Diversity in the IGH Locus of a South African Sub-Population

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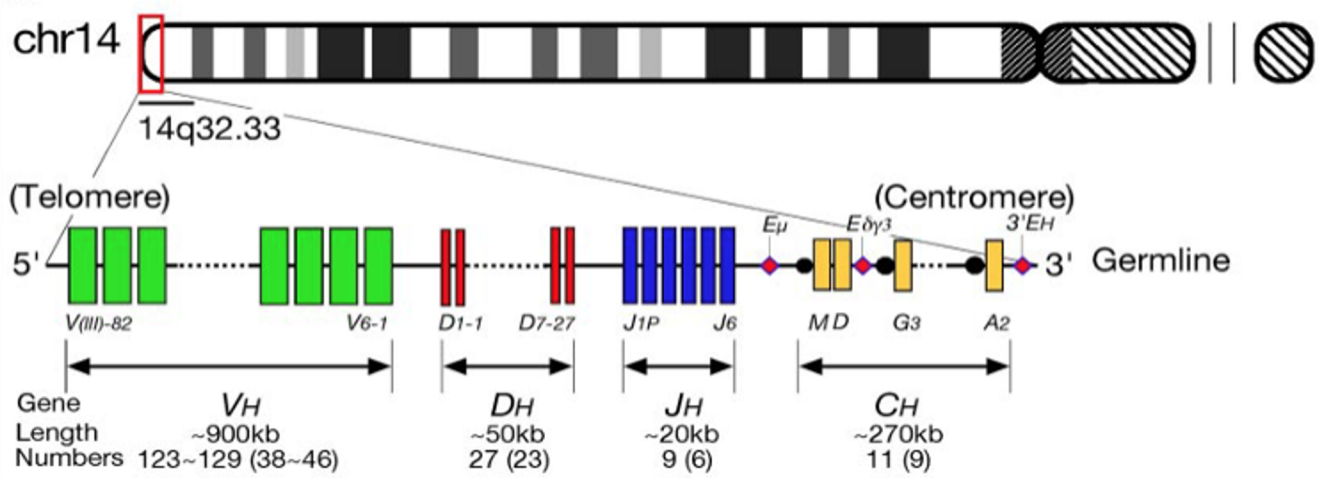
The Immunoglobulin Heavy Chain (IGH) Locus

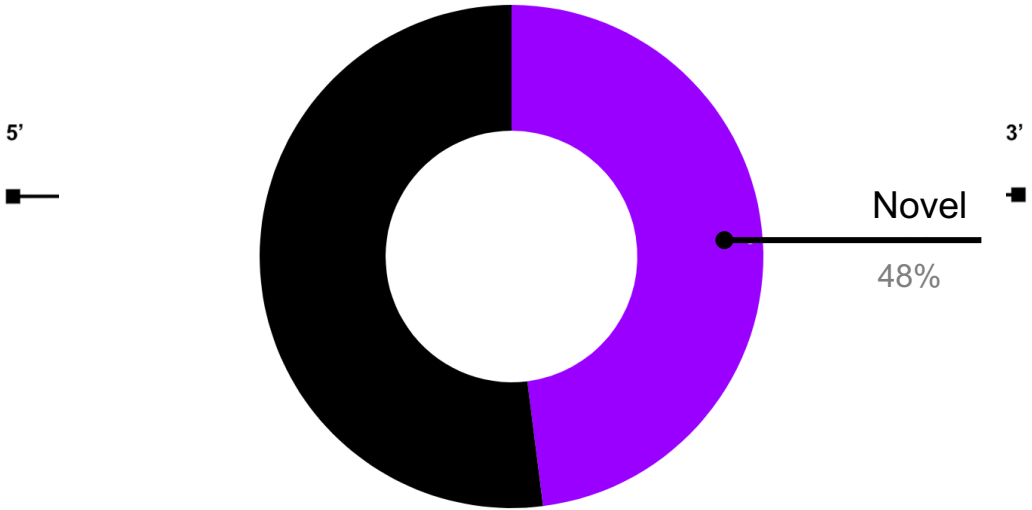


- ➔ 1.5 MB in size
- ➔ 200 genes many with multiple alleles
- ➔ Contains all the genes that code for the heavy chain
- ➔ One of the most polymorphic and complex loci in the human genome

Previous work

➔ We have previously sequenced a portion of IGHV genes in 28 women from rural and urban KwaZulu Natal

- **48%** of observed alleles had never been described before

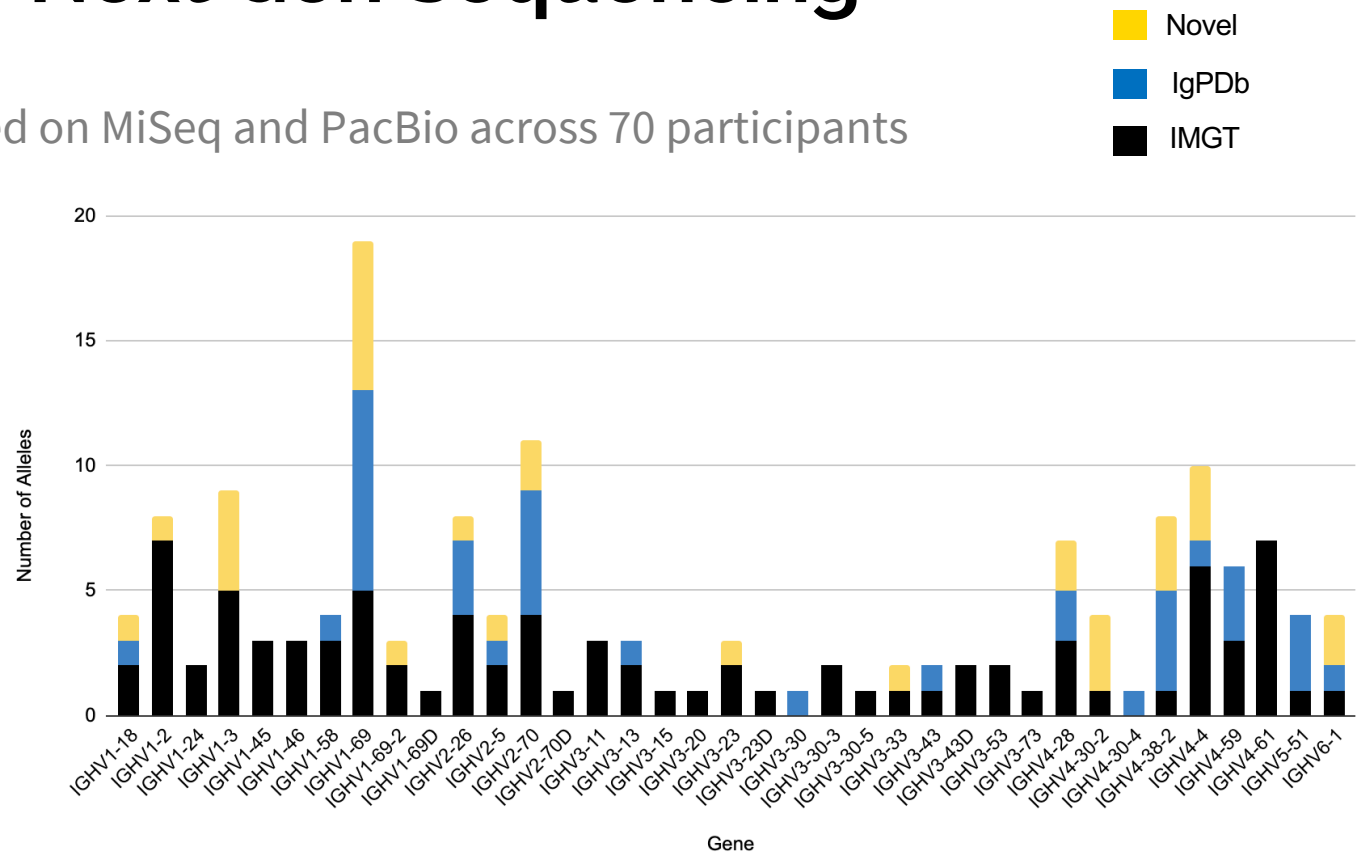


Scheepers, Cathrine, et al. 2015. “Ability To Develop Broadly Neutralizing HIV-1 Antibodies Is Not Restricted by the Germline Ig Gene Repertoire.” *The Journal of Immunology* 194 (9).

Aim:
To Investigate IGHV Polymorphism in a Larger Group

IGHV Next Gen Sequencing

Performed on MiSeq and PacBio across 70 participants



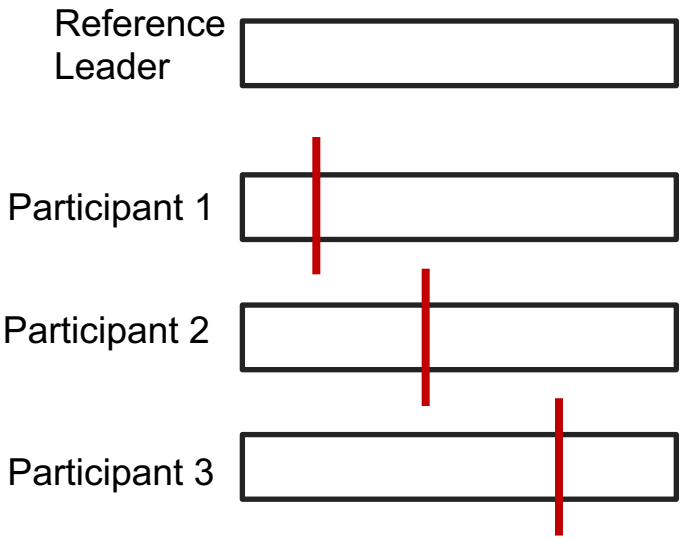
20.5%

Novel IGHV Allele Sequences

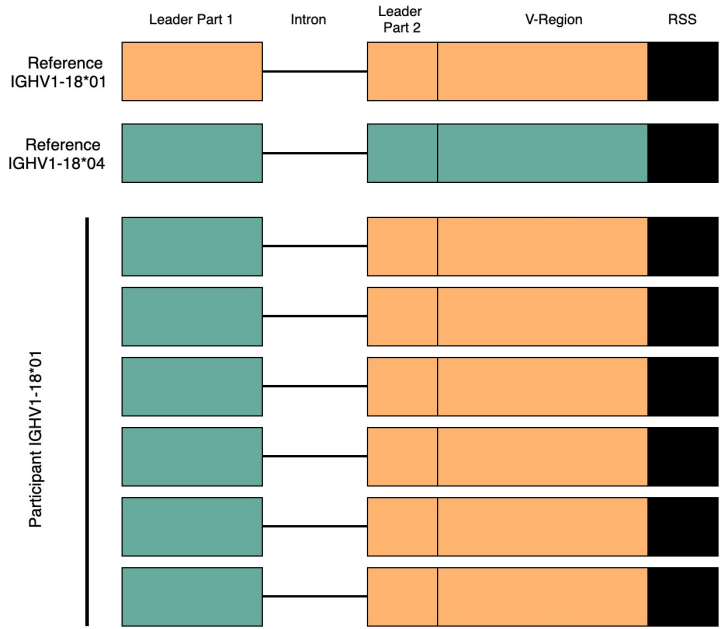
This was in addition to previous novel sequences

Types of Regulatory Variation

Single Nucleotide Variation



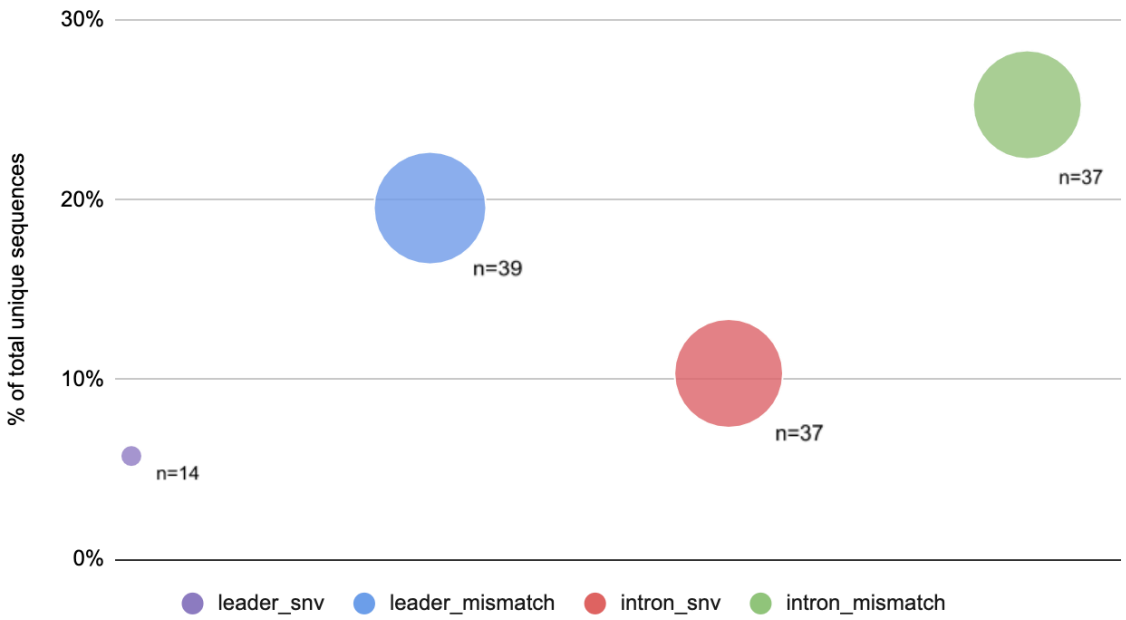
Mismatch



Regulatory region diversity

Diversity in regulatory regions was observed in **44.8%** of unique sequences

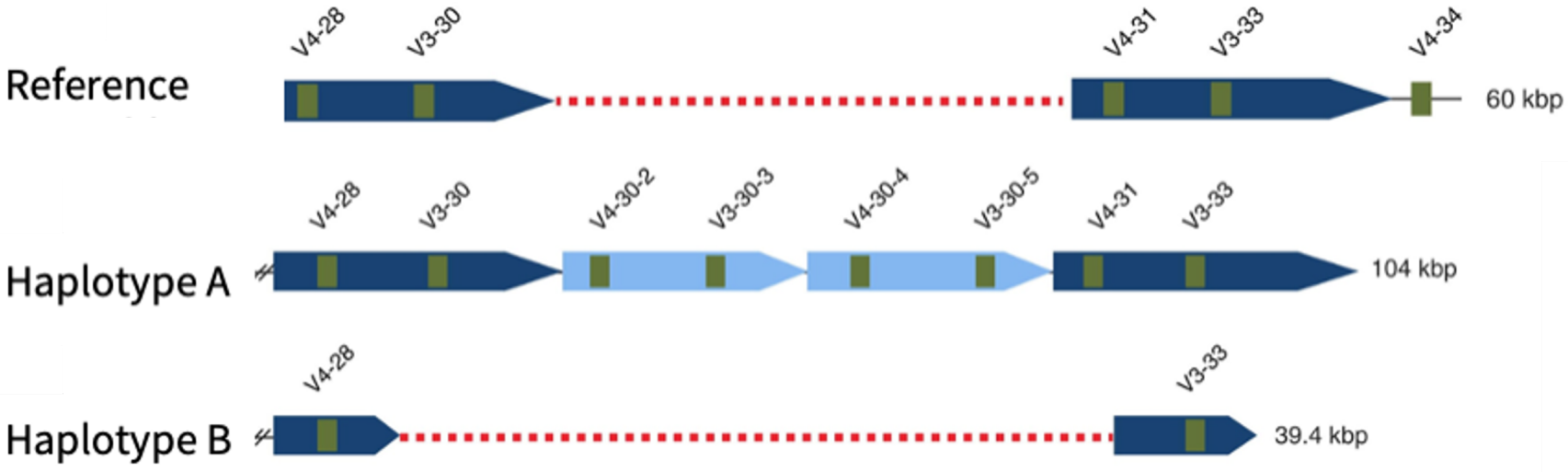
This may affect how antibodies are **secreted**



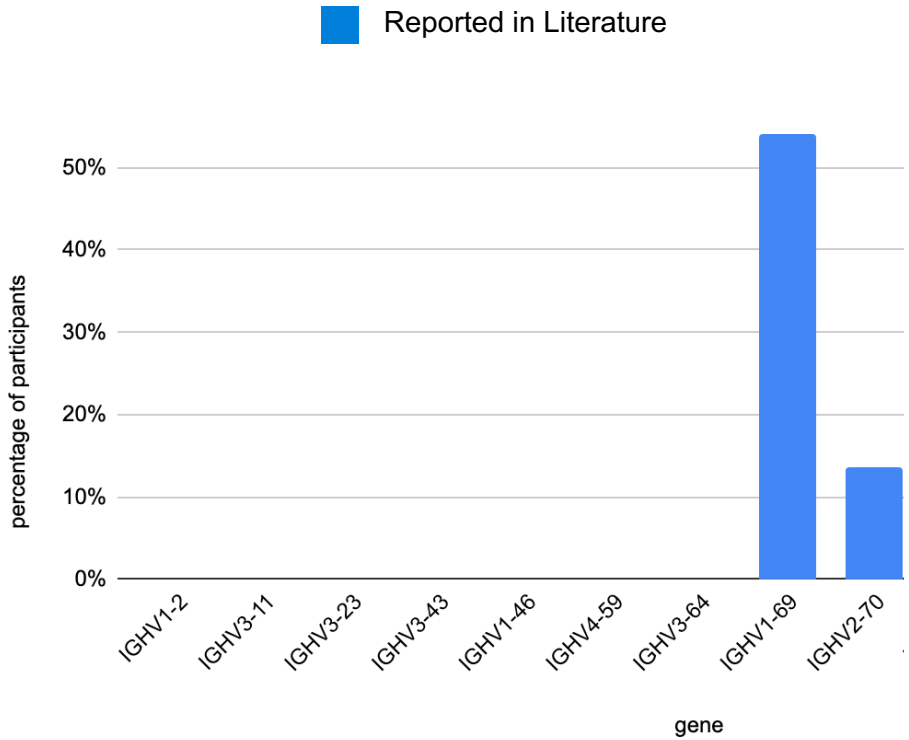
Aim:
To Examine Copy Number Variation and Structural Diversity

The IGH locus exhibits structural variation

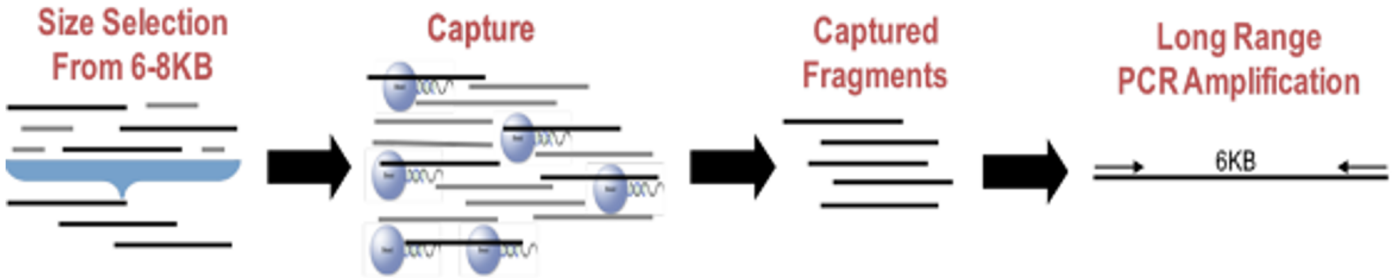
CNV caused by the rearrangement of the IGH locus leading to large indels



Common and Unreported IGHV Duplication



How do we resolve structural diversity?



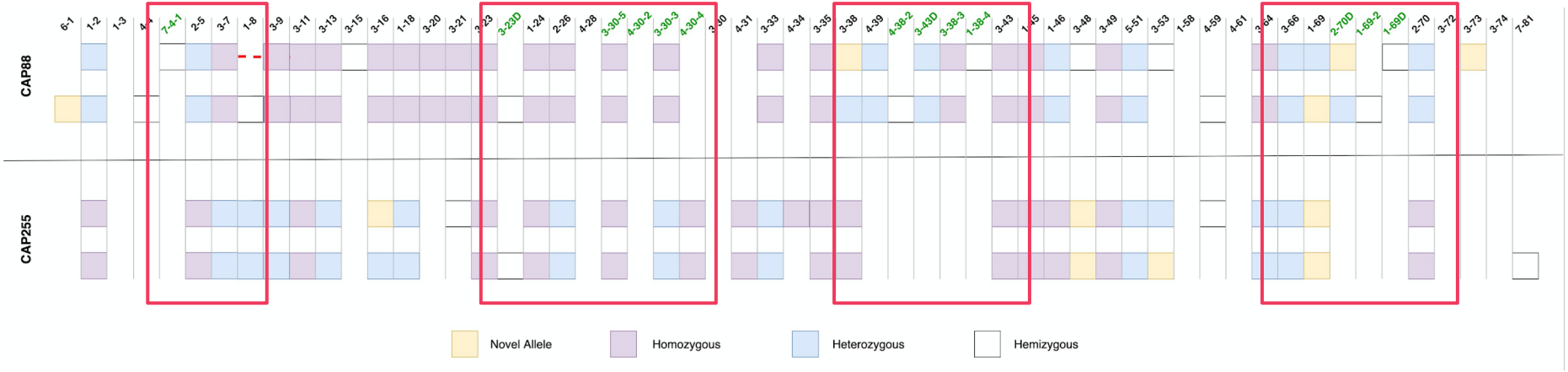
- ➔ Collaboration with Dr Corey Watson (University of Louisville)
- ➔ Uses magnetic probes that isolate IGH fragments from sheared gDNA
- ➔ Fragments (up to 8kb) are sequenced on PacBio
- ➔ Locus is reconstructed computationally

Rodriguez, Oscar L., et al. 2020. “A Novel Framework for Characterizing Genomic Haplotype Diversity in the Human Immunoglobulin Heavy Chain Locus.” *Frontiers in Immunology* 11: 2136..

IGH Capture revealed more genetic diversity

	CAP88	CAP255
Total SNVs	3235	3118
Intergenic	3116	3014
Coding	90	74
Regulatory	22	18
Total Indels	53	83
<50bp	45	69
>50bp	8	14

Haplotype reconstruction demonstrates structural diversity



Conclusions

- ➔ We detected more novel alleles and provided full-length data for several IgPDb alleles.
- ➔ Variation in the leader sequence was observed with frequent mismatch between different alleles.
- ➔ CNV was a common event with novel duplication in 4 genes and broad structural differences between participants.
- ➔ The phenotypic implications of this diversity in certain disease contexts are being currently investigated

Acknowledgments

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- Dr Arshad Ismail

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- Mr William Gibson
- Dr Oscar Rodriguez