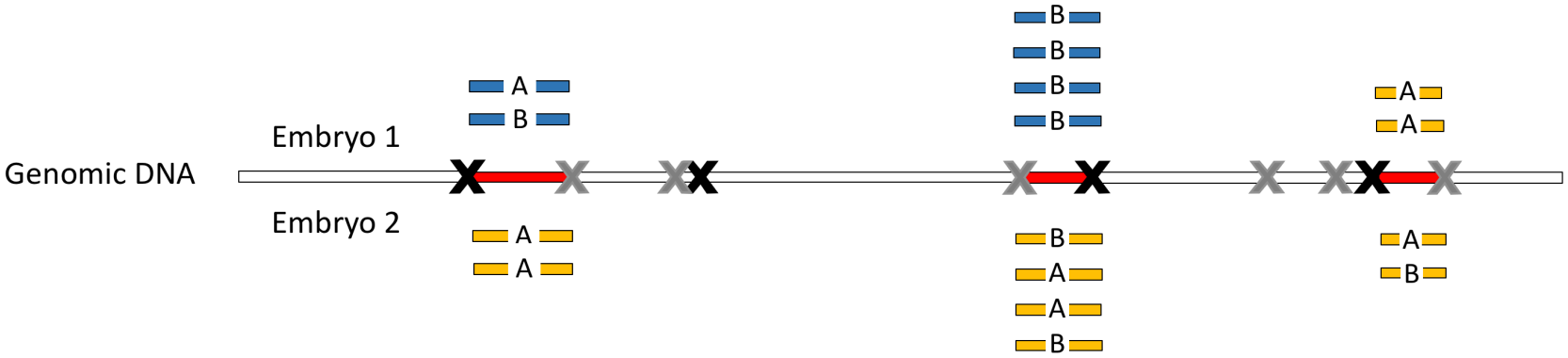
Haplotype phasing by SNVs

Table 1 Parental genotype combinations – informative SNPs

Example	Father	Mother	Informative?
1	AB	AA	Informative for father
2	AB	BB	Informative for father
3	AA	AB	Informative for mother
4	BB	AB	Informative for mother
5	AA	AA	Not informative
6	AA	BB	Not informative
7	AB	AB	Not informative
8	BB	BB	Not informative
9	BB	AA	Not informative

Genome wide haplotyping by SNP arrays

Haplotyping by double digest restriction-site associated DNA sequencing (ddRADseq)



Restriction enzyme 1

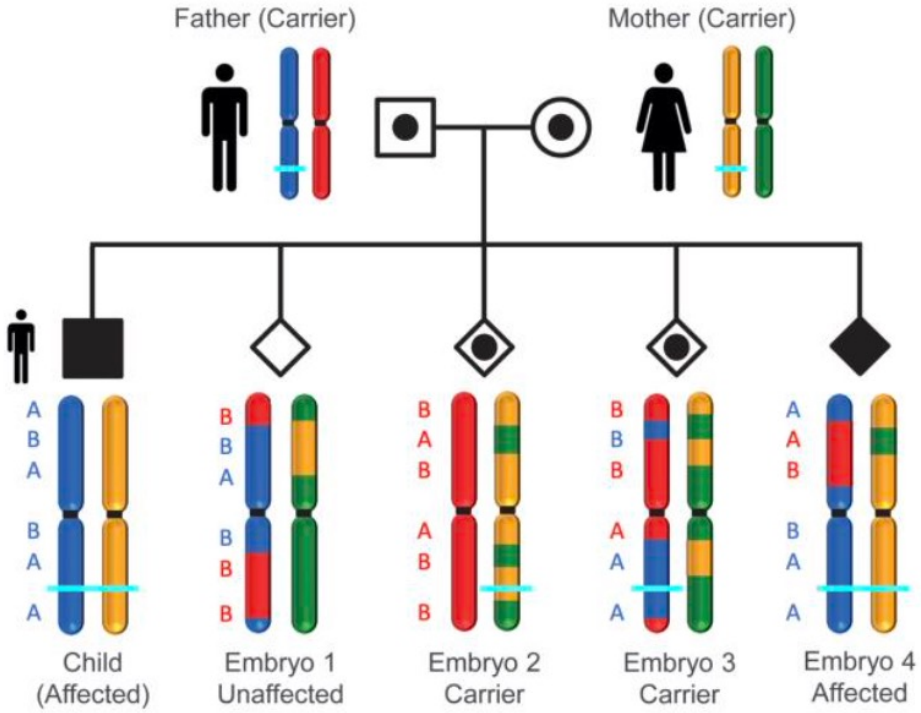
Restriction enzyme 2

ddRAD library

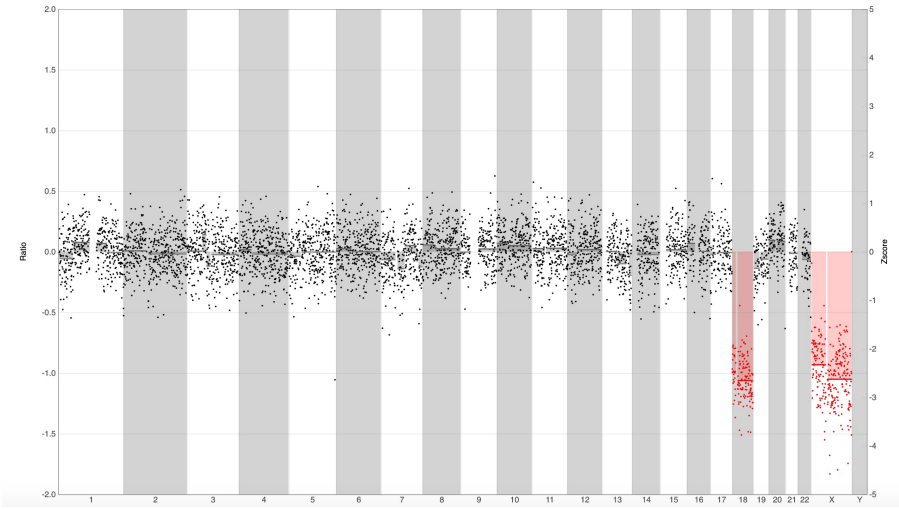
Sequence reads

Genome-wide haplotyping enables

genome wide phasing

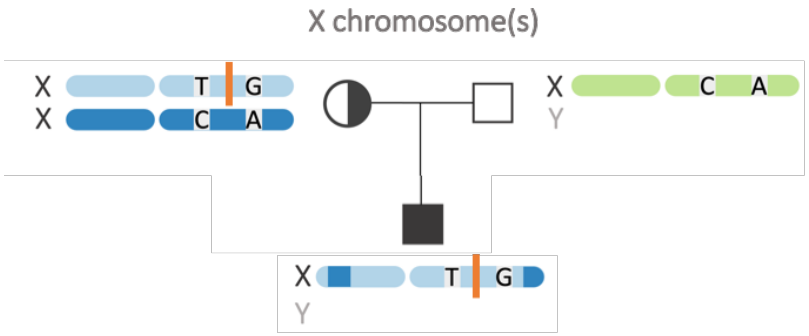


copy number analysis



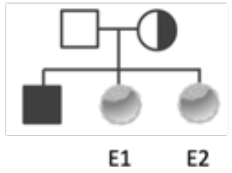
B-allele frequencies

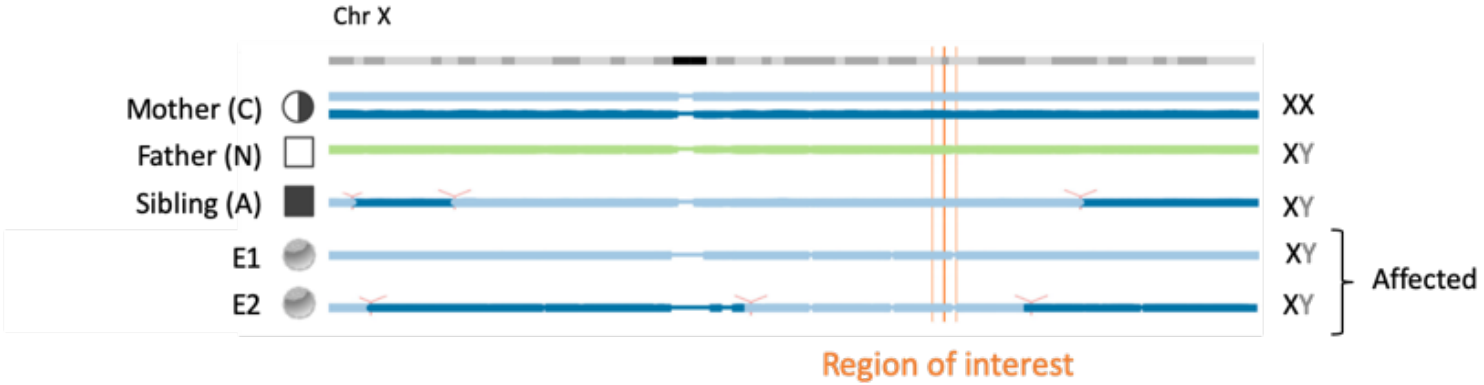
PGT-M + PGT-SR + PGT-A



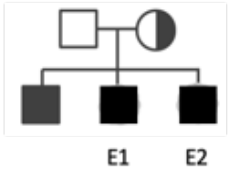
Direct mutation analysis

Region of interest

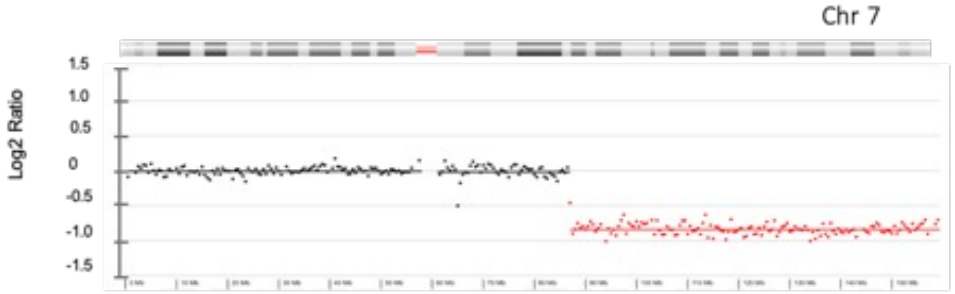

E1
E2


Chr X
Mother (C)
Father (N)
Sibling (A)
E1
E2
XX
XY
XY
XY
XY
Affected
Region of interest

PGT-M result


E1
E2

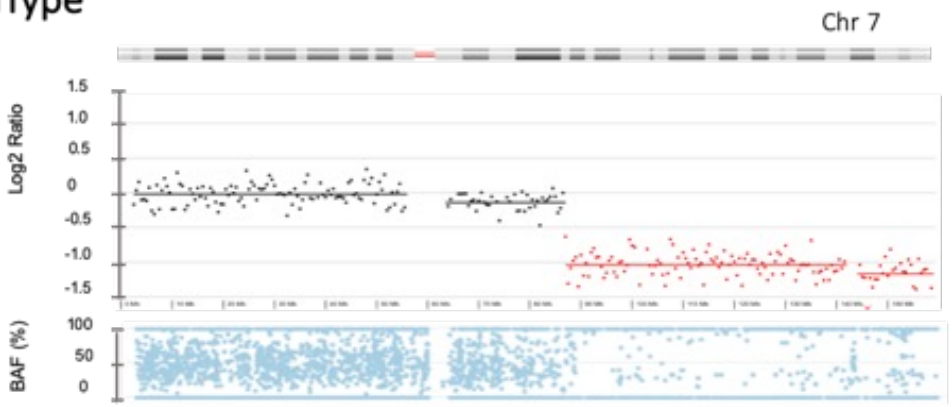
Reference method (*shallow whole genome sequencing*)

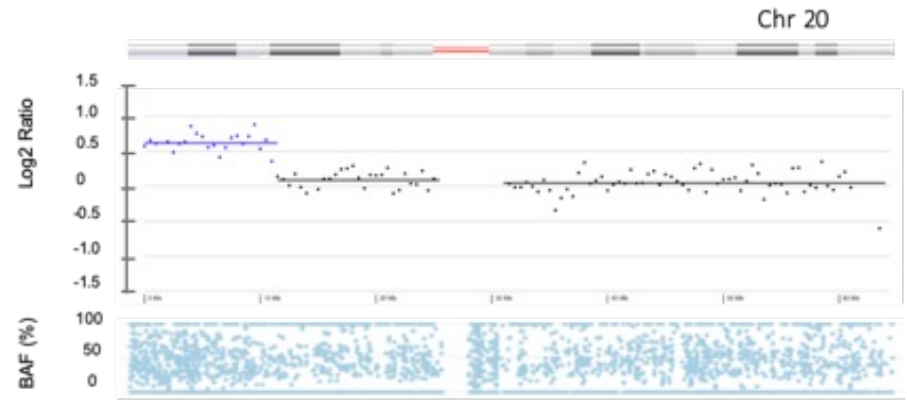


~70 Mb deletion

~10 Mb duplication

GENType



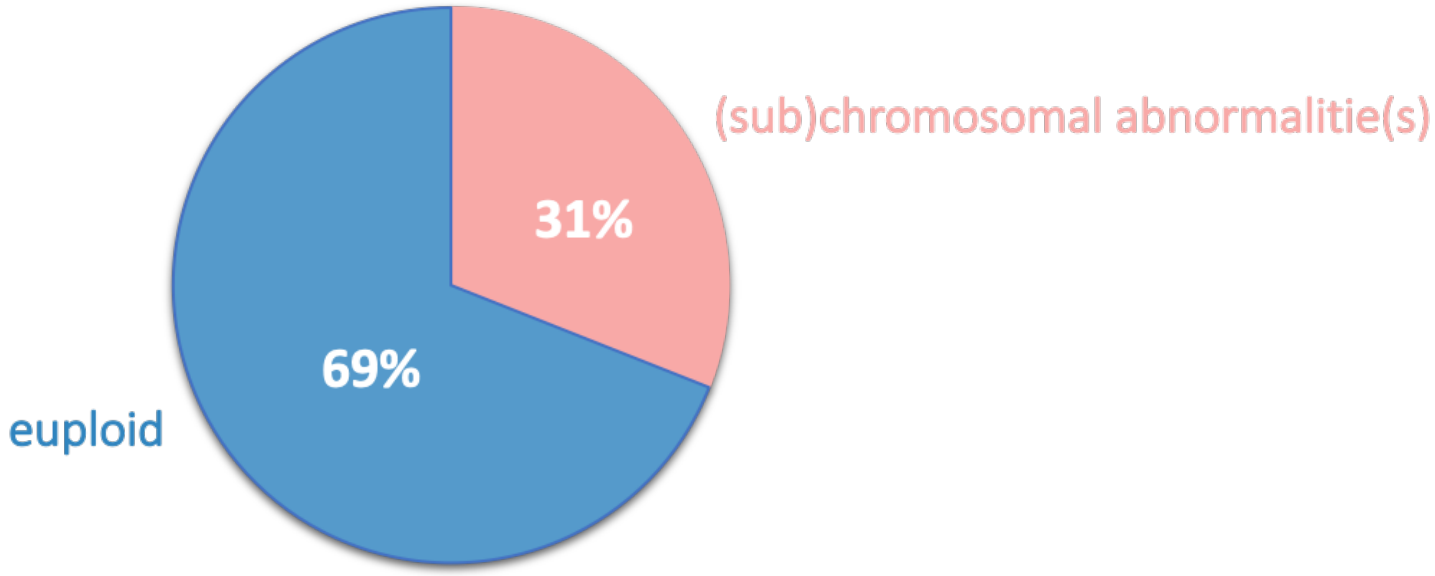


Diagnostic accuracy: 100%

Chromosome screening on PGT-M cohort

Among the embryos not affected by the monogenic disorder:

~ one third had at least one (sub)chromosomal abnormality

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- Share reports with family and friends
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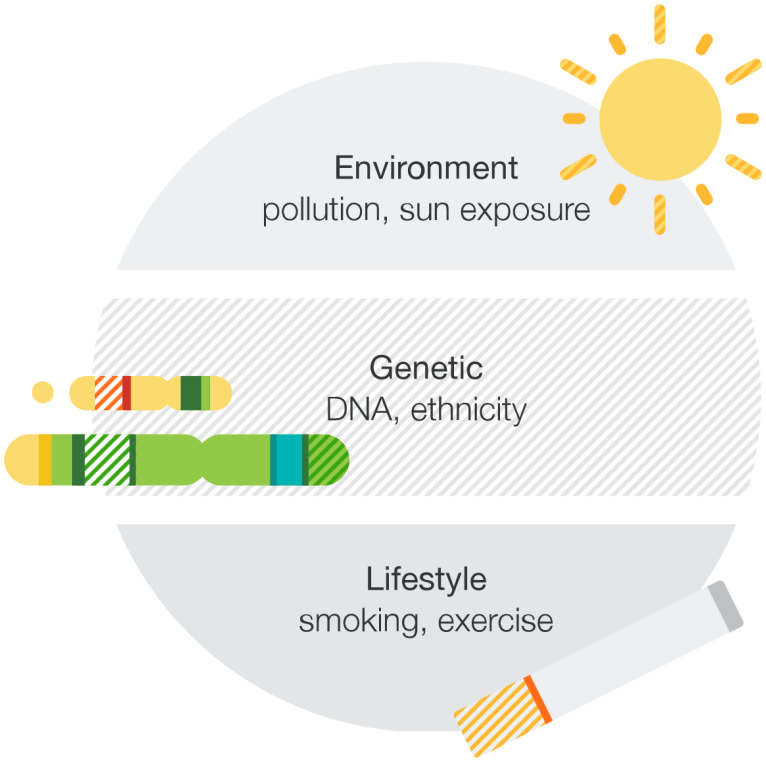

Why genetics is only part of the story.

When it comes to your health and traits, DNA is only part of the story. Your genes can raise your chances for many diseases, but they do not typically work alone. Health and longevity are influenced by other variables, including non-genetic factors, such as your environment and lifestyle. Let's take type 2 diabetes (T2D) for example, the most common — and to an extent preventable — form of diabetes.

Data from a few large studies estimate between 20-80 percent of the risk for developing the disease may be explained by genetics. That being said, your age, diet, weight, ethnicity, and activity levels all play a role.

To break it down a little further, your weight — or more specifically your Body Mass Index (BMI) — contributes to your chances of developing T2D, but your weight is also influenced by a complex mix of genetics, lifestyle, and your environment. An unhealthy diet and a sedentary lifestyle contribute to higher BMI, but obesity also runs in families, and families tend to share similar diet and lifestyle choices along with genetics.

All in all, it's important to recognize that your genetic predisposition, your DNA, is not your destiny, but knowing you may have a higher genetic likelihood for a disease such as T2D can help motivate you to make healthier choices.

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Lewis and Vassos *Genome Medicine* (2020) 12:44
https://doi.org/10.1186/s13073-020-00742-5

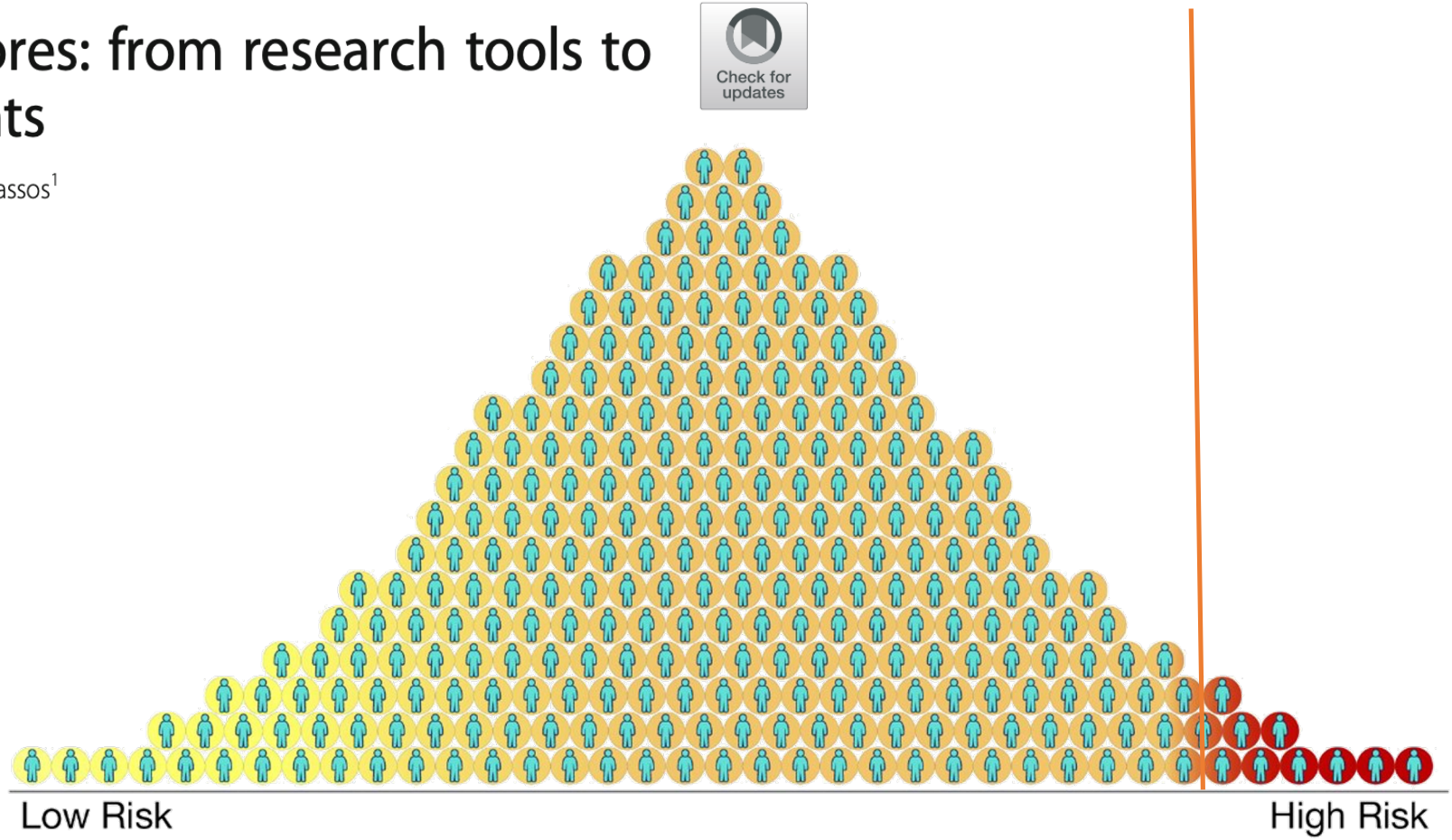
Genome Medicine

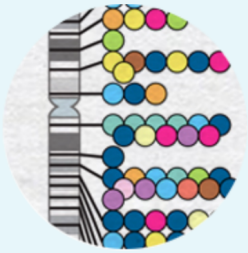
REVIEW Open Access

Polygenic risk scores: from research tools to clinical instruments

Cathryn M. Lewis[1,2*] and Evangelos Vassos[1]

threshold-liability model





GWAS Catalog

The NHGRI-EBI Catalog of human genome-wide association studies

Search the catalog

Examples: breast carcinoma, rs7329174, Yao, 2q37.1, HBS1L, 6:16000000-25000000

Coming soon! New format for GWAS summary statistics.
Read all about it in our **blog** and **preprint**.

Download

Download a full copy of the GWAS Catalog in spreadsheet format as well as current and older versions of the GWAS diagram in SVG format.

Summary statistics

Documentation and access to full summary statistics for GWAS Catalog studies where available.

Submit

Submit summary statistics to GWAS Catalog.

Documentation

Including FAQs, our curation process, training materials, related resources, a list of abbreviations and API documentation.

Diagram

Explore an interactive visualisation of all SNP-trait associations with genome-wide significance ($p \leq 5 \times 10^{-8}$).

Ancestry

An introduction to our ancestry curation process.

nature genetics

Article | Published: 07 March 2022

Assessing the contribution of rare variants to complex trait heritability from whole-genome sequence data

Pierrick Wainschtein, Deepti Jain, Zhili Zheng, TOPMed Anthropometry Working Group, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, L. Adrienne Cupples, Aladdin H. Shadyab, Barbara McKnight, Benjamin M. Shoemaker, Braxton D. Mitchell, Bruce M. Psaty, Charles Kooperberg, Ching-Ti Liu, Christine M. Albert, Dan Roden, Daniel I. Chasman, Dawood Darbar, Donald M. Lloyd-Jones, Donna K. Arnett, Elizabeth A. Regan, Eric Boerwinkle, Jerome I. Rotter, Jeffrey R. O'Connell, Lisa R. Yanek, ... Peter M. Visscher + Show authors

Nature Genetics **54**, 263–273 (2022) | Cite this article

t

data from genome-wide association studies on unrelated individuals have shown man traits and diseases, approximately one-third to two-thirds of heritability is y common SNPs. However, it is not known whether the remaining heritability is mperfect tagging of causal variants by common SNPs, in particular whether the nts are rare, or whether it is overestimated due to bias in inference from pedigree we estimated heritability for height and body mass index (BMI) from whole-genome sequence data on 25,465 unrelated individuals of European ancestry. The estimated heritability was 0.68 (standard error 0.10) for height and 0.30 (standard error 0.10) for body mass index. Low minor allele frequency variants in low linkage disequilibrium (LD) with neighboring variants were enriched for heritability, to a greater extent for protein-altering variants, consistent with negative selection. Our results imply that rare variants, in particular those in regions of low linkage disequilibrium, are a major source of the still missing heritability of complex traits and disease.

nature genetics

Comment | Published: 10 March 2021

The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation

Samuel A. Lambert, Laurent Gil, Simon Jupp, Scott C. Ritchie, Yu Xu, Annalisa Buniello, Aoife McMahon, Gad Abraham, Michael Chapman, Helen Parkinson, John Danesh, Jacqueline A. L. MacArthur & Michael Inouye

Nature Genetics **53**, 420–425 (2021) | Cite this article

nature genetics

Article

https://doi.org/10.1038/s41588-022-01192-y

Discovery of 42 genome-wide significant loci associated with dyslexia

Received: 28 August 2021

Accepted: 23 August 2022

Published online: 20 October 2022

Check for updates

Catherine Doust[1], Pierre Fontanillas[2], Else Eising[3], Scott D. Gordon[4], Zhengjun Wang[5], Gökberk Alagöz[3], Barbara Molz[3], 23andMe Research Team*, Quantitative Trait Working Group of the GenLang Consortium*, Beate St Pourcain[3,6,7], Clyde Francks[3,6], Riccardo E. Marioni[8], Jingjing Zhao[5], Silvia Paracchini[9], Joel B. Talcott[10], Anthony P. Monaco[11], John F. Stein[12], Jeffrey R. Gruen[13], Richard K. Olson[14,15], Erik G. Willcutt[14,15], John C. DeFries[14,15], Bruce F. Pennington[16], Shelley D. Smith[17], Margaret J. Wright[18], Nicholas G. Martin[4], Adam Auton, Timothy C. Bates[1], Simon E. Fisher[3,6] and Michelle Luciano[1]

Family studies of dyslexia suggest heritability up to 70%, yet few convincing genetic markers have been found. Here we performed a genome-wide association study of 51,800 adults self-reporting a dyslexia diagnosis and 1,087,070 controls and identifed 42 independent genome-wide signifcant loci: 15 in genes linked to cognitive ability/educational attainment, and 27 new and potentially more specifc to dyslexia.

The dyslexia PGS explained up to 3.6% of variance in the reading and spelling measures

PGS in psychiatric disorders

- Major Depressive Disorder: 15% lifetime prevalence, h^2 = 37%

  → PGS: 2% of variance in disease risk (AUC = 0.57)

- Schizophrenia: 1,5% prevalance, h^2 = 65-80%

  → PGS: 7% of trait variance and an AUC of 0.61

Lewis & Vassos 2022

PolyGenic (Risk) Score: the BOADICEA risk prediction algorithm

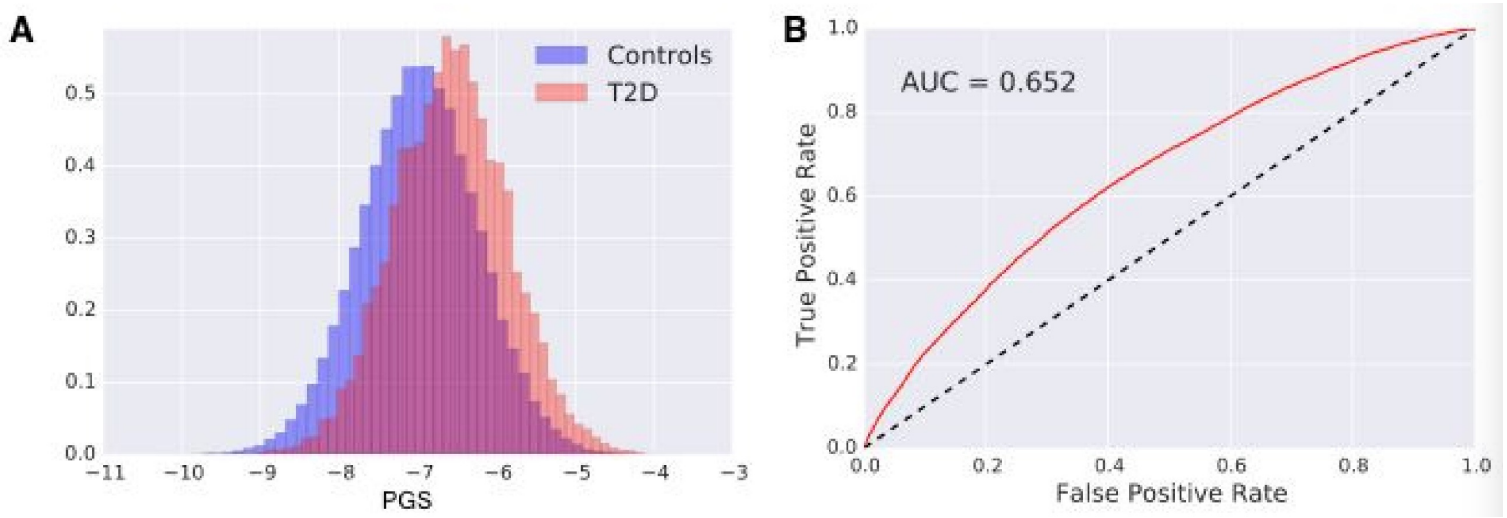
For breast cancer, PRSs can be used to more accurately quantify 10-year risk. For women aged 40–50 years with an unknown family history of disease, the average population risk of breast cancer is 1.7%. Using questionnaire-based risk factors and mammographic density, the BOADICEA risk prediction algorithm identifies 9.2% of the women in the population who would be classified at moderate or high risk of developing breast cancer (based on the UK's National Institutes of Clinical and Healthcare Excellence (NICE) guidelines[34]). A breast cancer PRS alone identifies 10%. As such, a PRS for breast cancer risk could be used to optimize screening initiation and the frequency of mammograms. An integrated model with PRS, questionnaire-based risk factors, and mammographic density identifies 13% of women with a moderate or high risk. BOADICEA v5 (as implemented in the CanRisk tool) already implements a 313-variant PRS and currently supports hundreds of thousands of women, doctors, and genetic counselors annually in >90 countries making treatment decisions[34,35]. PRS-guided mammographic screening is also being tested in the WISDOM and PERSPECTIVE I&I studies[36,37].

White Paper 23-19

The science behind 23andMe's Type 2 Diabetes report

Estimating the likelihood of developing type 2 diabetes with polygenic models

PGS Percentile	Odds Ratio	Relative Risk
0-5	0.322	0.332
5-10	0.448	0.459
50-55	1.033	1.031
90-95	2.217	2.103
95-100	3.152	2.876



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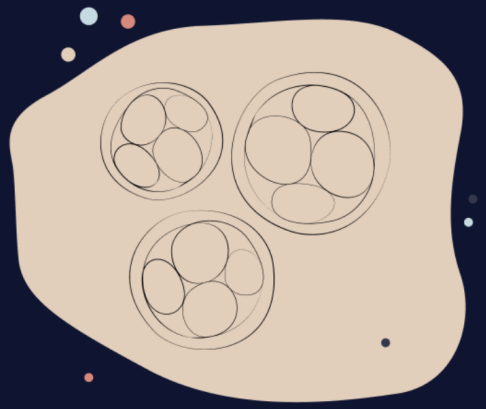

Identify your healthiest embryo

Mitigate your family's genetic predispositions with advanced genetic screening for your embryos

GET ACCESS

How Orchid Works

1

Tell your doctor

Tell your doctor you'd like to

2

Get your results

Receive advanced genetic

3

Consult with experts

Board-certified genetic

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○ COUPLE REPORT ● EMBRYO REPORT GET ACCESS

WHAT YOU'LL LEARN

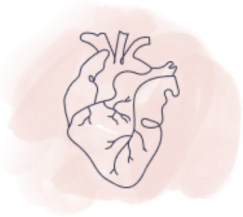
Protect your future child from genetic risks

Genetics influence the chance of developing disease later in life. Uncover risks and make an informed choice.

Orchid's advanced embryo screening measures:

Brain Health

- Schizophrenia
- Alzheimer's Disease



Heart Health

- Heart Disease
- Atrial Fibrillation
- Stroke

Cancers

- Breast Cancer
- Prostate Cancer

General Health

- Inflammatory Bowel Disease
- Type 1 & Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Problems with Using Polygenic Scores to Select Embryos

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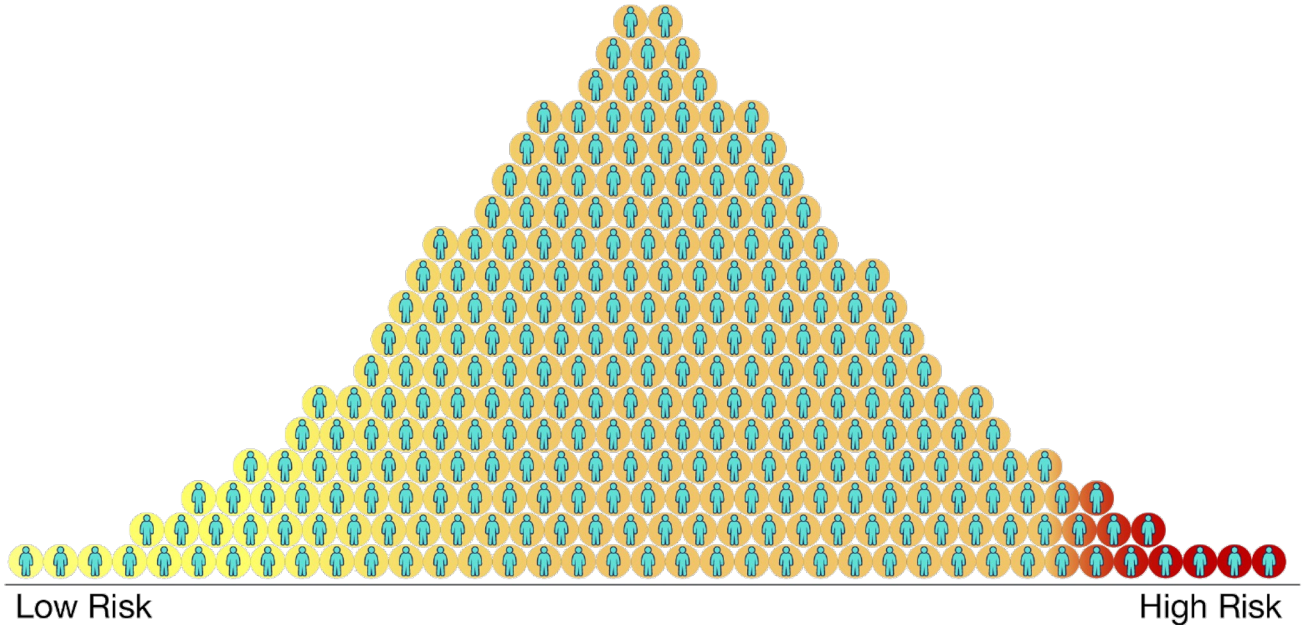

Preimplantation Genetic ~~Testing~~ → SELECTION

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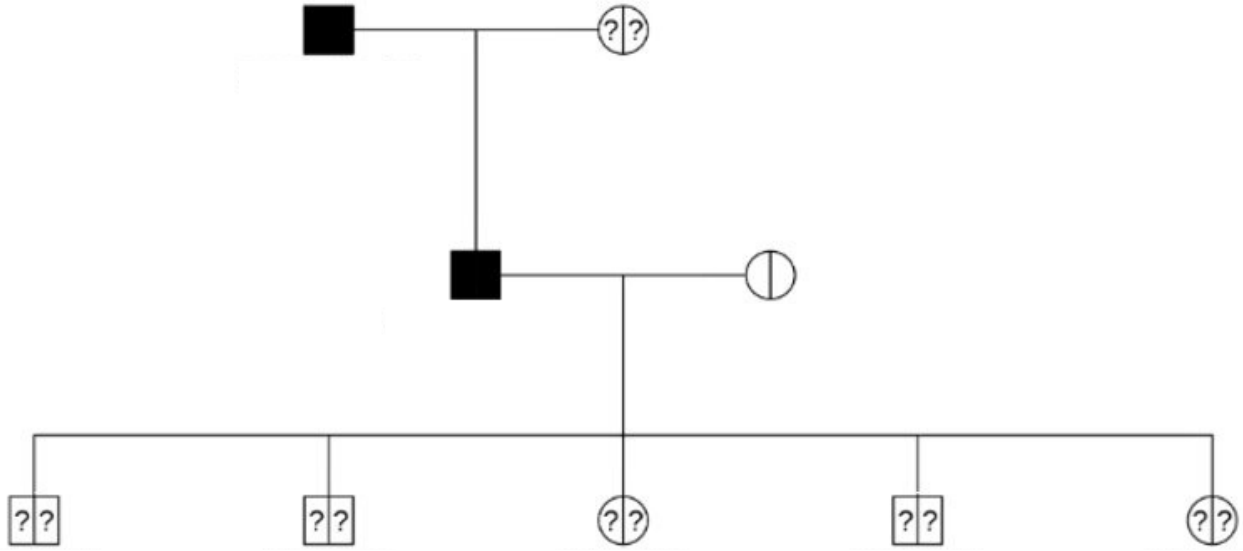
example 1

Familial Breast cancer (BRCA1)

Autosomal dominant inheritance (17q21.31)

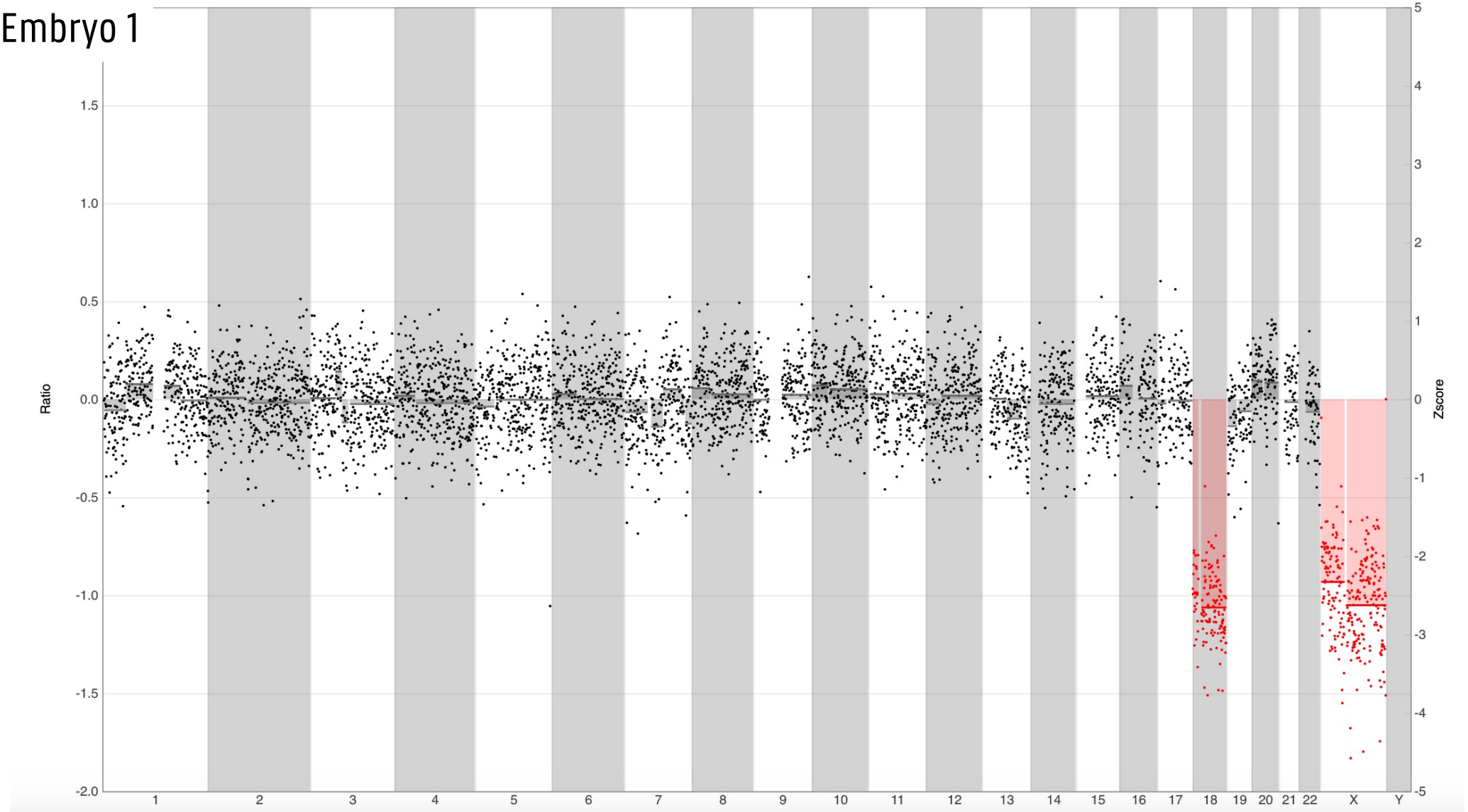
Family tree



Embryo 1


BAF (%)
100
50
0
chr1
chr2
chr3
chr4
chr5
chr6
chr7
chr8
chr9
chr10
chr11
chr12
chr13
chr14
chr15
chr16
chr17
chr18
chr19
chr20
chr21
chr22
chrX

Embryo 1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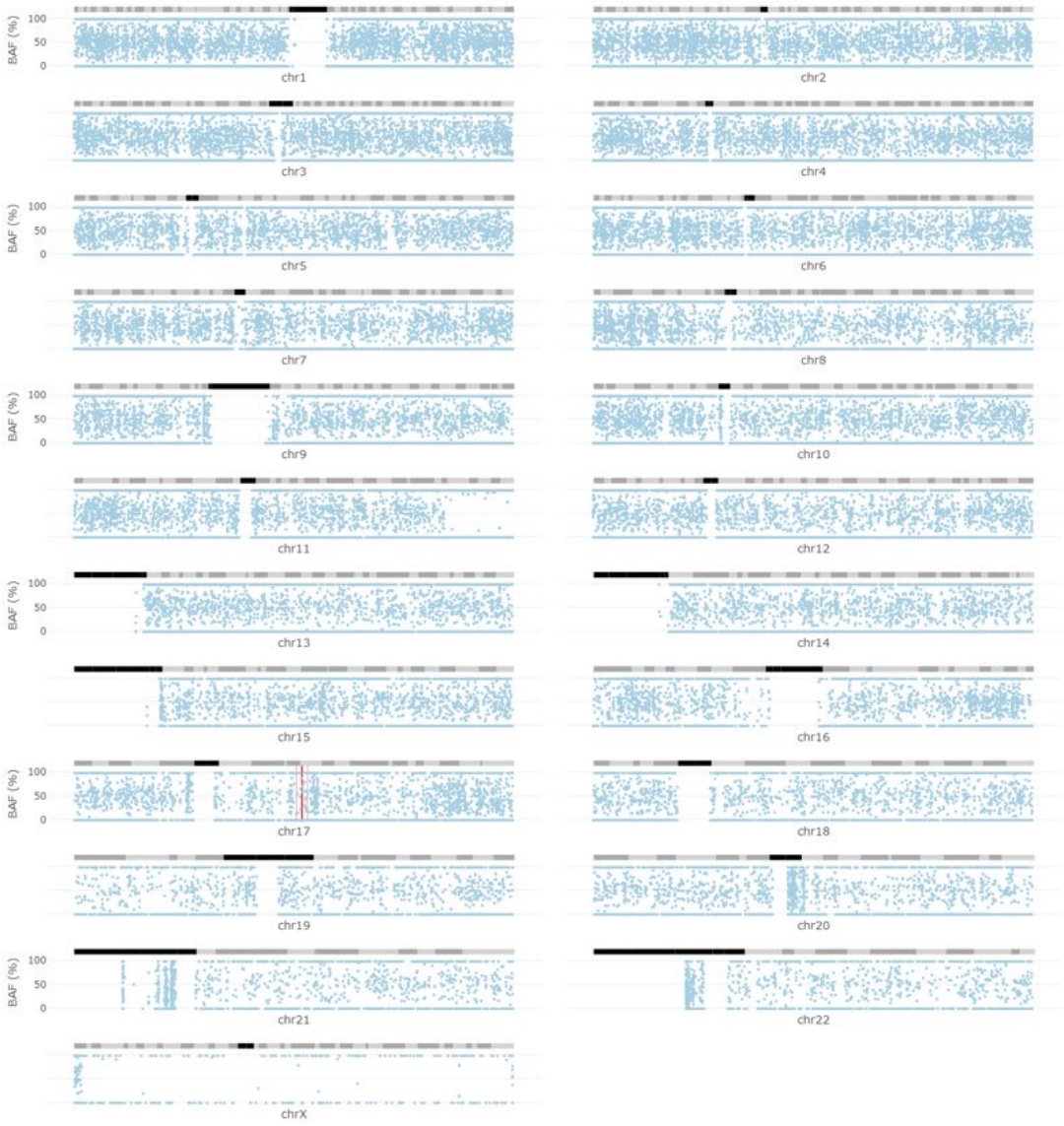
21
22
X
Y

Embryo 2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0
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chr2
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chr4
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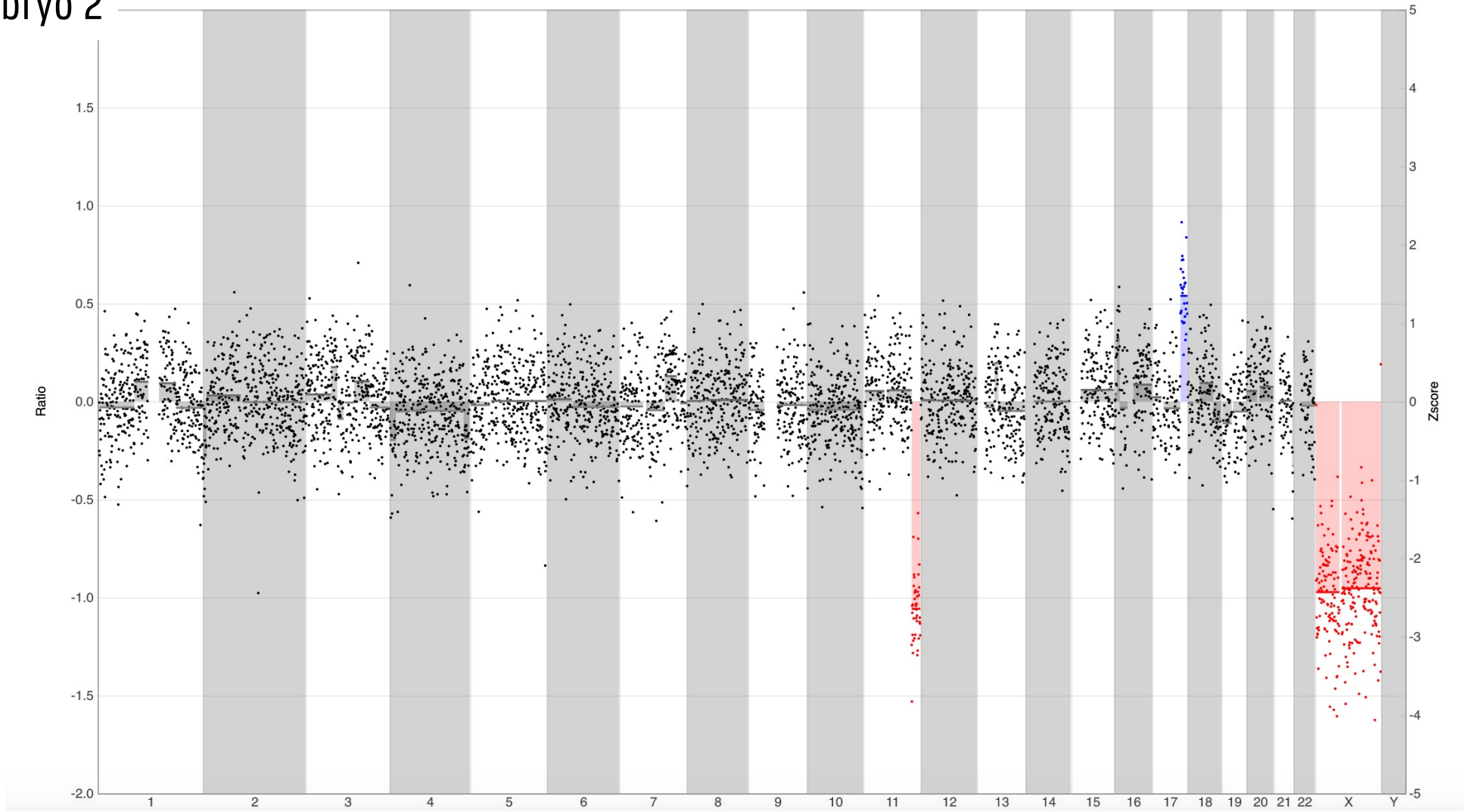
chr22
chrX

Embryo 2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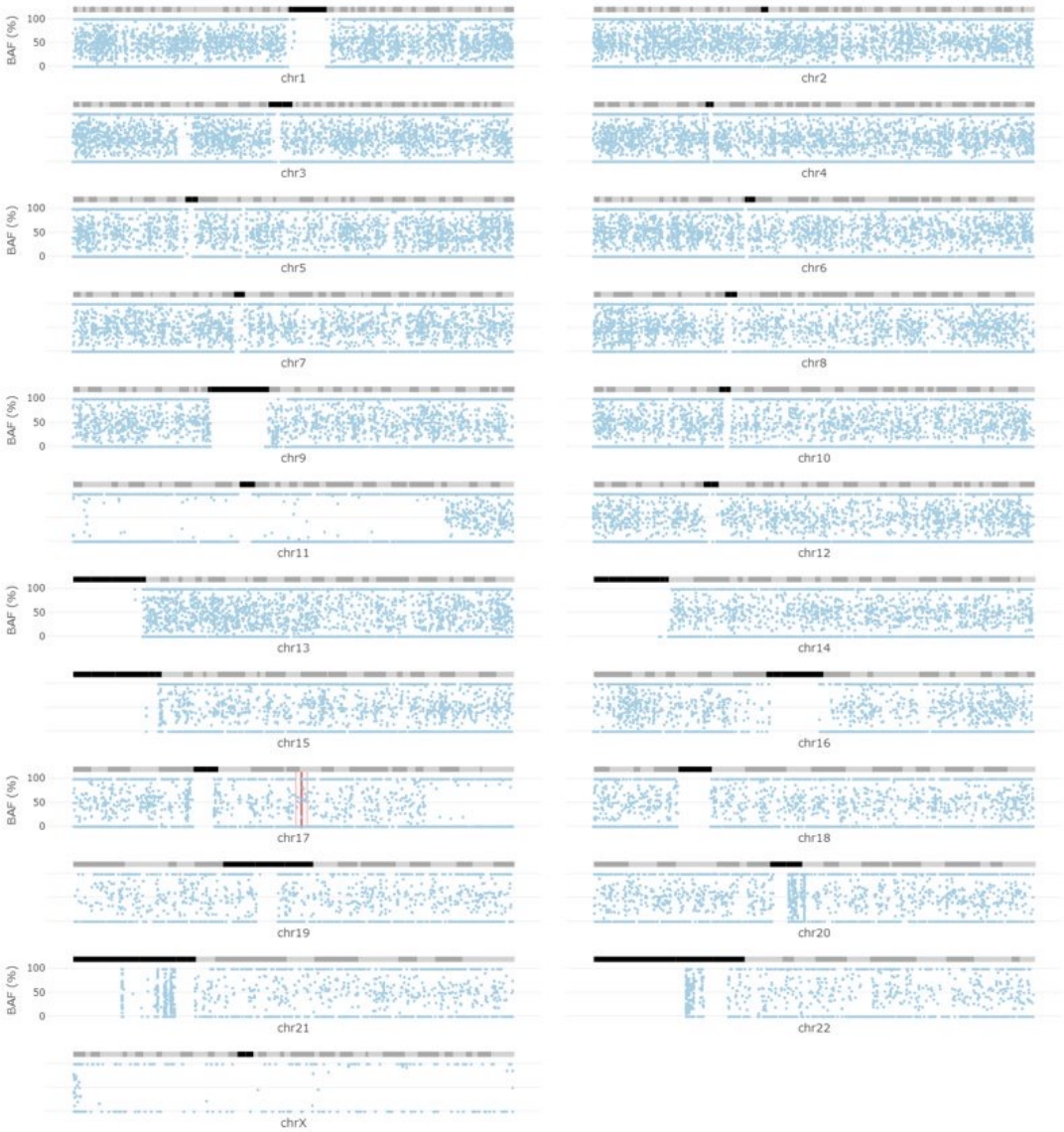
21
22
X
Y

Embryo 3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chr1
chr2
chr3
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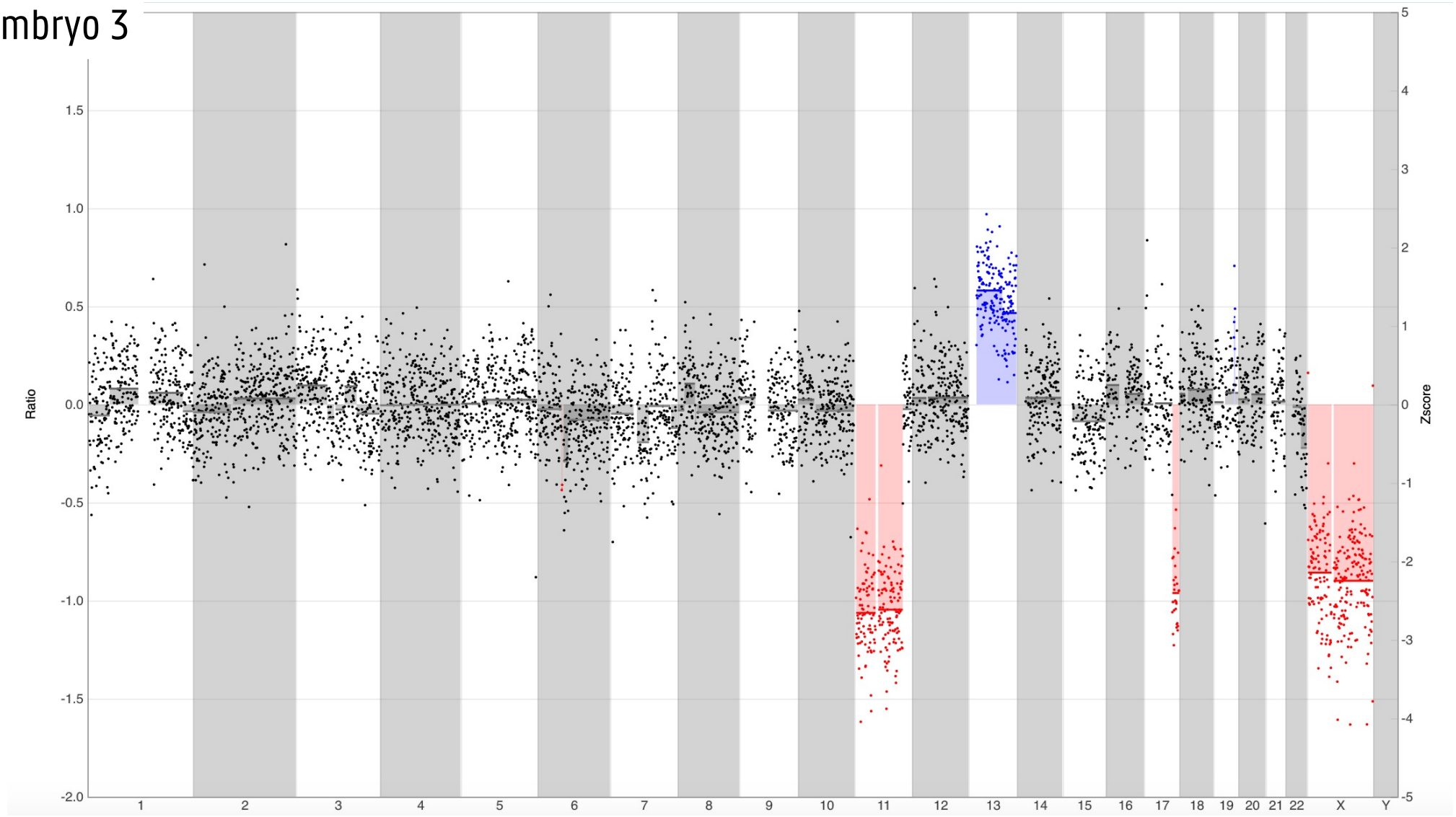
chr22
chrX

Embryo 3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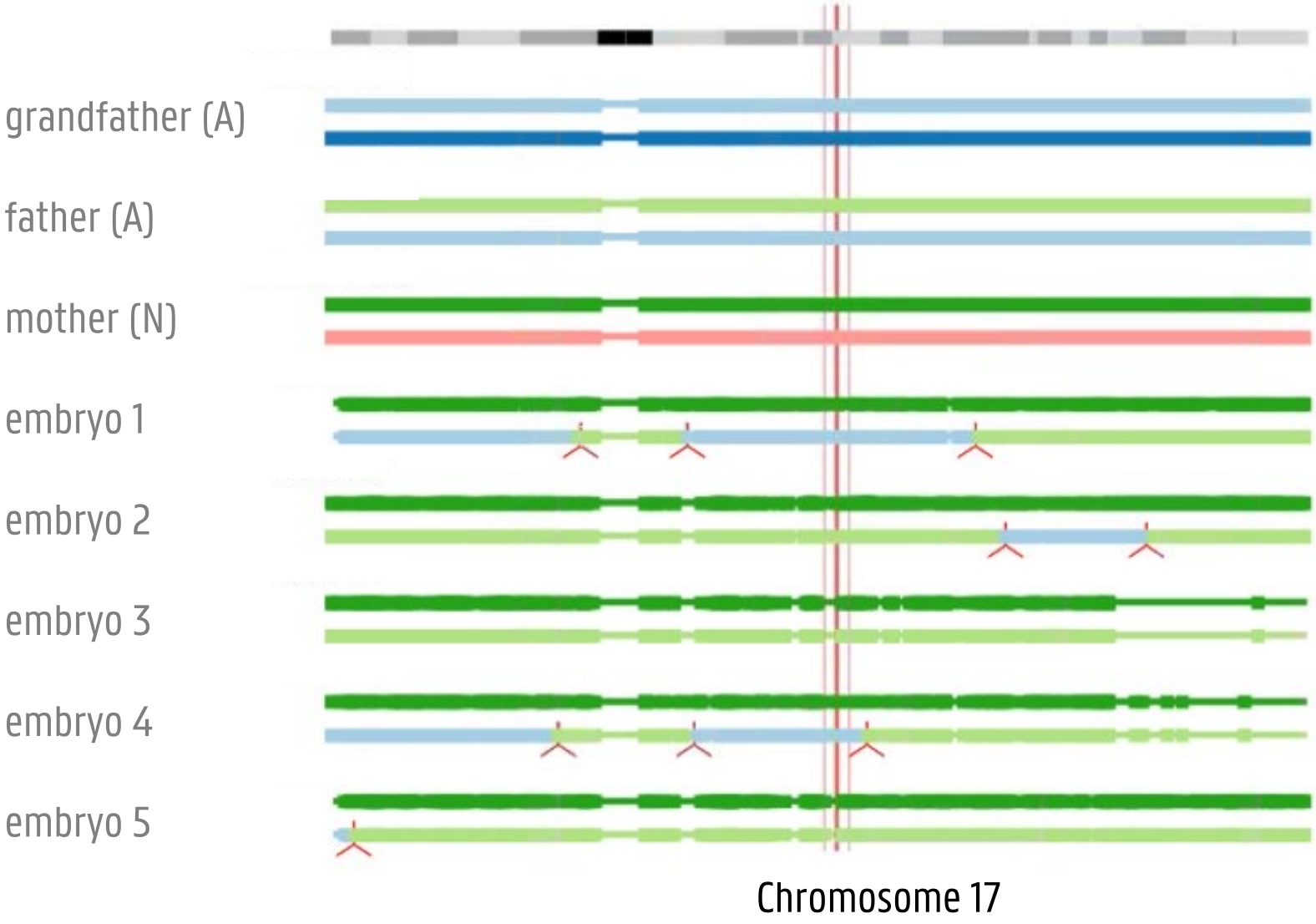
X
Y

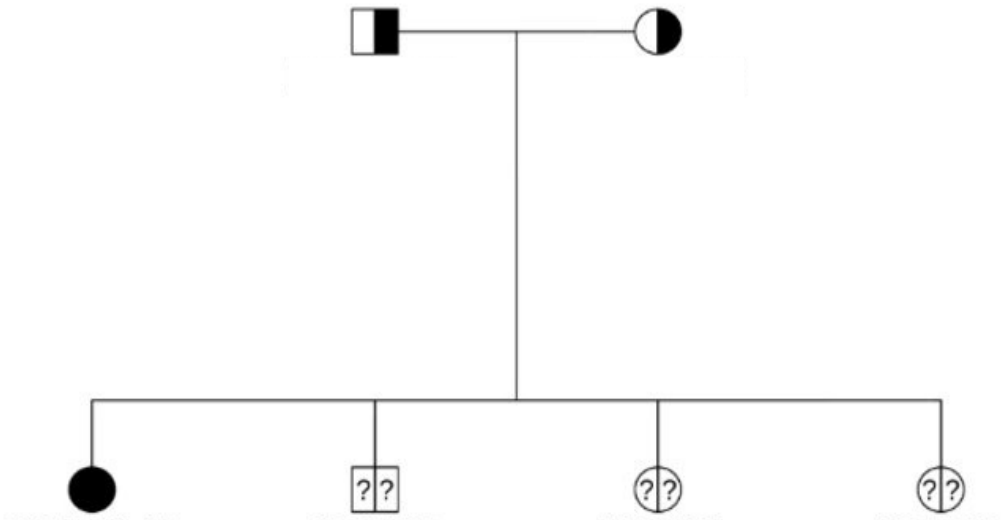

grandfather (A)
father (A)
mother (N)
embryo 1
embryo 2
embryo 3
embryo 4
embryo 5
Chromosome 17

example 2

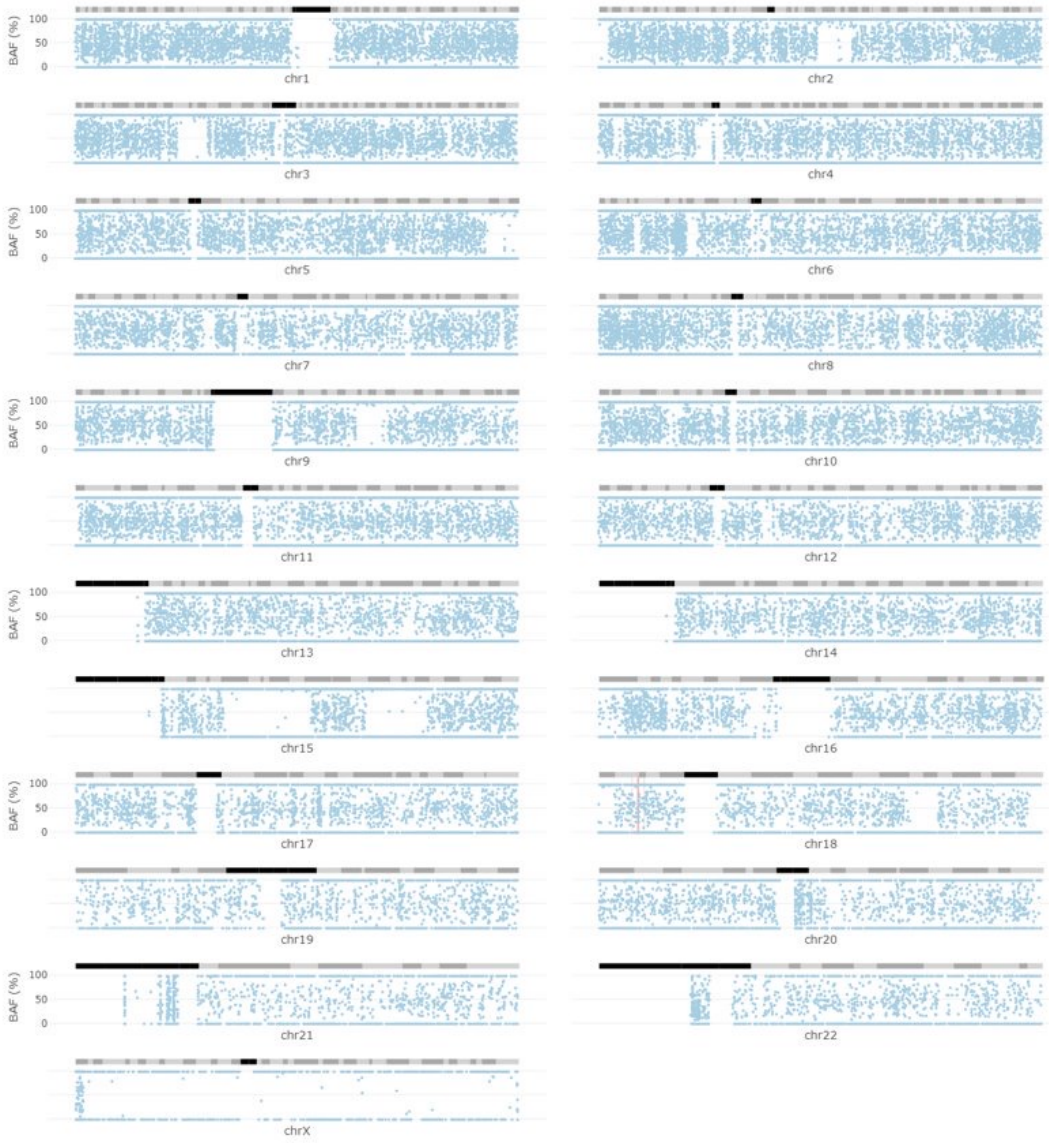
Poretti-Boltshauser syndrome (LAMA1)

Autosomal recessive inheritance (18p11.31)

Family tree



Embryo 1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chr1
chr2
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chr4
chr5
chr6
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chr8
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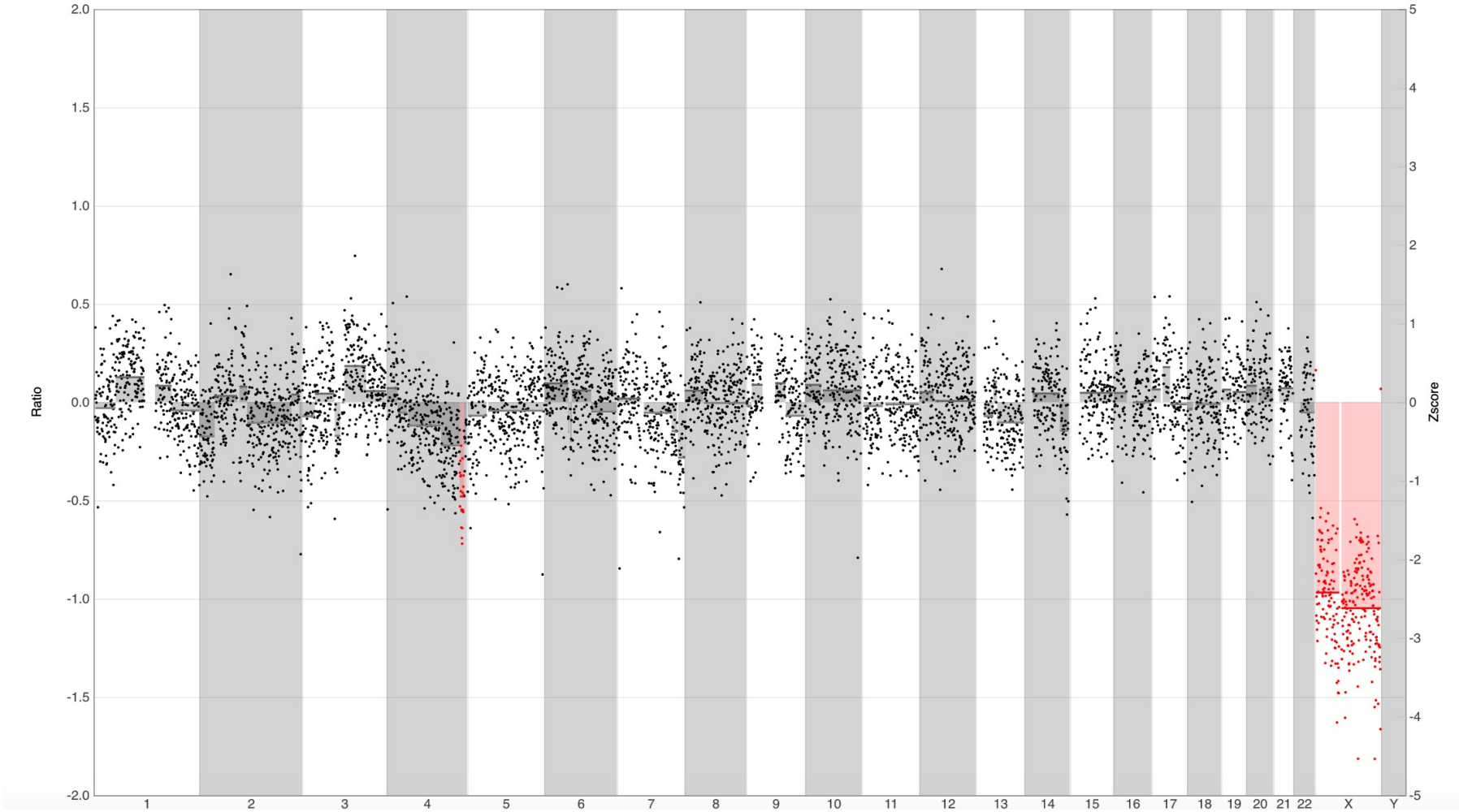
chr21
chr22
chrX

Embryo 1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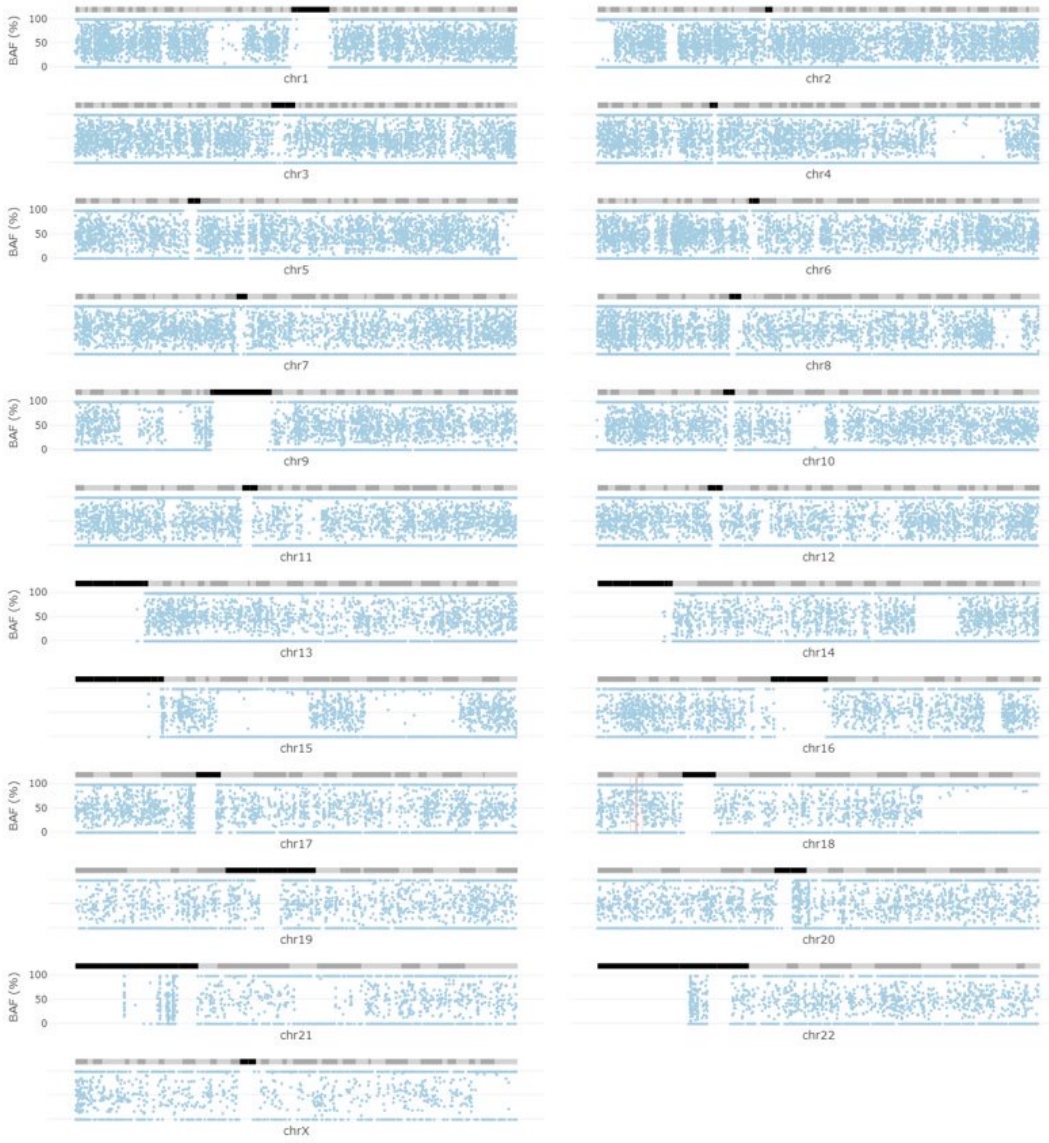
X
Y

Embryo 2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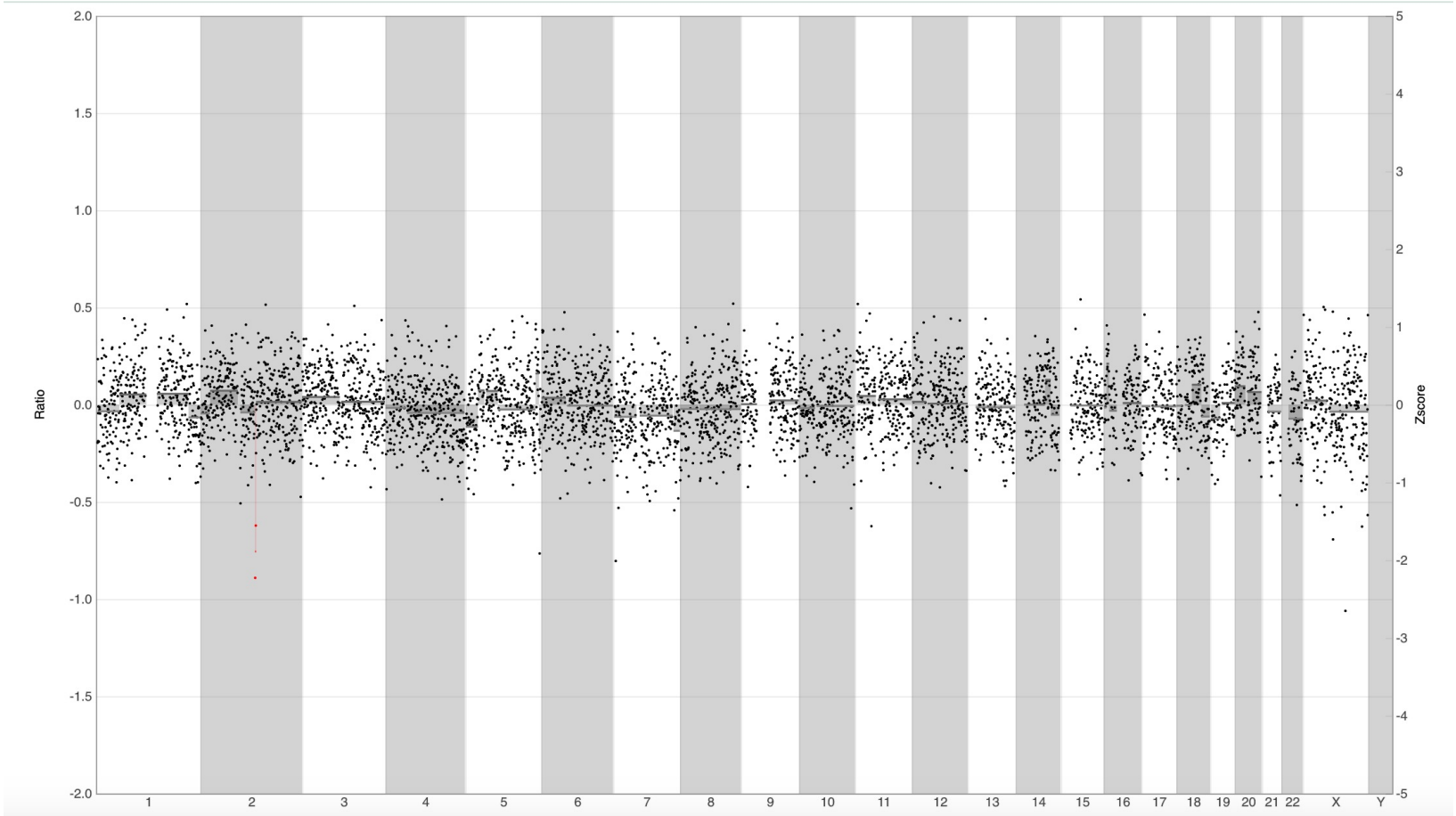
Embryo 2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Embryo 3


BAF (%)
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chr1
chr2
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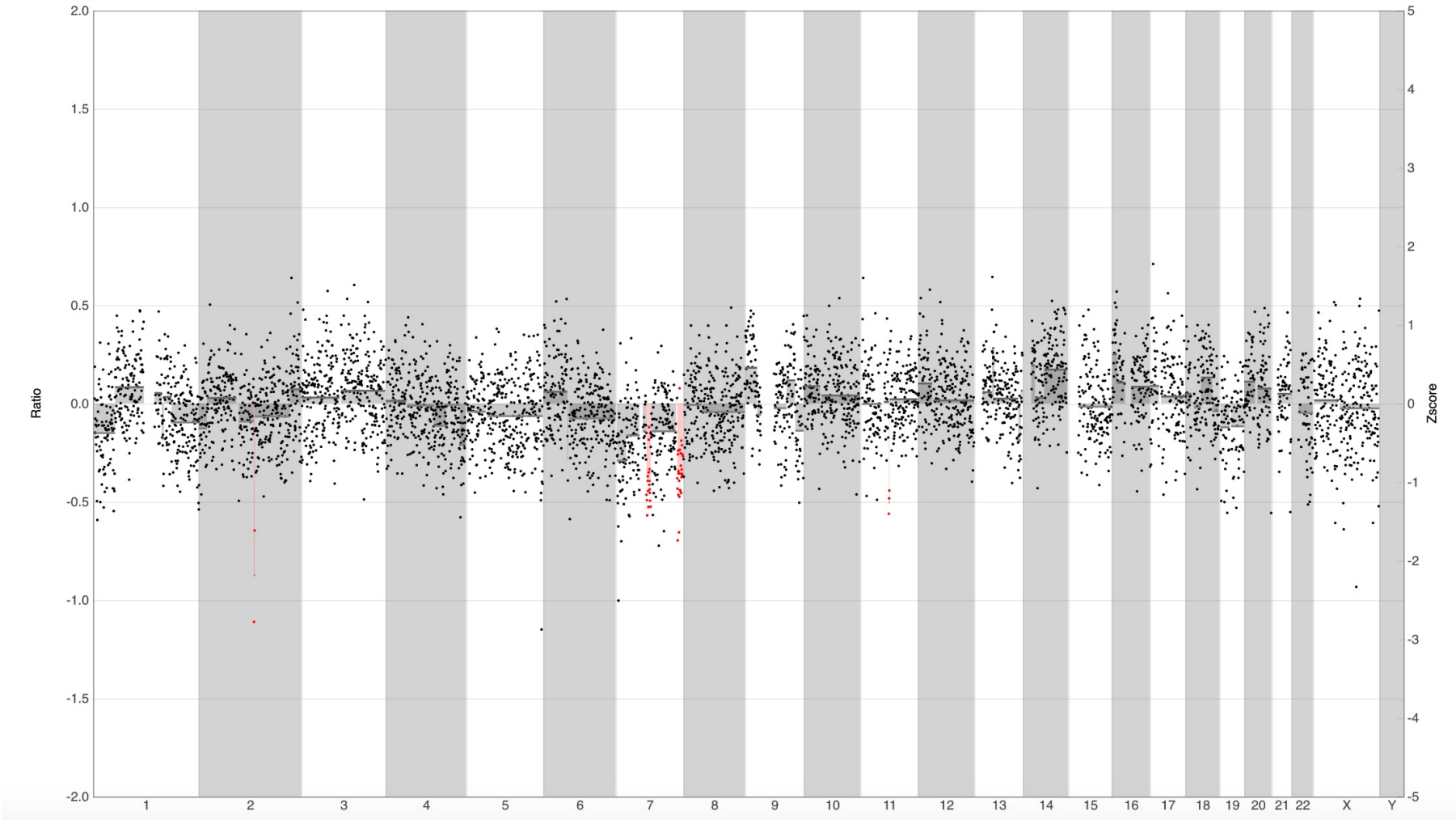
Embryo 3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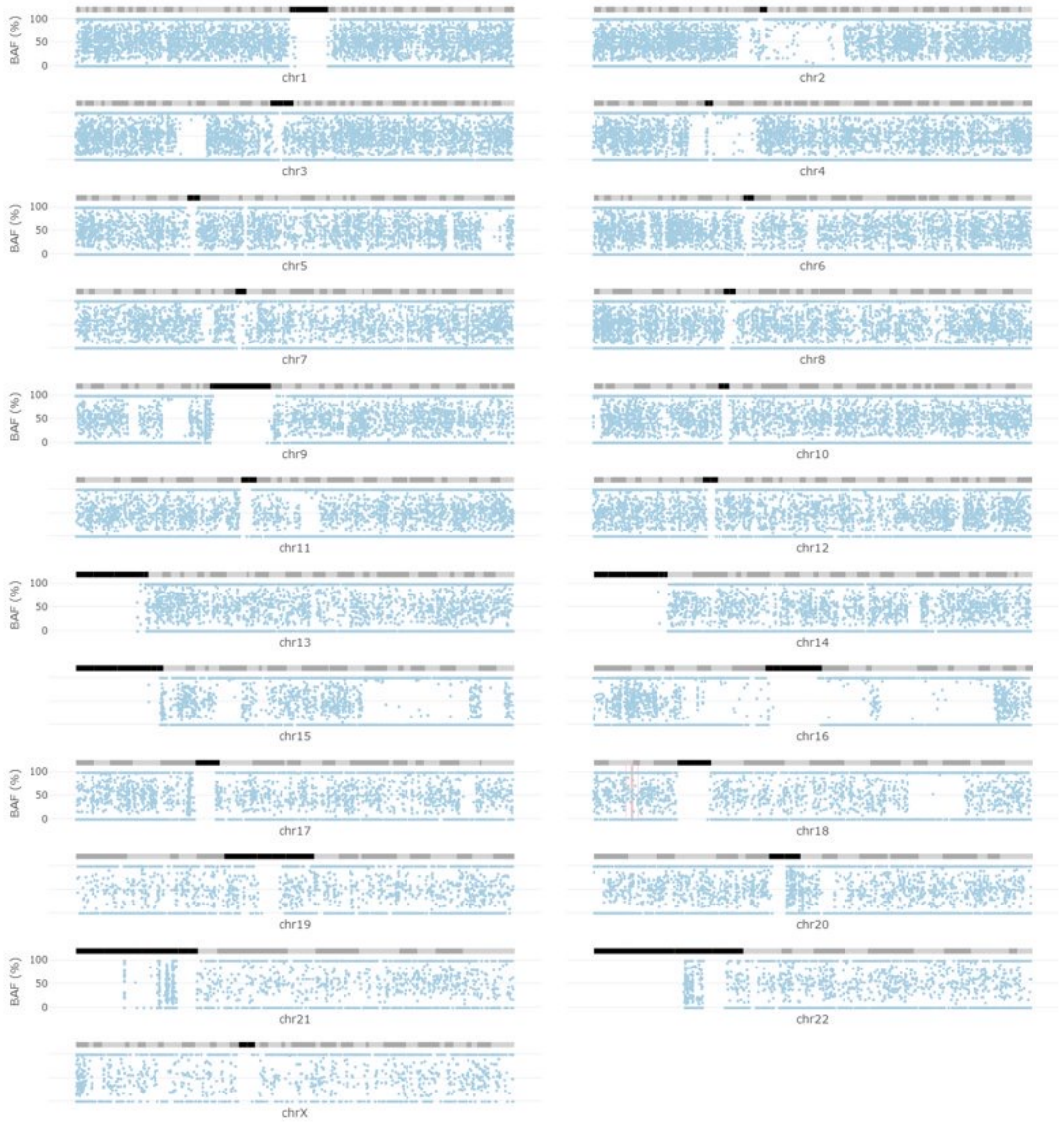
→ LOH by consanguinity



Difficult cases

- de novo aberrations / mutations
- Single parent
- Small deletions / duplications
- pseudogenes

Difficult cases

- de novo aberrations / mutations
- Single parent
- Small deletions / duplications
- pseudogenes

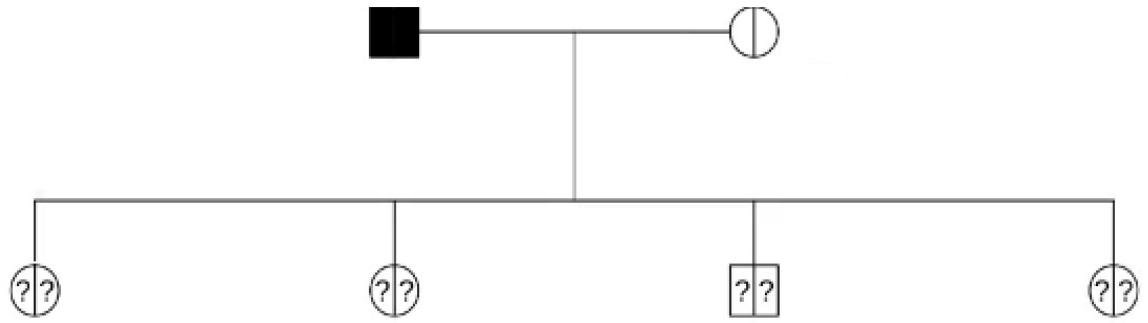
- Uniparental disomie

example 2

Deafness, autosomal dominant 5 (GSDME)

Autosomal dominant inheritance (7p15.3)

Family tree



Sanger sequencing

Gene: GSDME

accession number: chromosome:GRCh38:7:24697851:24758613:1

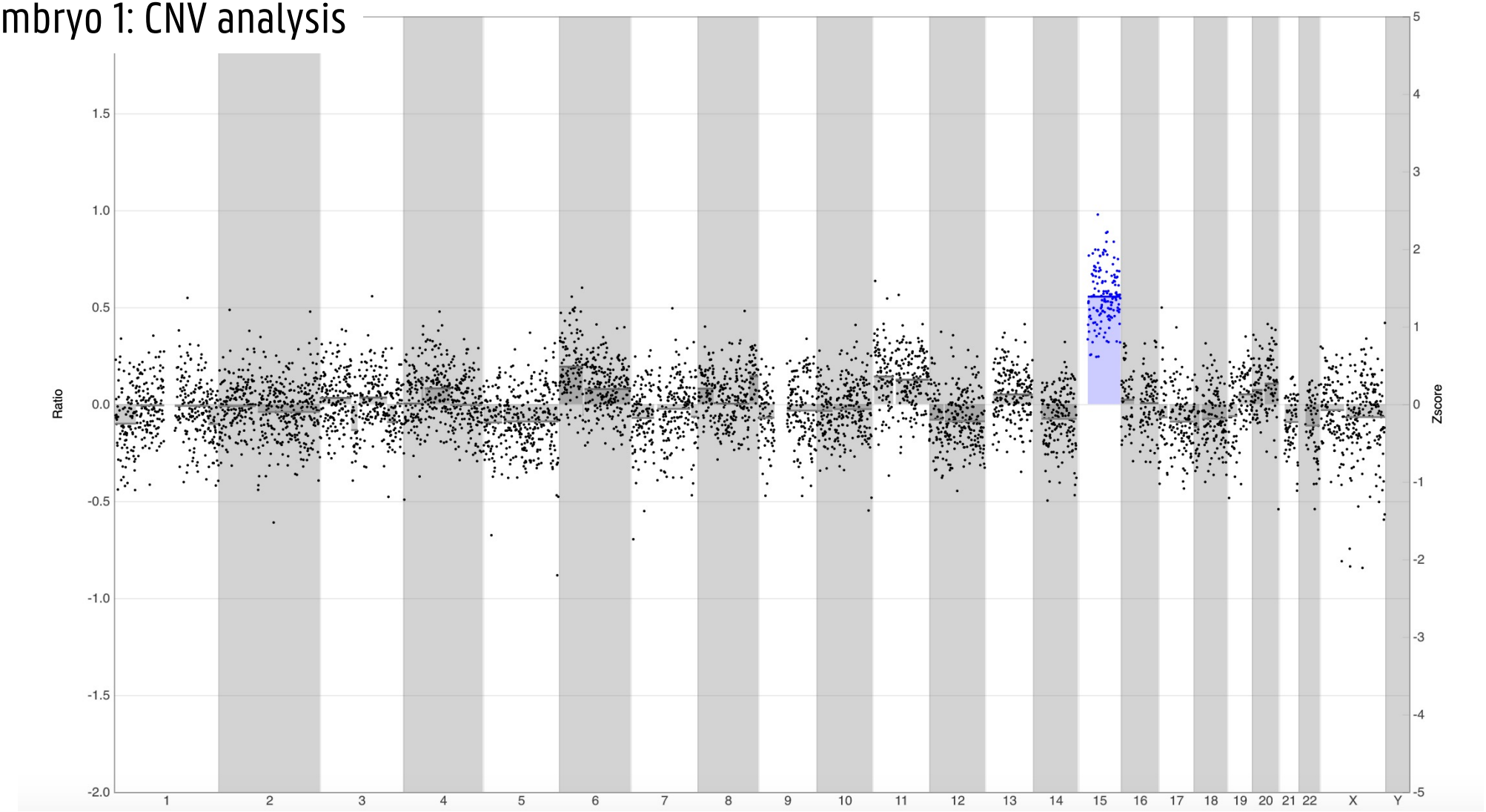
sequence version: chromosome:GRCh38:7:24697851:24758613:1

Result:

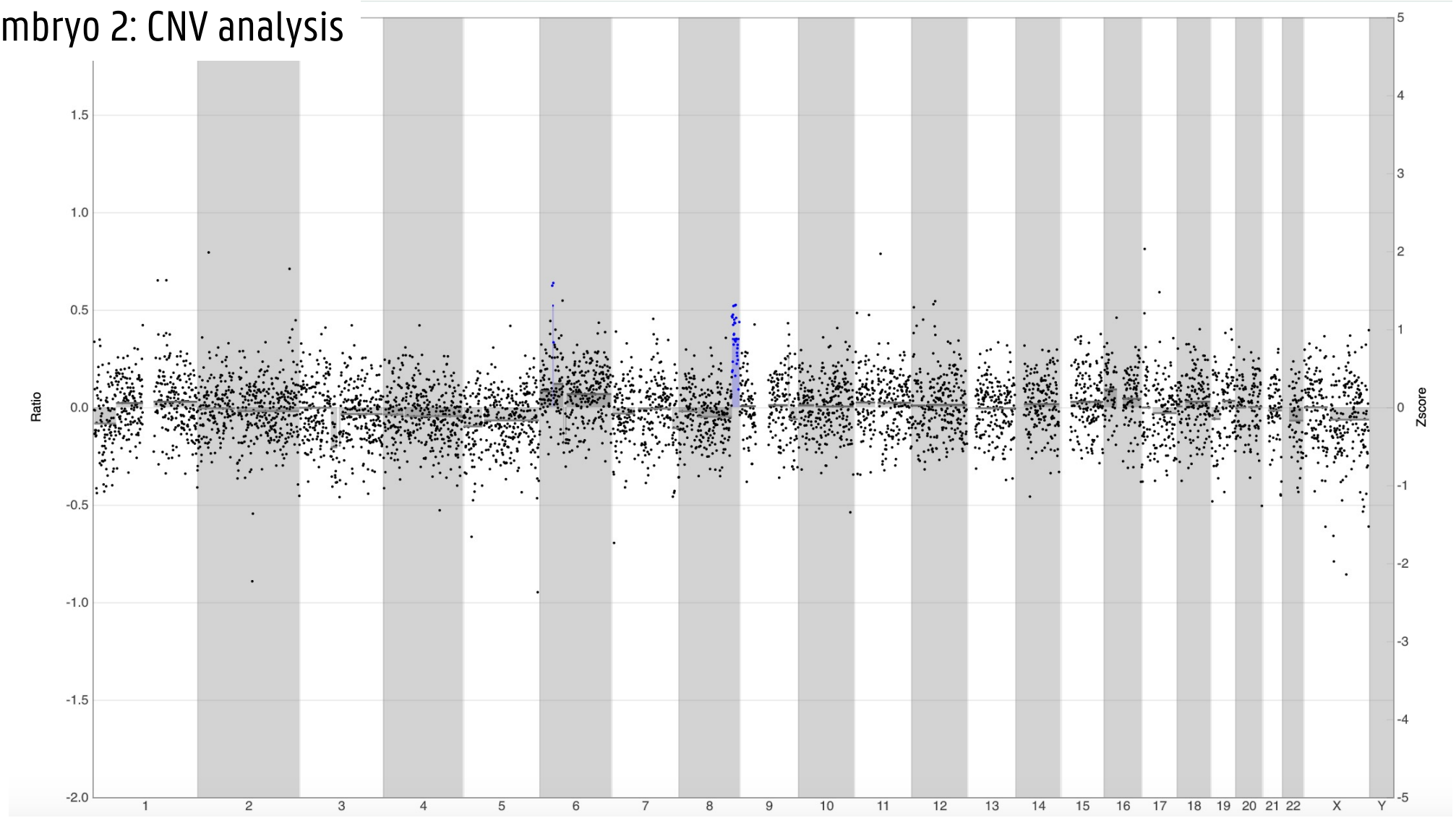
Index	Location	Position	Type	Nuc Change	AA Change	Web Ref	Mut Ref	Mut Effect
1	E8	171 (1161)	C	C -> T	Y -> Y (387)		c.1161C>T	

	1									
	het									
mother										
father	het									
Embryo 1A	het									
Embryo 1B	het									
Embryo 2A										
Embryo 2B										
Embryo 3A										
Embryo 3B										
Embryo 4A	het									
Embryo 4B	het									
Negative control										

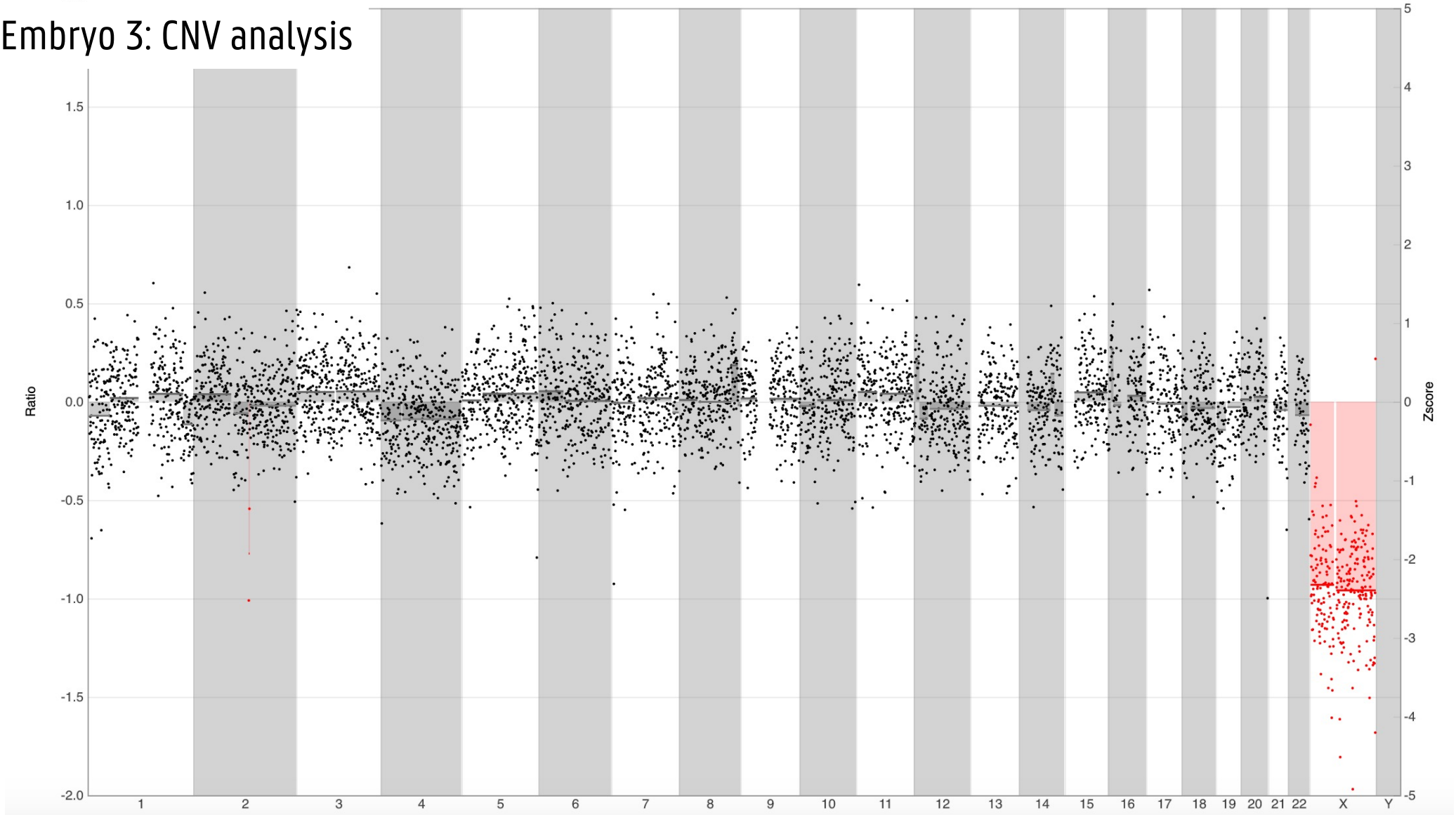
Embryo 1: CNV analysis



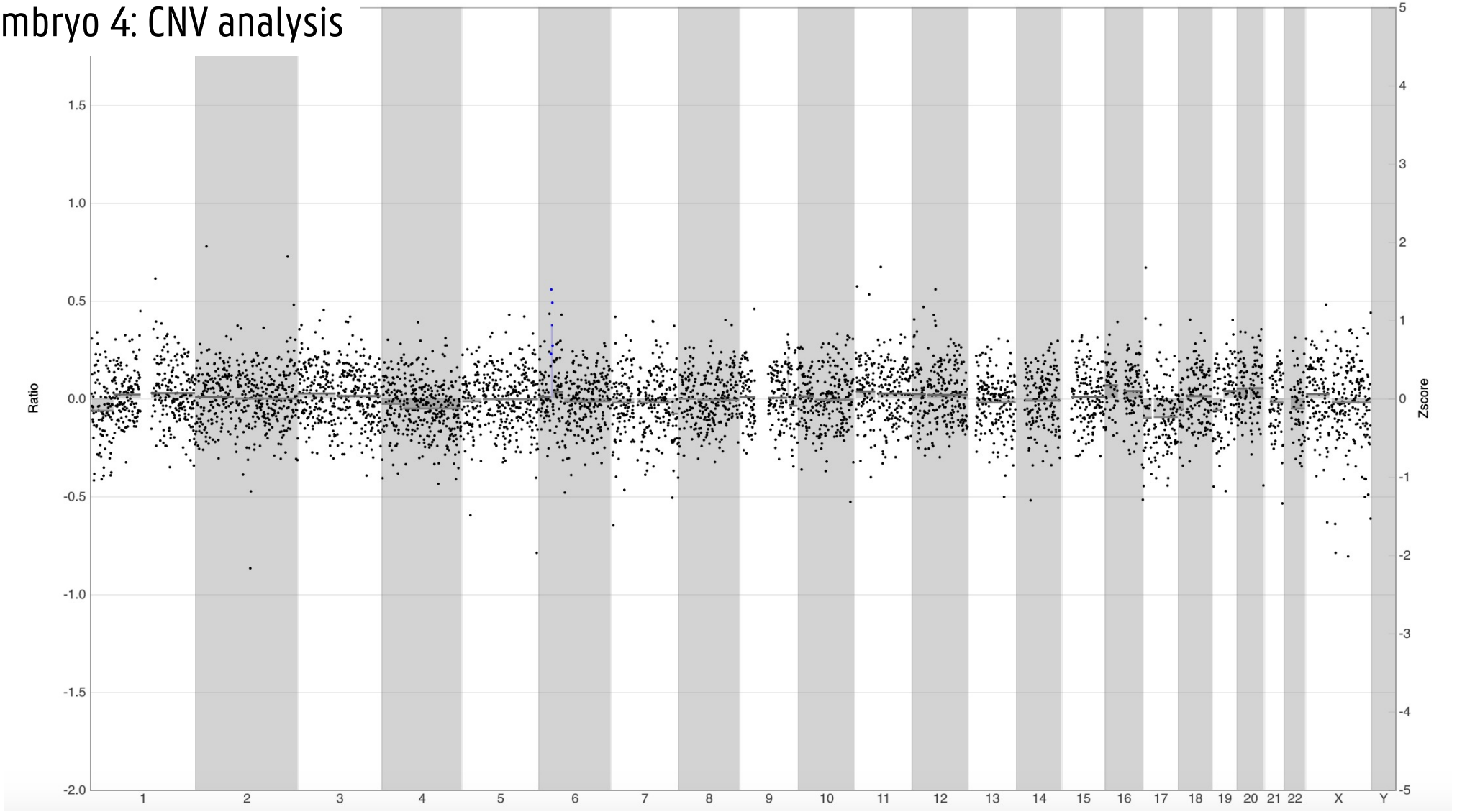
Embryo 2: CNV analysis



Embryo 3: CNV analysis



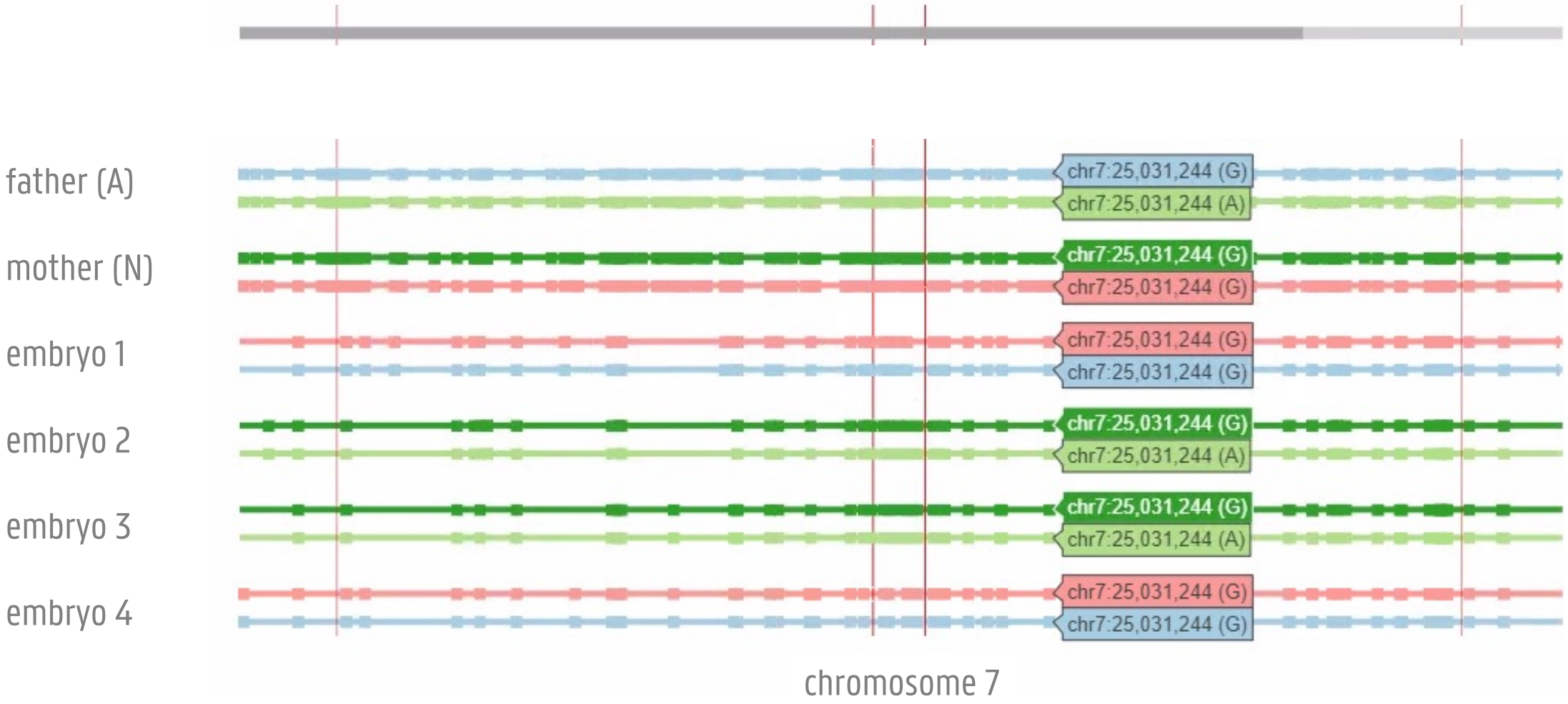
Embryo 4: CNV analysis



Results

	Sanger	Hopla	CNV analysis	Conclusion
Embryo 1	affected		trisomy 15	no
Embryo 2	unaffected		8q duplication	no
Embryo 3	unaffected		normal	Yes
Embryo 4	affected		normal	no

GENType + HOPLA analysis



Results

	Sanger	Hopla	CNV analysis	Conclusion
Embryo 1	affected	affected	trisomy 15	no
Embryo 2	unaffected	unaffected	8q duplication	no
Embryo 3	unaffected	unaffected	normal	Yes
Embryo 4	affected	affected	normal	no

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Center for Medical Genetics

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Lisa De Witte
Annelies Dheedene
Lennart Raman
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