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Innovative use of SNPs in PGT-A allows to distinguish meiotic trisomies without parental DNA sample support

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21.PGDIS
Kuala Lumpur
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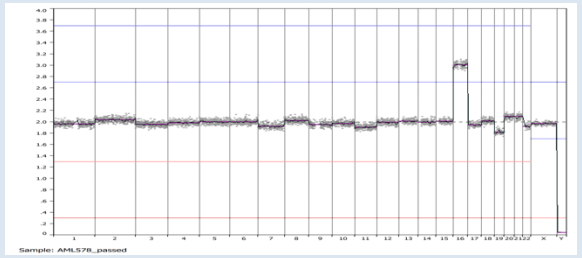
Use of SNPs in preimplantation genetic testing for aneuploidies (PGT-A)

CNV

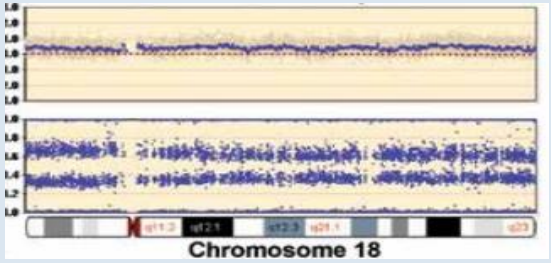
NGS



- Mosaicism detection
- High resolution
- Segmental aneuploidies

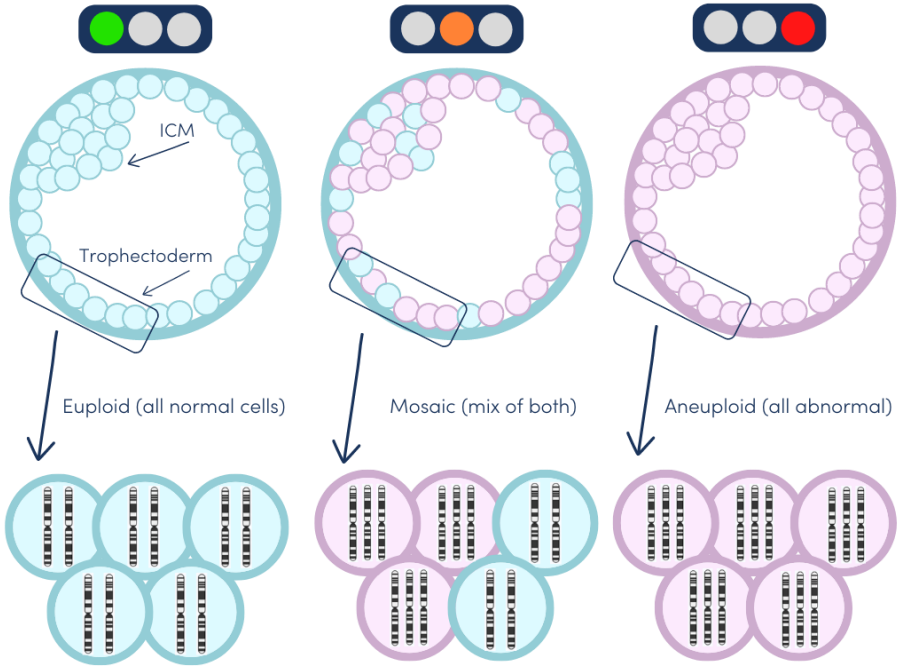
CNV + SNP analysis

NGS, SNP array



- Triploids/haploids detection
- Reduced false calls
- Fingerprinting
- Origin of aneuploidy (meiotic,mitotic, pat., mat.)

PGT-A



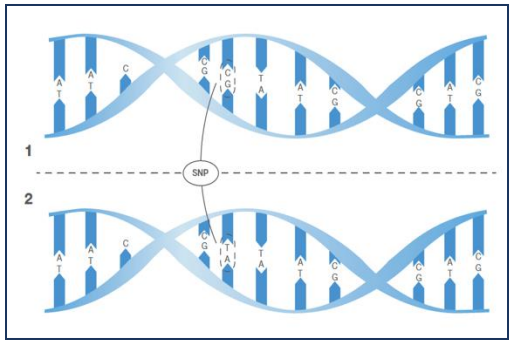
✓ Recommended for transfer

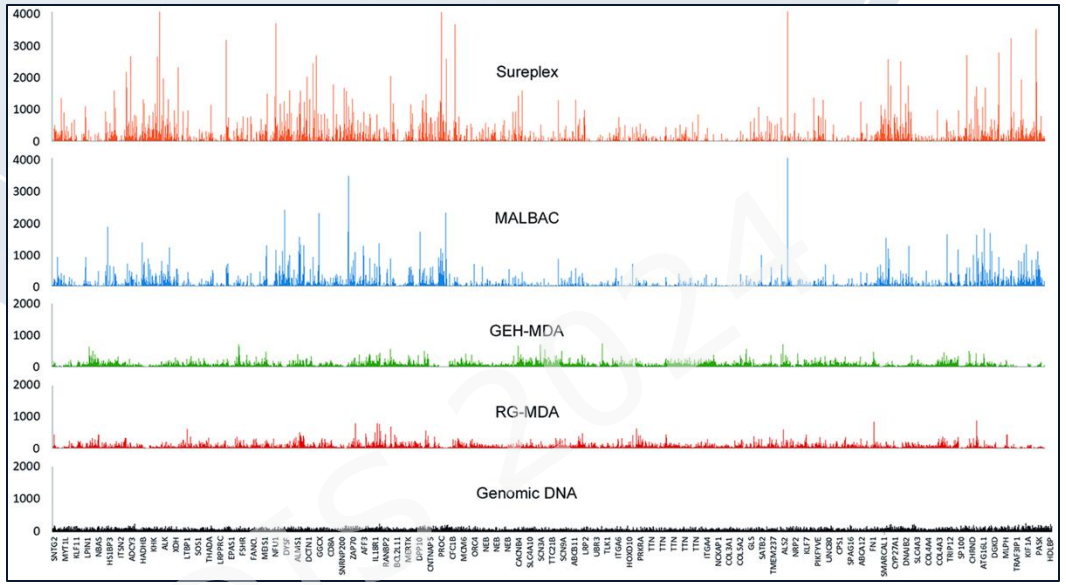
! Genetic counselling

✗ Not recommended

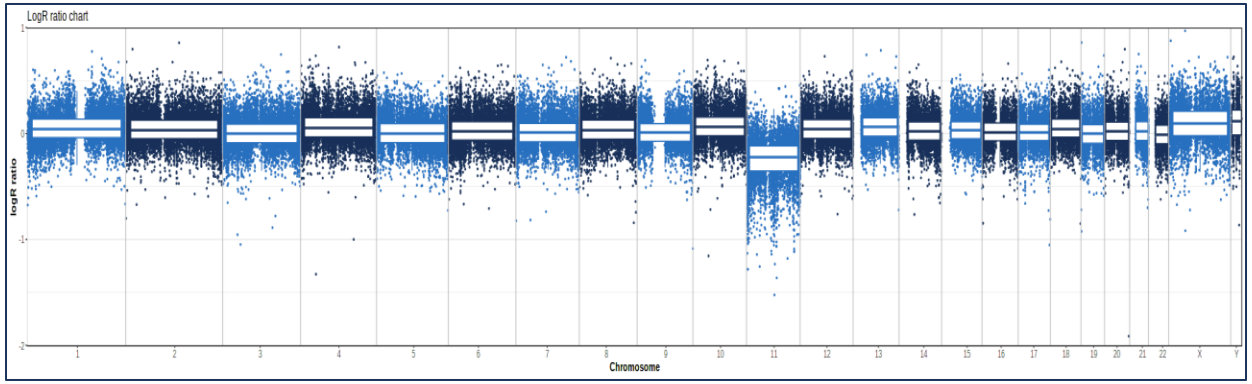
PGT-A + SNP analysis

- Infinium™ Global Screening Array-24 v3.0 BeadChip
- 654,027 SNP markers
- Multiple Displacement Amplification (MDA)

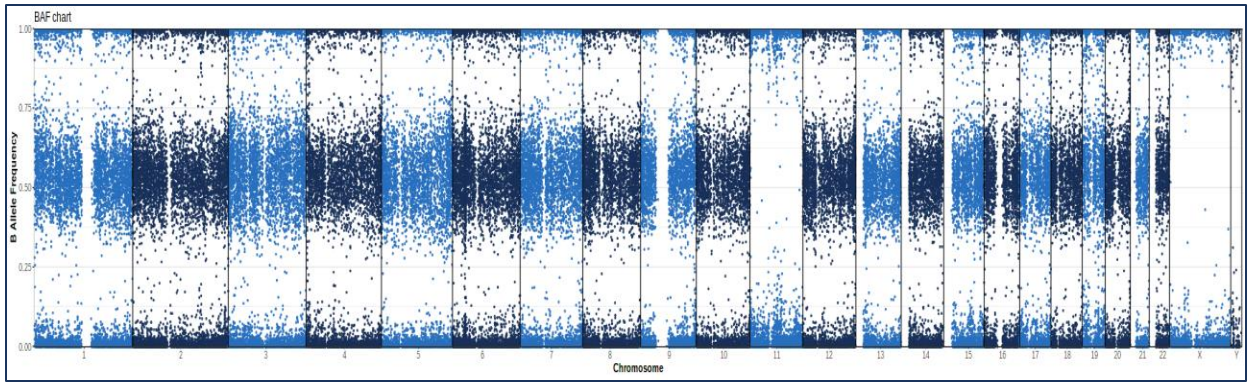




Rey et al., 2018



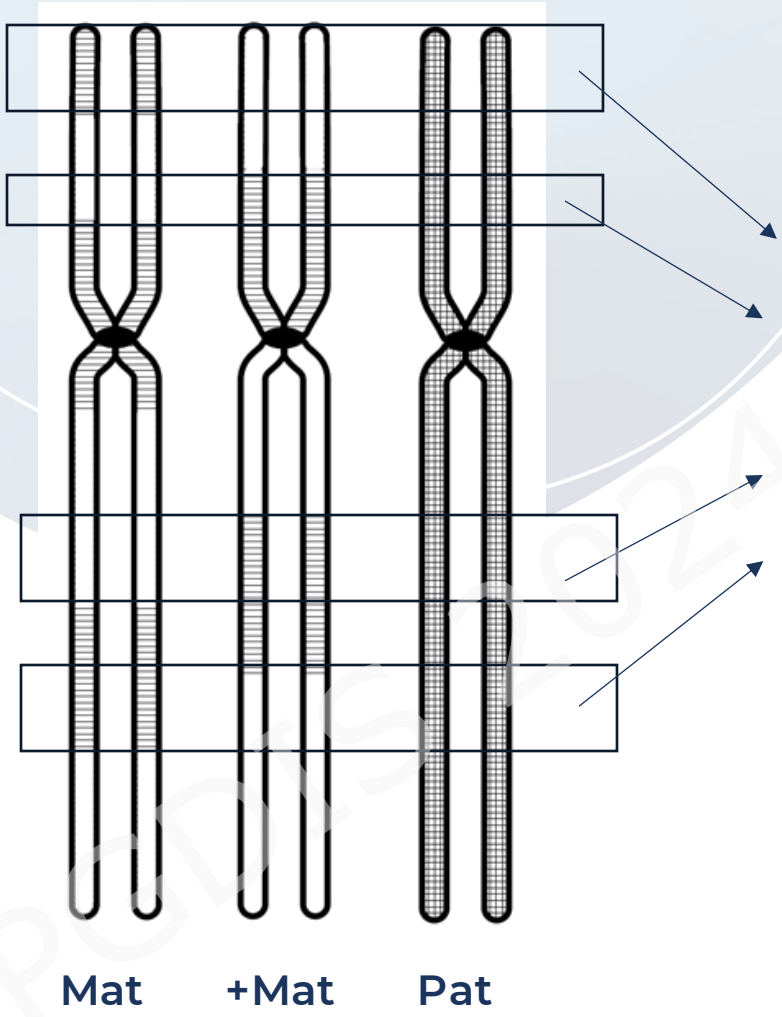
LogR (CNV)



BAF

Meiotic vs. mitotic trisomies without parental DNA sample support?

Meiotic trisomy

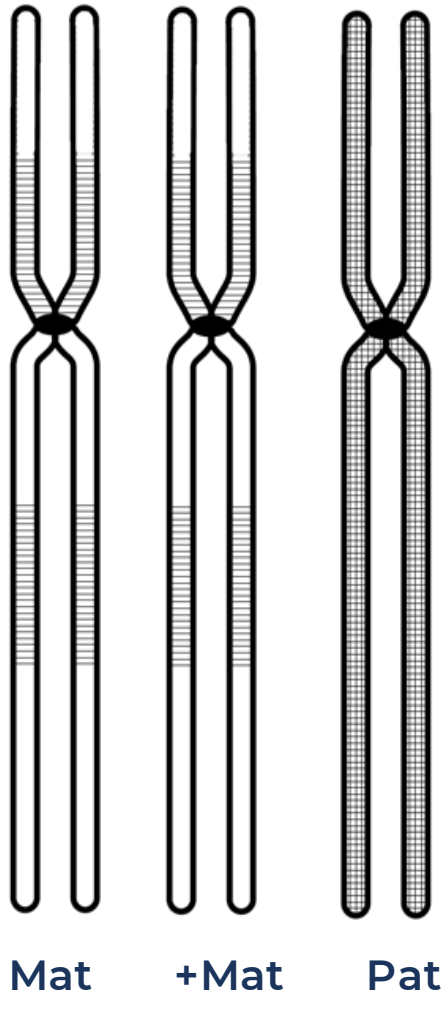


(presence of 3 homologs)

Increased heterozygosity

GSA +46% (st.dev ± 11,8 %)

Mitotic trisomy



(presence of 2 homologs)

heterozygosity level

not increased

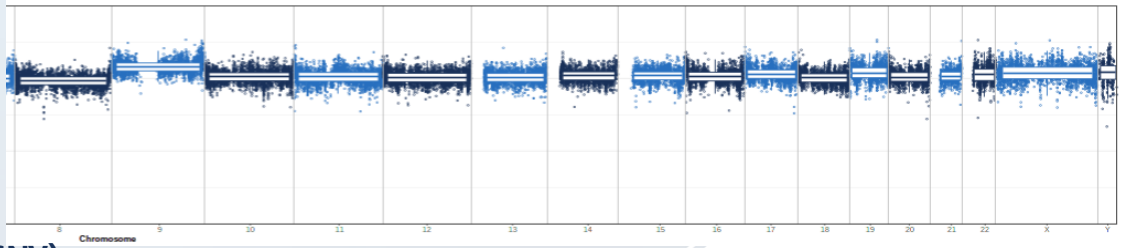
PGT-A meiotic vs. mitotic trisomies without parental DNA sample support?

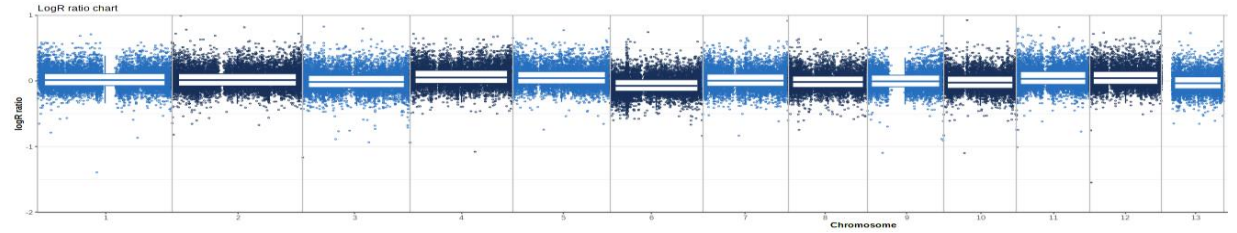
Meiotic trisomy

Mitotic trisomy

Normalised heterozygosity increase in TE samples enables to distinguish between meiotic a mitotic trisomy without parental DNA sample support

LogR (CNV)





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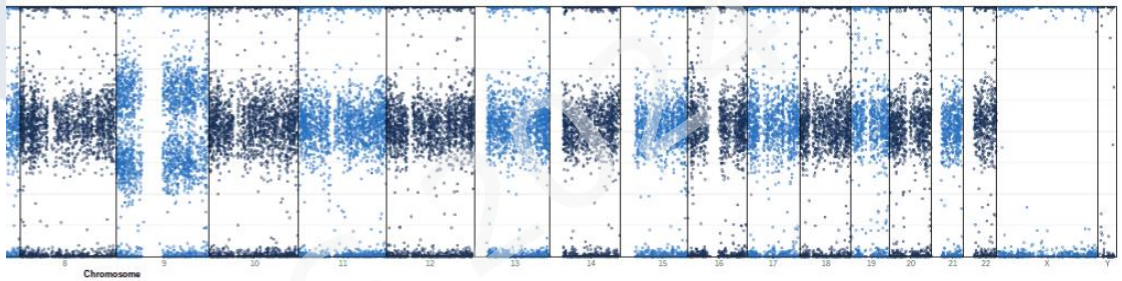
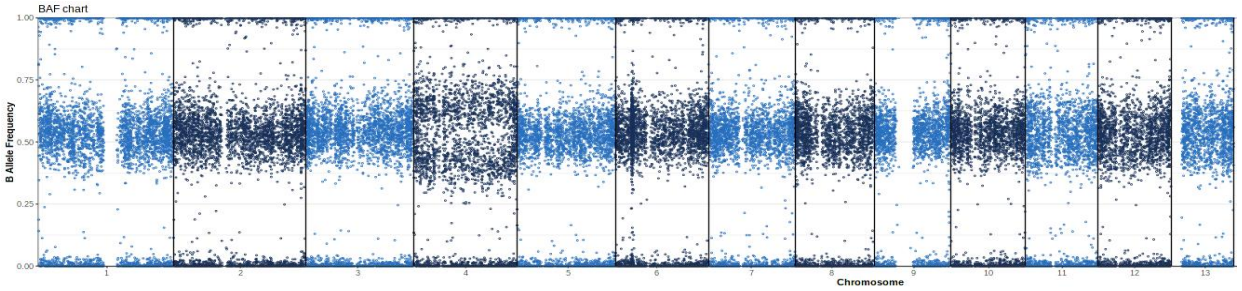
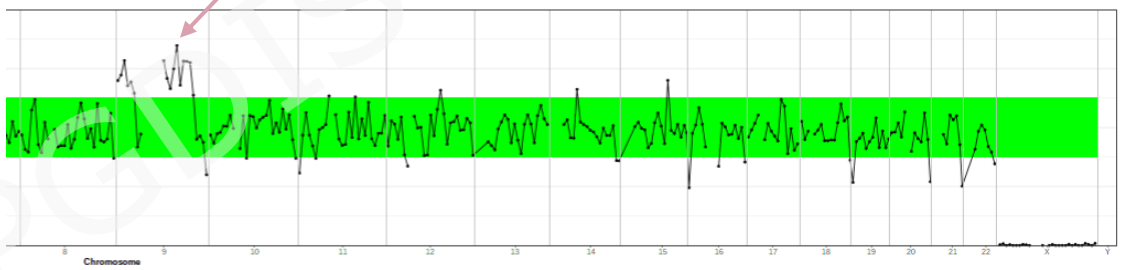
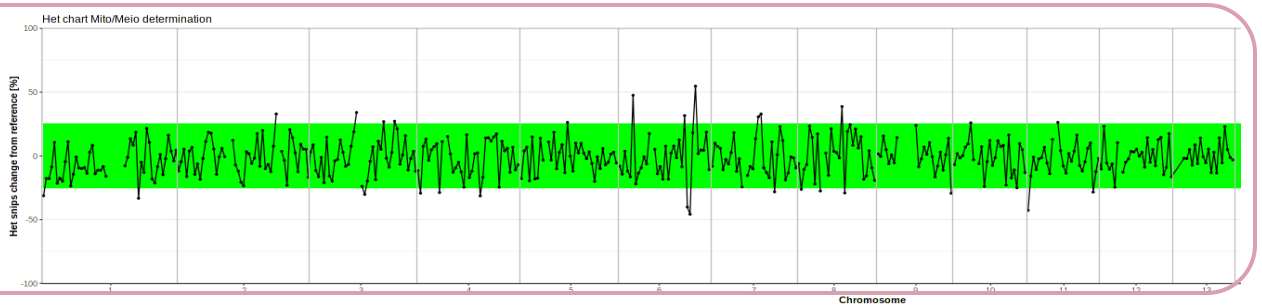




GOH



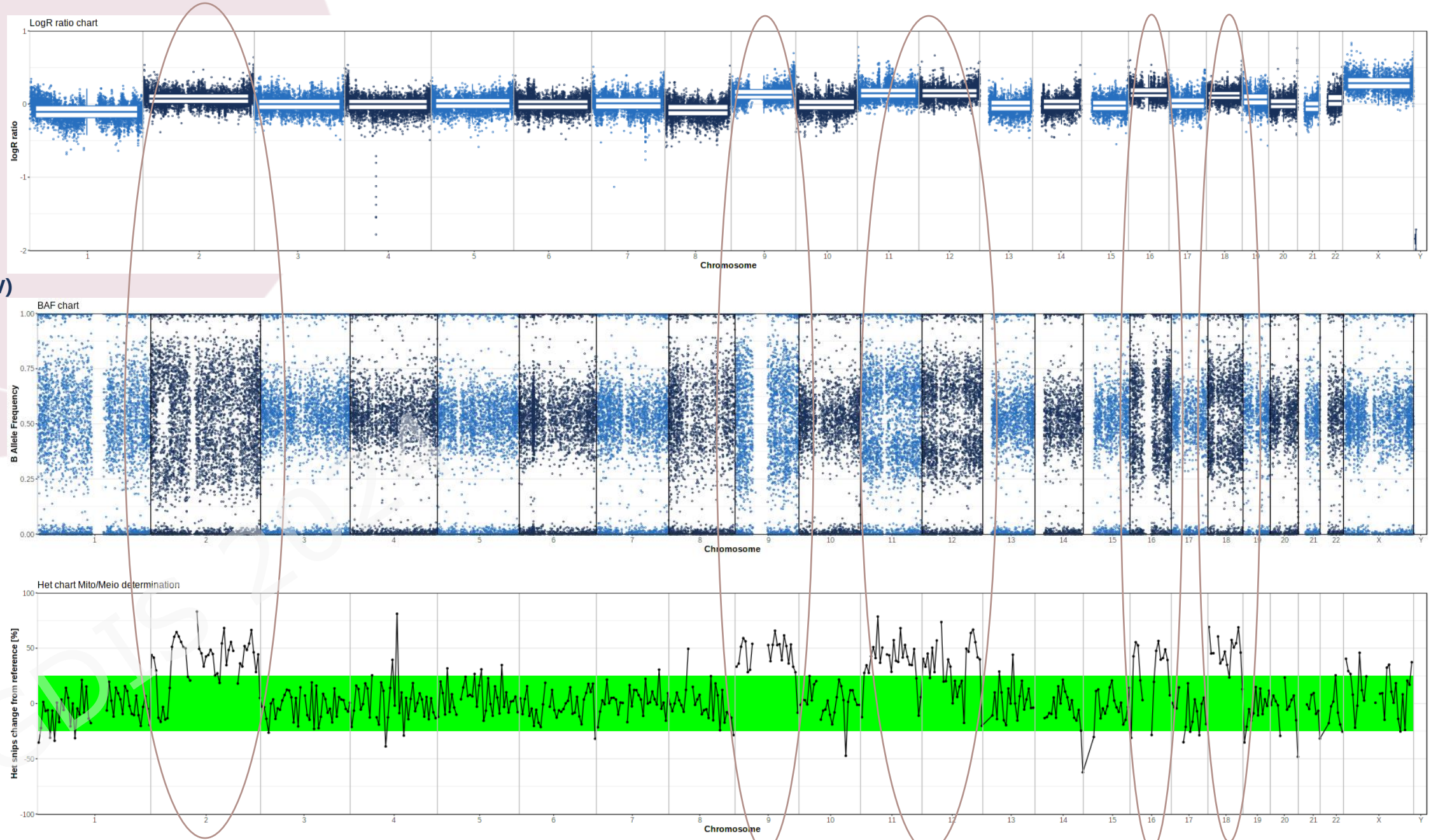


Trophectoderm sample - meiotic trisomy signature

LogR (CNV)

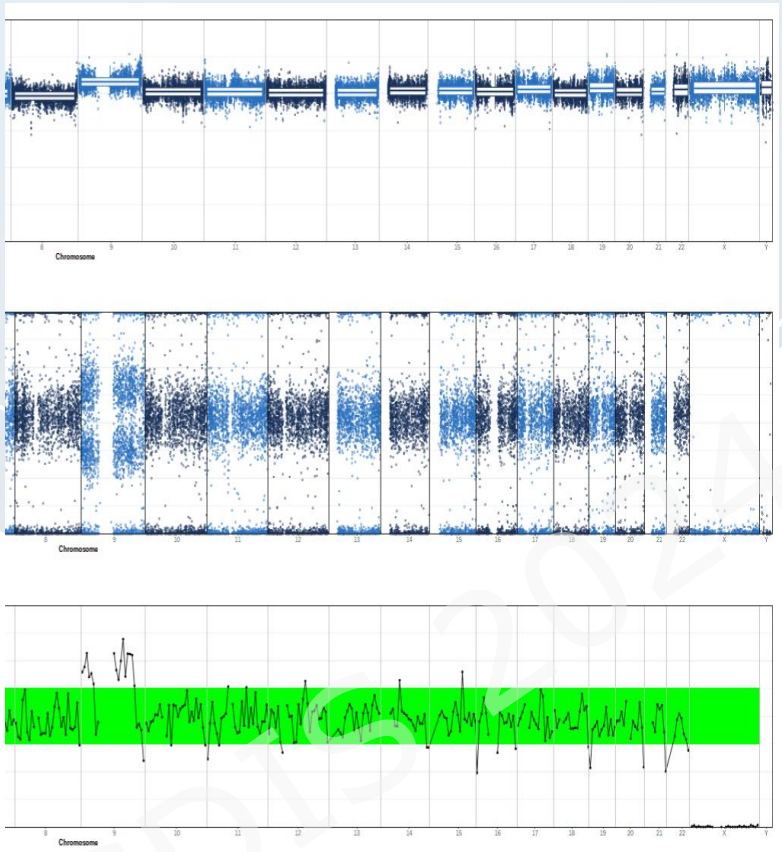
BAF

GOH

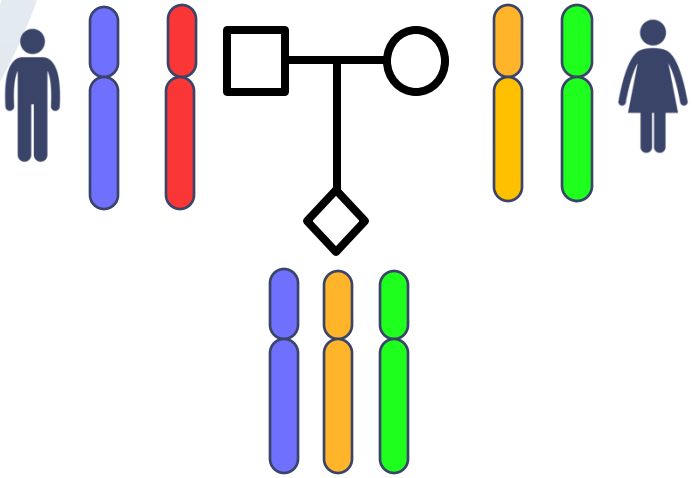


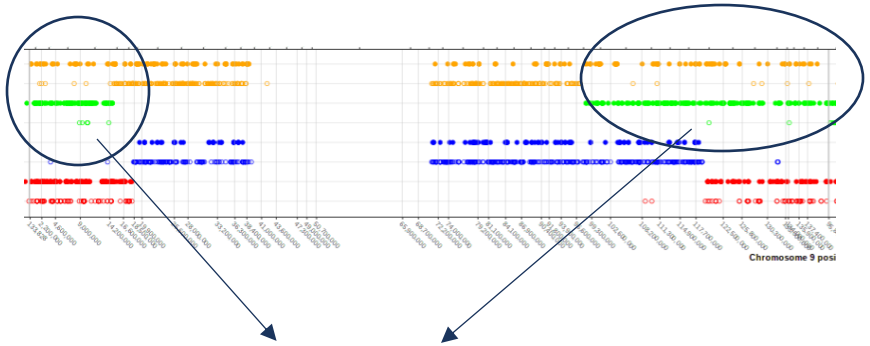
Validation of the algorithm

Trophectoderm sample -> meiotic pattern → Parental DNA samples analysis (biparental haplotypes)



Infinium™ Global Screening Array-24 v3.0 BeadChip

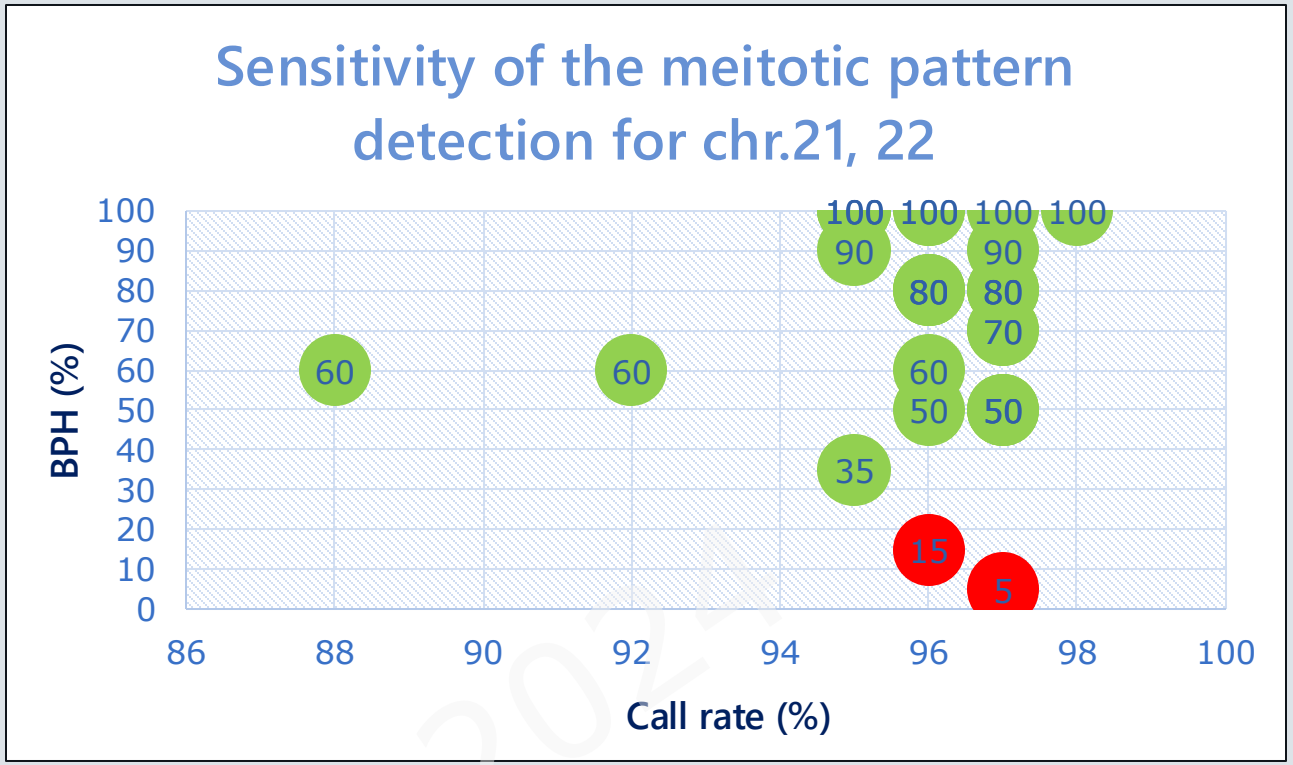




BPH = biparental hapotypes

38/38 meiotic trisomies confirmed
= 100% concordance between heterozygosity increase and biparental haplotypes (BPH)

Validation of the sensitivity (meiotic pattern)

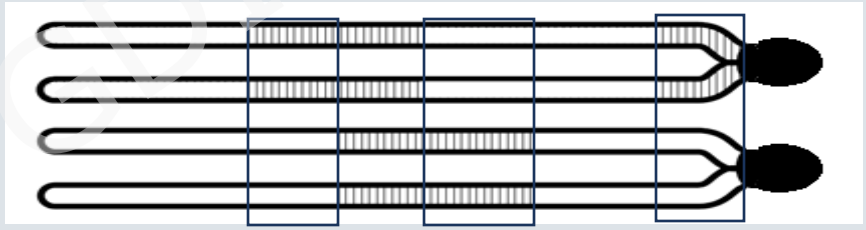


- Twenty meitotic trisomies of chr. 21, 22 (confirmed by karyomapping)

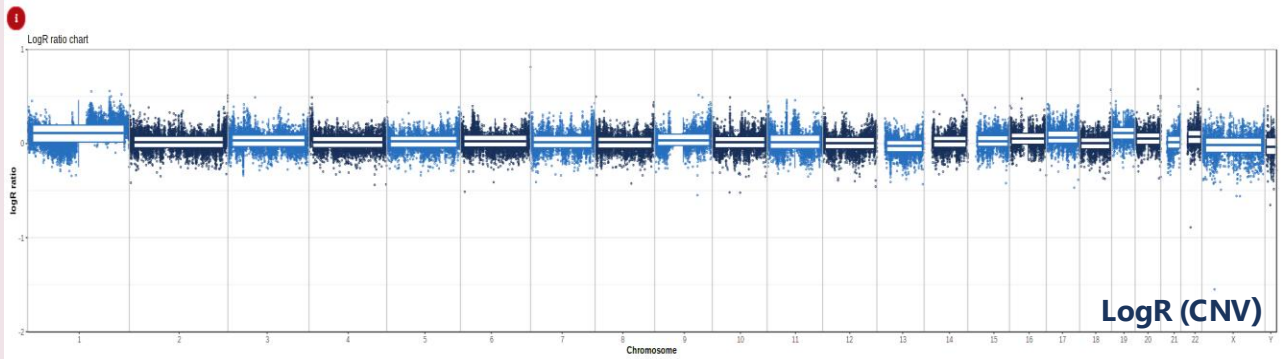
- 18/20 (90%) of meiotic trisomies confirmed by the heterozygosity analysis

Overall sensitivity 95-98%

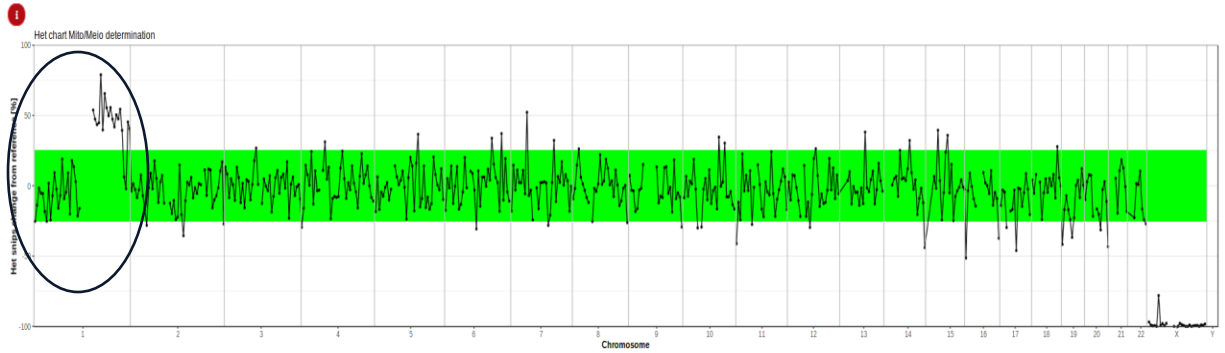
BPH(%) = BPH / BPH + SPH



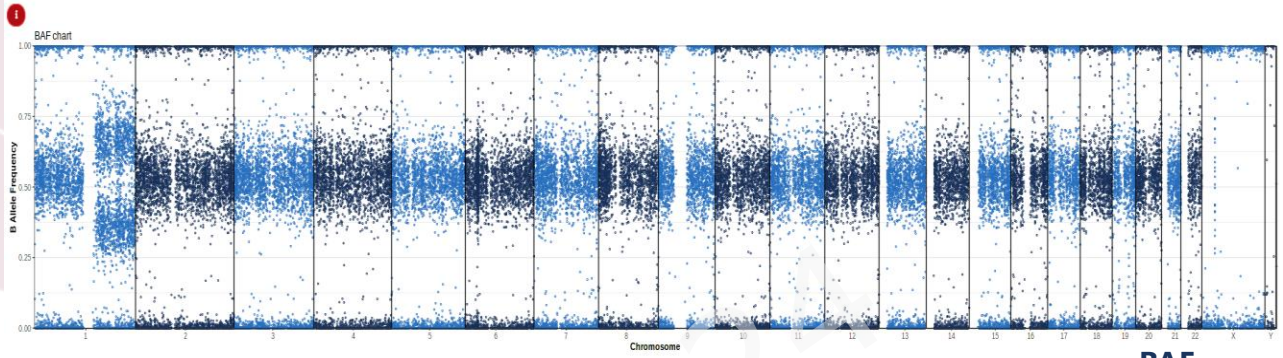
Segmental aneuploidy – Gain of heterozygosity algorithm



LogR (CNV)



GOH



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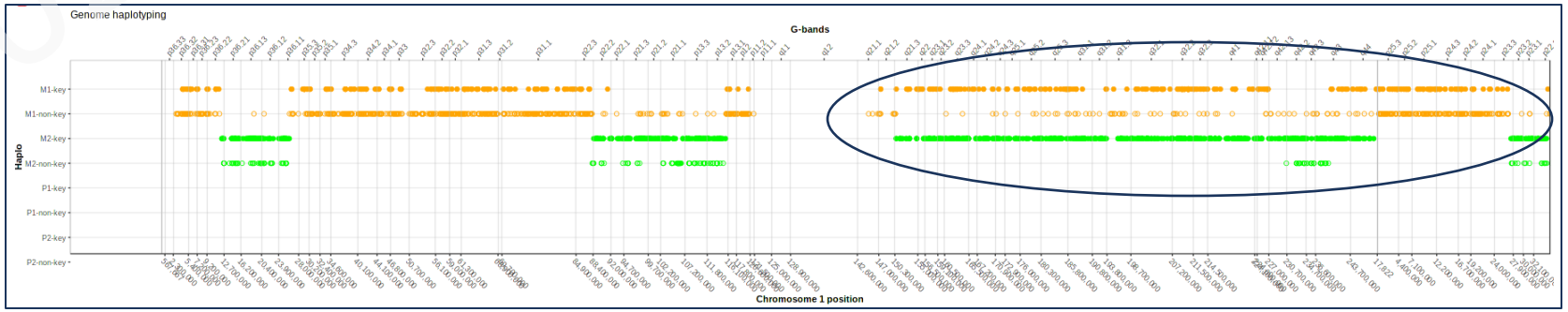
Improved diagnostics of segmentals



Haploblock analysis

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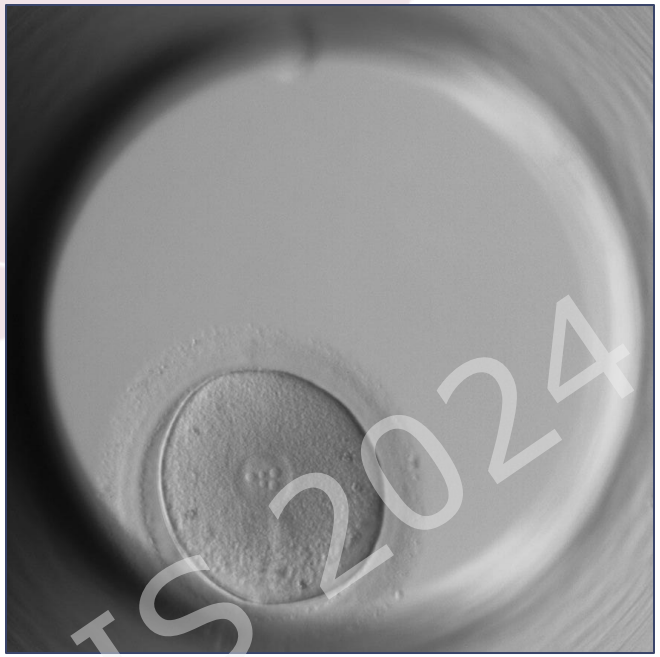
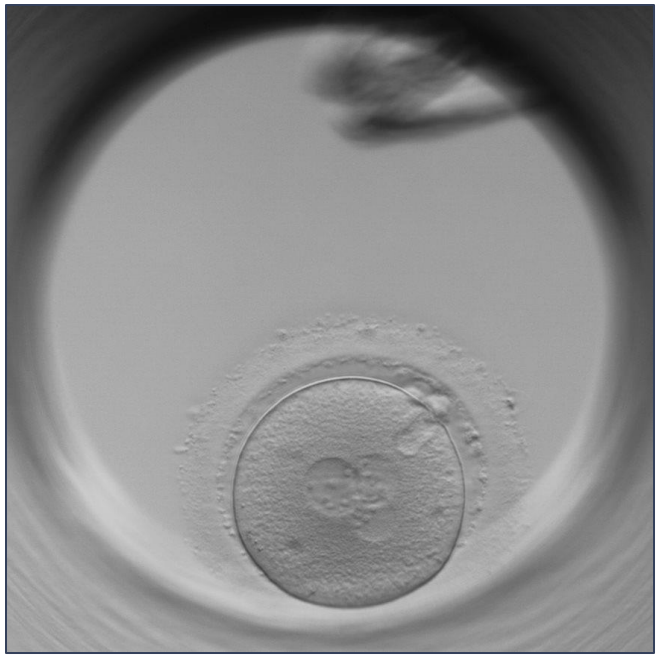
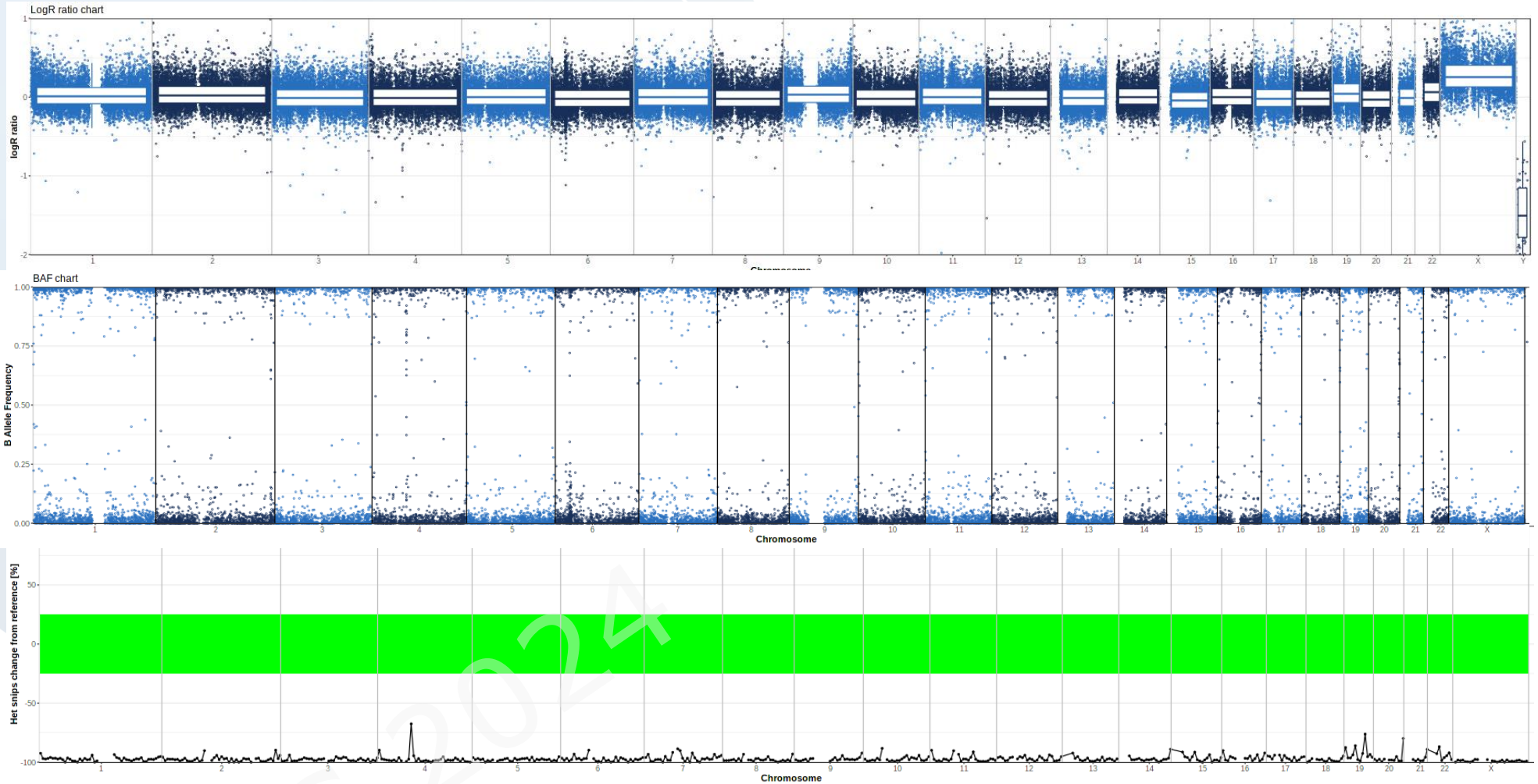
Polyploidy detection – Gain heterozygosity algorithm

- detection of haploid embryos (1 PN check)
- detecton of triploid embryos (3 PN check)





Repromeda, embryology lab



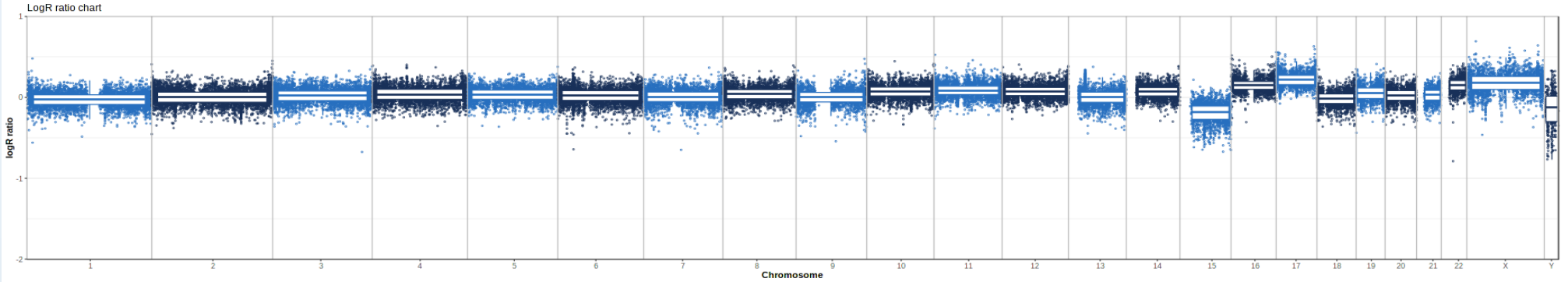
Haploid TE sample

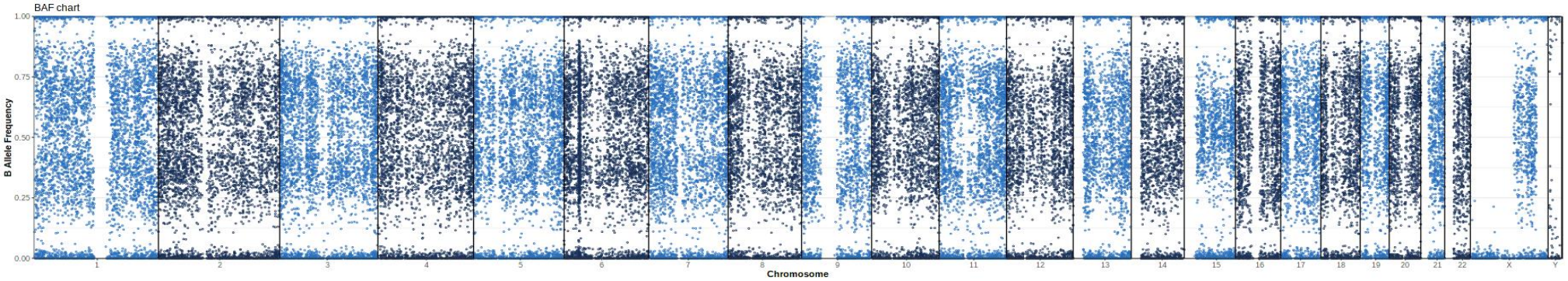
chr. constitution = 23,X

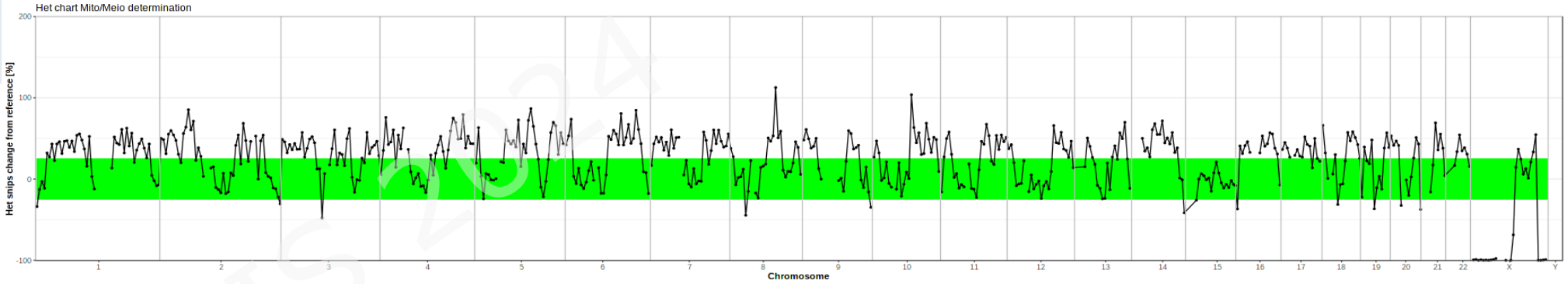
LogR (CNV)

BAF

Heterozygosity analysis







Triploid TE sample

chr. constitution = 69,XXY

LogR (CNV)

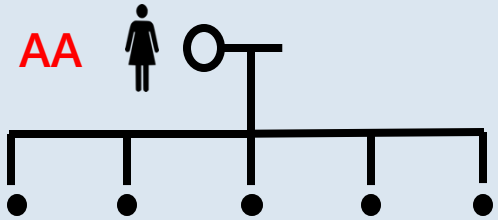
BAF

GOH

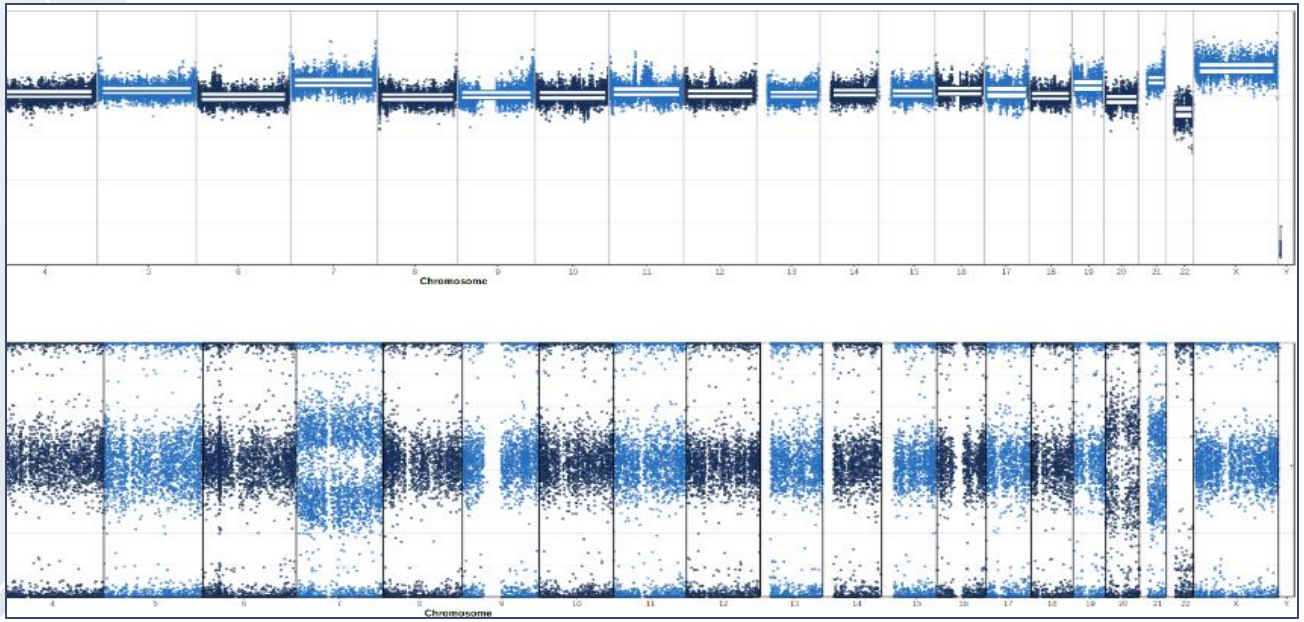
Extended SNP analysis with maternal DNA sample PGT-A+

SNP analysis

Haplotypy (SNP array)



- Parental BAF chart
- Chart of increased heterozygosity
- Chromosome aneuploidy origin



LogR (CNV)

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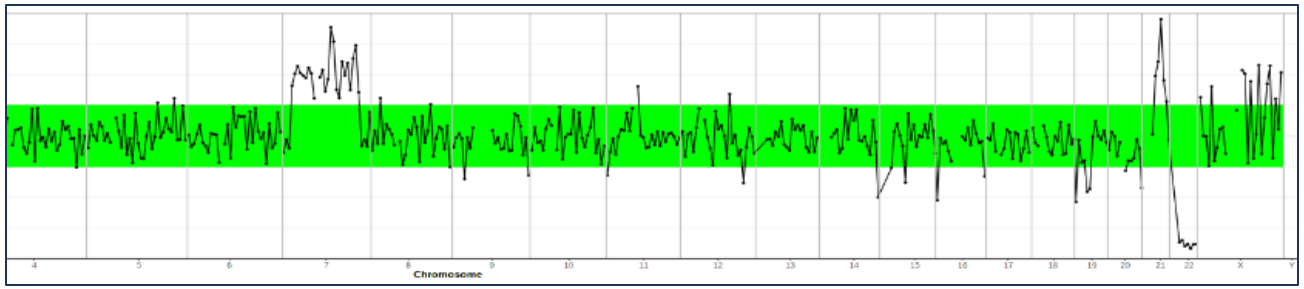
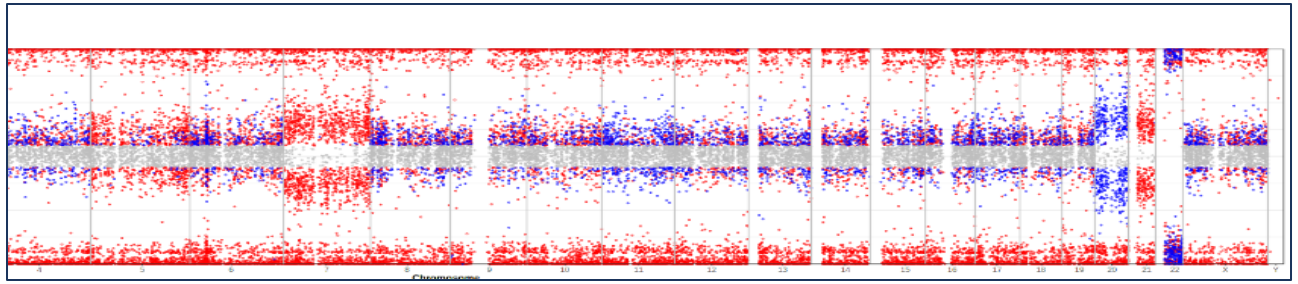


Heterozygosity analysis



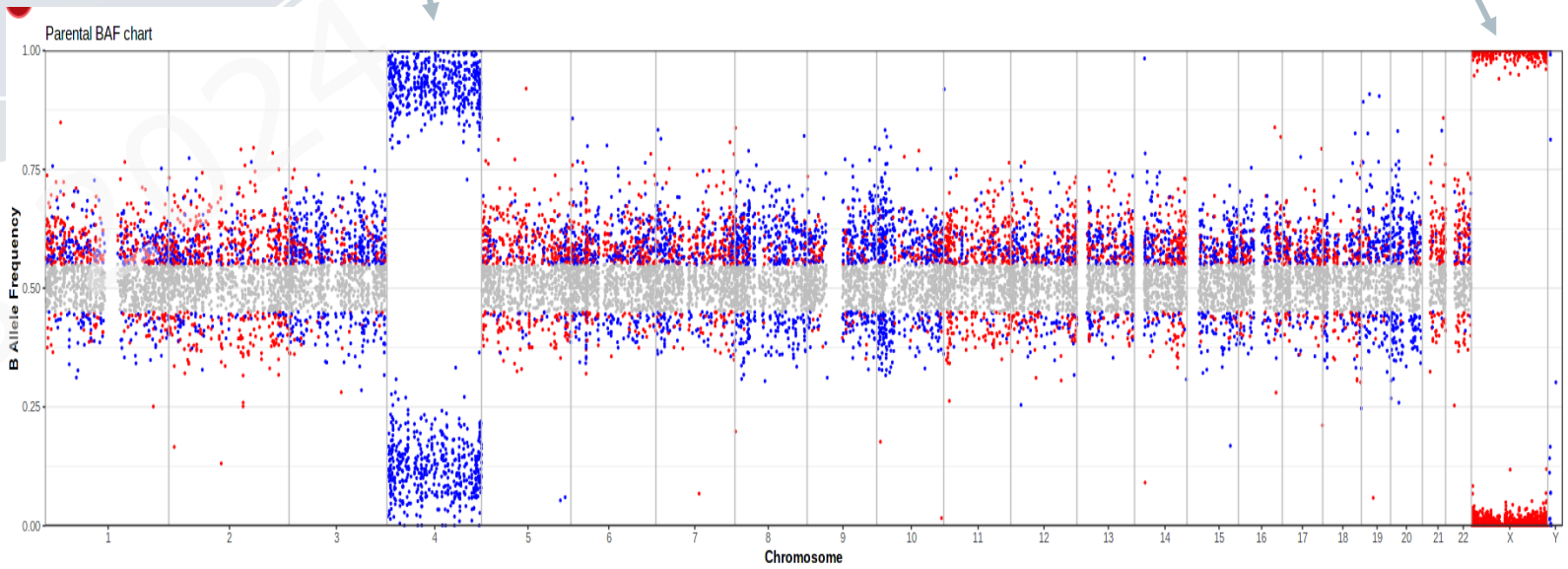
Aaneuploidy origin (mat/pat)

Extended SNP analysis with maternal DNA sample PGT-A+

- Mozaicism analysis
- Improved detection of high mosaic versus full aneuploidy – 90 % border for monosomies

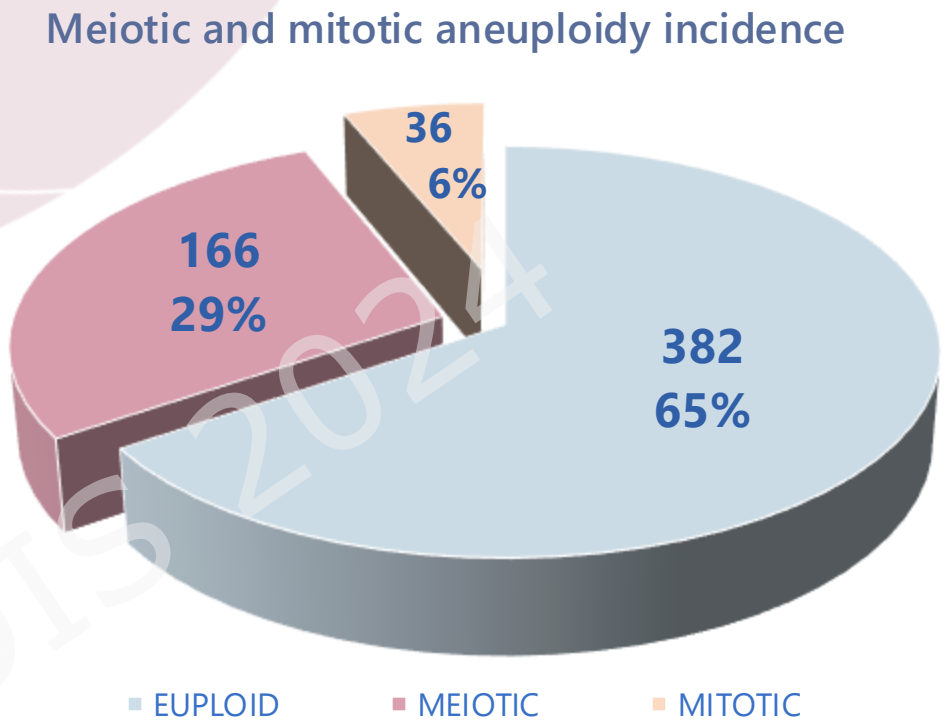
90 % mosaic monosomy:
- 9:1 MDA DNA ratio
  monosomy chr. 4 : disomy chr.4

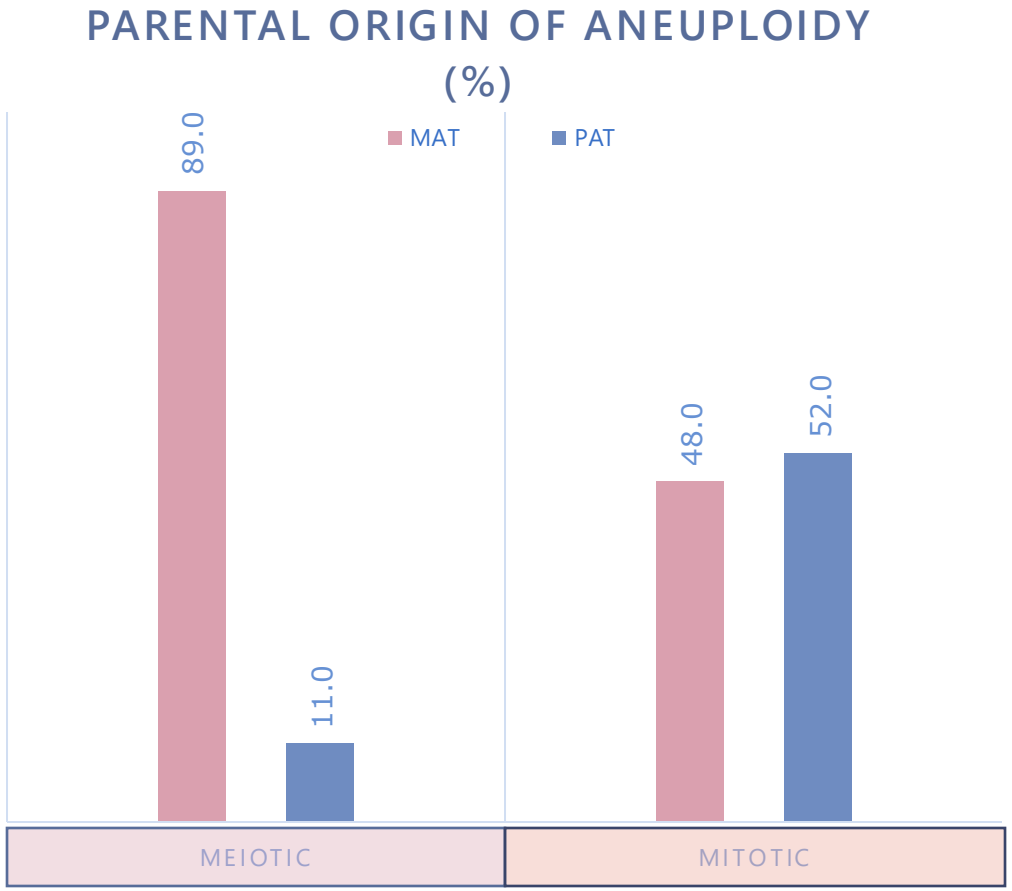
100 % „monosomy“ of chr. X



Aneuploidy statistics – whole chromosome errors

Average maternal age: 34,2 years
Embryos analysed: 625





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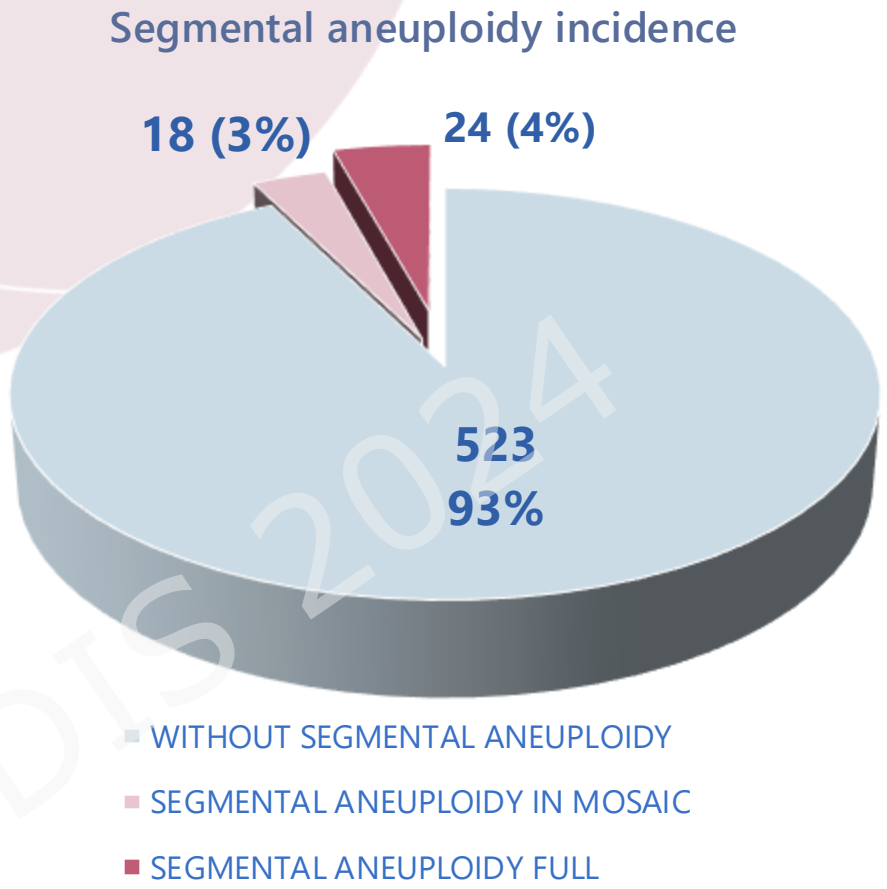
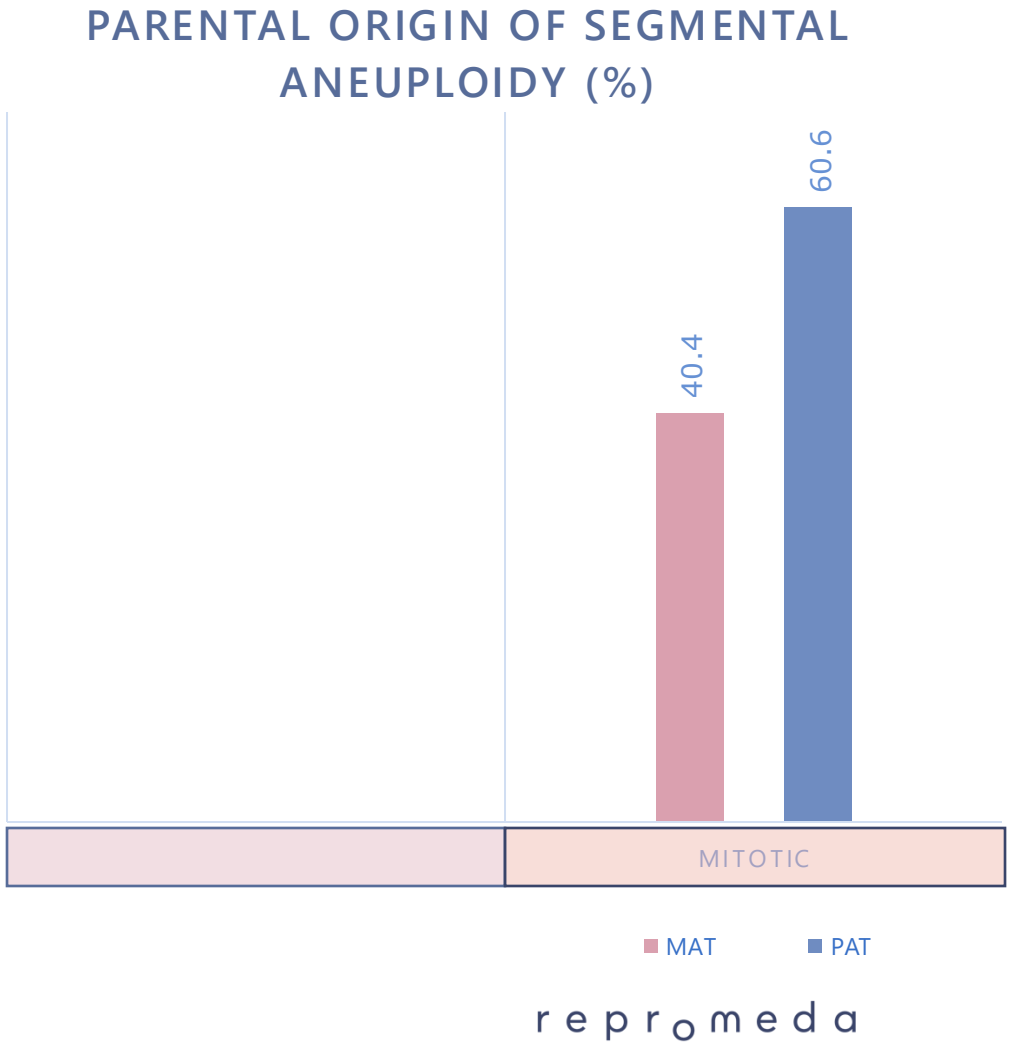
Aneuploidy statistics – segmental errors

Average maternal age: 34,2 years
Embryos analysed: 625





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Summary

- SNP analysis improve diagnostics
- Gain of heterozygosity analysis – patent pending (NGS / SNP arrays, preimplantation / prenatal samples)
  - meiotic vs. mitotic trisomy analysis
  - triploidy detection
- Analysis of aneuploidy origin – maternal DNA sample
- Recombination rate = 70% of BPH in meiotic trisomies and triploid samples
- Embryo transfer recommendation:
  - ✓ - euploid, segmentals in mosaic
  - ! - mosaic embryos, full segmentals -mitotic
  - ✗ - meiotic trisomies, triploids, haploids, segmental gains (meiotic pattern)

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Thank you for your attention

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