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Complete haplotype-resolved assembly of the 22q11.2 region by de novo assembly and adaptive sampling

The origin of 22q11.2 deletion syndrome

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DNA is organized into 2 sets of 23 chromosomes

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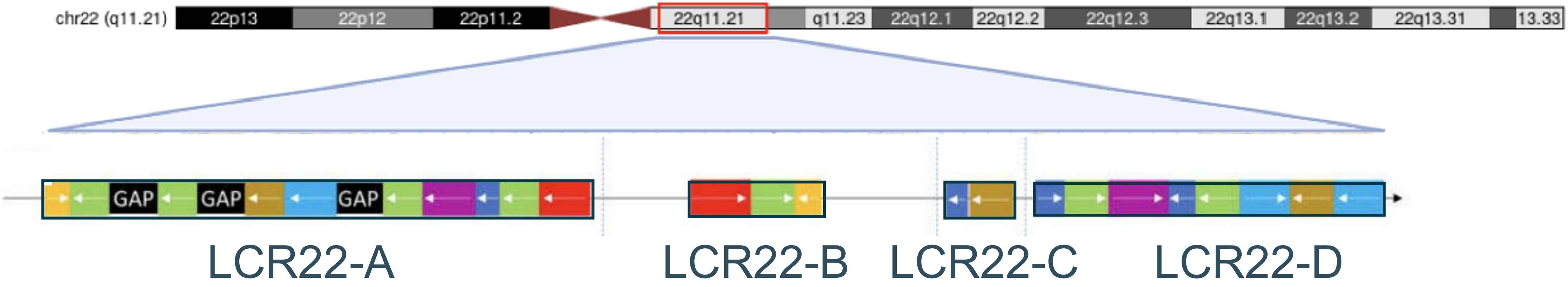
The four low copy repeats in 22q11.21 region on chromosome 22 (LCR22s)



Low copy repeats (LCRs) are:

- Long almost identical segments of DNA (> 95% identical)

Adapted from Vervoort and Vermeesch, Genes, 2022

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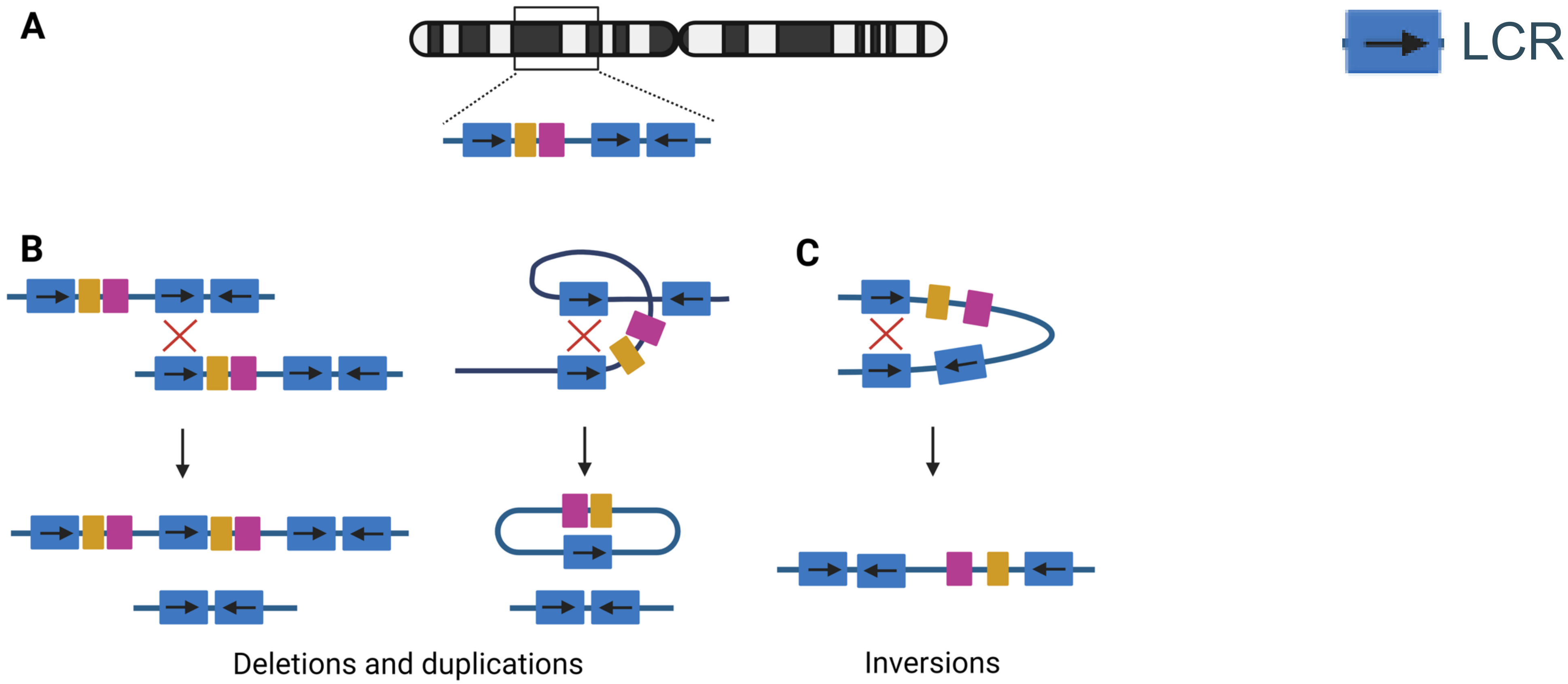
How do most deletion or duplication syndromes arise?

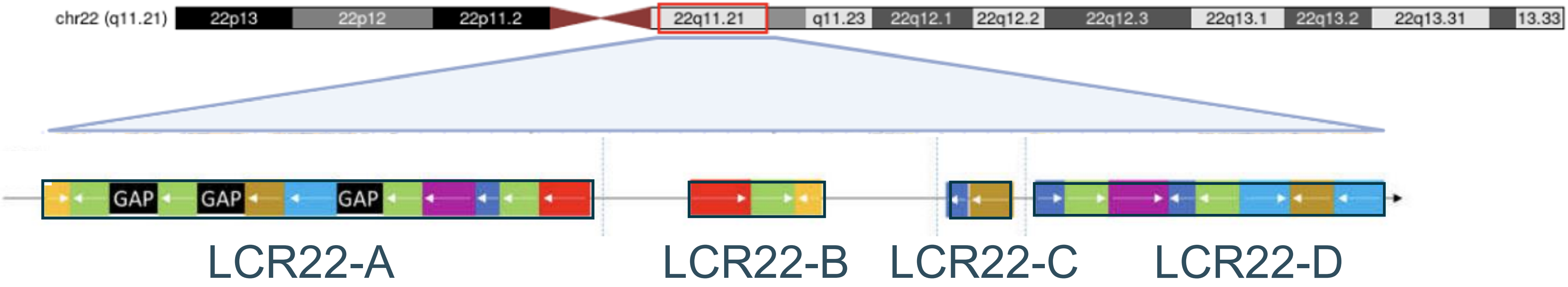
Due to rearrangements between low copy repeats

Rearrangements occur upon missalignment during the creation of our germ cells



Vervoort and Vermeesch, Explorations in Medicine, 2023

22q11.2DS is caused by rearrangements between low copy repeats on chromosome 22 (LCR22s)



22q11.2 deletion syndrome (22q11.2DS) subtypes

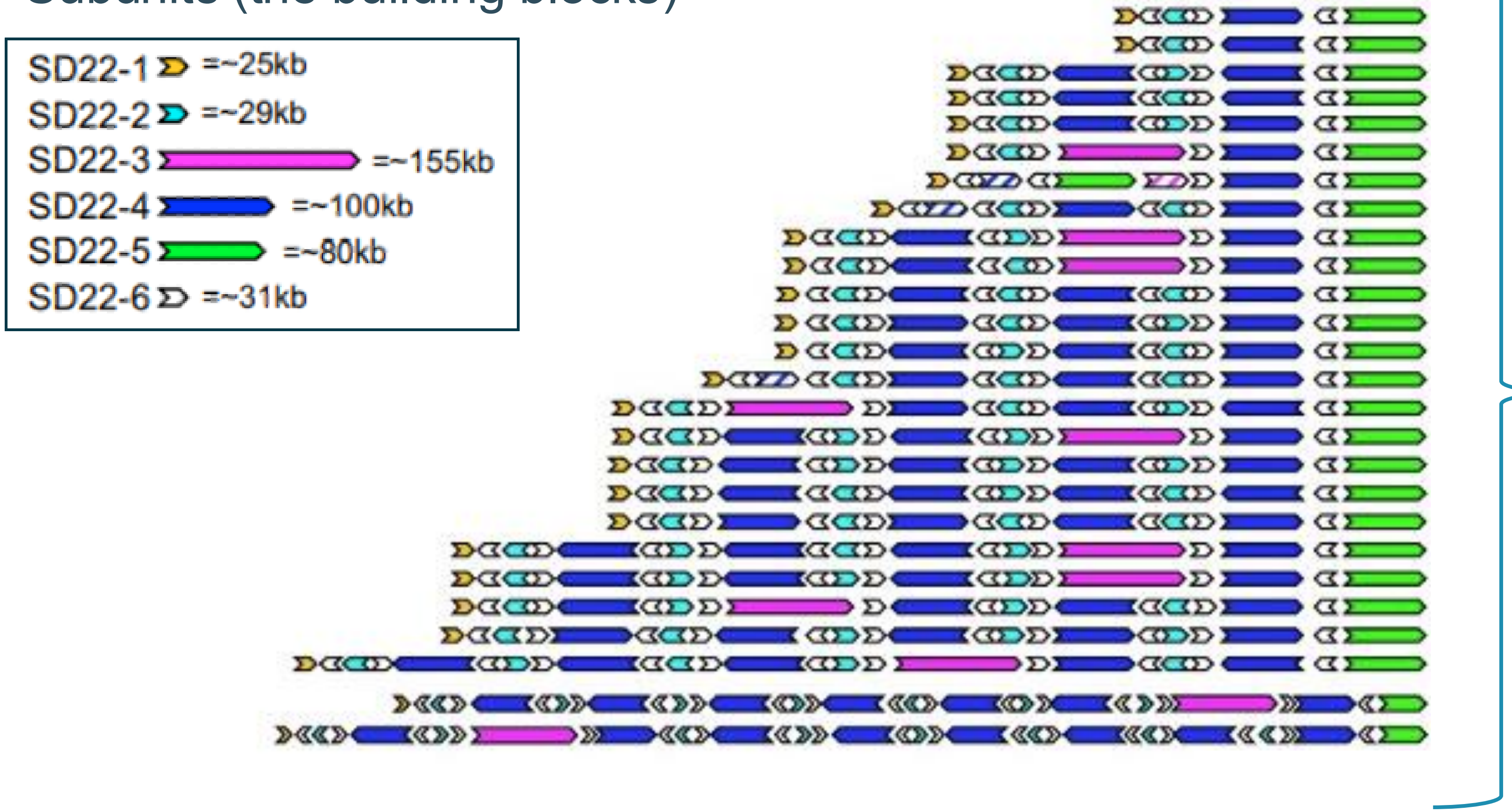
- LCR22-A/D deletion (85% of cases)
- LCR22-A/B deletion (5%)
- LCR22-B/D deletion (4%)
- LCR22-A/C deletion (2%)
- LCR22-C/D deletion (1%)

Adapted from Vervoort and Vermeesch, Genes, 2022

LCR22-A is hypervariable in the human population

Subunits (the building blocks)

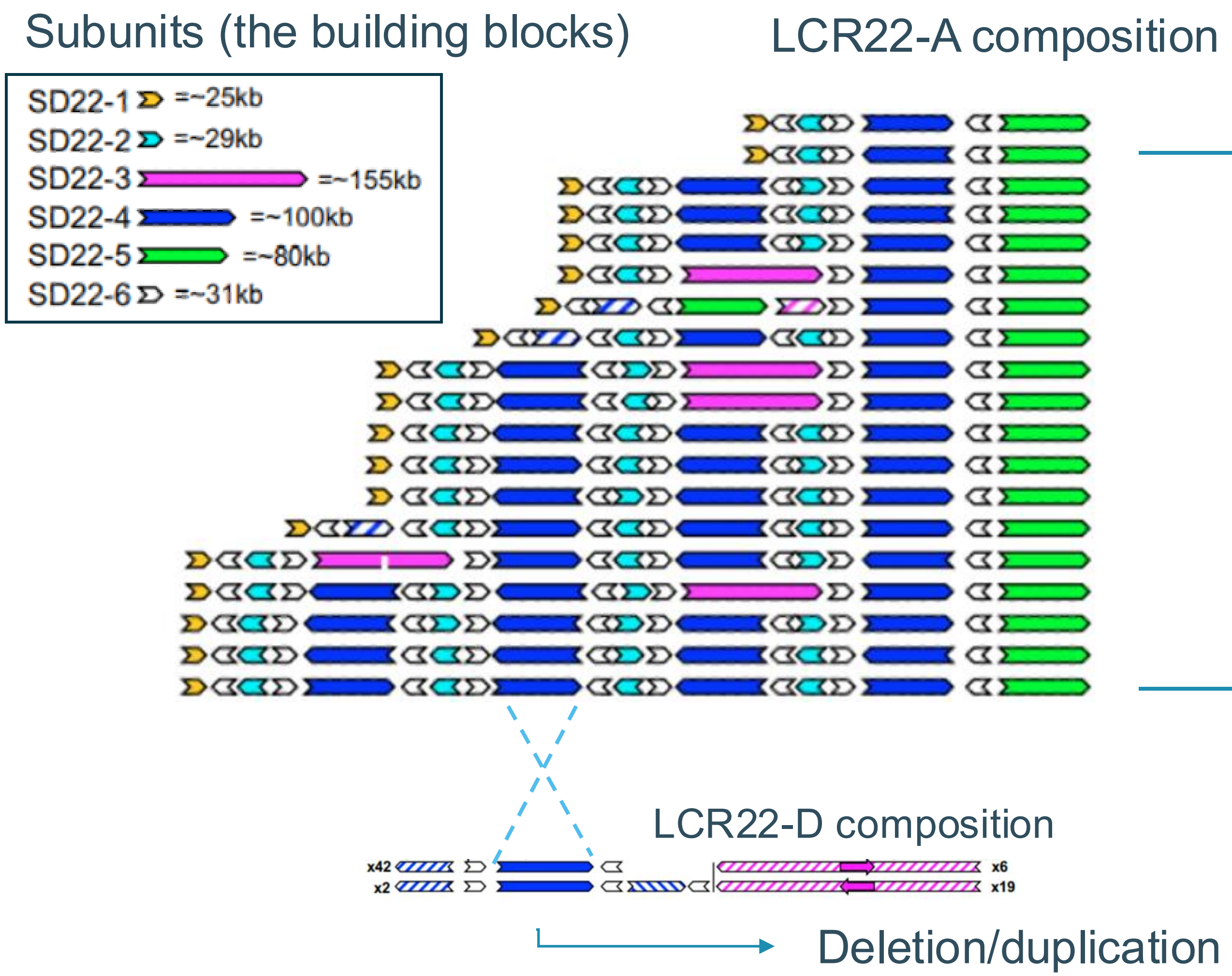
LCR22-A composition



Different “haplotypes”

Demaerel et al., Genome Research, 2019

LCR22 haplotypes predisposing for rearrangement may exist



→ Deletion/duplication risk decreases?

↓

Protective haplotype?

→ Deletion/duplication risk increases?

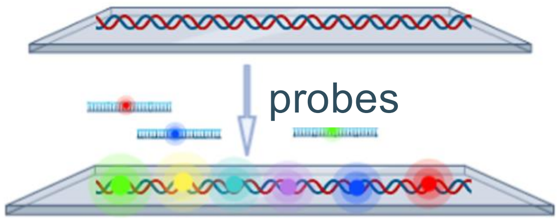
↓

Predisposing haplotype?

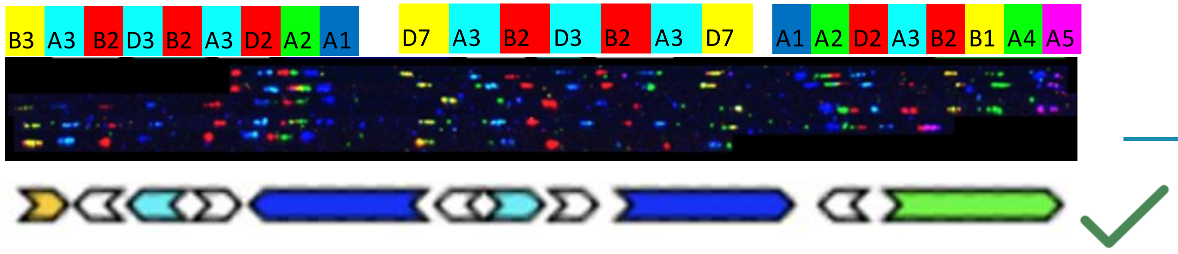
Demaerel et al., Genome Research, 2019

Can we read through the LCR22s?

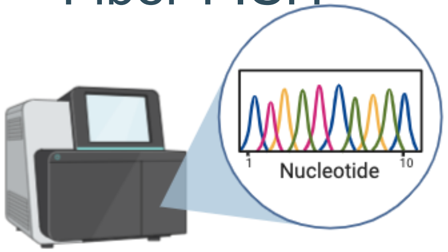
Novel technologies allow to read the LCR22 sequence



Fiber-FISH

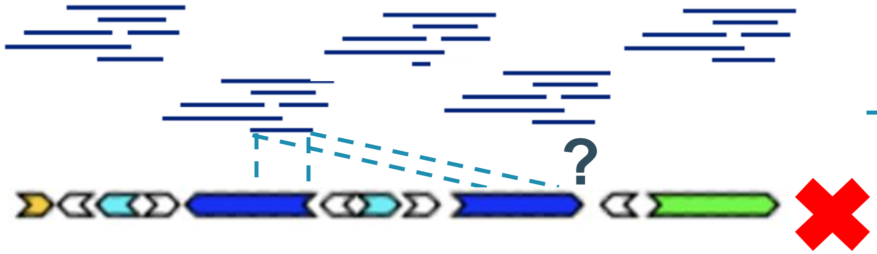


Subunit level information

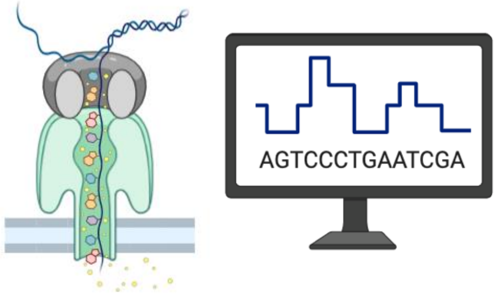


Short read sequencing

300 basepair reads

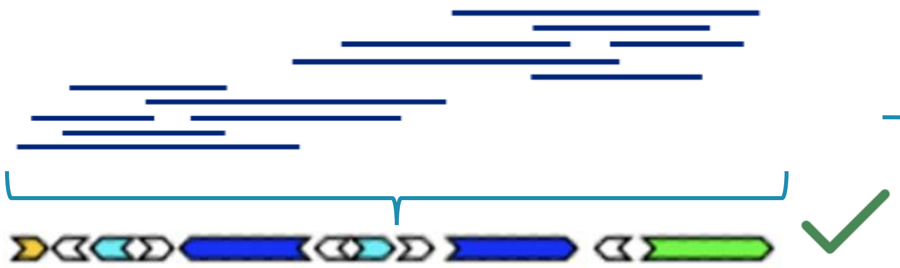


No LCR22 information



Long read sequencing

>30.000 basepair reads



Sequence level infomation

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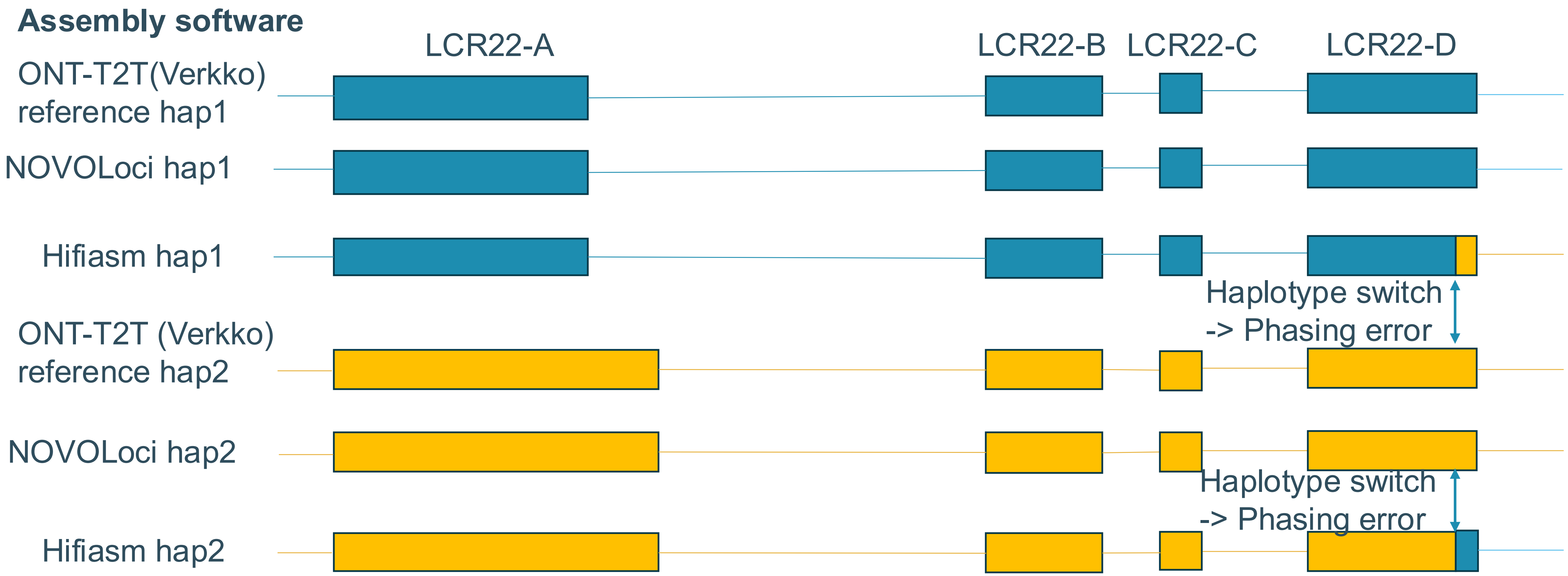
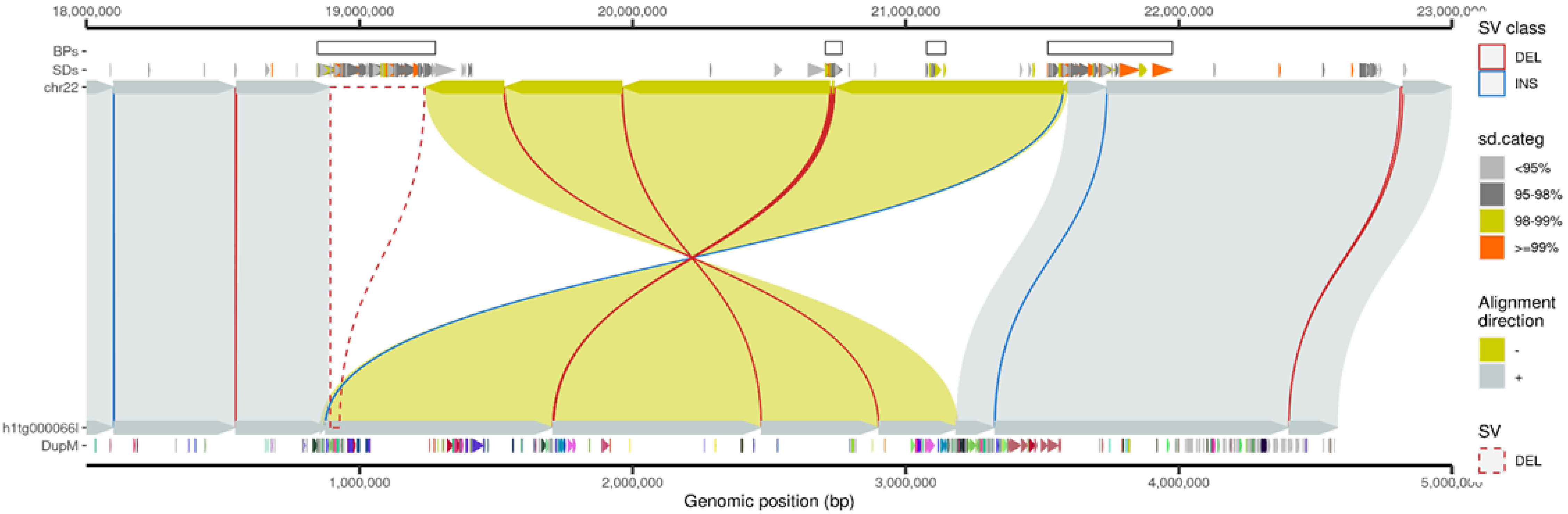
NOVOLoci shows complete concordance with the H9 reference assembly on the 22q11.2 region



22q11 region inversions exist in the population

LCR22-A LCR22-B LCR22-C LCR22-D



-> Can an inversion be a predisposing factor for a deletion?

Porubsky et al., BioRxive, 2025

Vervoort et al., Genome Research, 2025

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How to study predisposition?

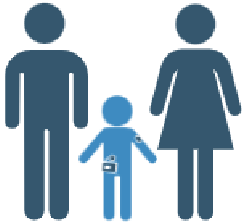
Reference cohort (n=500 individuals)

GOE

Genome of Europe

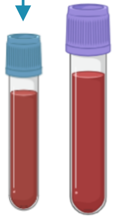
BGB Belgian Genome Library

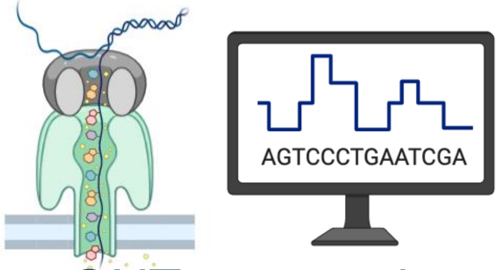
22q11DS families (n=100 trios)



Which structures are more common in the parent of origin?

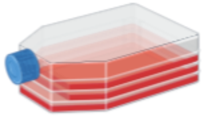
Which structures are more common in the parent of origin?
Larger SD22s? Inversions? Specific duplicons?



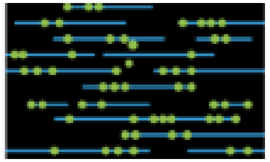


ONT sequencing

De novo assembly of LCR22 haplotypes



Cell lines



Validation techniques

Conclusions

- New technologies and algorithms allowed to completely assemble the 22q11 region using data from a single sequencing run
- NOVOLoci showed superior phasing compared to hifiasm
- This cost-effective approach enables large scale characterization of the LCR22s in 22q11 families at sequence level to identify predisposing haplotypes and discovering risk factors for neuropsychiatric phenotype in 22q11.2DS

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Collaborations

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Prof. Beata Nowakowska (Imid, Warsaw)

Prof. Anne Bassett (University of Toronto)

Prof. Donna McDonald-McGinn (University of Philadelphia)

All 22q11.2DS patients and parents contributing to our studies

-> We are still looking for more families ;)

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FONDS DE SOUTIEN/STEUNFONDS MARGUERITE-MARIE DELACROIX

Questions? Collaborations?

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How to study brain phenotype associations?