

Beyond the Linear Reference: an ALPL Pangenome to Improve Variant Interpretation in Hypophosphatasia

Giulio Bianca, Zoe Cataldi, Sofia Sisti, Mirko Coggi, Guglielmo Bruno,
Beatrice Branchini, Guido Walter Di Donato



SCAN OR FIND US
AT BOOTH 302

CONTEXT

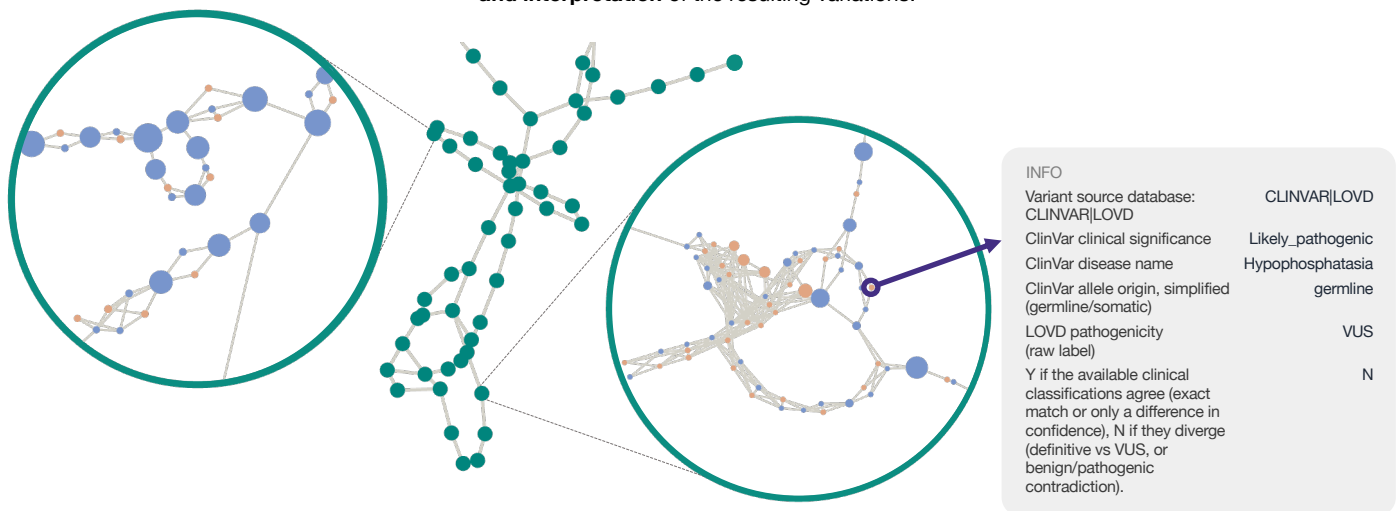
Hypophosphatasia is a **rare inherited disorder** caused by ALPL variants, with a broad spectrum ranging from severe perinatal disease to mild skeletal and dental signs in adulthood¹. Conventional diagnostic workflows still rely on a single linear reference genome, **limiting the ability to capture the full complexity** of variations.

OBJECTIVE

Construct an **ALPL locus-specific pangenome** on the **GENOGRAM** platform, combining the GRCh38 reference with variants from multiple VCF resources and genotypic, phenotypic and clinical annotations. The aim is to **capture broader variation**, improving the interpretation of disease-associated variants and **hypophosphatasia diagnosis**.

INTERACTIVE PANGENOME EXPLORATION WITH THE GENOGRAM PLATFORM

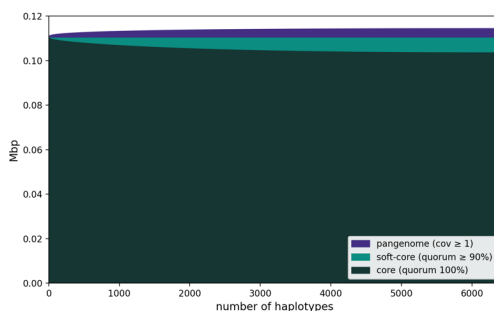
The **GENOGRAM** platform enables interactive visualization of the graph generated from the input data and support the filtering of millions of variants through **automated selection** based on genomic regions or annotation criteria. This allows **rapid, target-specific exploration and interpretation** of the resulting variations.



ALPL PANGENOME: STRUCTURE AND VARIANT CONTENT

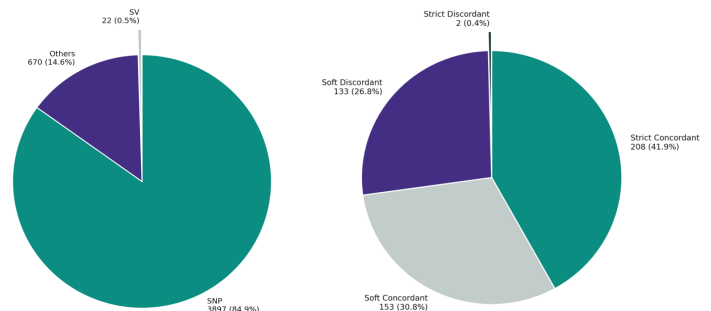
A compact locus with a closed pangenome

Adding haplotypes grows the ALPL pangenome only marginally: total sequence **saturates at ~114.5 kbp** and the strict core **stabilises at ~103.5 kbp**, the closed behaviour of a single compact locus. The **~11 kbp gap** is accessory, rare sequence that a linear reference omits but the graph retains as alternative haplotype paths.



A multi-class variant catalogue

The graph encodes **4,589 variants: 3,897 SNPs (84.9%), 670 small and complex (14.6%)** and **22 structural (0.5%)**, the latter often missed by a linear reference but **kept as alternative paths**. Cross-database analysis revealed **discordant pathogenicity for 27.2% of variants**, harmonized in a dedicated tool² for direct comparison.



SUMMARY

The **ALPL locus-specific pangenome** integrates diverse variant classes with VEP-derived consequences and pathogenicity evidence, giving a **more complete and interpretable view of ALPL variation** to support **improved variant interpretation** and **more accurate diagnosis of hypophosphatasia**. Further variants, clinical evidence and genotype-phenotype integration will strengthen its validation, particularly for discordantly classified variants.

REFERENCES

- ¹ Morret E. Hypophosphatasia. *Metabolism*. 2018 May;82:142-155. doi: 10.1016/j.metabol.2017.08.013. Epub 2017 Sep 20. PMID: 28939177.
² De Grandis L, Bianca G, Di Donato GW, Santambrogio MD. A Scalable Tool to Harmonize Genomic Variant Data from Heterogeneous Sources