The Genome Aggregation Database (gnomAD)

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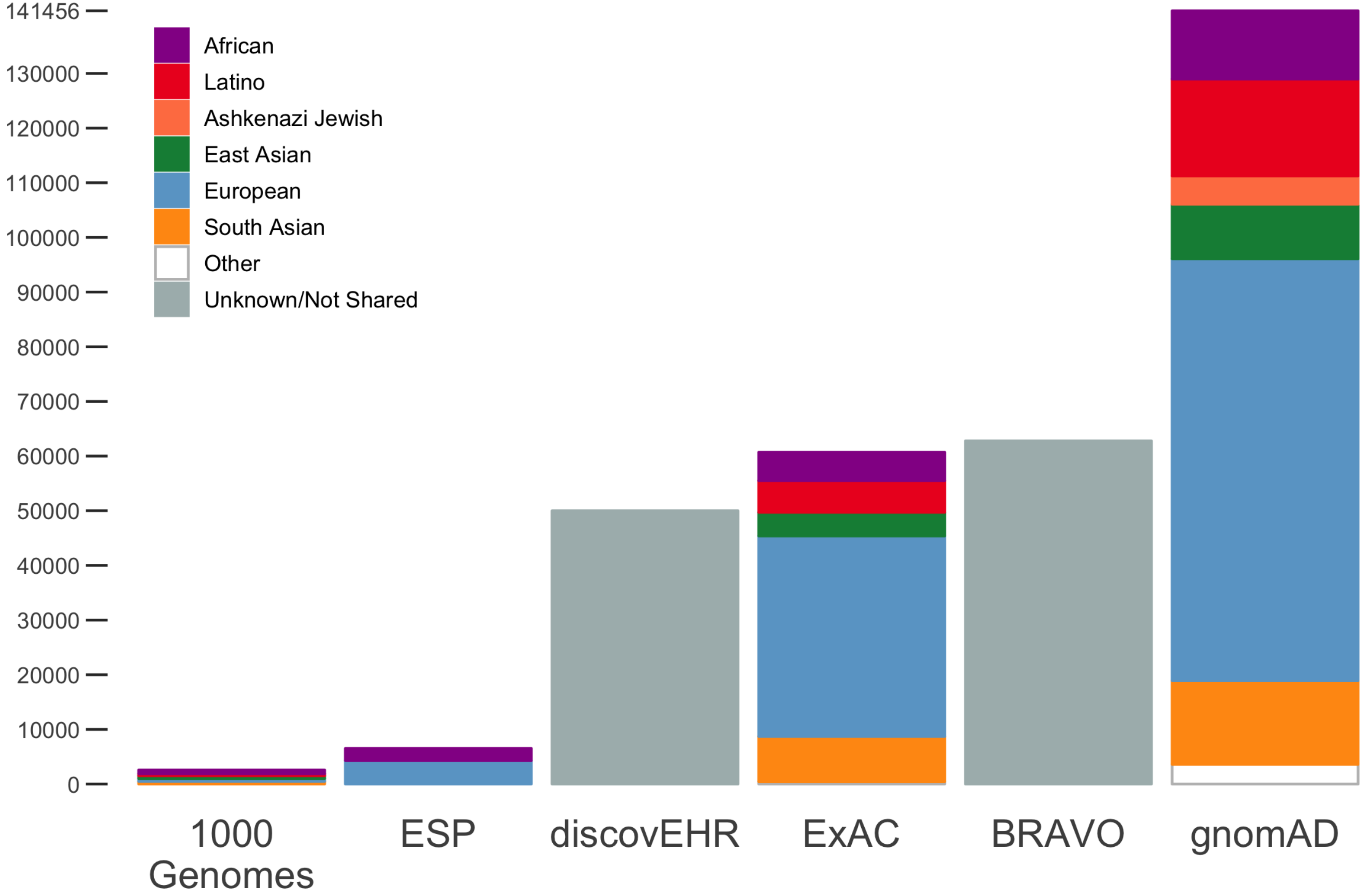
broad.io/gnomad_lof

@konradjk

When interpreting whether a variant is associated with a disease, two of the most important pieces of information are its:

- Frequency
- Functional consequence

Increasing the scale of reference databases



- **gnomAD:** 125,748 exomes and 15,708 whole genomes

gnomAD 2.1.1

- Data provided by 109 PIs
  - 1.3 and 1.6 petabytes of BAM files
- Uniformly processed and joint called
  - 12 and 24 terabyte VCFs
- Developed a novel QC pipeline
  - Complete pipeline publicly available: broad.io/gnomad_qc
- All QC and analysis performed using Hail: hail.is
  - Scalable to thousands of CPUs
  - Enabled rapid iteration (few hours for each component, few days for entire process)

Broad Genomics Platform
Broad Data Sciences Platform

Grace Tiao

Laurent Francioli

Cotton Seed

Tim Poterba

gnomAD 2.1.1

- Sub-continental ancestry
- Subsets:
  - controls-only
  - non-neuro/non-psychiatric
  - non-cancer
  - non-TOPMed Bravo

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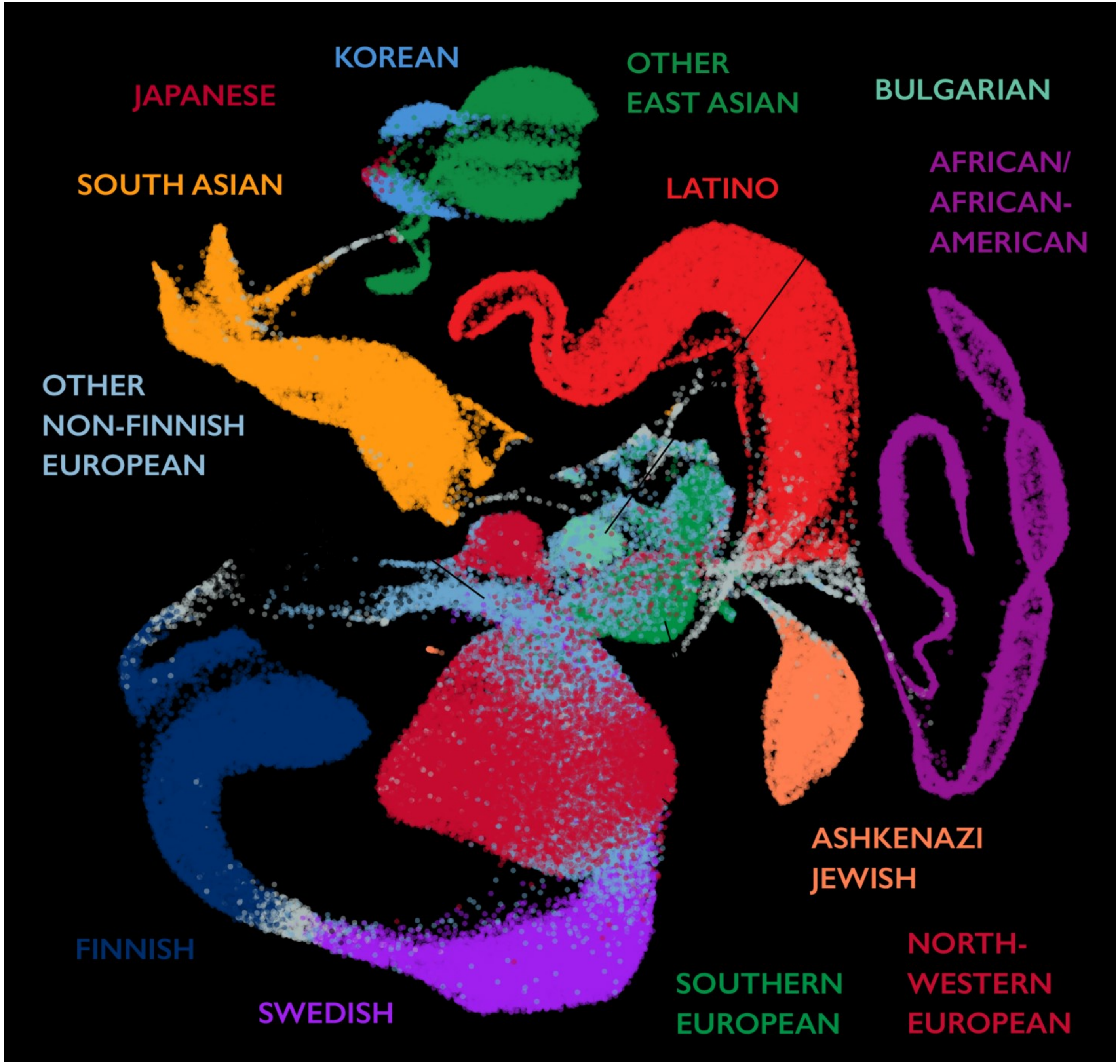
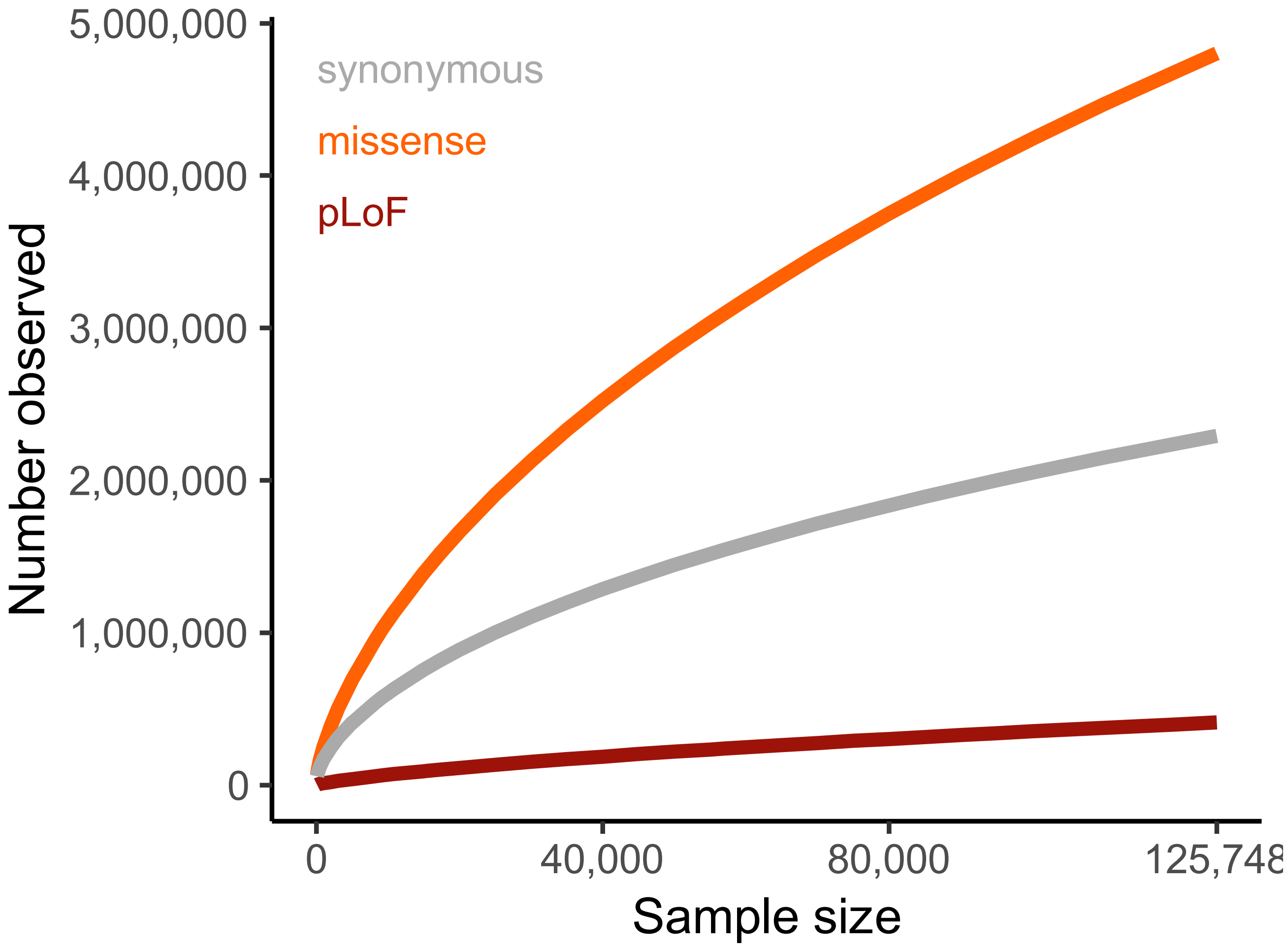
http://gnomad.broadinstitute.org



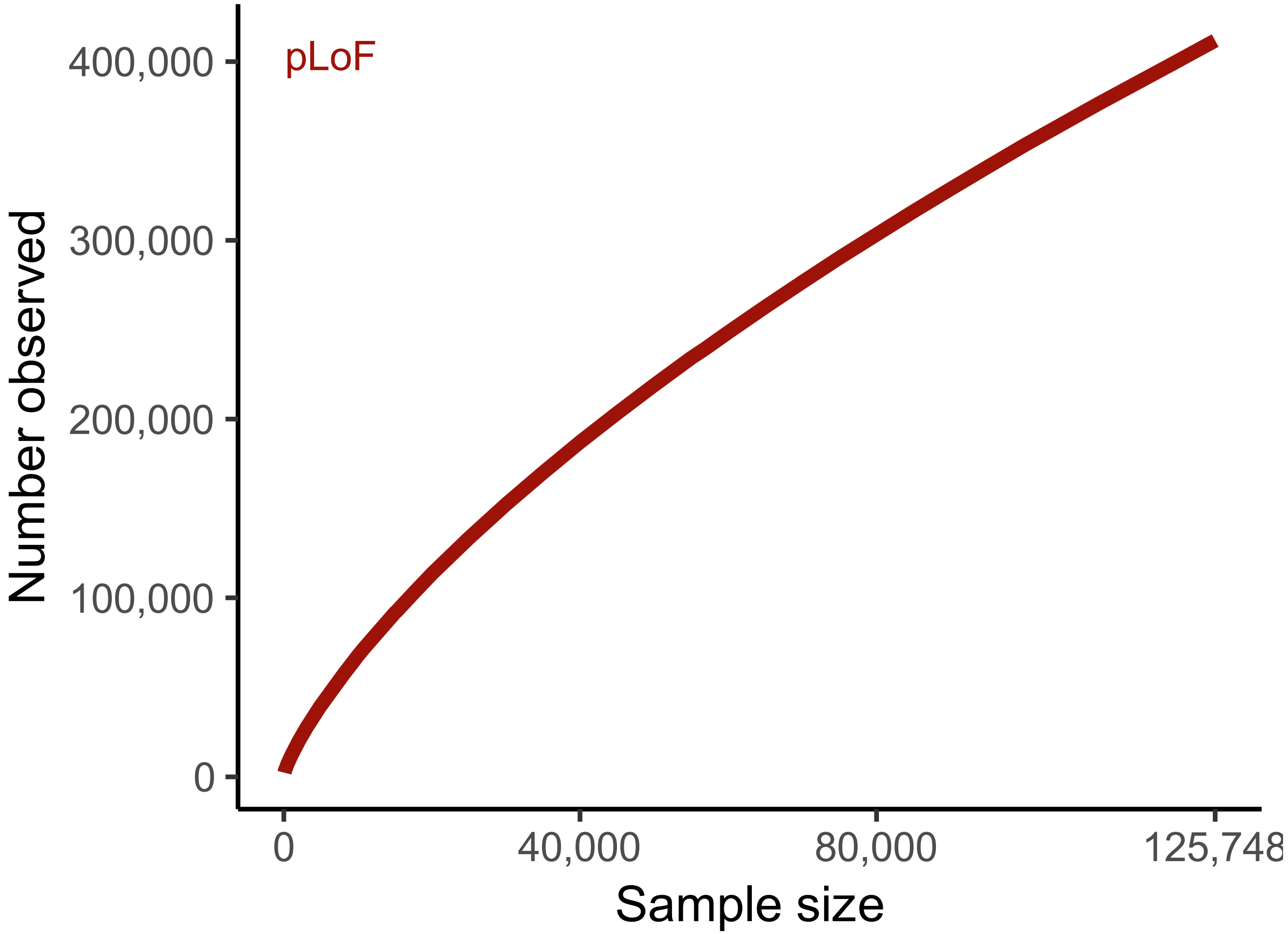
Staggering amounts of variation

- gnomAD 2.1 contains:
  - 230M variants in 15,708 genomes
  - 15M variants in 125,748 exomes



Staggering amounts of LoFs

- gnomAD 2.1 contains:
  - 230M variants in 15,708 genomes
  - 15M variants in 125,748 exomes
- Of these, we observe 515,326 loss-of-function (LoF) variants
  - Stop-gained
  - Essential splice
  - Frameshift indel

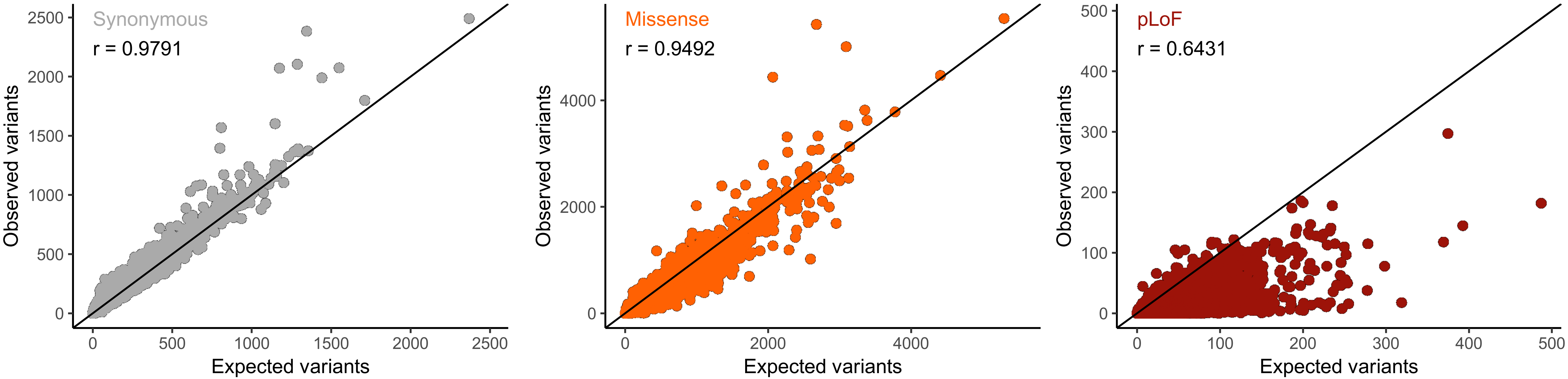


Detecting genes depleted for LoFs

(Samocha *et al*. 2014;
Lek *et al*. 2016)

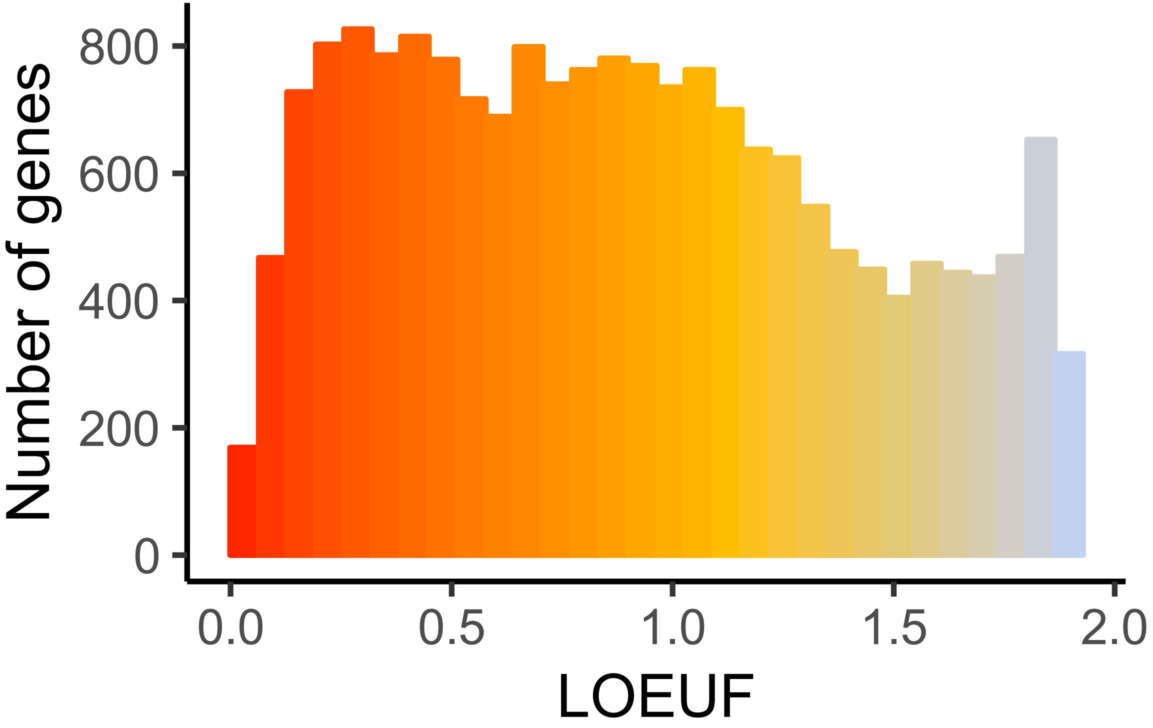
Kaitlin Samocha

- Mutational model that predicts the number of SNVs in a given functional class we would expect to see in each gene in a cohort



Most genes are depleted of LoF variation

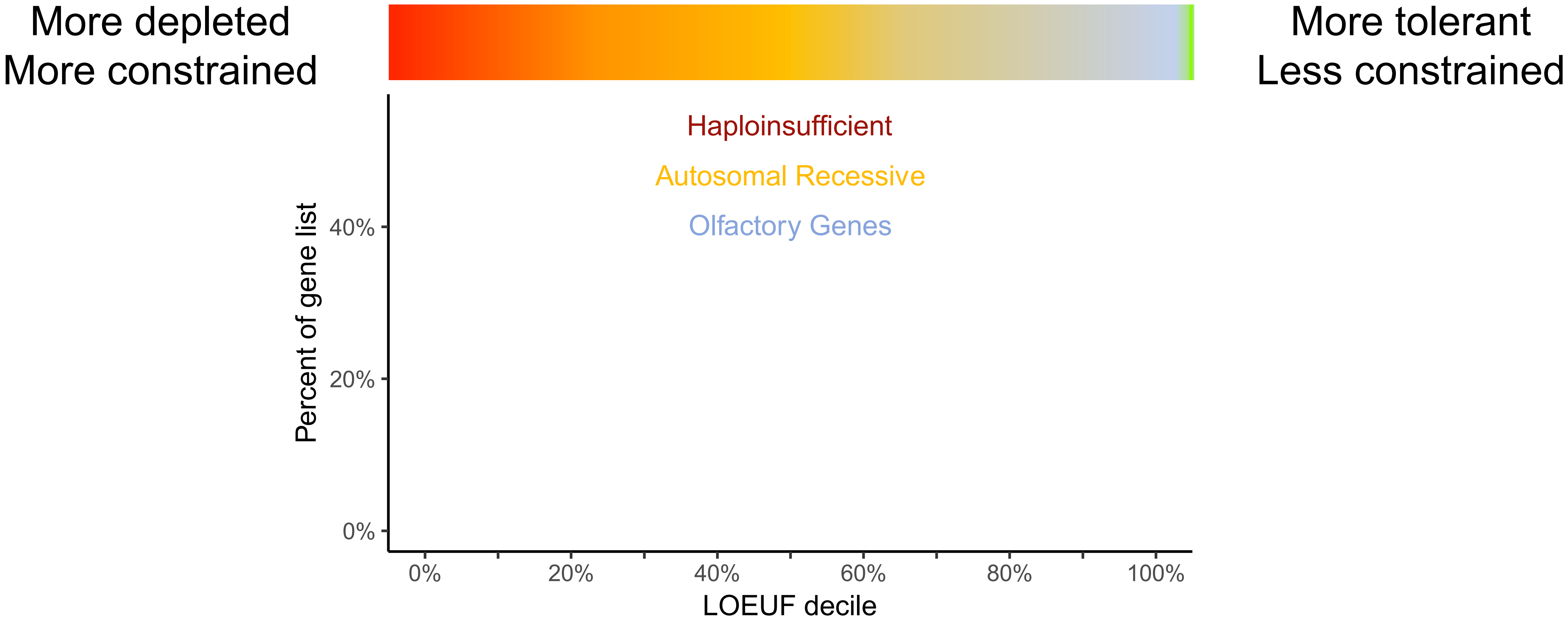
- Many are extremely depleted (<20% observed compared to expected)
    - Including most known dominant Mendelian genes
- Using upper bound of confidence interval corrects for small genes



	MED13L		
Phenotype	Severe Intellectual Disability		
	Observed	Expected	Obs/Exp (CI)
Synonymous	462	465	0.993 (0.92-1.07)

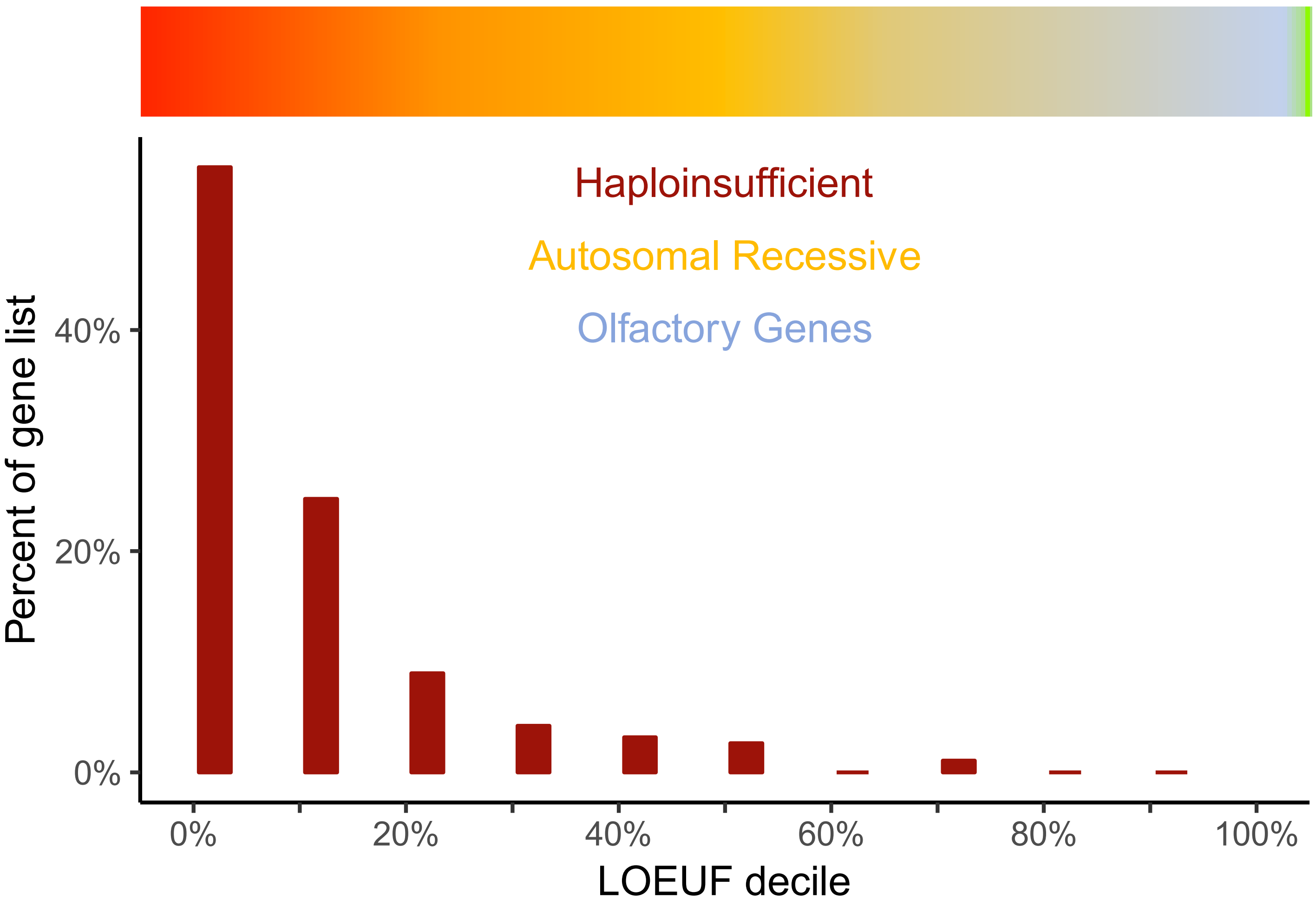
Resolving the spectrum of LoF intolerance

- Binning this spectrum into deciles



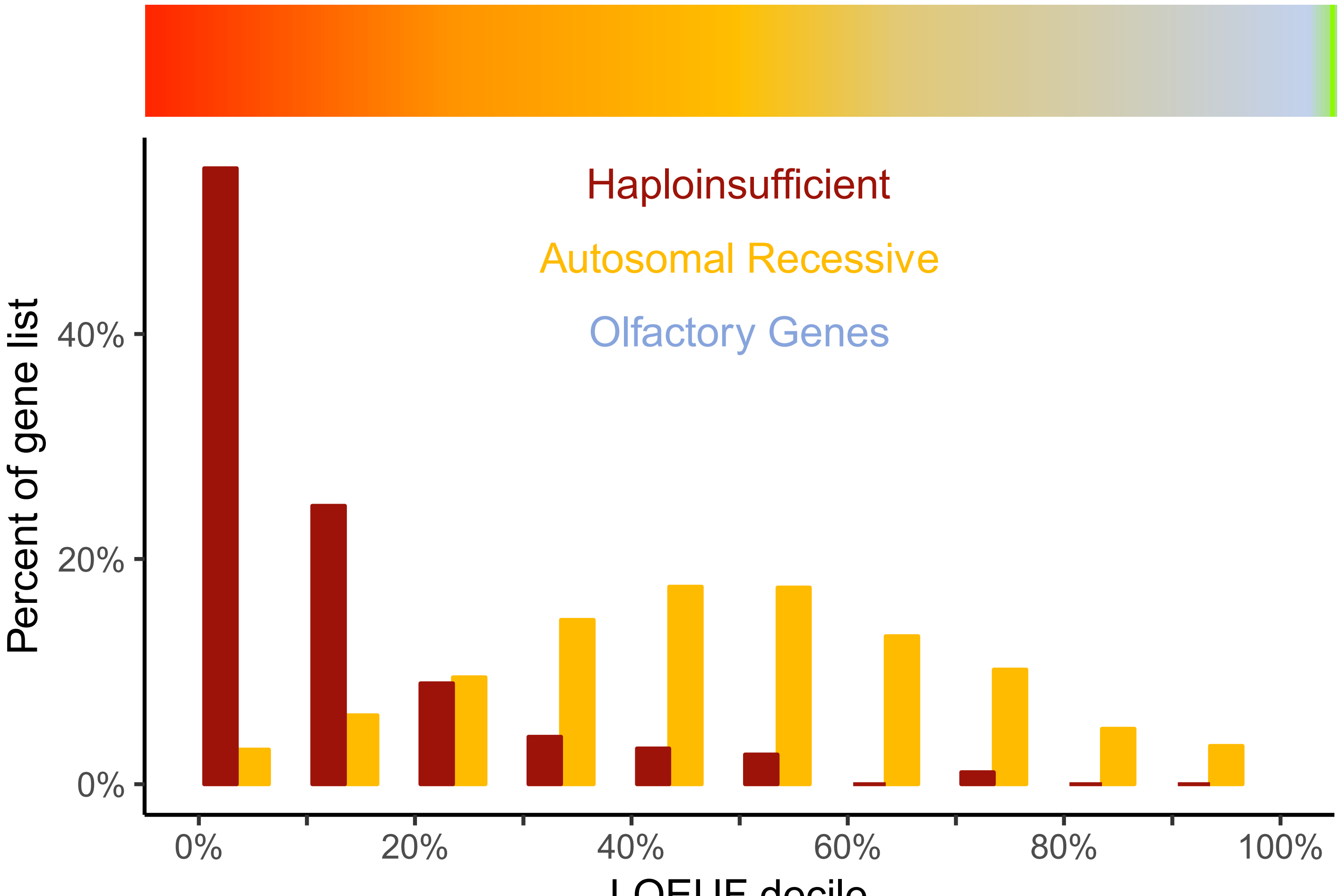
Resolving the spectrum of LoF intolerance

- Known haploinsufficient genes have ~10% of the expected LoFs



Resolving the spectrum of LoF intolerance

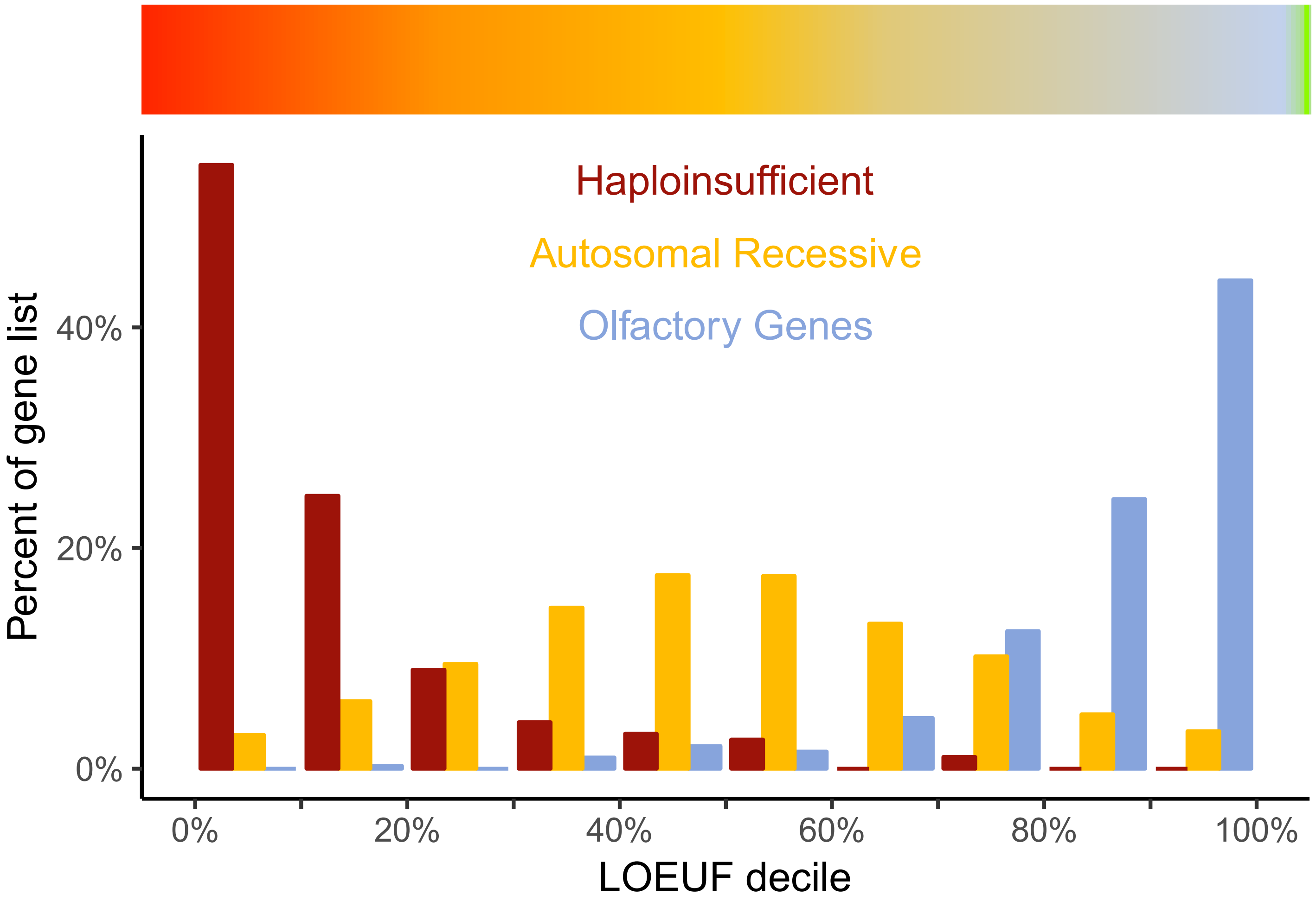
- Autosomal recessive genes are centered around 60% of expected



Gene list from:
Blekhman et al., 2008
Berg et al., 2013

Resolving the spectrum of LoF intolerance

- Some genes, e.g. olfactory receptors, are unconstrained



Data publicly released with no publication restrictions

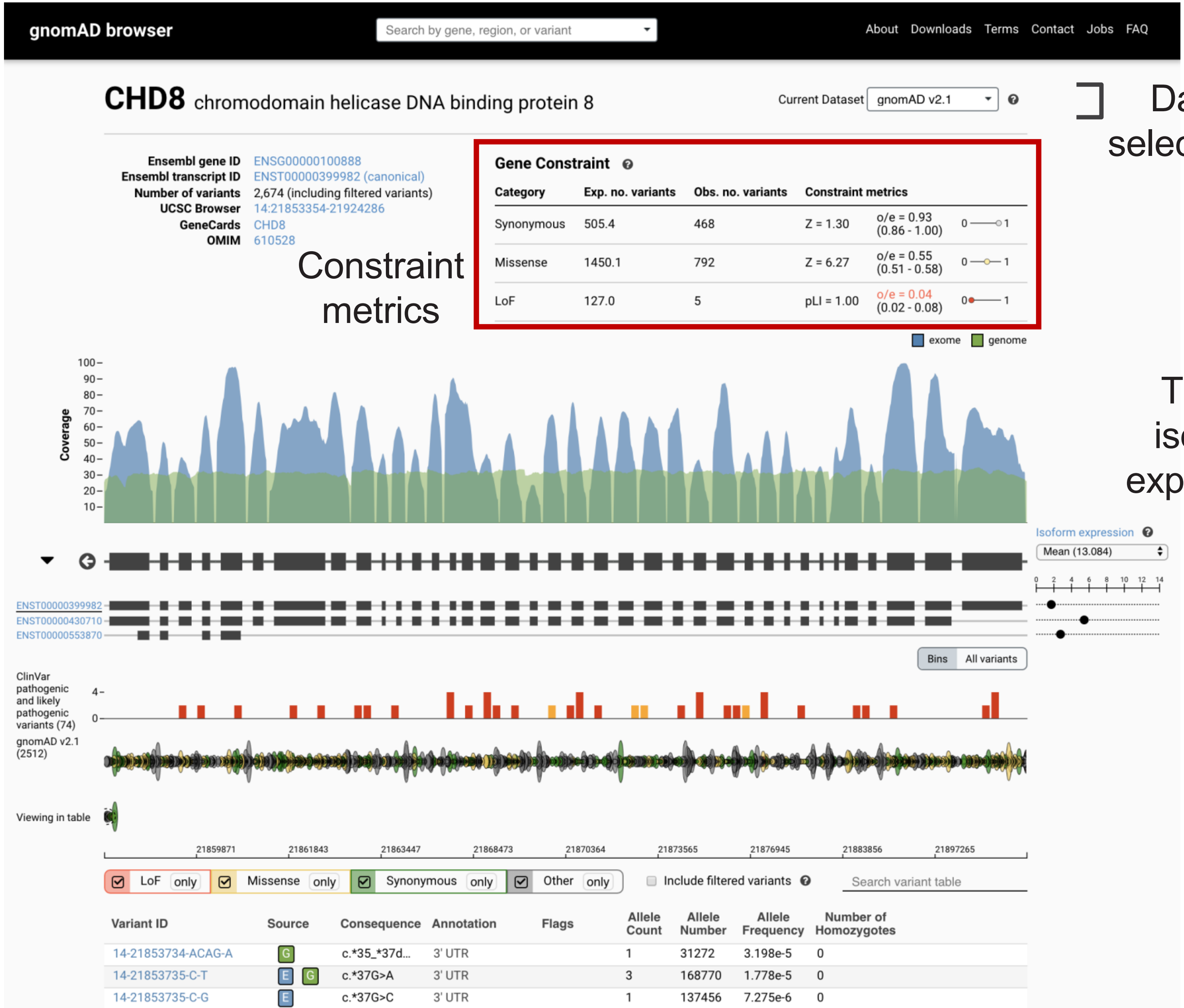
gnomad.broadinstitute.org

Matt Solomonson

Nick Watts

Gene model with transcripts

Pathogenic Clinvar Variants



gnomAD browser

Search by gene, region, or variant

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CHD8 chromodomain helicase DNA binding protein 8

Current Dataset: gnomAD v2.1

Ensembl gene ID	ENSG00000100888
Ensembl transcript ID	ENST00000399982 (canonical)
Number of variants	2,674 (including filtered variants)
UCSC Browser	14:21853354-21924286
GeneCards	CHD8
OMIM	610528

Constraint metrics

Gene Constraint

Category	Exp. no. variants	Obs. no. variants	Constraint metrics		
Synonymous	505.4	468	Z = 1.30	o/e = 0.93 (0.86 - 1.00)	0 — 1
Missense	1450.1	792	Z = 6.27	o/e = 0.55 (0.51 - 0.58)	0 — 1
LoF	127.0	5	pLI = 1.00	o/e = 0.04 (0.02 - 0.08)	0 — 1

☑ LoF only ☑ Missense only ☑ Synonymous only ☑ Other only □ Include filtered variants

Search variant table

Variant ID	Source	Consequence	Annotation	Flags	Allele Count	Allele Number	Allele Frequency	Number of Homozygotes
14-21853734-ACAG-A	G	c.*35_*37d...	3' UTR		1	31272	3.198e-5	0
14-21853735-C-T	E G	c.*37G>A	3' UTR		3	168770	1.778e-5	0
14-21853735-C-G	E	c.*37G>C	3' UTR		1	137456	7.275e-6	0

Dataset selection box

Tissue isoform expression