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Creation of a dense, public allele frequency resource

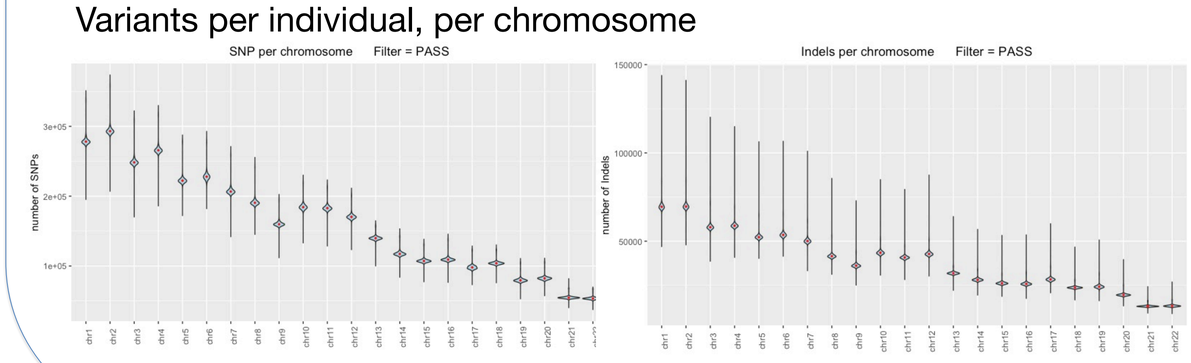
Data Available

Sequence from 59,464 individuals (release 5.1) has been analysed and 677,003,512 variants have been called on GRCh38.
Basic quality control has been applied:

Sample filtering:
- cross-contamination < 5%
- mapping rate > 75%
- mean sample coverage > 20
- insert size < 250

The variant PASS flag is set if:
- missingness < 5%
- coverage >= 10
- genotype quality >=15
- genotypes passing allelic imbalance test >= 0.25

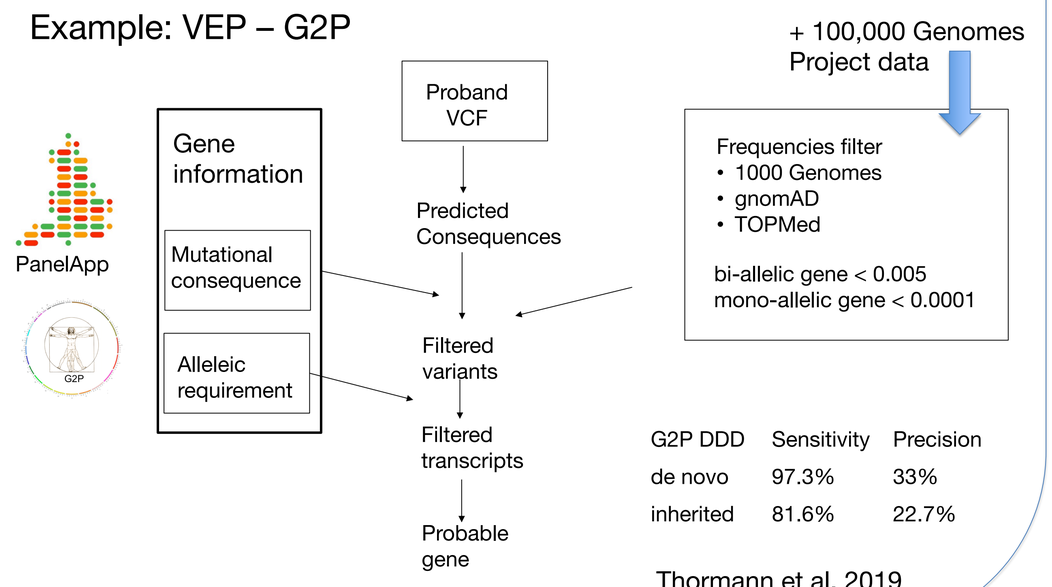
Variants per individual, per chromosome



Data Importance

The 100,000 Genomes Project will create a deep collection of population frequency data
- These data will enable an improved understanding of constraint in the genome
- Allele frequency distributions at this scale can accelerate diagnosis of rare disease

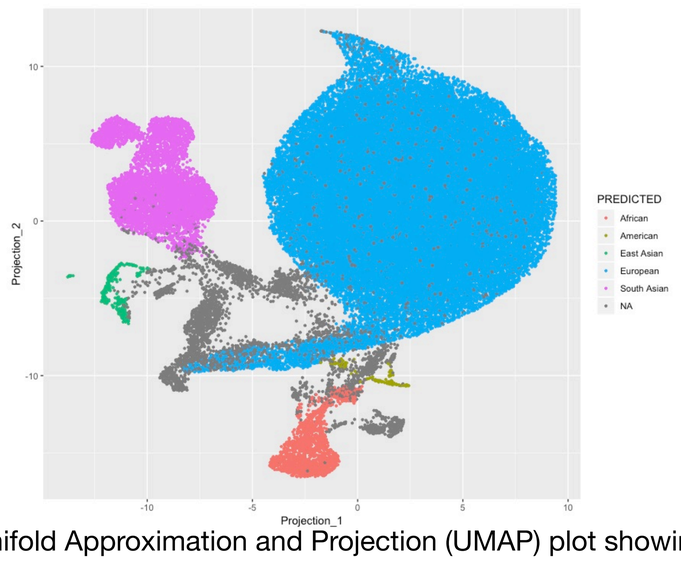
Example: VEP – G2P



G2P DDD	Sensitivity	Precision
de novo	97.3%	33%
inherited	81.6%	22.7%

Thormann et al. 2019

Ancestry prediction

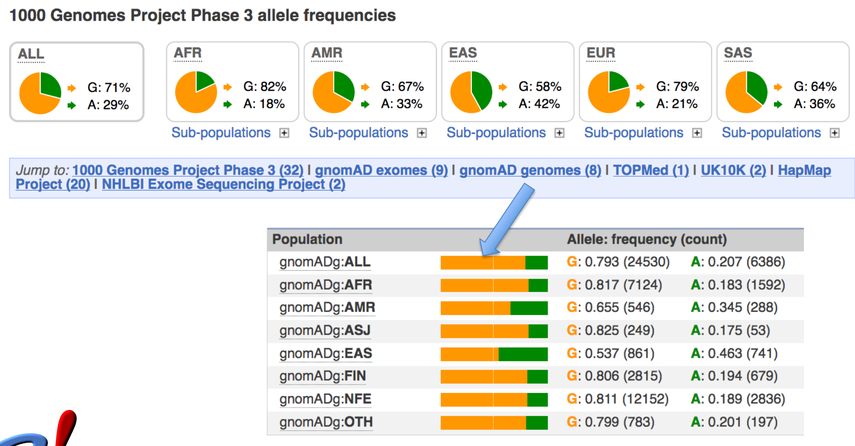


Uniform Manifold Approximation and Projection (UMAP) plot showing inferred ancestries.

Ancestries were inferred using the R-package randomForest, and data from the 1000 Genomes project (1kGP3) as the truth. The 1kGP3 study participants were split into broad ancestries (African, American, East Asian, European, and South Asian). Based on the similarity of the first 6 PCs between the 1kGP3 dataset and the 100,000 Genomes dataset, probabilities of each sample in the 100,000 Genomes dataset belonging to any one of the broad ancestries were calculated. A threshold of T=0.9 was applied for assignment. Participants below this threshold are shown in grey. For further details, see data freeze folder:
/gel_data_resources/main_programme/aggregated_illumina_gvcf/GRCH38/20190228

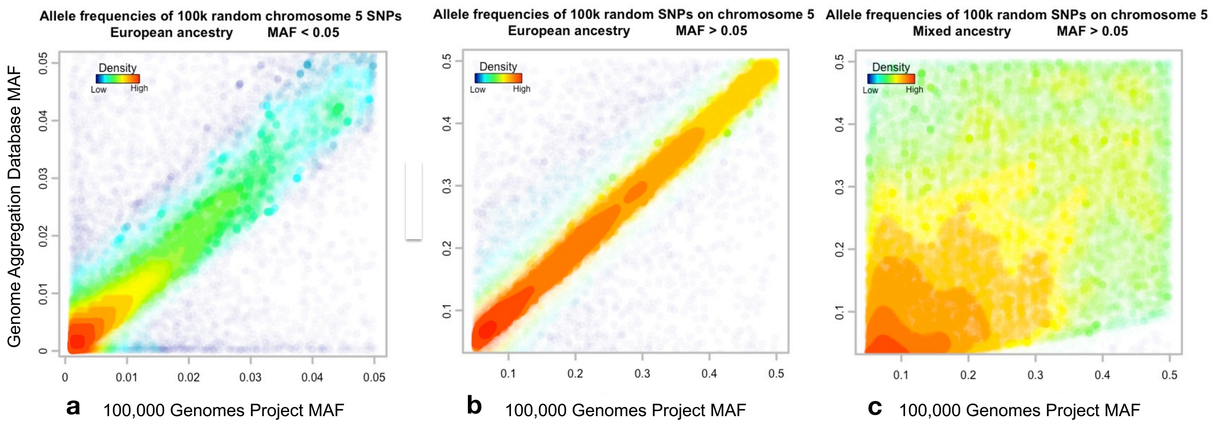
Data Distribution

- A 100,0000 Genomes Project data browser is planned
- Frequencies will be also displayed alongside other large scale data in the Ensembl browser and available in Ensembl VEP



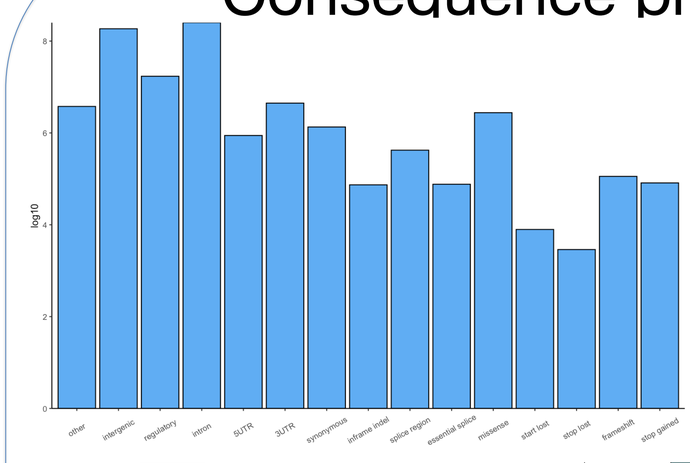
Example of current Ensembl frequency distribution views

Minor allele frequency comparison

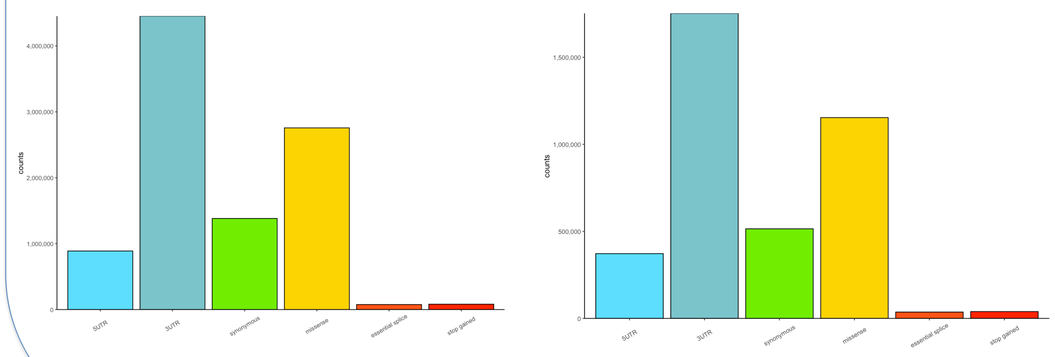


Minor allele frequencies (MAF) across cohorts, for variants with MAF below (**a**) or above (**b**) 5%, for individuals of European ancestry or between individuals of European and African ancestry **(c)**.
Every dot represents a pair of minor allele frequencies.
Colour indicates the proportion of SNPs with a pair of MAFs (red: common, blue: rare).
Data from unrelated participants was stratified by inferred ancestry
When allele frequencies across different ancestries are compared **(c)**, we see reduced concordance between the datasets as expected.

Consequence prediction



Most severe consequence per variant in the most supported Ensembl transcript per gene, as calculated with Ensembl VEP, version 98.
Passed variants only



All passed variants, major transcript consequences only.

Only singletons, major transcript consequences only.

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