

Analysis of Genetic Inheritance in a Family Quartet by Whole- Genome Sequencing

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Background

- Genotyping vs Resequencing
- Sequencing errors
- Power to detect candidate genes

Data

- Family: mother, father and two siblings (both offspring have two recessive disorder: Miller syndrome and primary ciliary dyskinesia)
- DNA was extracted from peripheral blood cells and sequenced at Complete Genomics, Inc.
- Reads were mapped to the NCBI ref. genome

Data

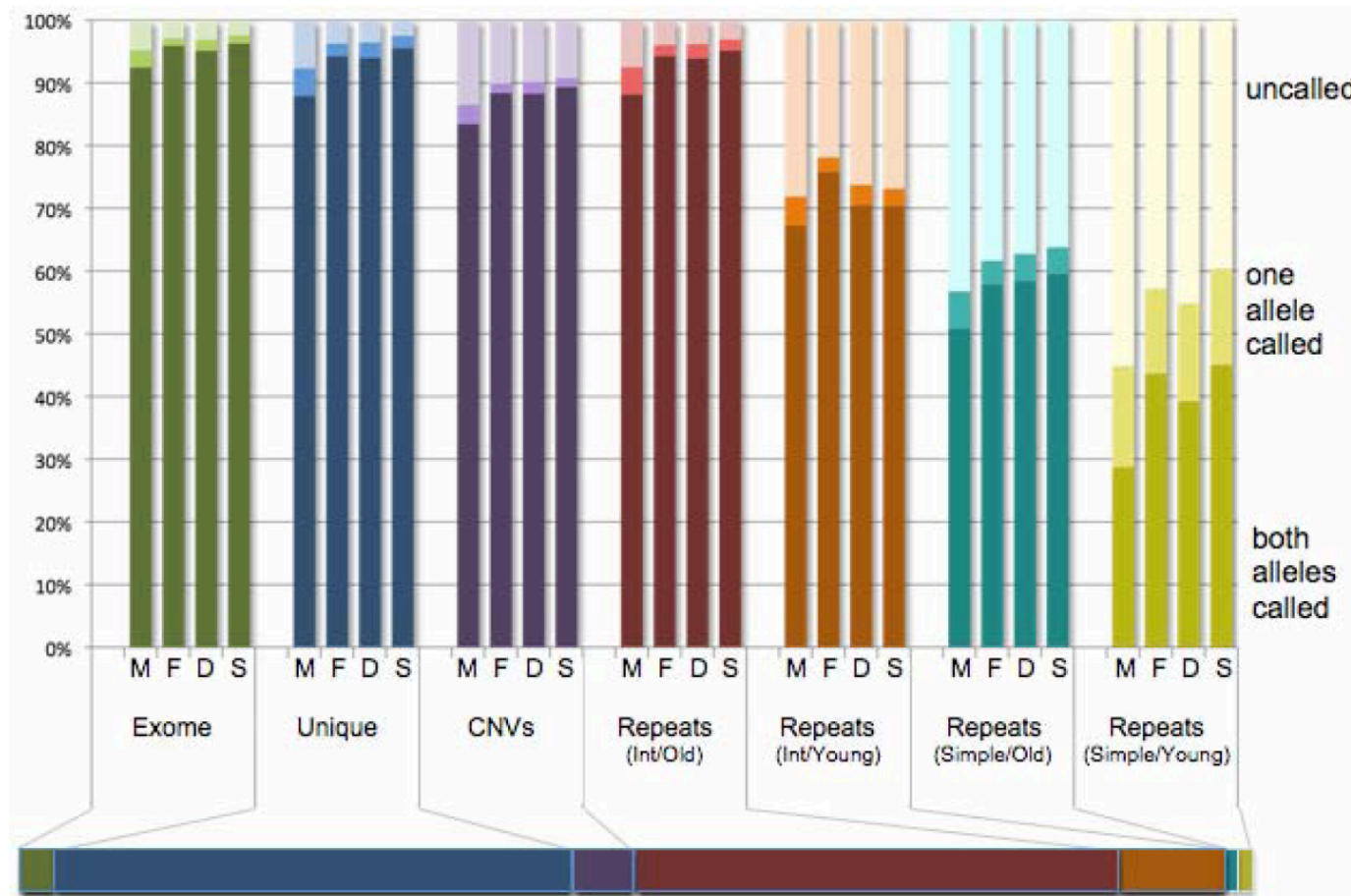
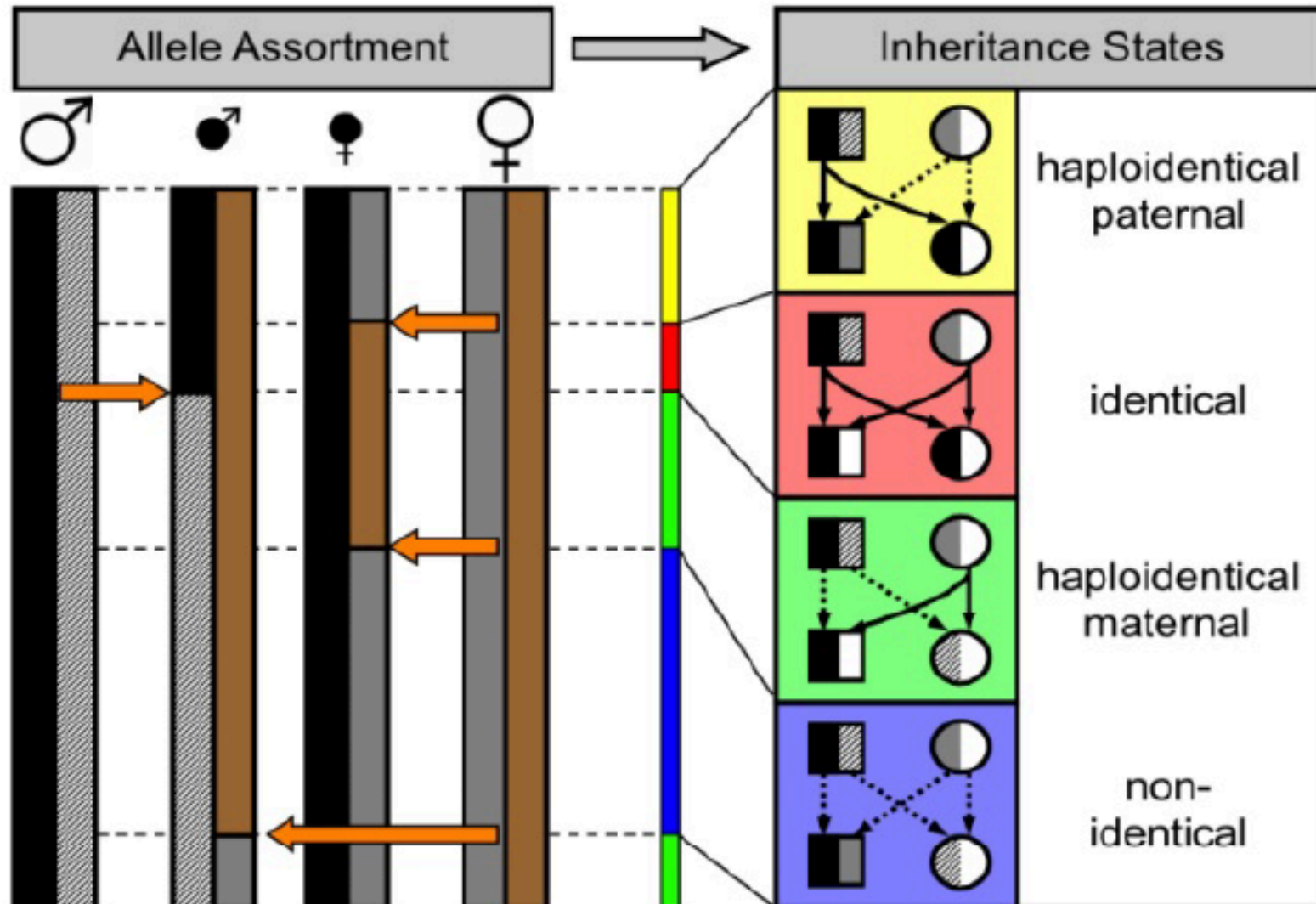
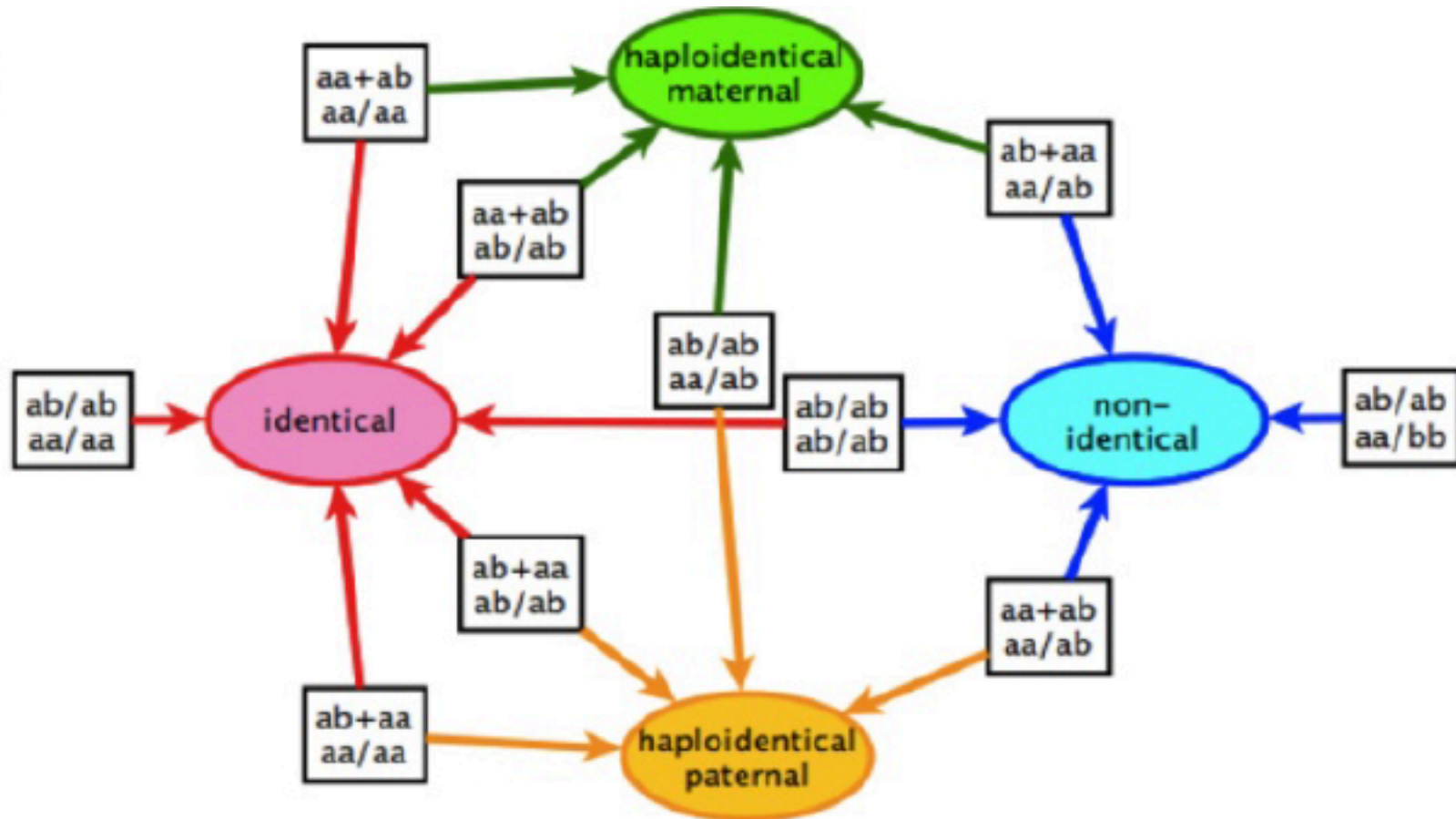


Figure S1. Called coverage in all 4 genomes. **M** mother; **F** father; **D** daughter; **S** son. Int (complex sequence repeats ranging from 100bp to over 10kb), Simple (short stretches of low complexity sequence or tandem repeats), Young (<10% diverged from consensus) and Old (\geq 10% diverged from the consensus).

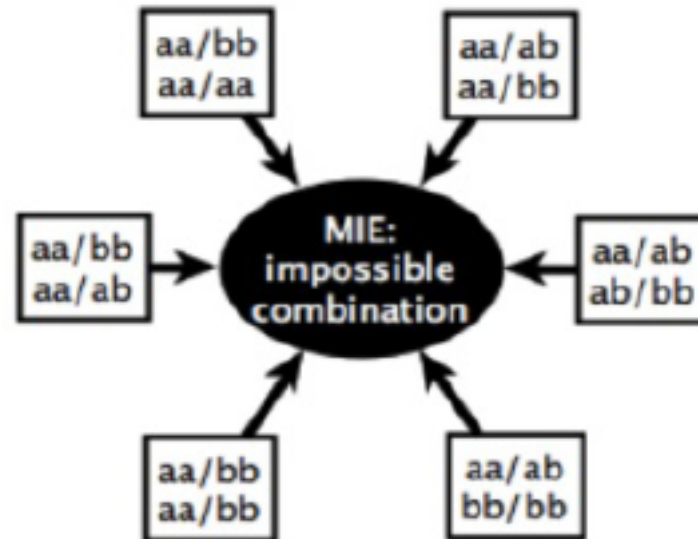
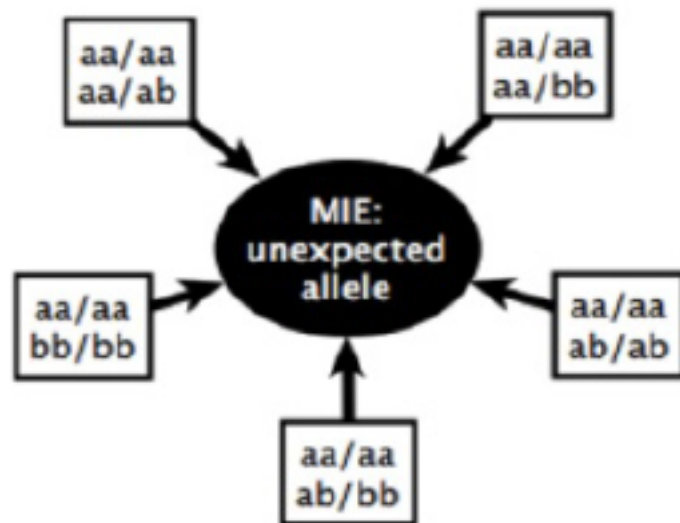
Inheritance patterns



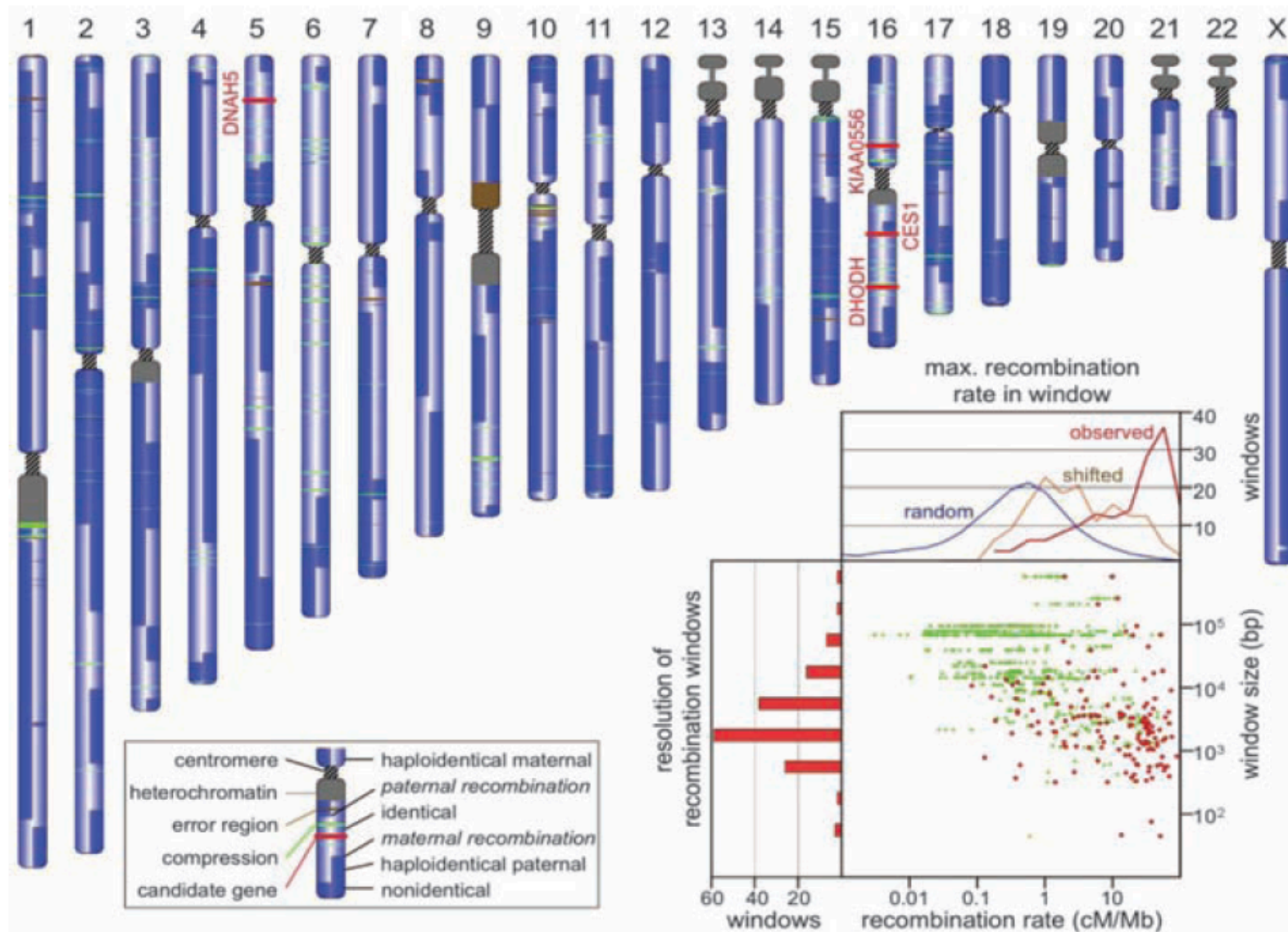
Inheritance patterns



Inheritance patterns



The landscape of recombination



Inheritance states in six scenarios

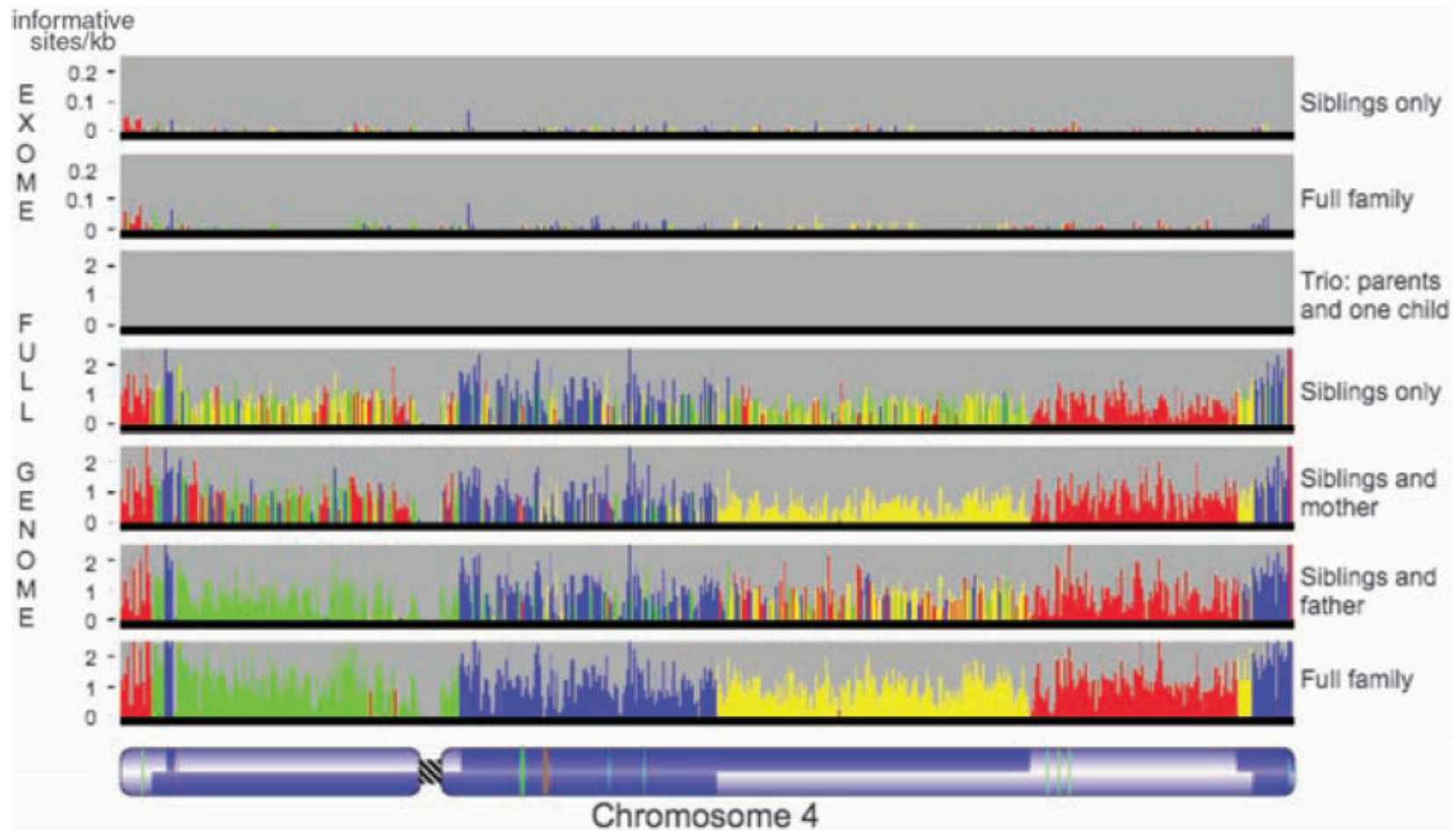


Figure 2. Red – identical; blue – nonidentical; green – haploidentical maternal; yellow – haploidentical paternal

Number of candidate SNPs

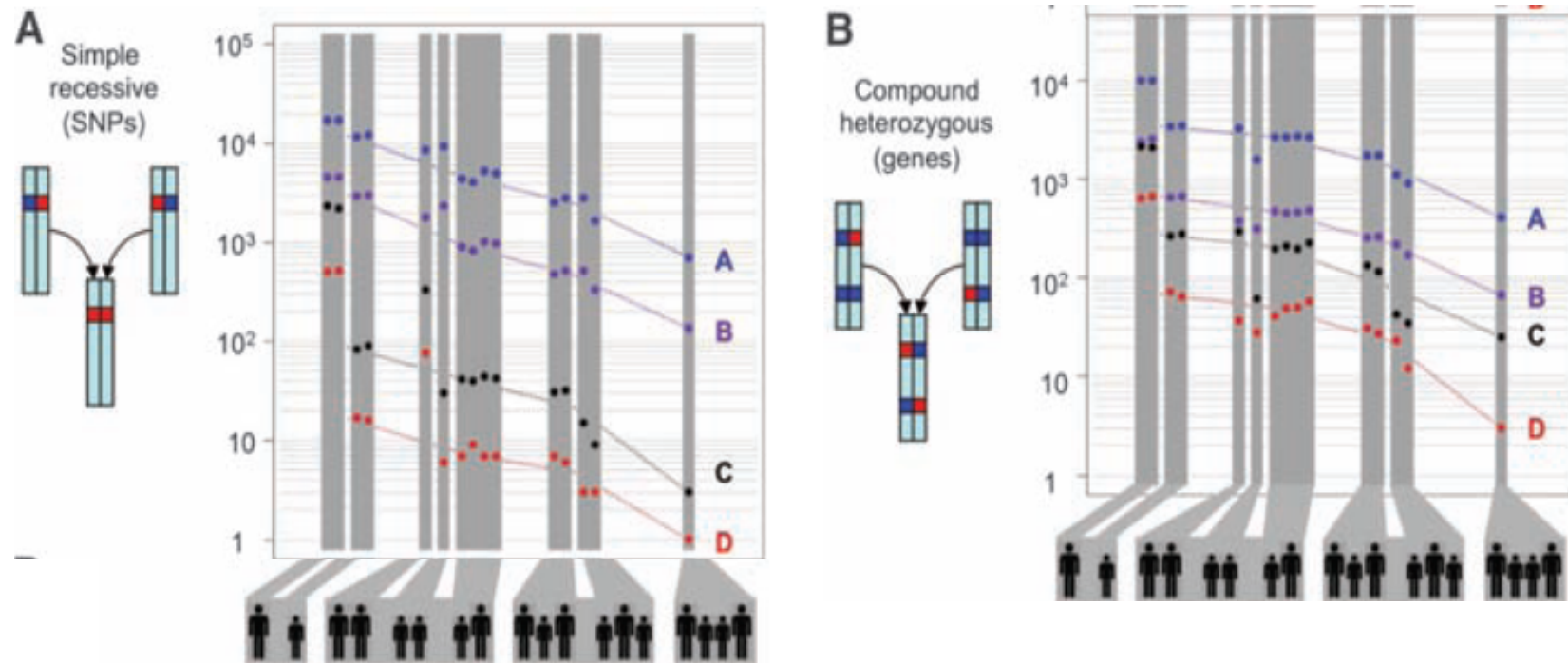


Figure 3. “A” all probably detrimental SNPs; “B” all possibly detrimental SNPs; “C” rare possibly detrimental SNPs; “D” rare probably detrimental SNPs.

Probably detrimental - missense, nonsense, splice defect, non-initiation

Possibly detrimental - missense, nonsense, splice defect, non-initiation, UTR, noncoding, splice region

Conclusion

Family sequencing helps to correct sequencing errors and reduce the search space for the disease-causing variants.

Reference

Roach, J.C. *et al.*

" Analysis of genetic inheritance in a family quartet by whole-genome sequencing."

Science. 2010 Apr 30;328(5978):636-9

THANK YOU

Mutations

- Human intergeneration mutation rate $\sim 1.1 \times 10^{-8}$ per position per haploid genome.
- 28 de novo mutations (verified with mass spectrometry)