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Use of Arrays in PGD/PGS
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Karyomapping: a universal method for genome wide analysis of genetic disease based on mapping crossovers between parental haplotypes

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Single nucleotide polymorphisms (SNPs)

- 10 million SNPs across human genome
- Many biallelic (AA, AB, BB)
- Major contribution to genetic diversity, inherited disease and variants associated with common multifactorial conditions

Molecular cytogenetics using SNP arrays

Molecular cytogenetics

Intensity profiling
Loss of heterozygosity
B allele ratio

Targeted genotyping of family

Karyomapping

Family genotyping

Genome wide parental haplotyping and crossover mapping

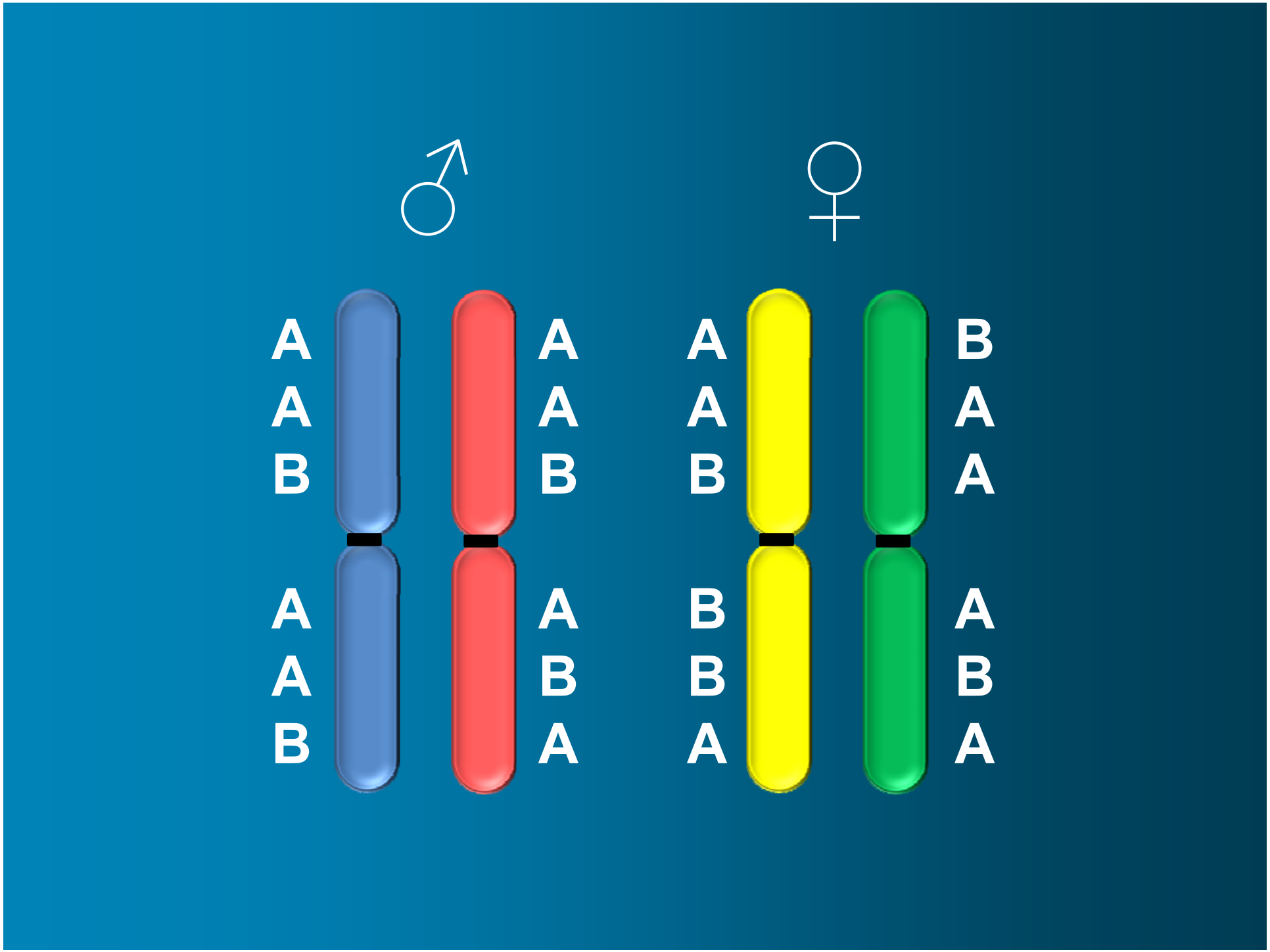
Construction of karyomaps

Principles of Karyomapping

- High density genome wide single nucleotide polymorphisms (SNP) genotyping of proband, parents and appropriate family member(s) to establish phase (Illumina Human CNV 370 Infinium-II Quad and Duo >300K SNP loci)

- Mendelian analysis and karyomapping of the parental and grandparental haplotypes for each chromosome or chromosome segment in recombinant chromosomes

Handyside et al (2009) J Med Genet, in press


♂
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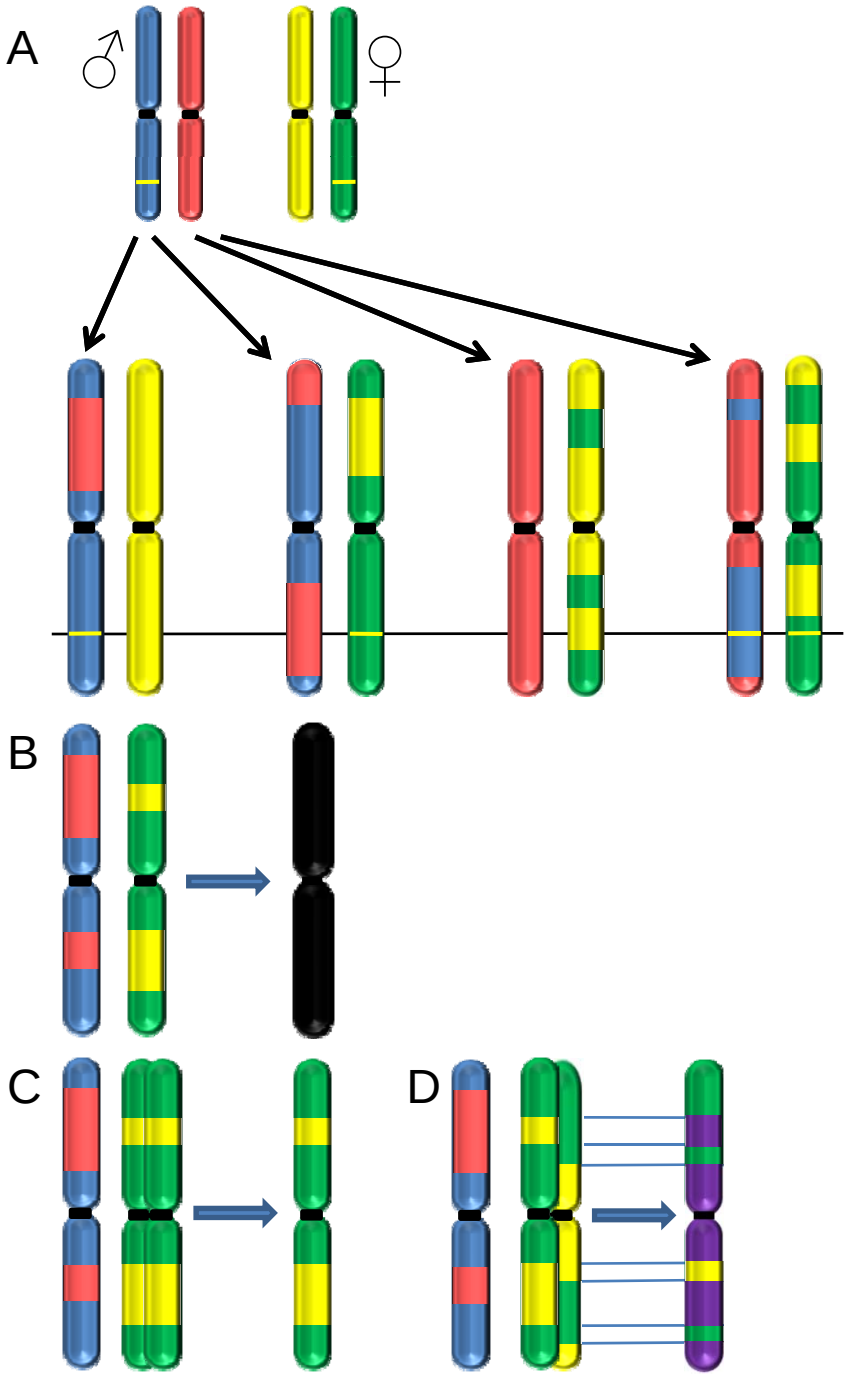
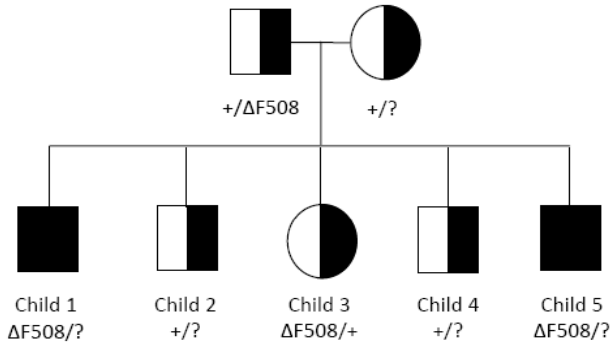
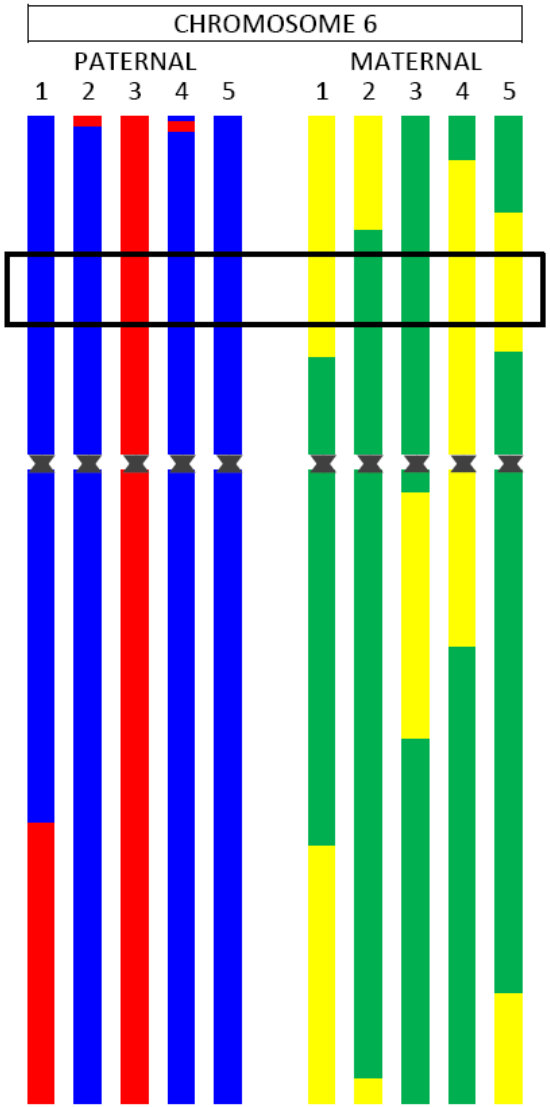
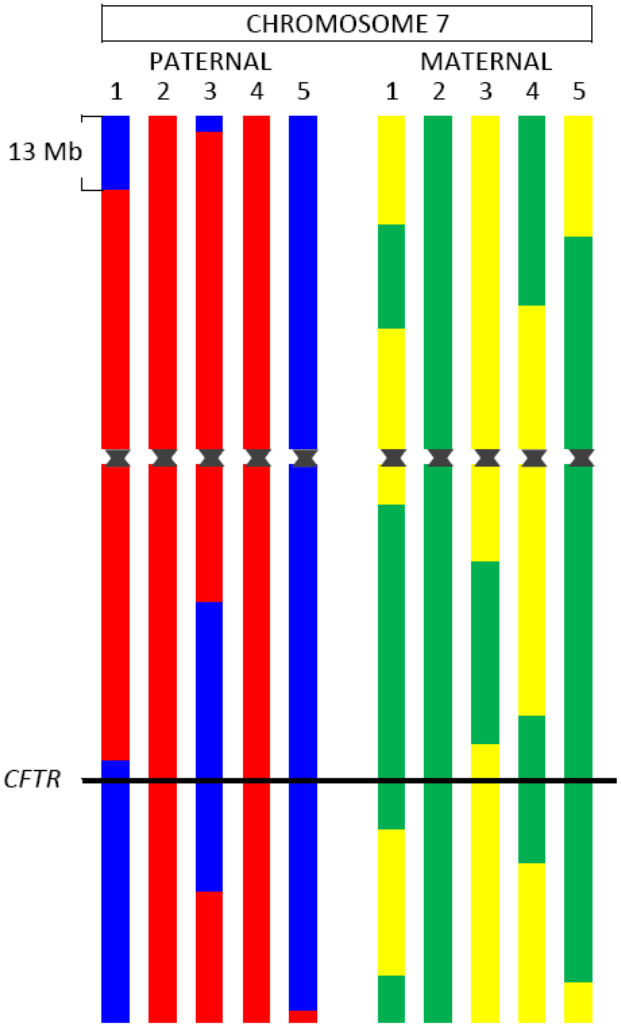
Karyomapping combines genome wide linkage based detection of single gene defects (A) with chromosomal aneuploidy including monosomy/deletions (B) and trisomies involving inheritance of two different meiotic chromosomes from one parent (D). Chromosome duplication is not detected (C).



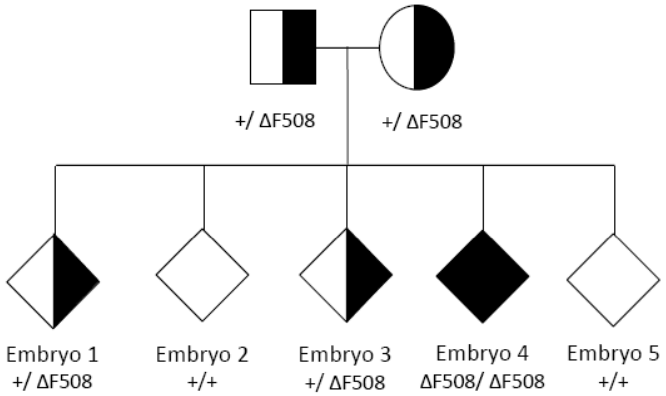
Family 1


+/ΔF508
+/?
Child 1
ΔF508/?
Child 2
+/?
Child 3
ΔF508/+
Child 4
+/?
Child 5
ΔF508/?

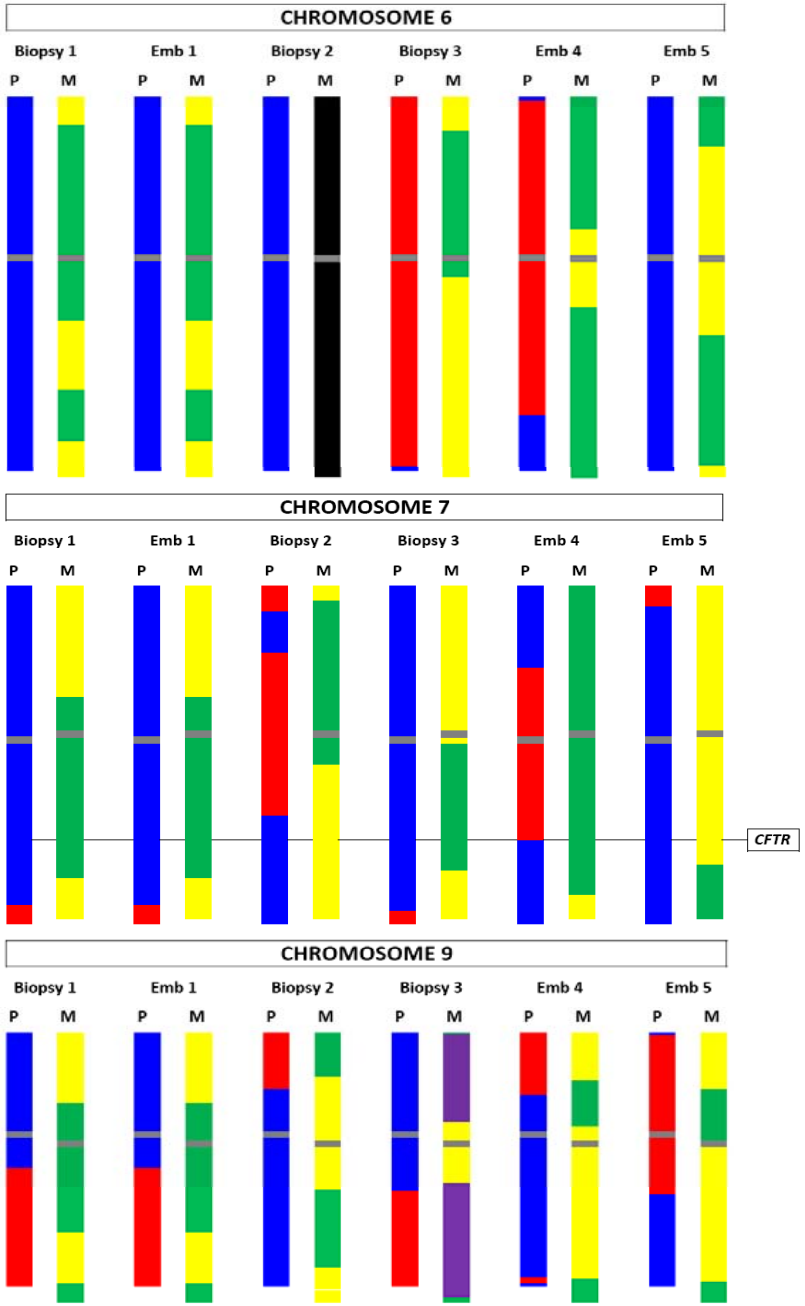

CHROMOSOME 6
PATERNAL
MATERNAL
1 2 3 4 5
1 2 3 4 5


CHROMOSOME 7
PATERNAL
MATERNAL
1 2 3 4 5
1 2 3 4 5
13 Mb
CFTR

Family 2
Preimplantation genetic diagnosis for cystic fibrosis



Whole genome amplification by isothermal multiple displacement amplification of 2-10 cells in each biopsy/embryo



	Mutation detection	Multiplex PCR and minisequencing	Preimplantation genetic haplotyping	Fluorescence in situ hybridisation	Array CGH	Quantitative SNP array analysis and Karyomapping
Single gene defects						
Single or combination	✓	Any	✓			Any
Exclusion	✗	✓	✓			✓
SGD + HLA typing	✗	✓	✗			✓
Chromosome screening						
Aneuploidy			✗	✓ (5-12 chr)	✓ (24 chr)	✓ (24 chr)
Meiotic aneuploidy				✓ (PB only)	✓ (PB only)	✓ Trisomy only
With parental origin		✓		✗	✗	✓
With meiotic origin		✗		✗	✗	✓
Mosaicism				✓	✓✗	✓✗
Duplications/deletions				✗	✓✗	✓✗
Uniparental disomy				✗	✗	✓
Translocation chromosome imbalance						
Reciprocal/Robertsonian		✓		✓	✗	✓
Normal vs balanced		✗		✗	✗	✓
With 24 chr aneuploidy		✗		✗	✗	✓
Other						
Multifactorial recurrence risk						✓
Copy Number Variants						✓
Errors						
Allele dropout		✓	✓			✓
Contamination		✓	✓			✓

SNP analysis and Karyomapping

- A universal method for genome wide analysis of genetic defects and their parental origin
- Complementary to standard methods of SNP data analysis for molecular cytogenetics
- Parental origin of aneuploidies and meiotic phase of origin of trisomies identified
- Inheritance and parental origin of copy number variants and structural chromosomal abnormalities can be analysed
- Enhanced linkage based analysis of loci genome wide for diagnosis of single gene defects and analysis of recurrence risk of multifactorial conditions
- Applicable at the single cell level for preimplantation genetic diagnosis (PGD)

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