Genome-wide characterization of copy number variants in epilepsy patients

Human Genetics Research Day

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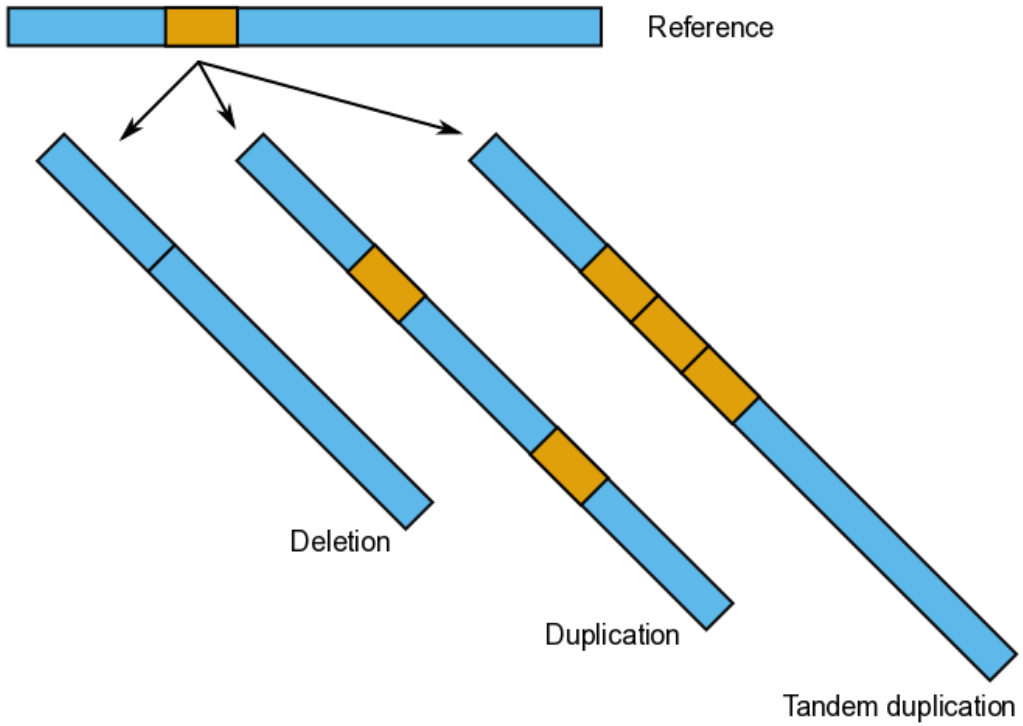
Copy Number Variation (CNV)

Imbalanced genetic variation involving more than 500bp.



Epilepsy

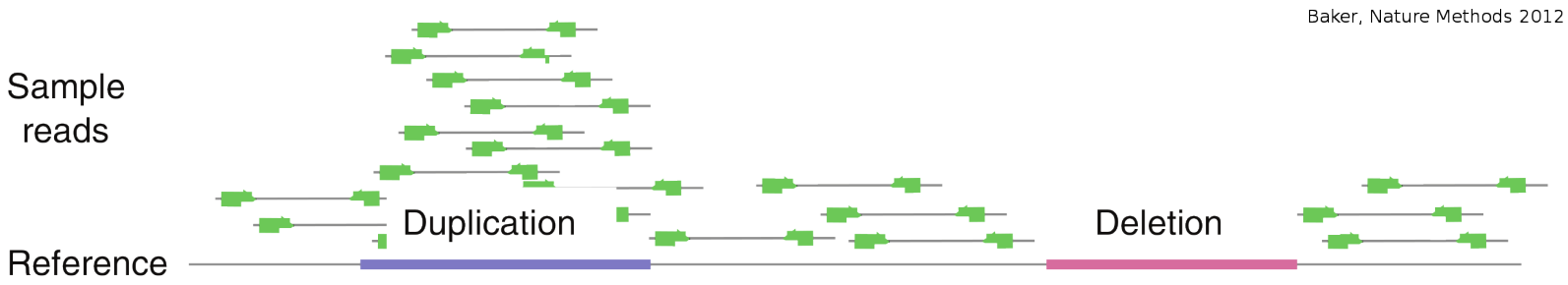
- Neurological disorder characterized by recurrent and unprovoked seizures.
- Incidence 3%.

- Rare large CNVs were associated with epilepsy (array-based studies).

- The Canadian Epilepsy Network (CENet) conducted **whole-genome sequencing** of epilepsy patients to identify **genetic variants** that predispose individual to **epilepsy** or **drug response**.

Detecting CNV in Whole-Genome Sequencing

Read coverage variation



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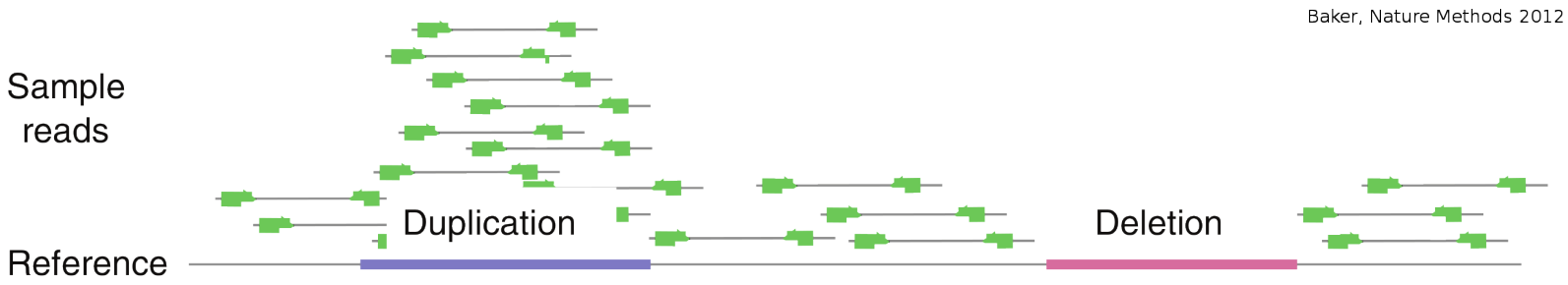
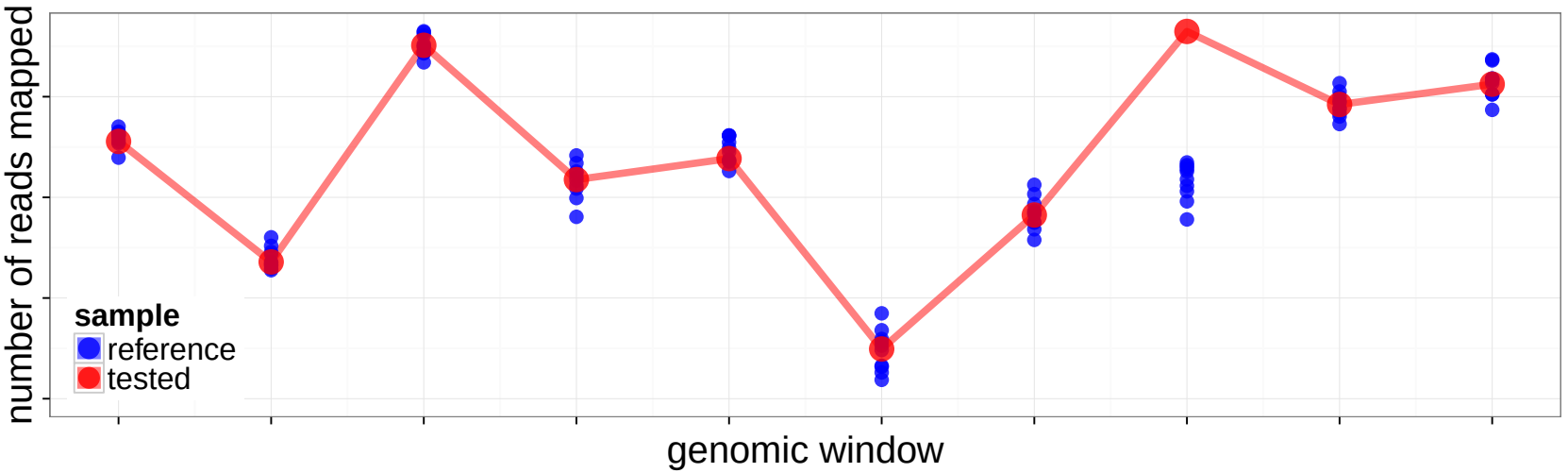
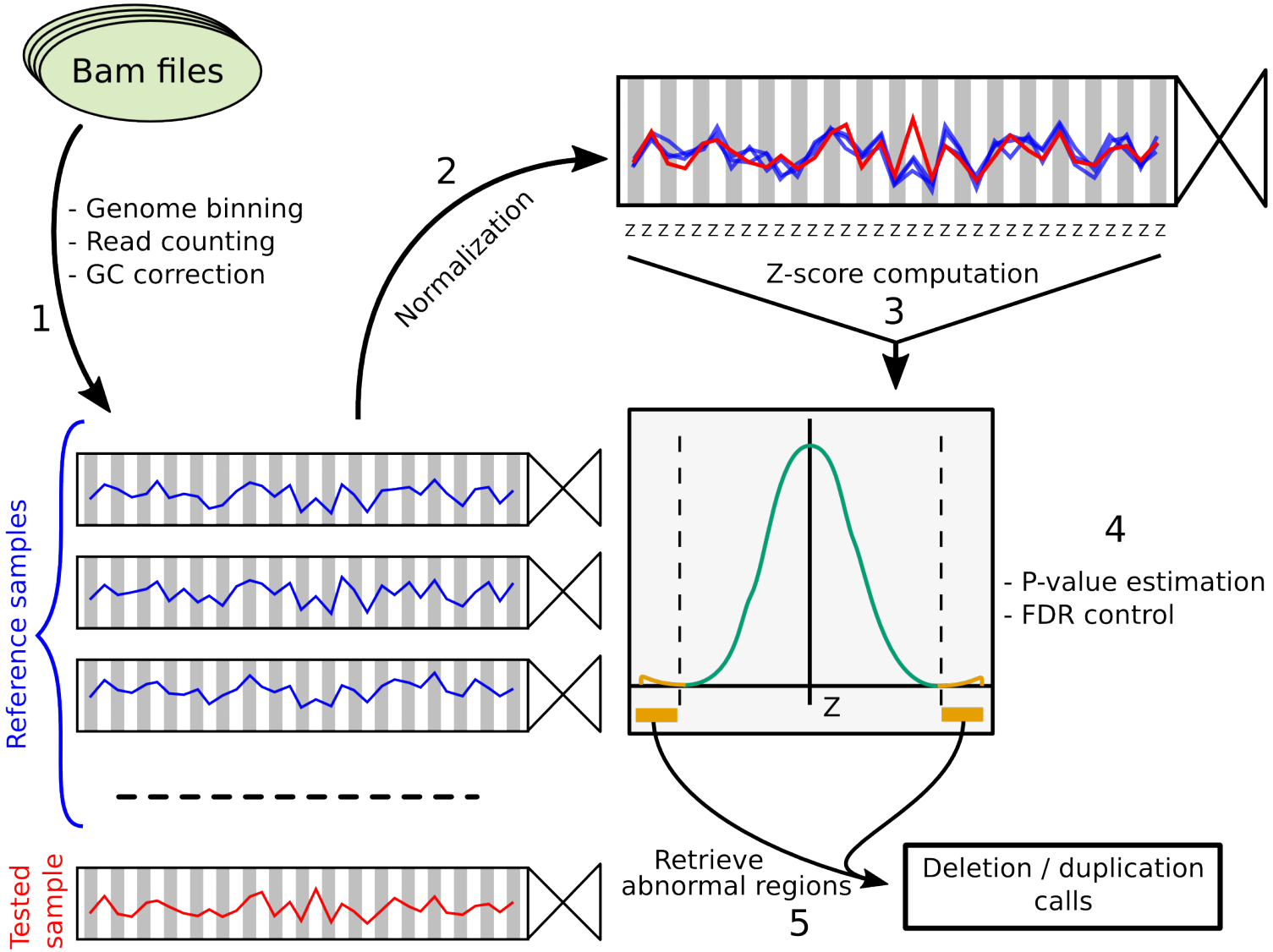


PopSV: Population-based approach

Use a set of **reference experiments** to detect abnormal patterns.

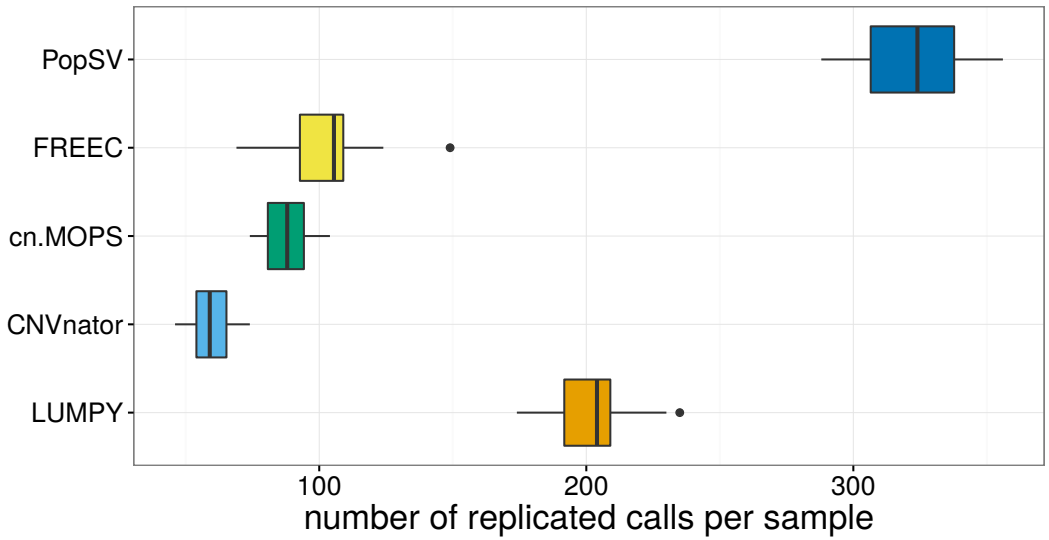


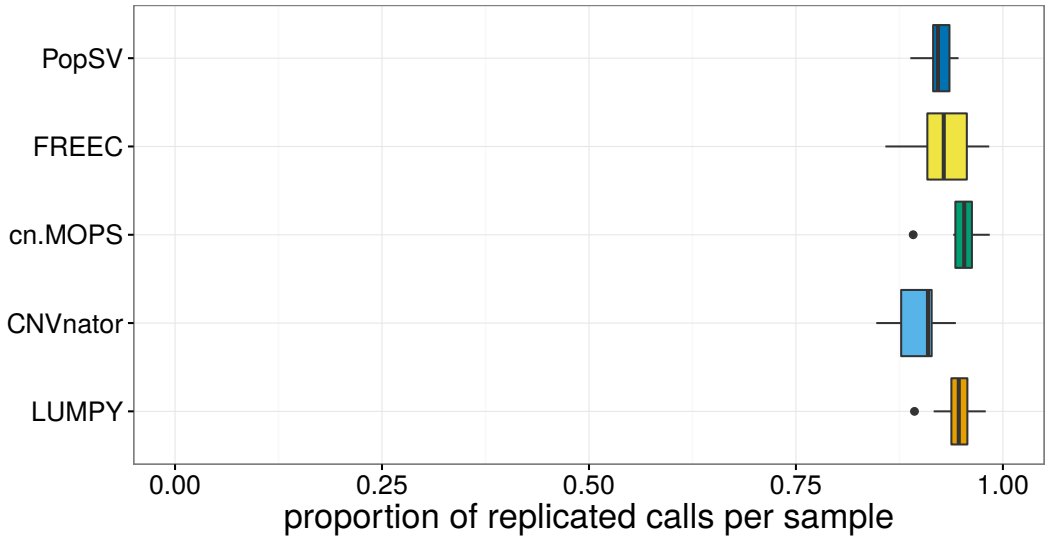
PopSV's workflow



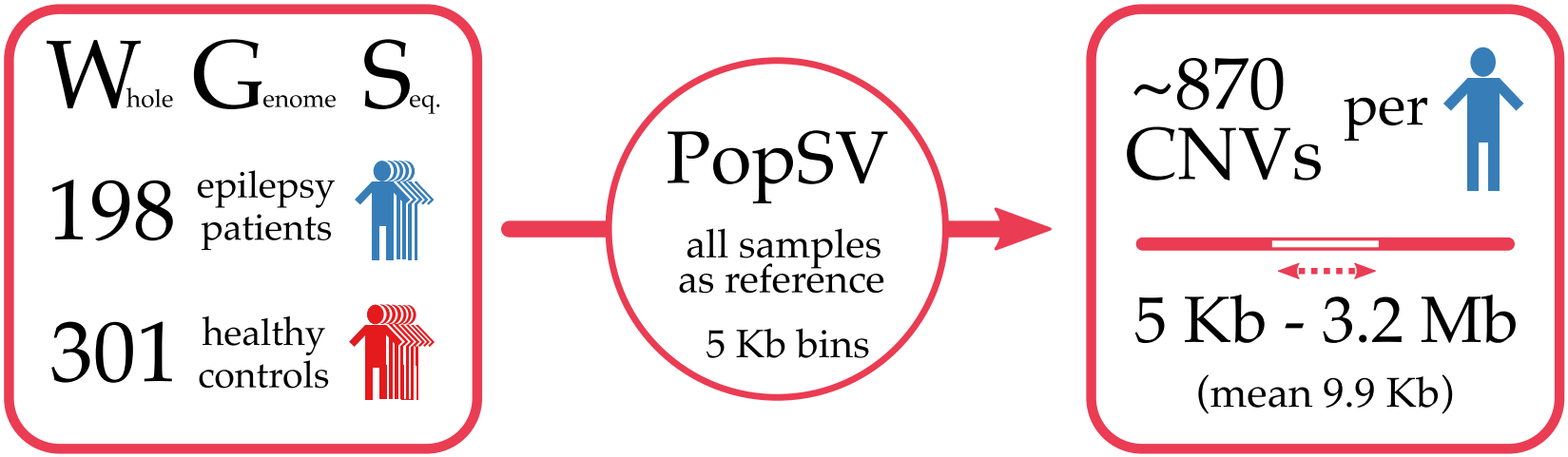
PopSV is more sensitive than other methods

Twin dataset, normal/tumor cancer dataset and RT-PCR validation.





Application to the CENet dataset



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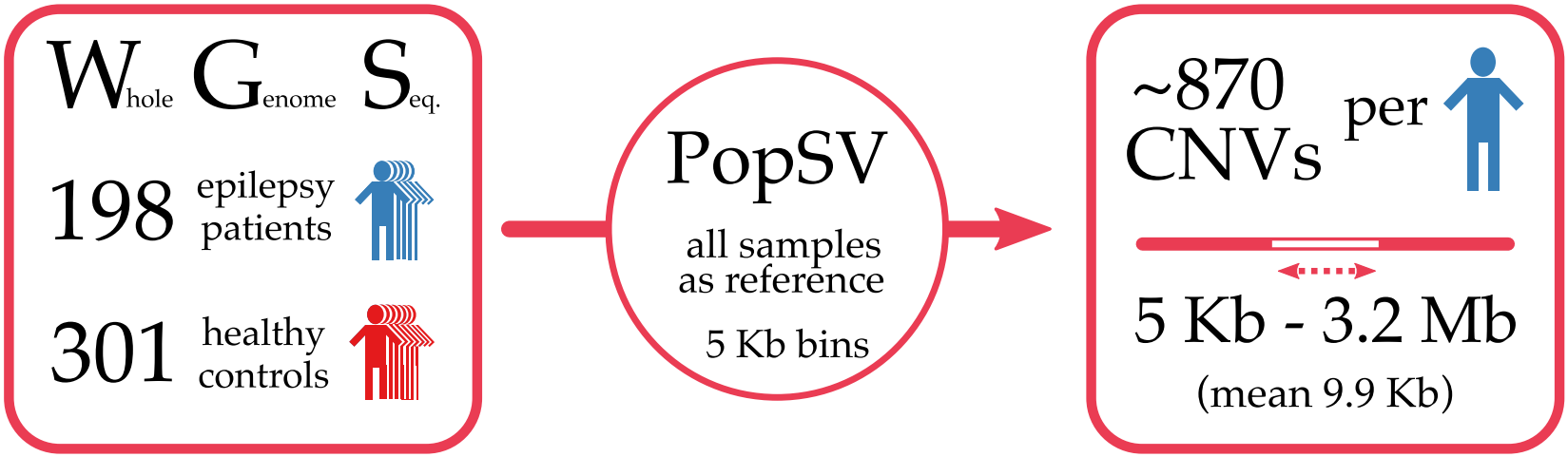
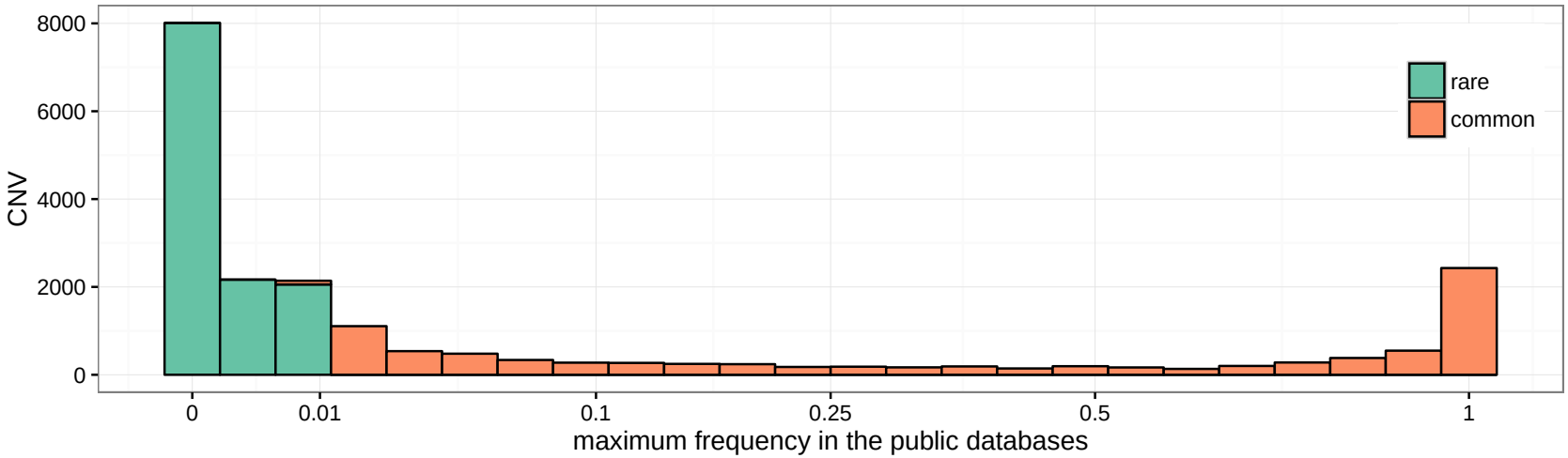
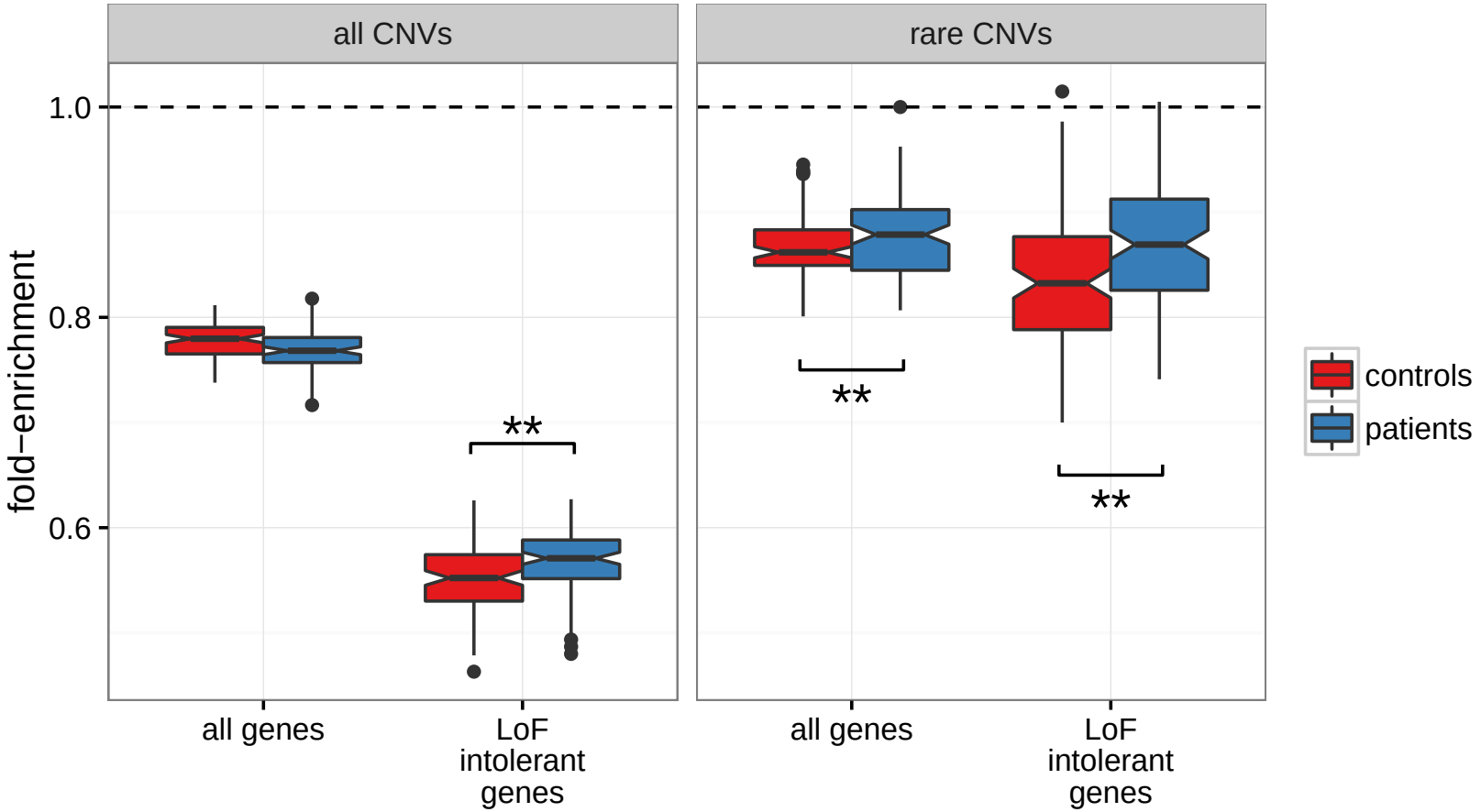


- Frequency from 5 public WGS-derived SV databases.
- *Rare* means frequency < 1% in all 5 databases.



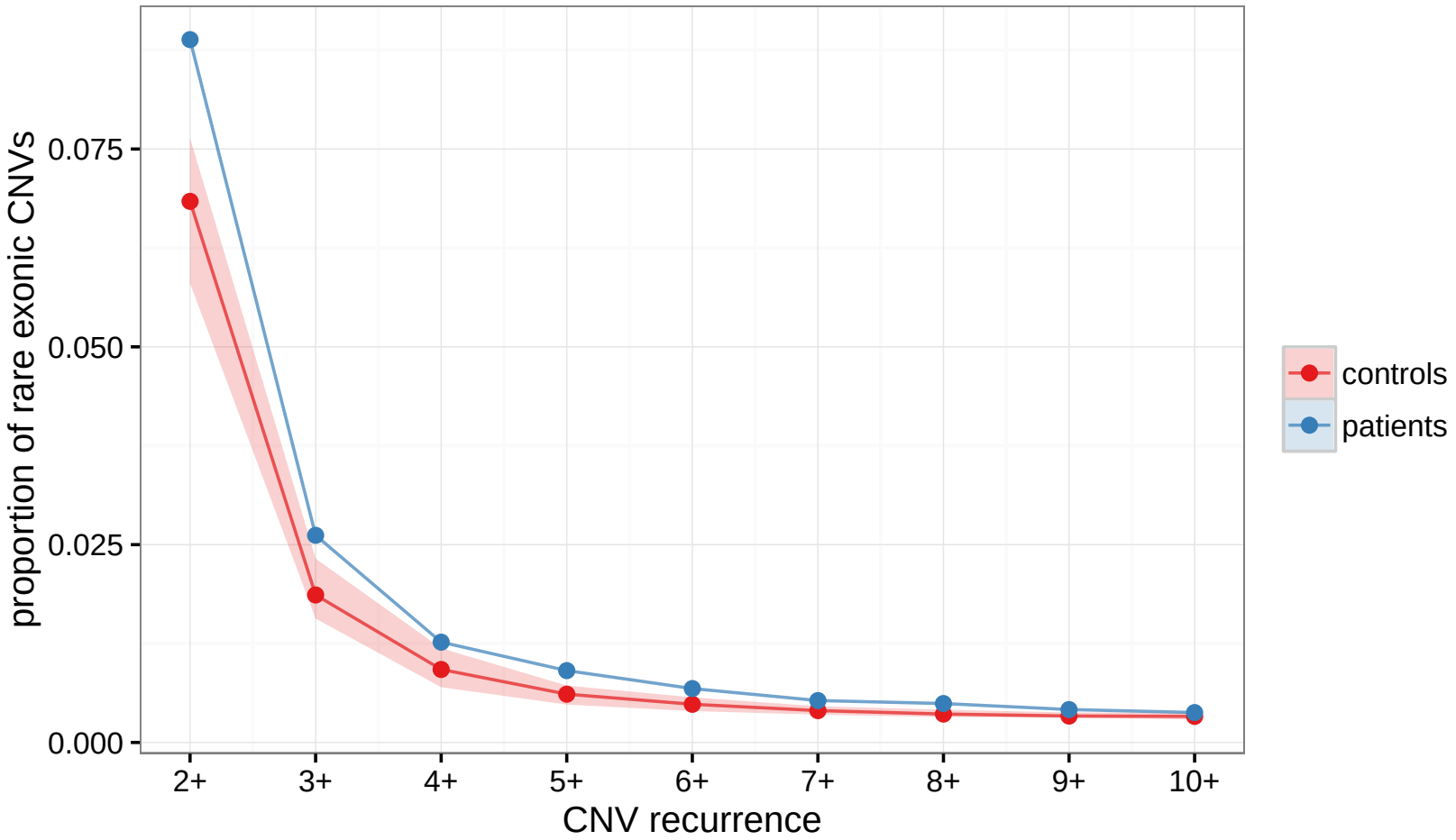
Slight enrichment of rare CNVs in exons



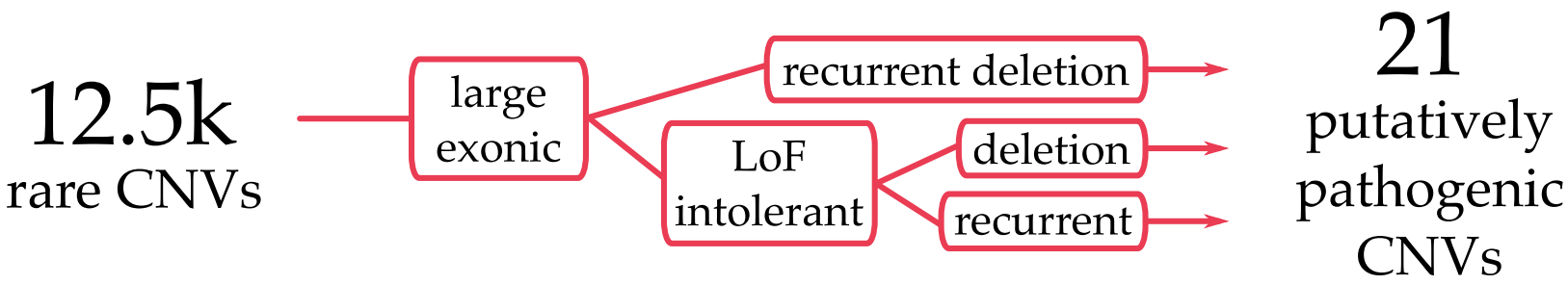
fold-enrichment: how many CNVs overlap an exon compared to expected by chance.

Loss-of-Function intolerant genes from ExAC consortium.

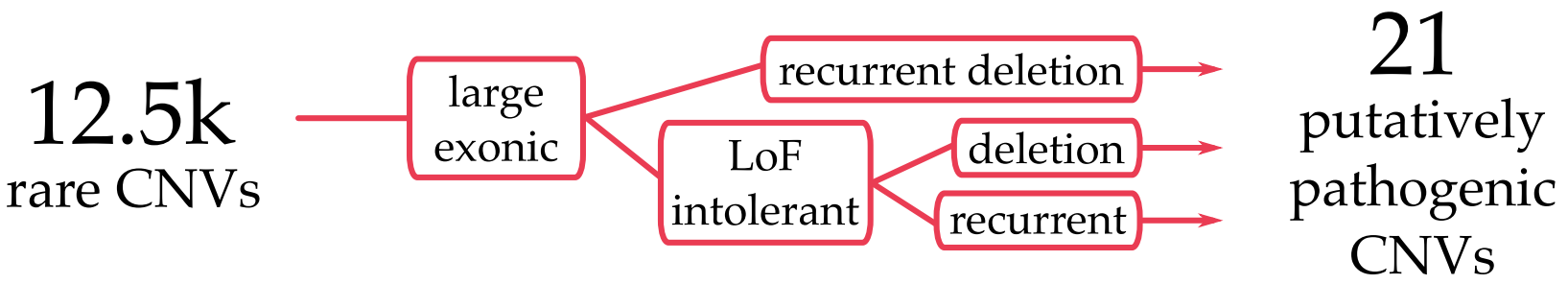
Rare exonic CNVs are more recurrent in the epilepsy cohort



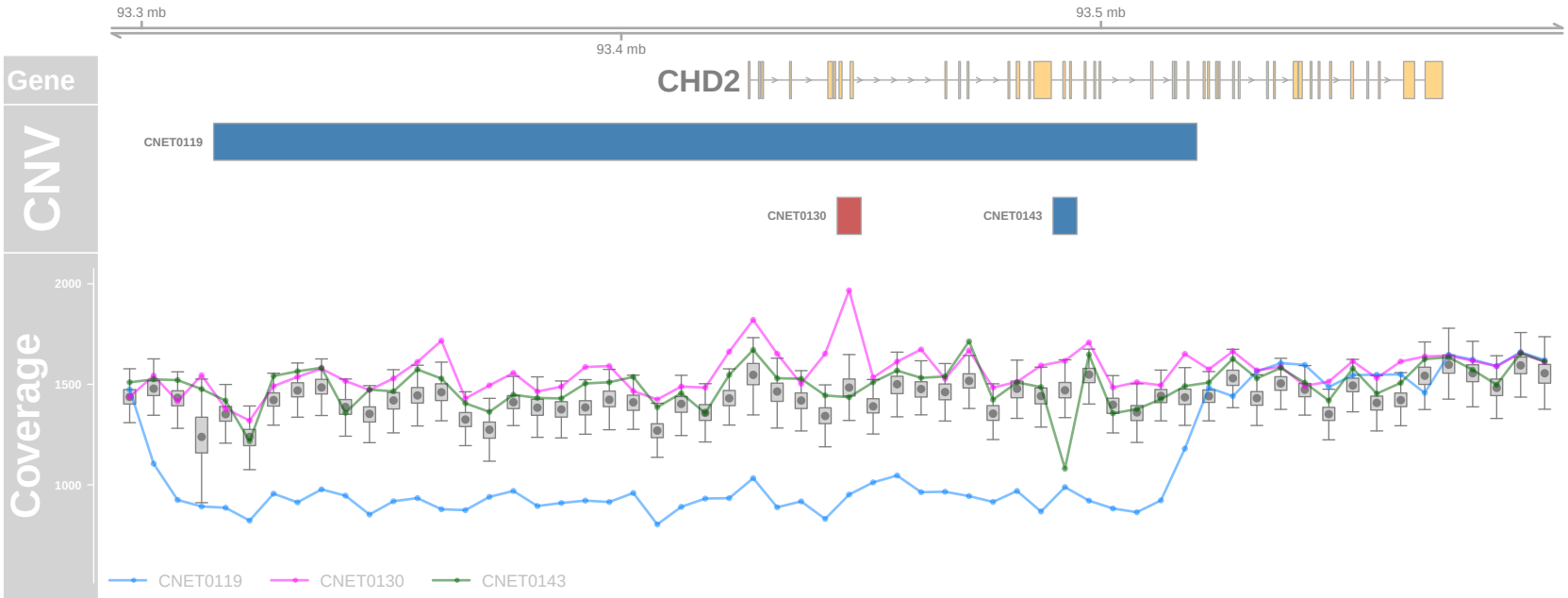
Putatively pathogenic exonic CNVs



Putatively pathogenic exonic CNVs

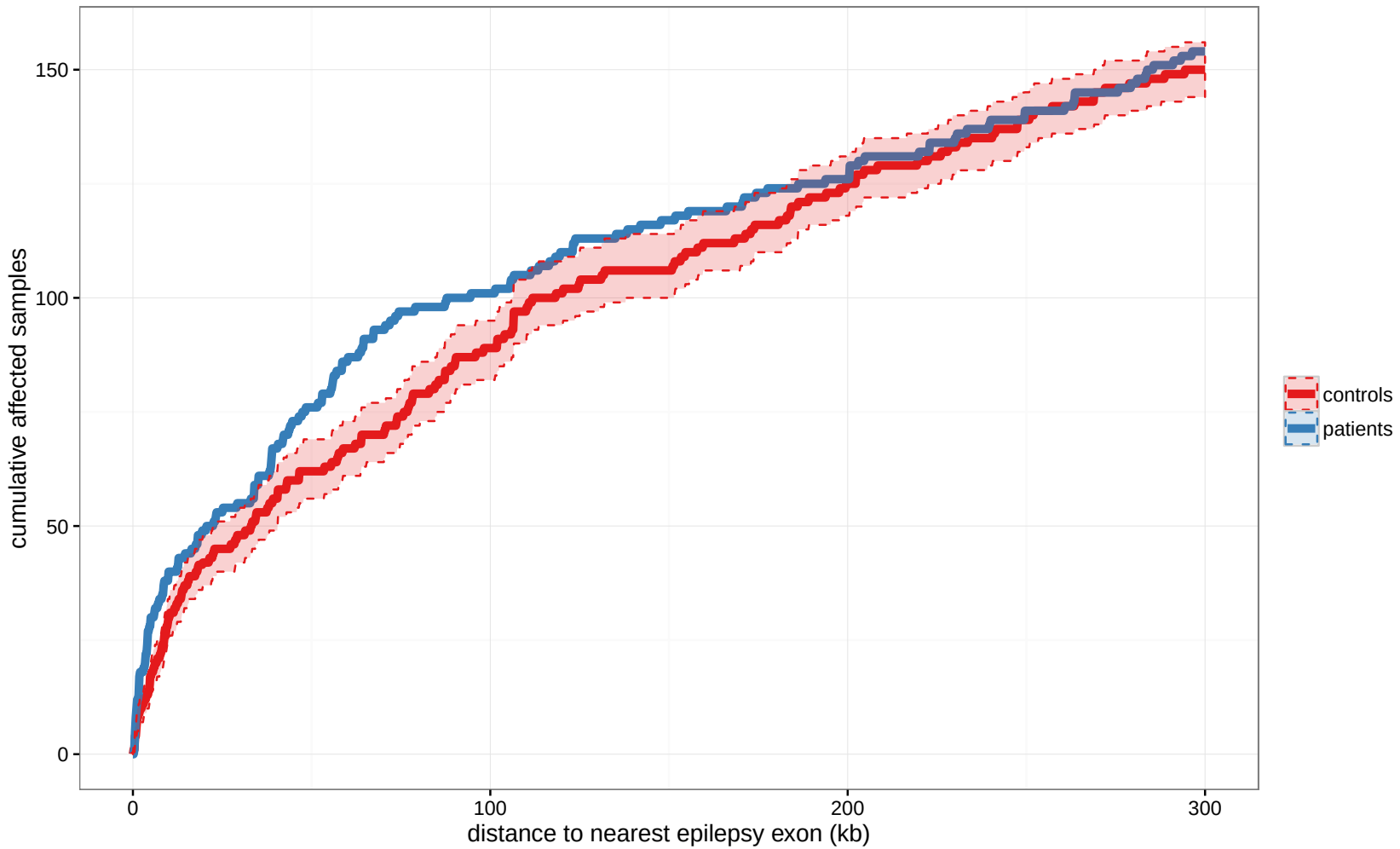


- 8/21 affect a known epilepsy-associated gene *(Ran NAR 2015)*.

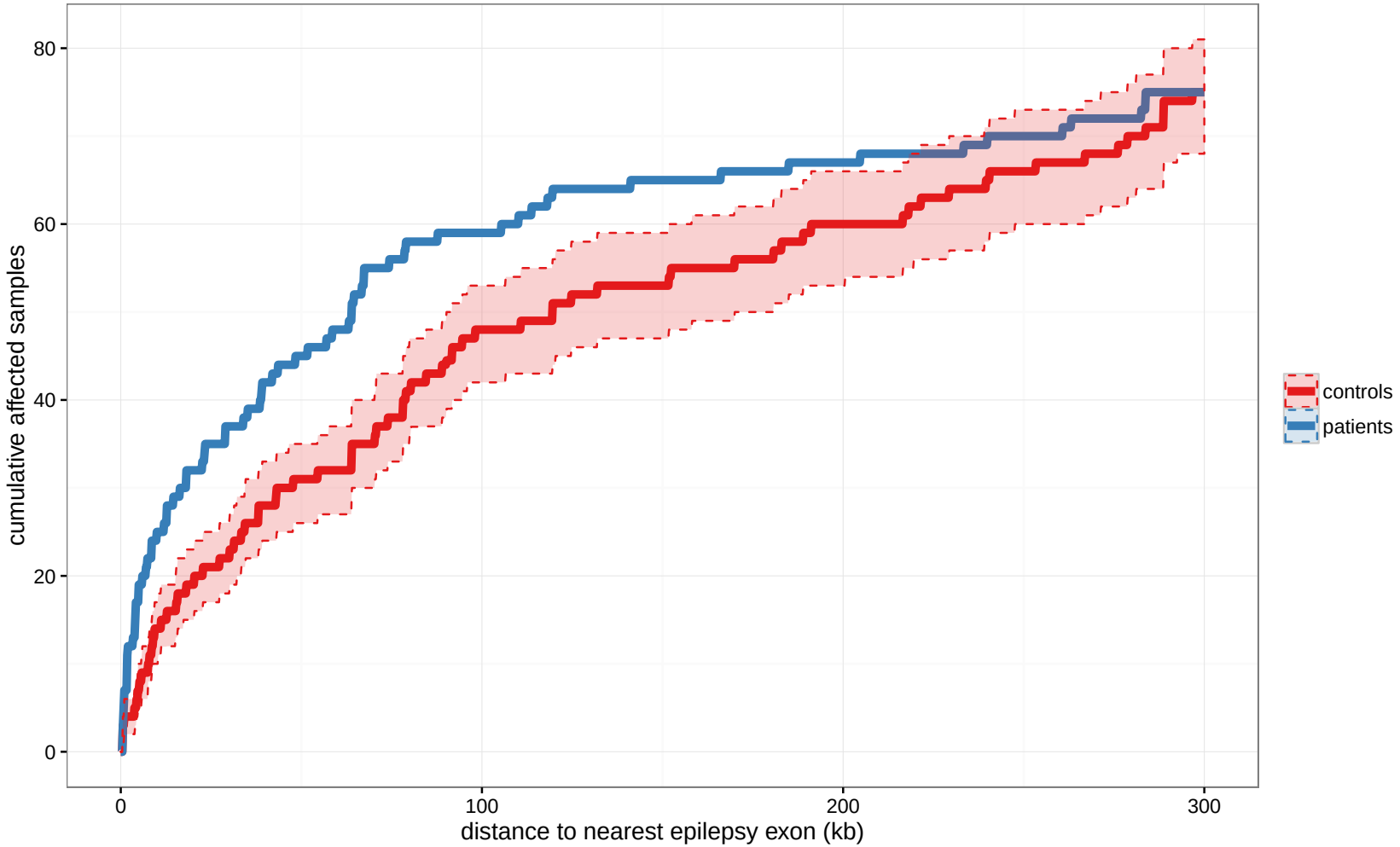


- Two recurrent CNVs were replicated in an additional cohort (325 patients and 380 controls).

Rare non-coding CNVs enriched close to epilepsy-associated genes



Even more if in enhancers of the epilepsy gene



Enhancer: eQTL or DNase site associated with the epilepsy gene.

Conclusions

- **Rare exonic CNVs are enriched and more recurrent** in epilepsy patients compared to controls.
- Identified **putatively pathogenic exonic CNVs**, some replicated in an additional cohort.
- **Rare non-coding CNVs are enriched close to epilepsy-associated genes.**
- We show the importance of **small and non-coding CNVs** in epilepsy.
- Comprehensive profiling of CNVs could help **explain a larger fraction of epilepsy cases**.

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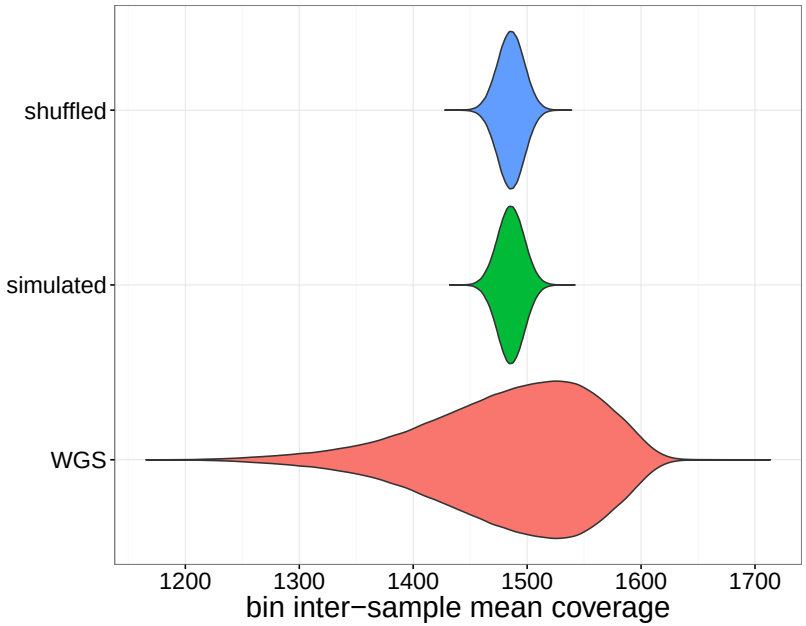
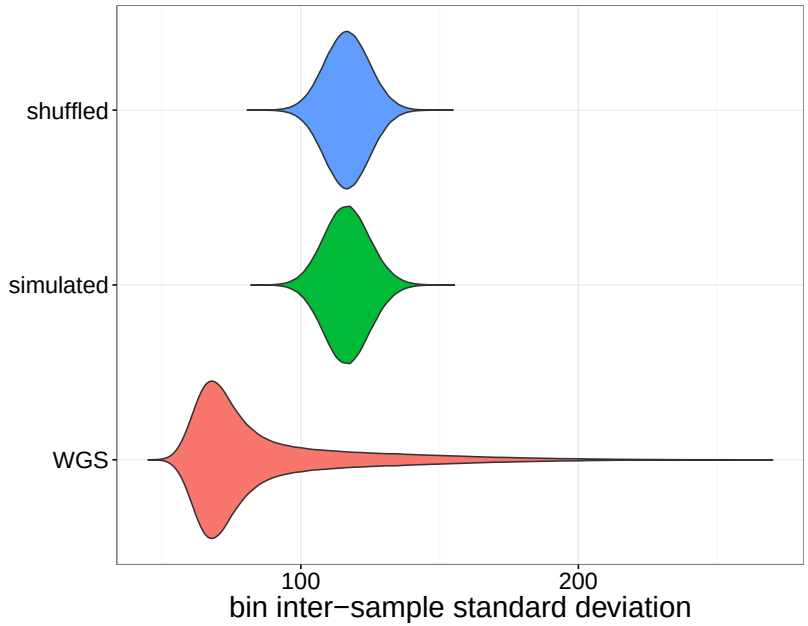
Technical bias in WGS





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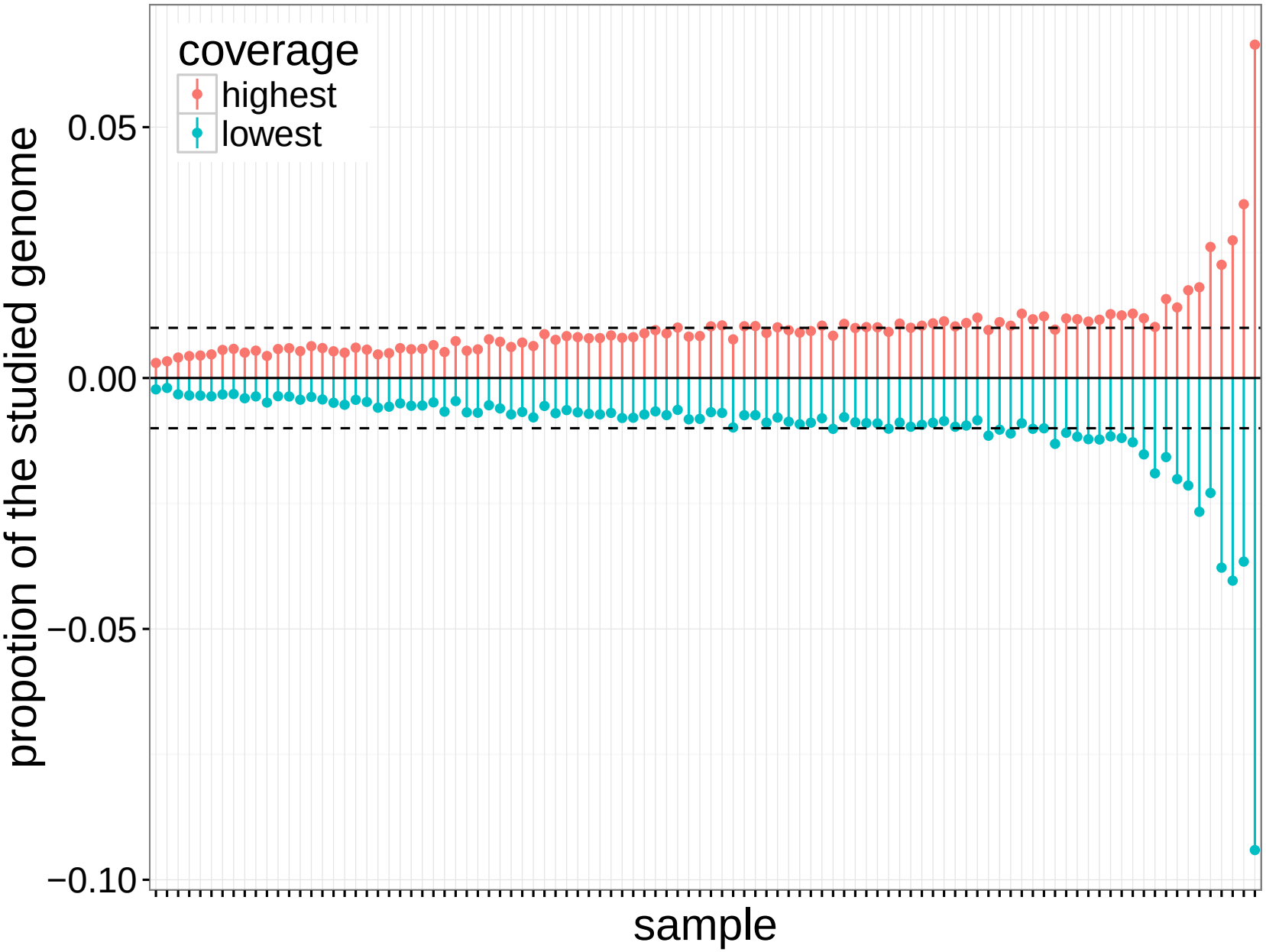
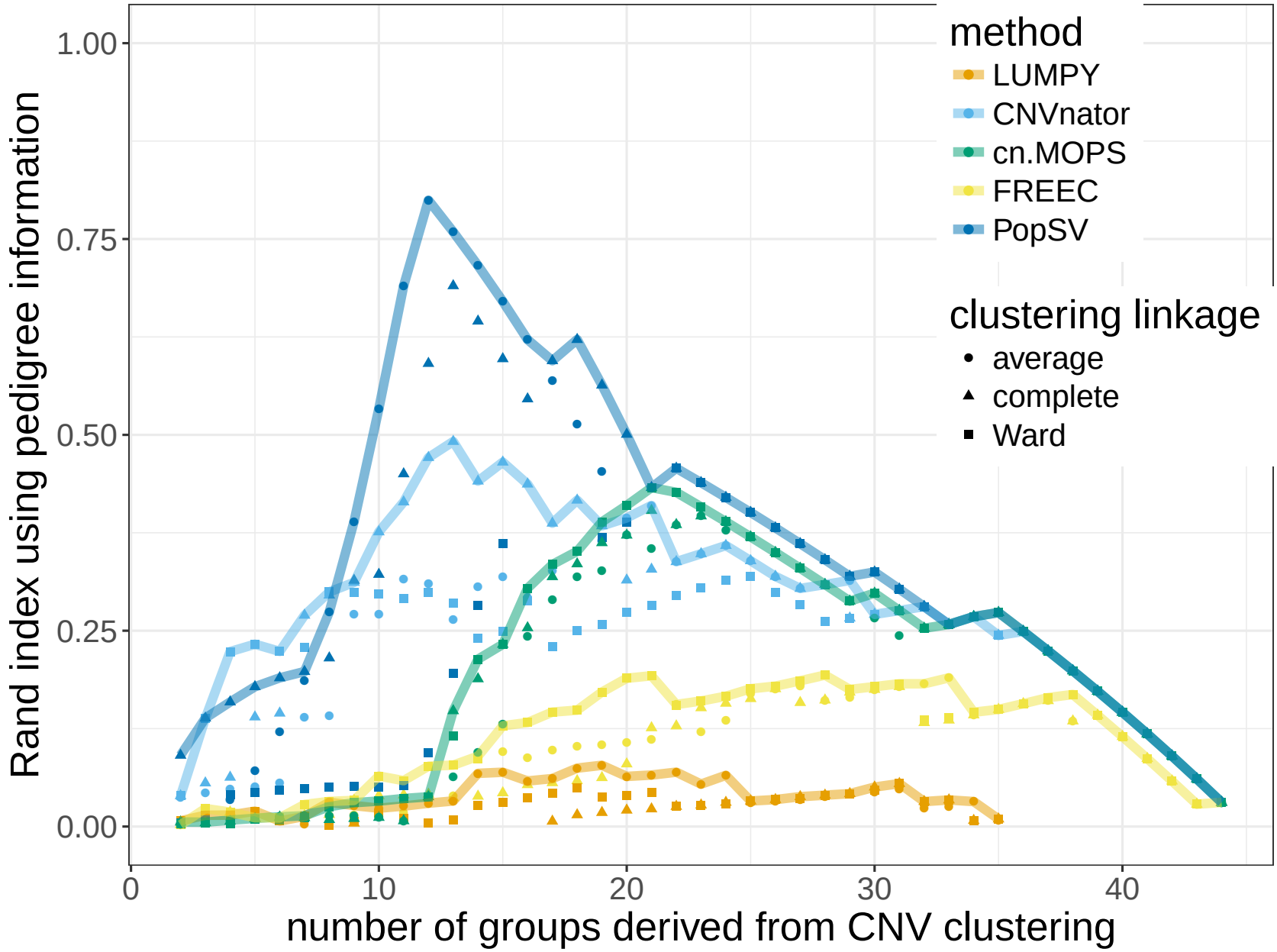


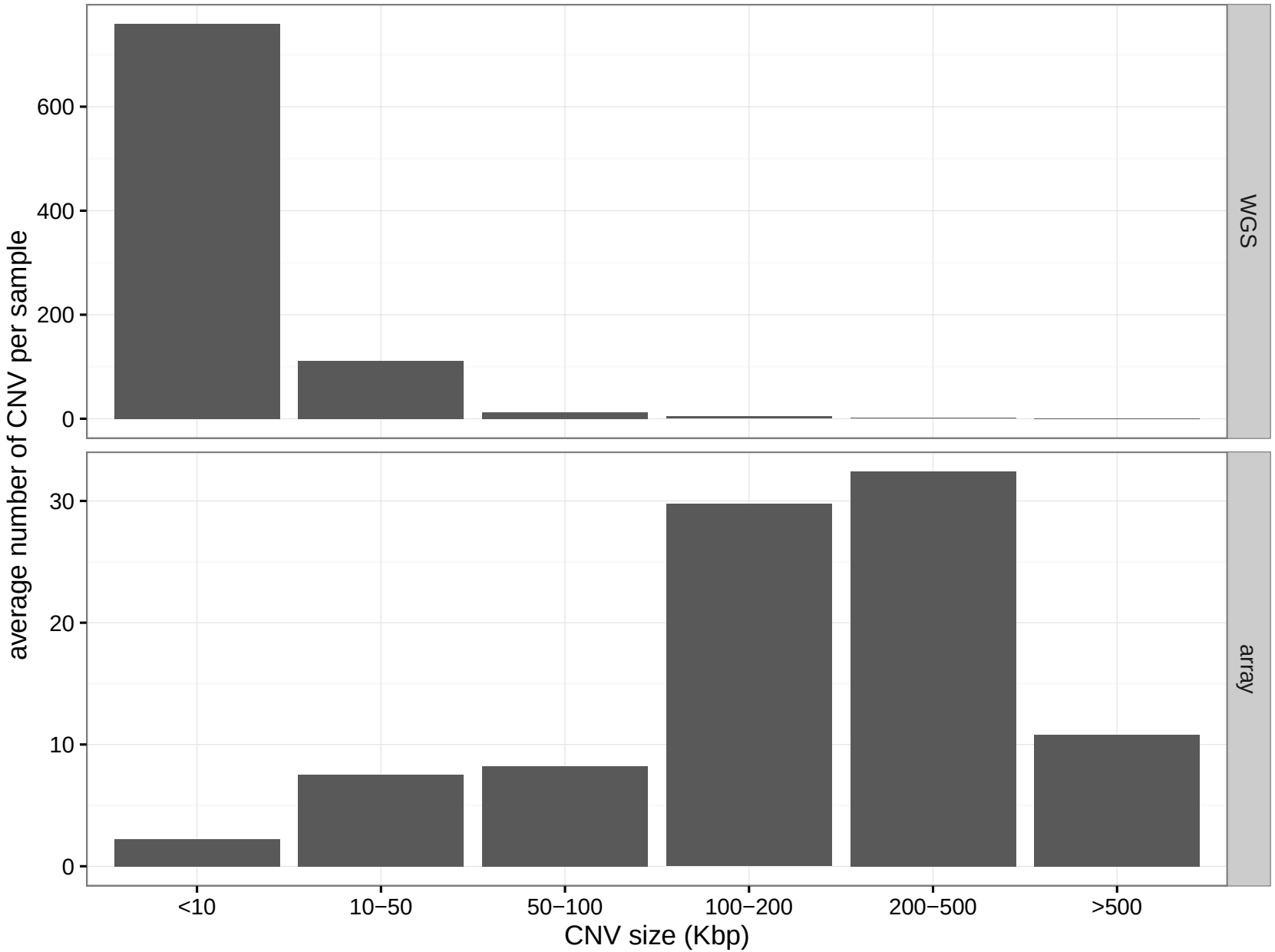
Twin pedigree concordance



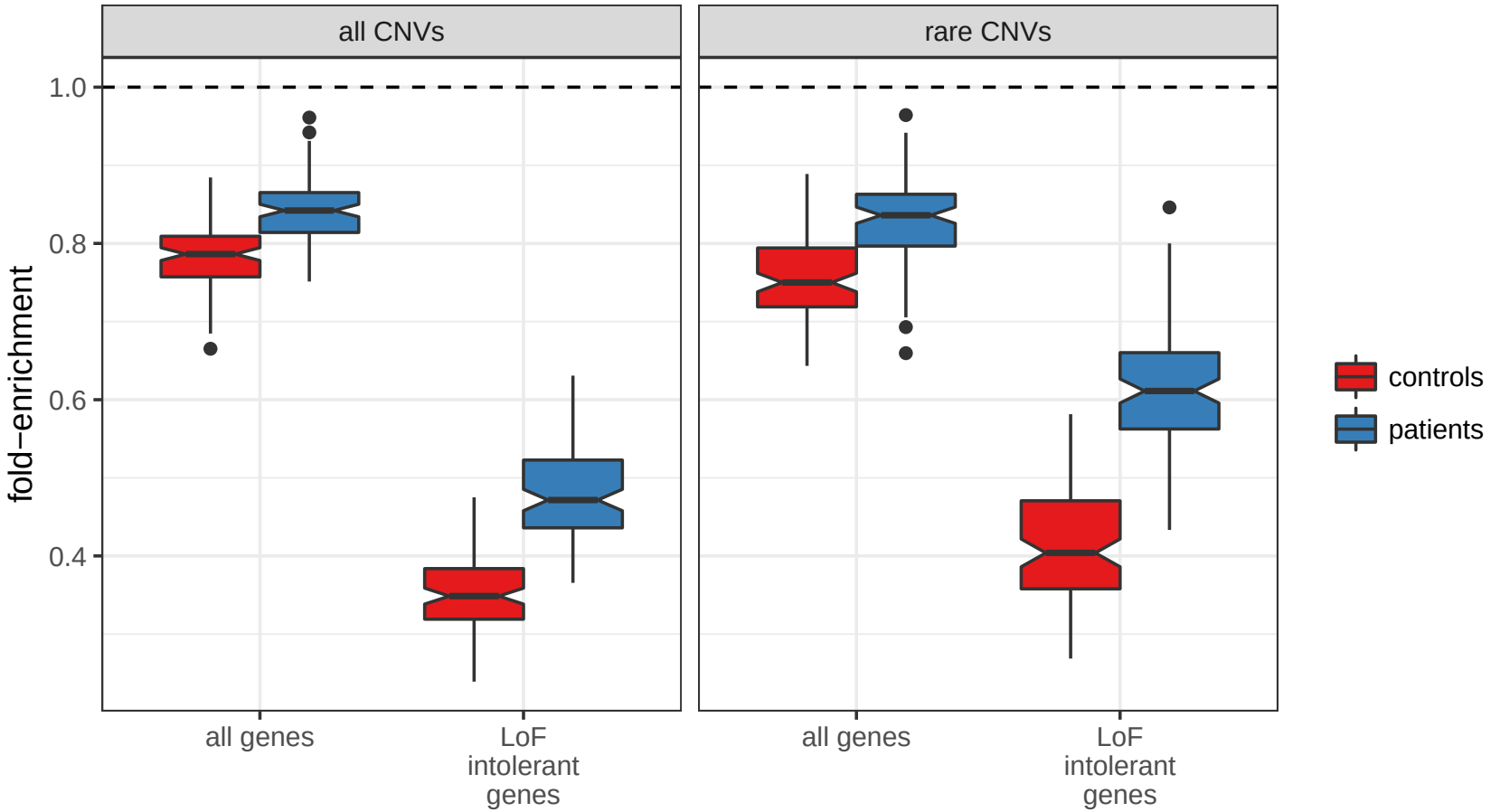
RT-PCR validation rates

	Region	Validation rate
Total	151	0.907
CNV type		
Deletion	102	0.902
Duplication	49	0.918
Frequency in database		
0	26	0.923
$(0, 0.01]$	24	0.833
$(0.01, 1]$	101	0.921
Size (Kbp)		
< 20	73	0.849
$(20, 100]$	38	0.974
> 100	40	0.950

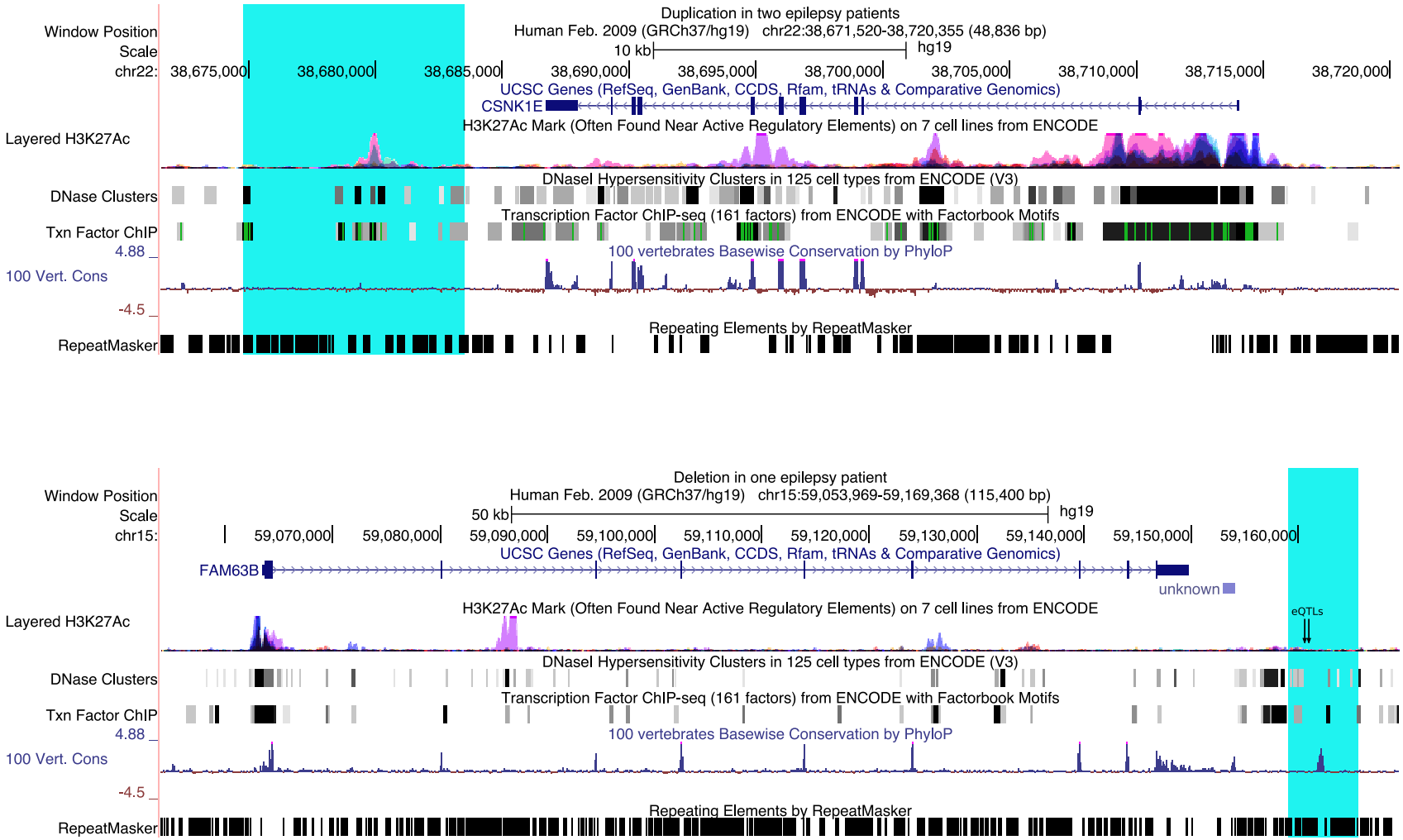
Size distribution



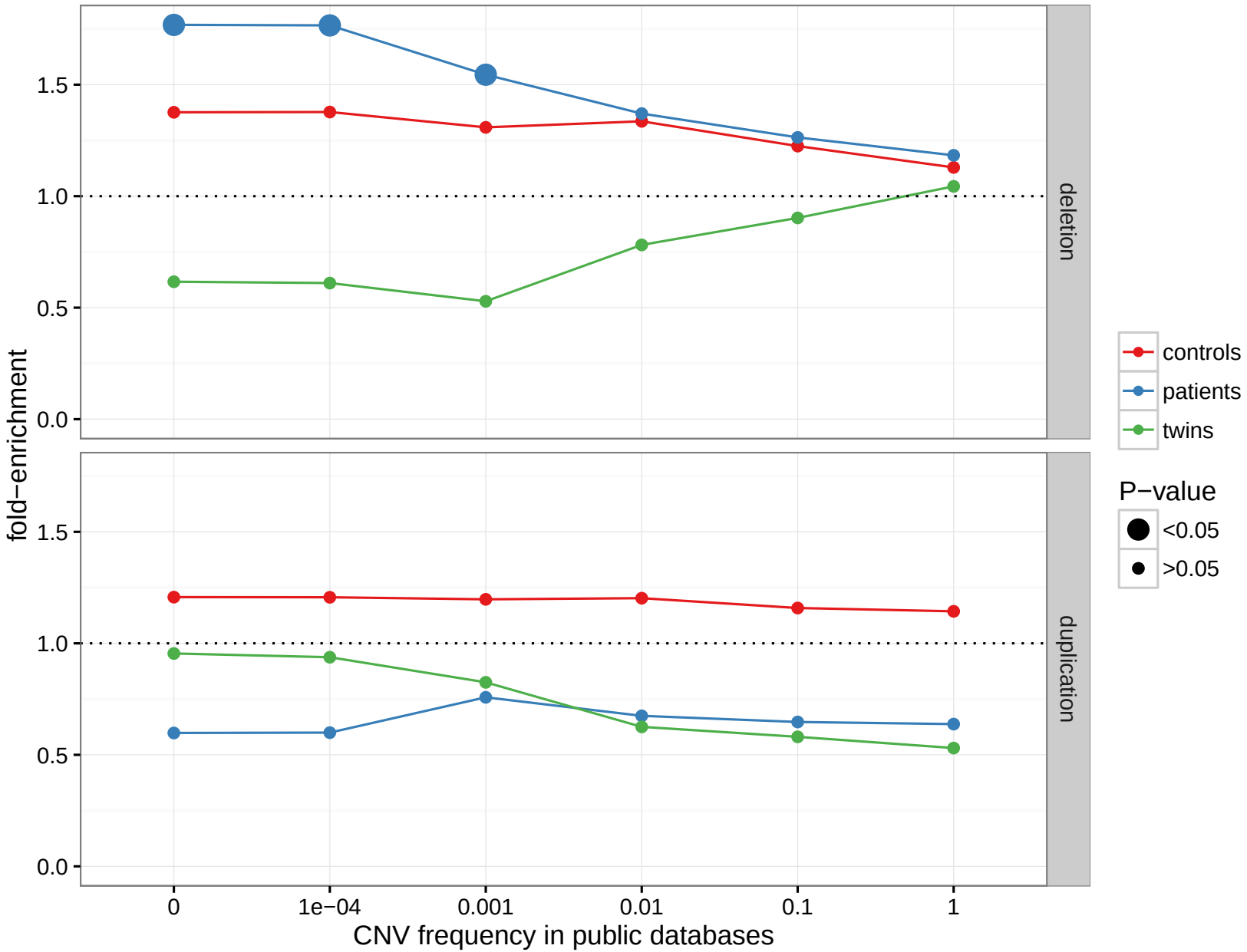
Large CNV enrichment in epilepsy patients



Non-coding CNVs of high interest



Rare deletions enriched in epilepsy-associated genes



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