The role of structural variation in human local adaptation

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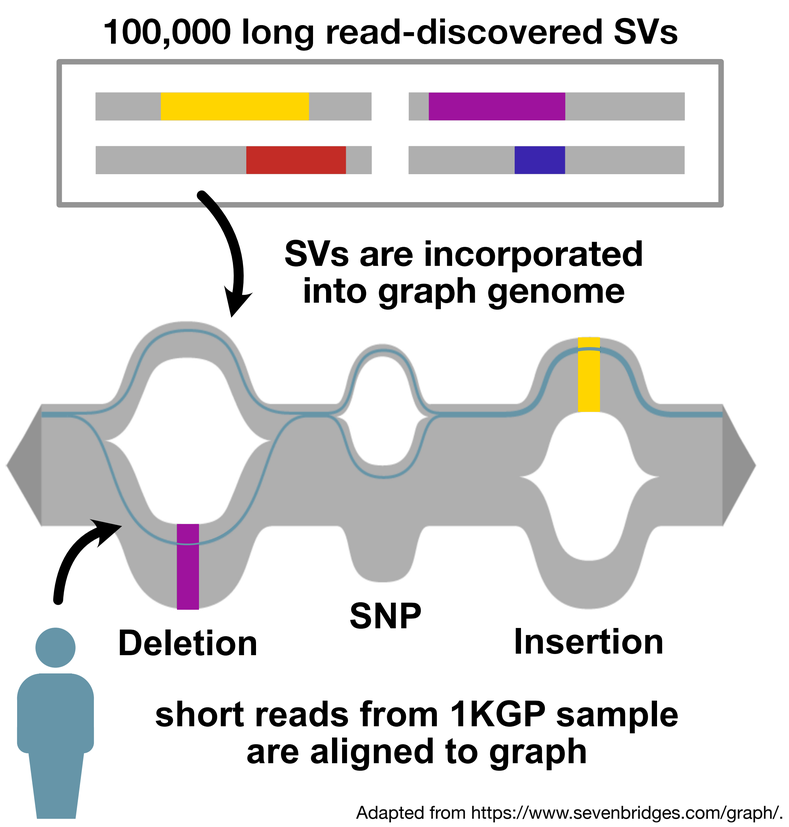
Background

- Structural variants (SVs)—large insertions, deletions, or inversions (>50bp)—may be prominent but hidden targets of positive selection.
- Long-read sequencing studies have expanded the catalog of SVs segregating in human populations[1], but have not yet been applied to study SVs on a large scale.

Population-wide SV genotyping

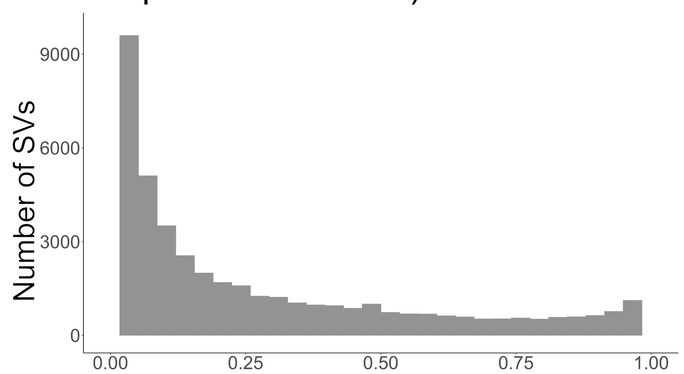
- We used Paragraph[2], a variant graph genotyper, to genotype long read-discovered SVs in short-read samples from three populations (CEU, CHB, YRI) in the 1000 Genomes Project.



Adapted from https://www.sevenbridges.com/graph/.

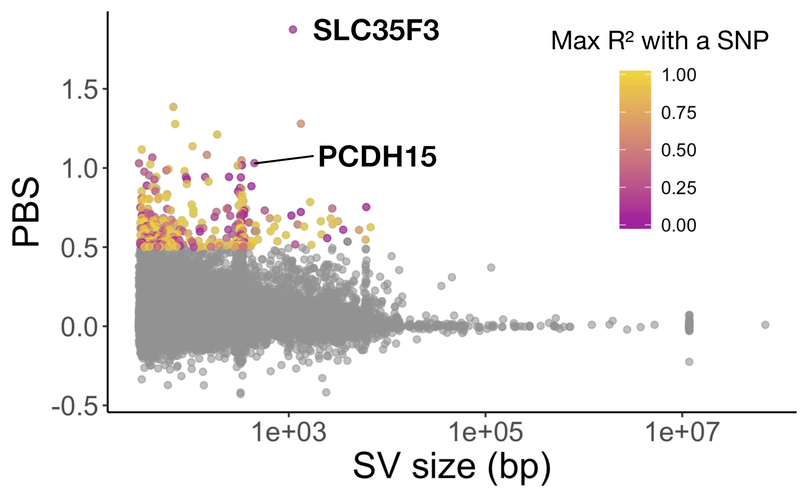
Most SVs are in weak LD with known SNPs

- We required all SVs to be genotyped in at least 98% of samples. We removed variants with excess heterozygote calls (Hardy-Weinberg equilibrium p-value < 0.0001).

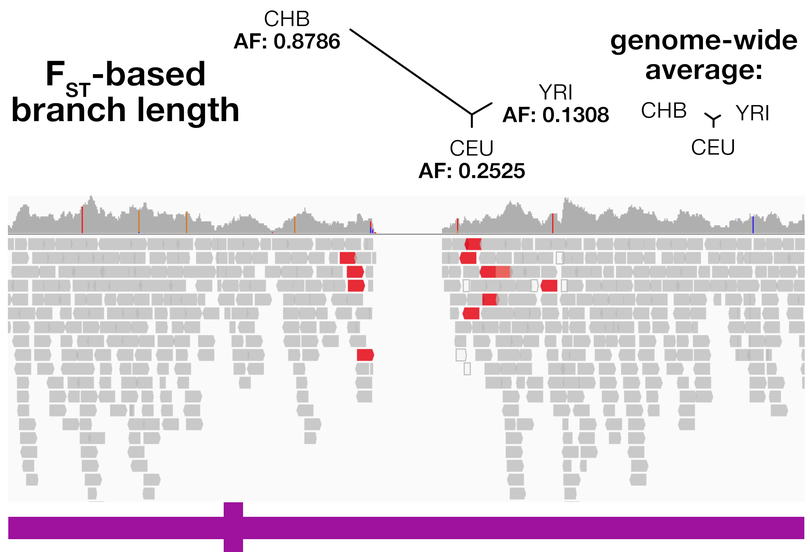


Identifying SVs with signatures of positive selection

- We used the population branch statistic (PBS) to identify 330 SVs with extreme allele frequency differentiation between populations (PBS > 0.5).



A 447bp deletion in PCDH15



- Codes for protocadherin-15, a protein involved in retinal and cochlear function.[3]

Conclusions

- We applied variant graph genotyping to genotype structural variants on a population-wide scale. Several SVs show signatures of positive selection.
- Many SVs are not strongly linked to known SNPs, indicating that they could constitute previously unknown adaptive loci.

Acknowledgments

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References

1. Audano *et al.* (2019). Characterizing the Major Structural Variant Alleles of the Human Genome. *Cell* **176**, 663-675.e19.
2. Chen *et al.* (2019). Paragraph: a graph-based structural variant genotyper for short-read sequence data. *Genome Biol.* **20**, 291.
3. https://ghr.nlm.nih.gov/gene/PCDH15.