

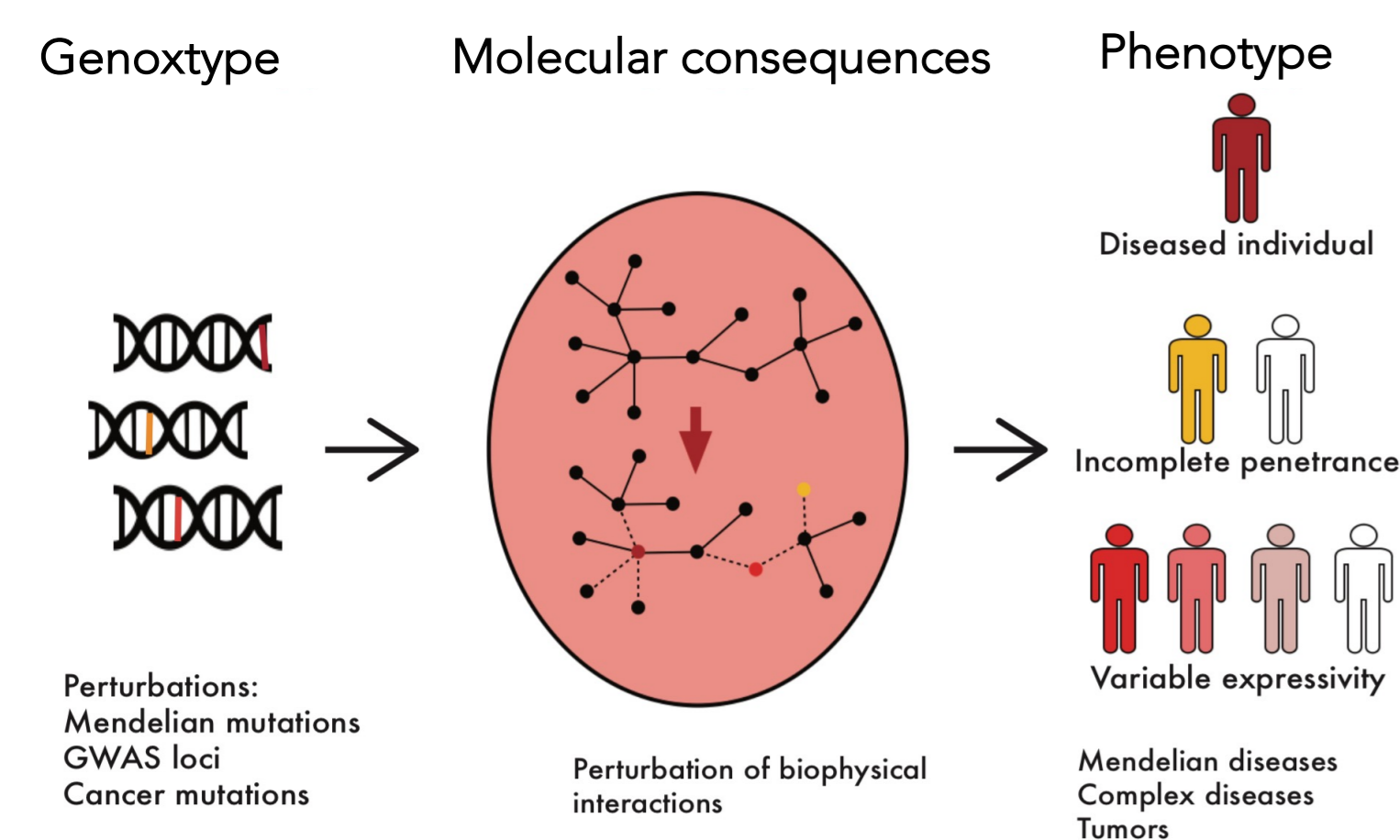
Uncovering Molecular Impacts of Missense Variants in Rare Disease Genes: A High-Throughput Framework for Variant Functionalization

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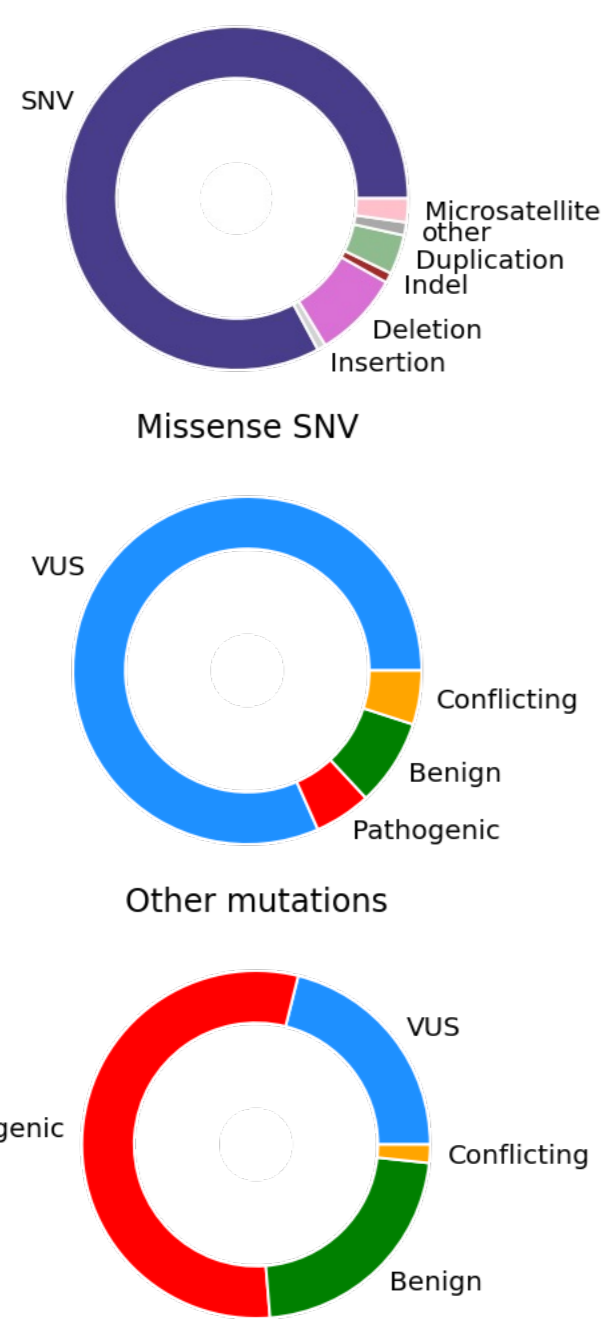
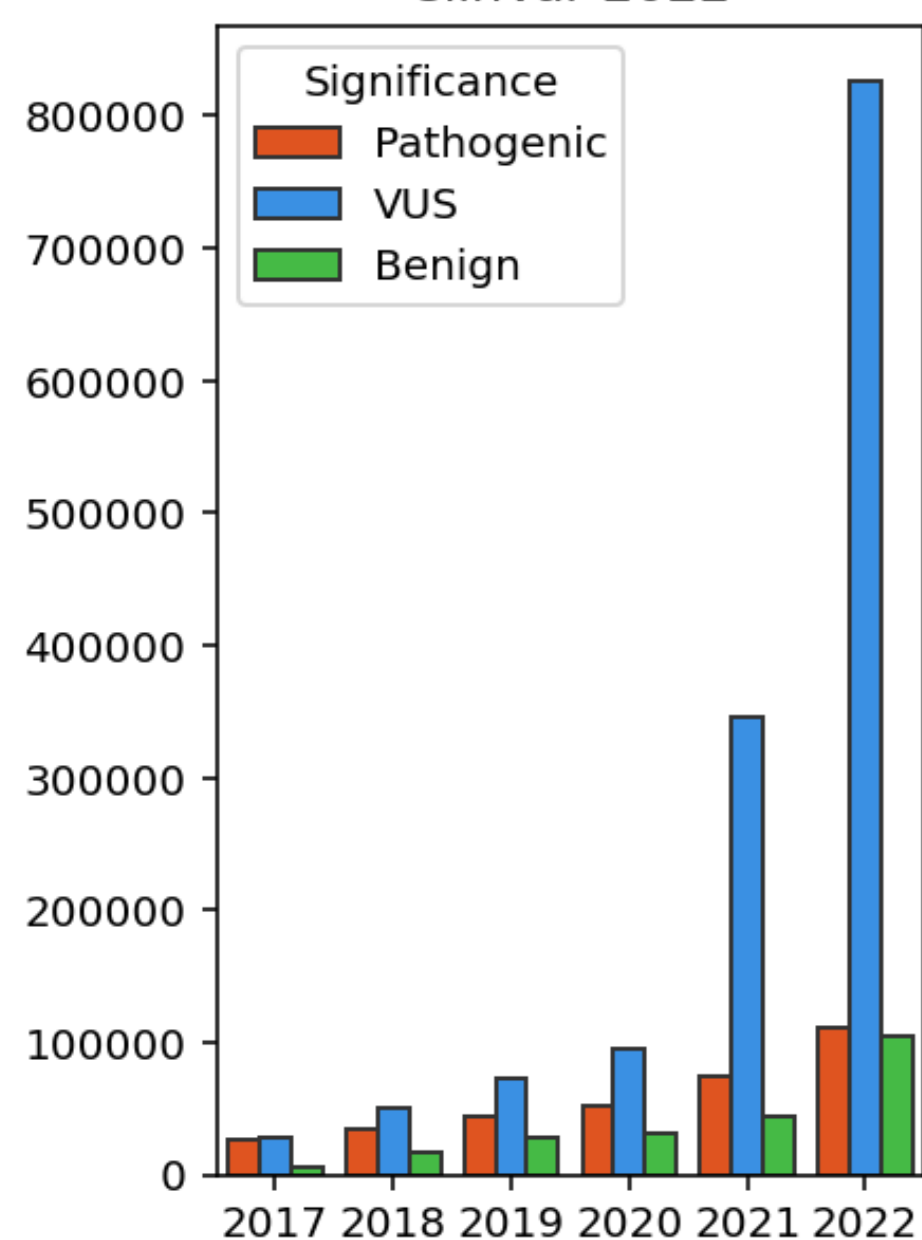
Uncertainty around missense variants

- Complex genotype to phenotype relationships in Mendelian disorders



- Drastic increase of variants of uncertain significance (VUS)

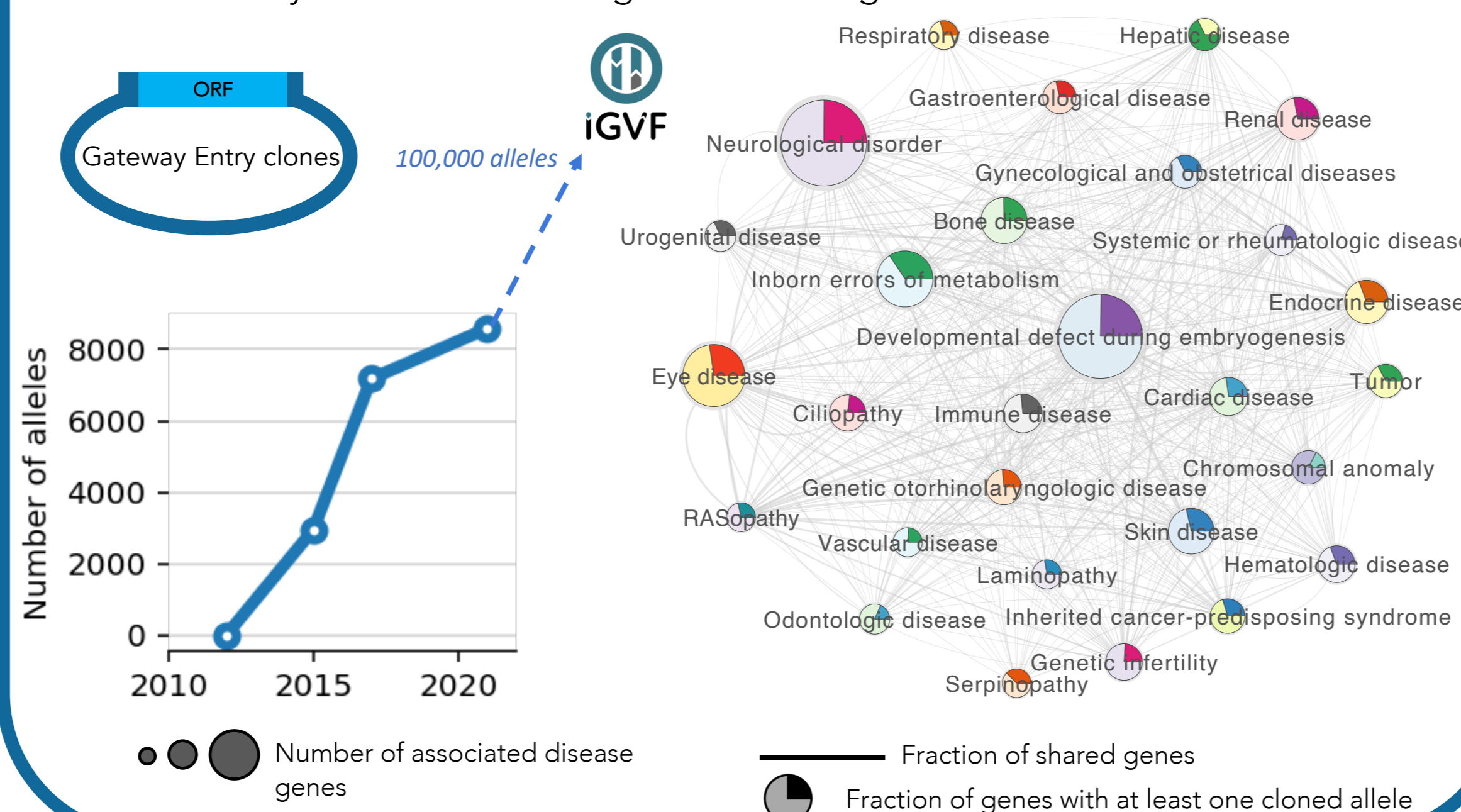
ClinVar 2022



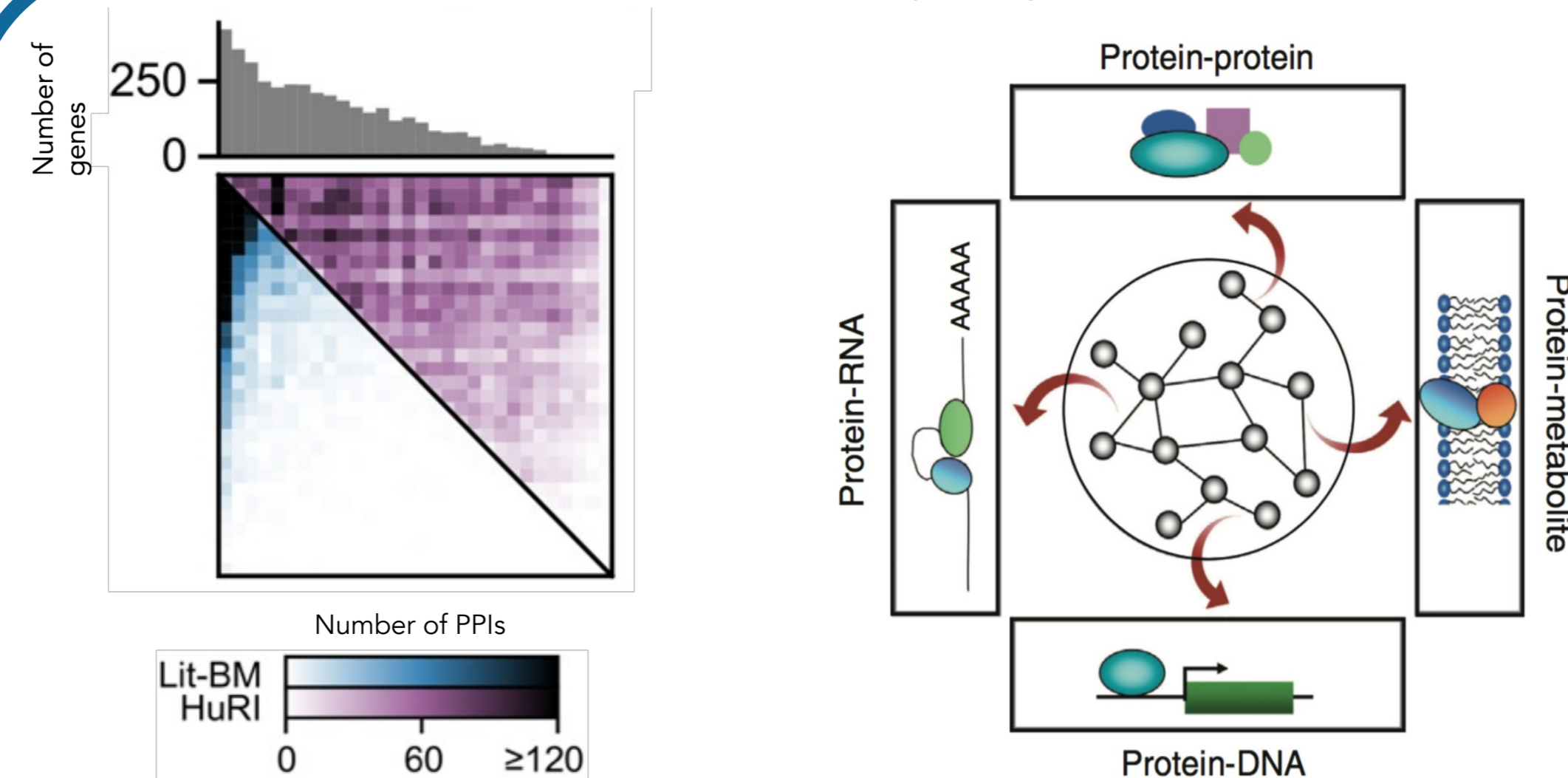
- Need of a systematic, unbiased, high throughput approach to study molecular impacts of single nucleotide variants (SNVs)

Comprehensive allele collection

- 9,000 sequence confirmed alleles in Gateway Entry clones
- IGVF long-term plan: cloning 100,000 alleles
- Covering 36% of all disease associated genes
- Uniformly distributed among disease categories



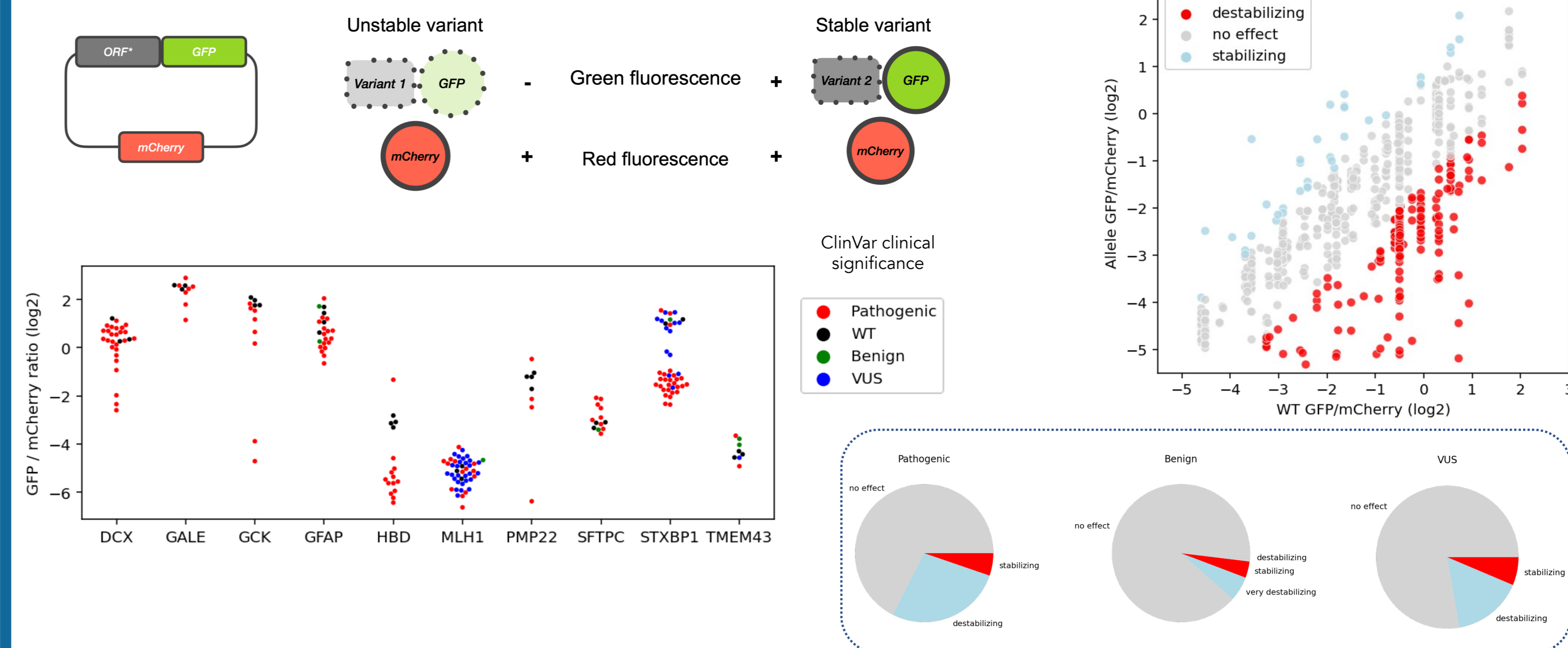
Molecular phenotyping approach



- Unbiased systematic human reference interactome (HuRI)
- 55,000 protein-protein Interactions (PPIs)
- Stability
- Cell viability
- Subcellular localization
- PPI perturbation

Systematic study of variants in Mendelian disease genes

- Node level - Impact of SNVs on stability using bi-fluorescent assay:



- Edge level - Perturbations of protein-protein interactions using Yeast Two-Hybrid (Y2H):

