Using 1000 genomes data in disease studies

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Two parallel goals in complex disease genetics

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Two parallel goals in complex disease genetics

For a given disease, can we:

1. Explain heritability (prediction/prognosis?)
2. Understand biology (treatment?)

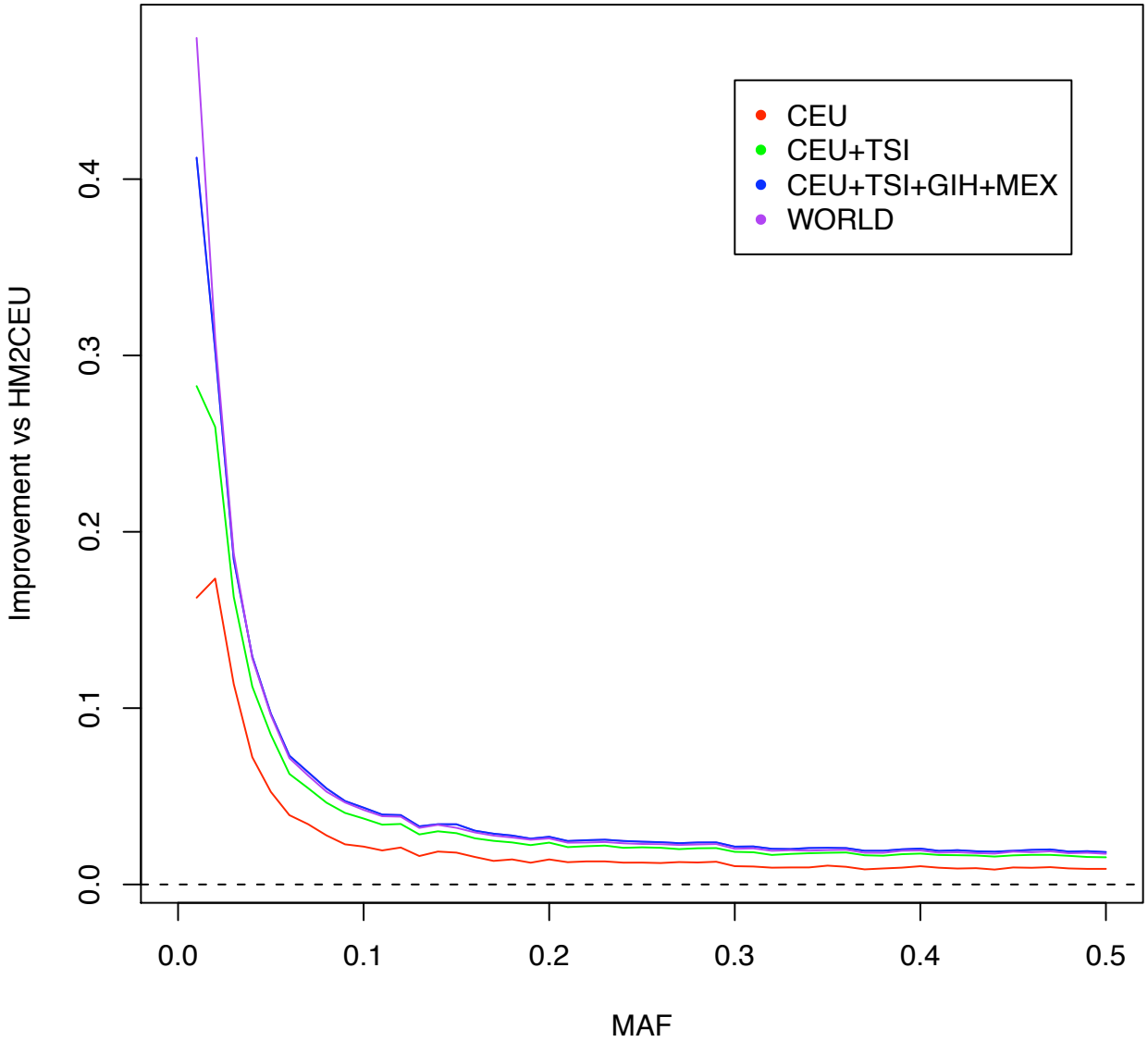
Two parallel goals in complex disease genetics

For a given disease, can we:

1. Explain heritability (imputation)
2. Understand biology (annotation)

1000 genomes data can play an important role in both these goals.

Accurate and deep reference sets are key to imputing low frequency variants



Imputation software

- IMPUTE v2 (Howie & Marchini)
  `mathgen.stats.ox.ac.uk/impute/impute_v2.html`
- BEAGLE (Browning & Browning)
  `faculty.washington.edu/browning/beagle/beagle.html`
- MACH & Minimac (Li, Fuchsberger & Abecasis)
  `www.sph.umich.edu/csg/abecasis/MACH/`
  `genome.sph.umich.edu/wiki/Minimac`

Imputation is computationally heavy duty

- Imputing into $\approx 16,000$ WTCCC samples using combined SNP/indel pilot data
- Formatting files, aligning strands, etc. can be fiddly
- IMPUTE v2 'factory default' settings
- Genome split into ≈ 600 chunks, each chunk submitted as a job to Sanger farm, each job requiring 4–6 GB memory
- Total processing time > 2 CPU years

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- 1–2 CPU hours per sample (scales approx linearly with sample size)

Pre-phasing can save a great deal of time

- Simplistically, imputation aims to match skeletal target haplotypes to more complete (in terms of variation) reference haplotypes.
- In the past, target datasets have been unphased genotype data (e.g. basic GWAS output). This requires a combination of phasing and matching, which underlies much of the computational burden.
- Phasing target data in advance (and saving the result) means imputation, and re-imputation with other references, is much faster (comparing haplotypes to each other, rather than genotypes to pairs of haplotypes).
- Implemented via flags in IMPUTE v2, BEAGLE and via Minimac for MACH.

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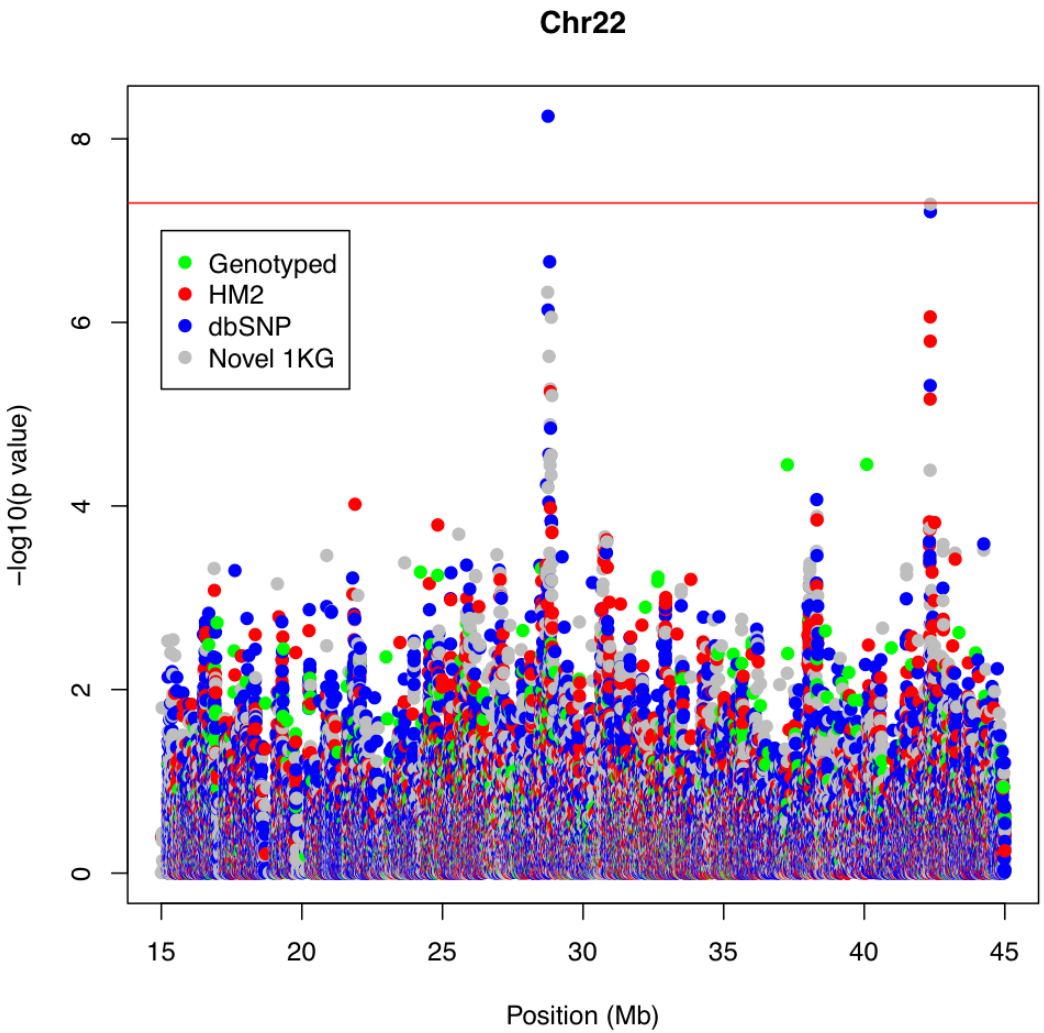
- Future: 1000 genomes complete data (2,500 samples, 30(?) million SNPs, indels, SVs). Phased releases of data integrated from all platforms (low coverage sequence, high coverage exomes, genotyping arrays, arrayCGH. . .)

Example: Crohn's disease



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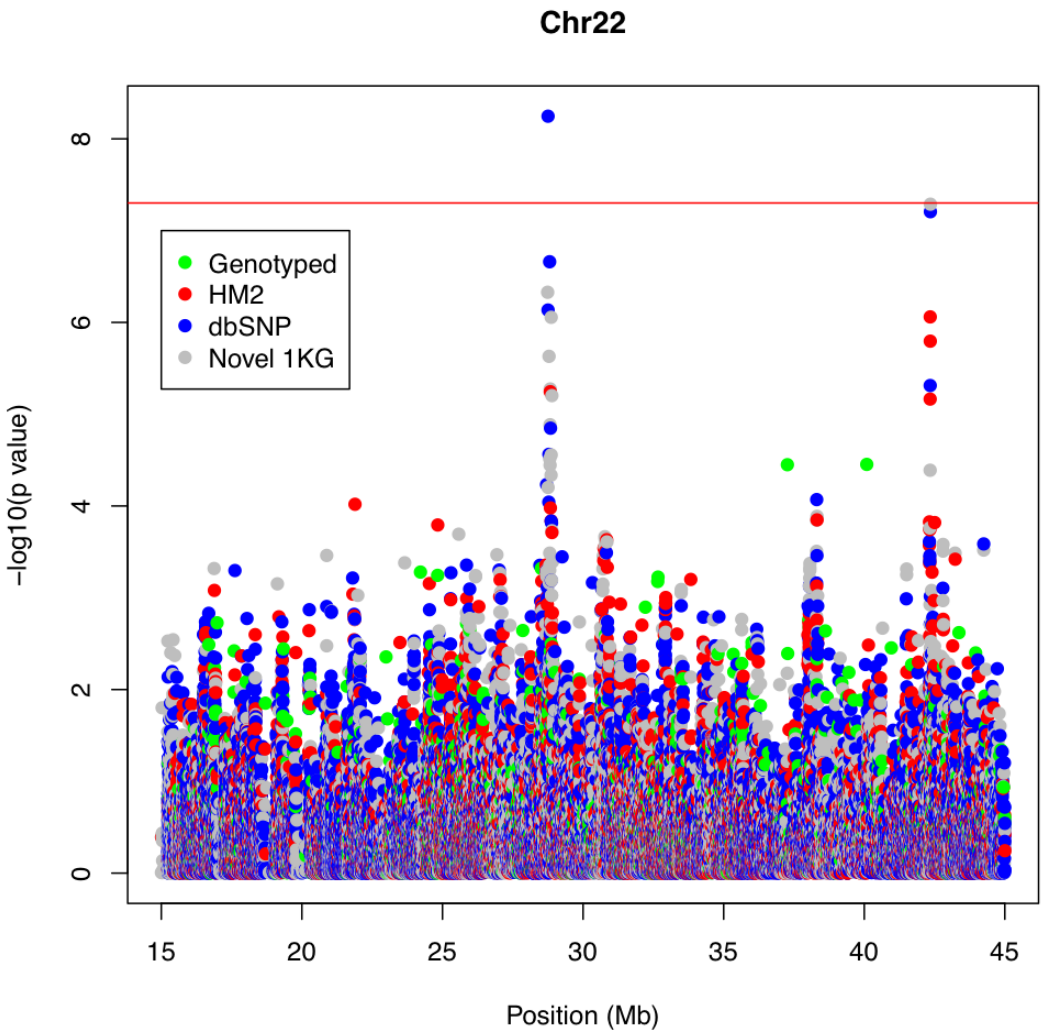

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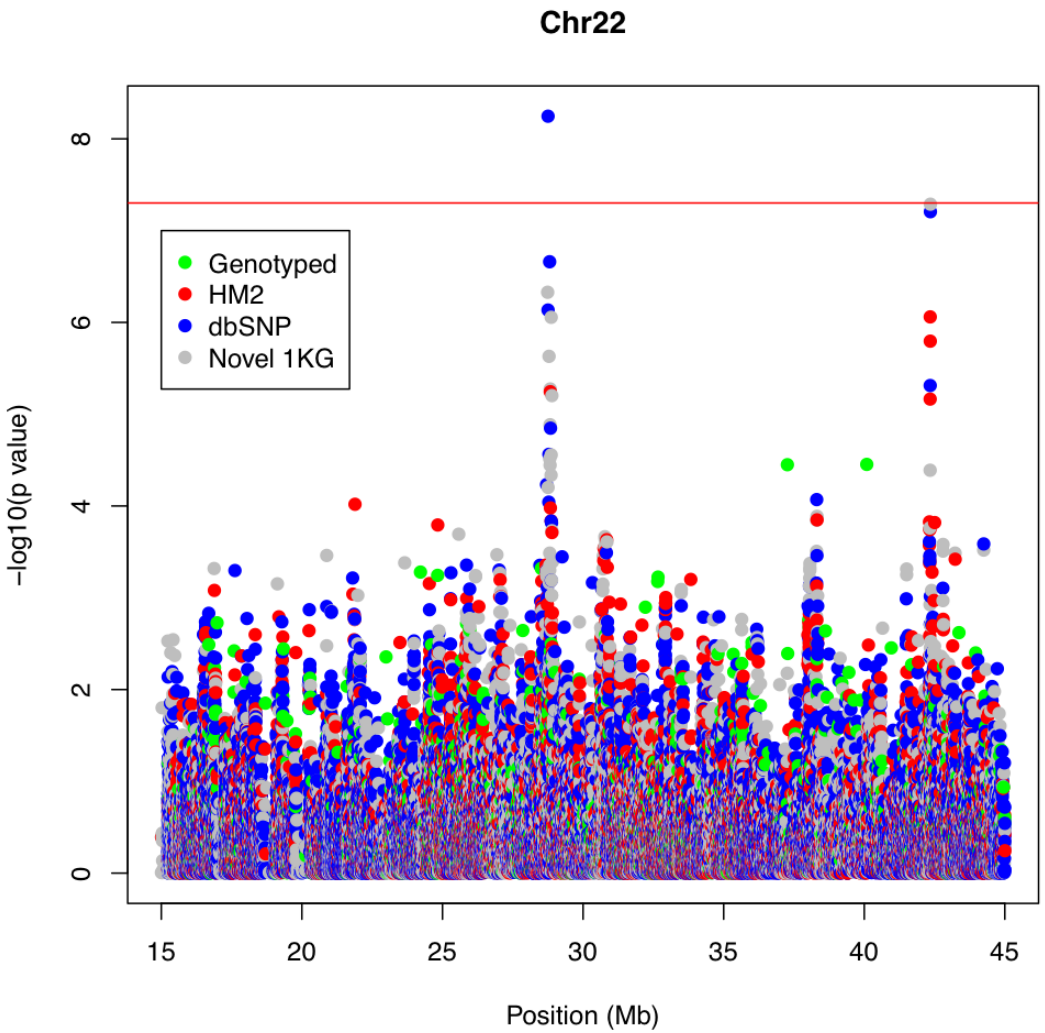

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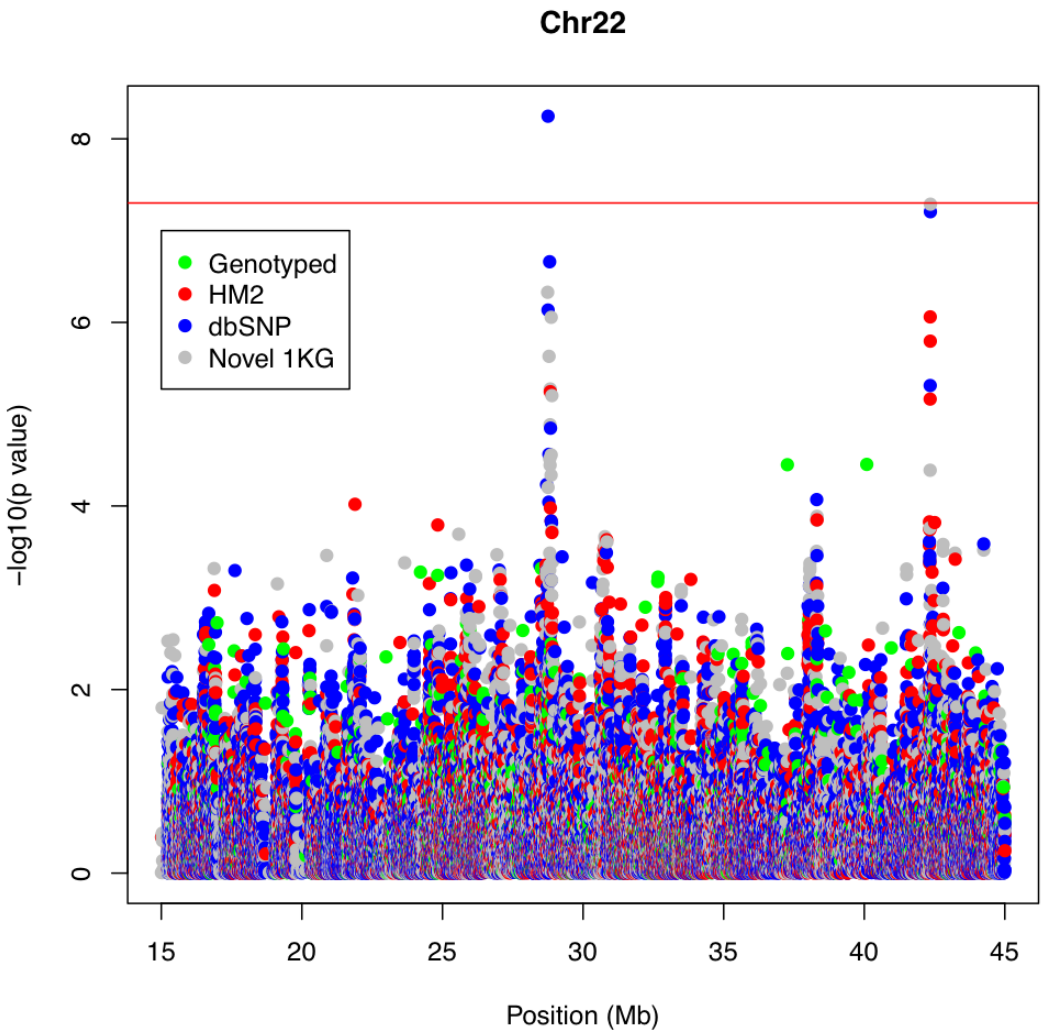

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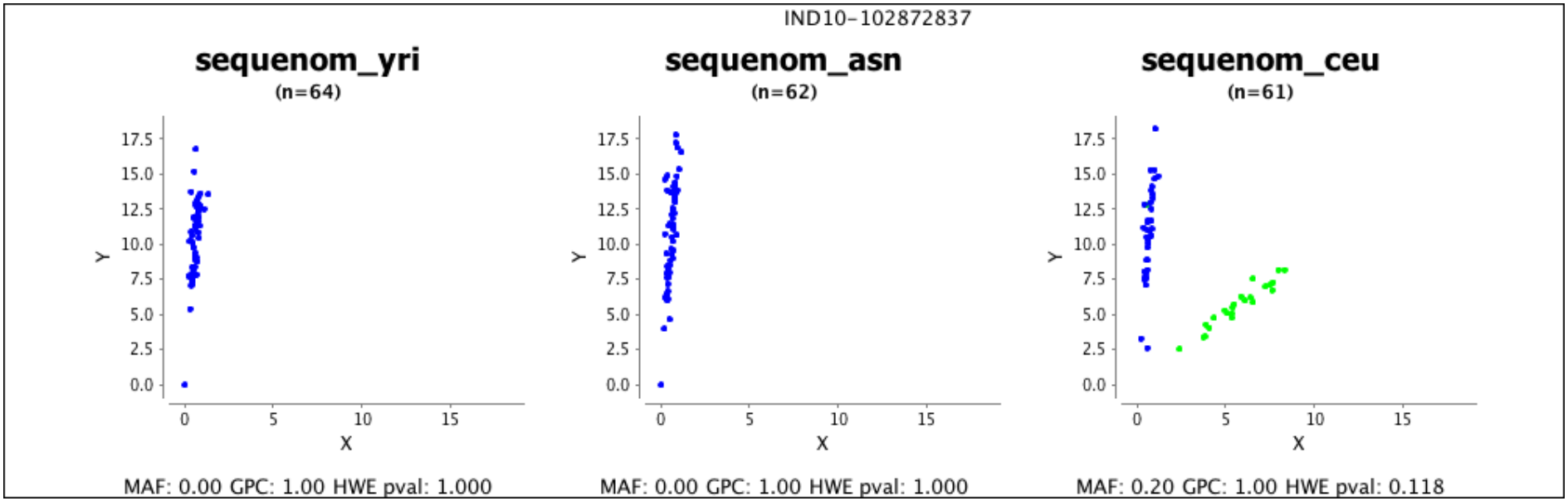
- Hit at 42 MB not supported at all in meta-analysis...

Validation and 'gold standards'



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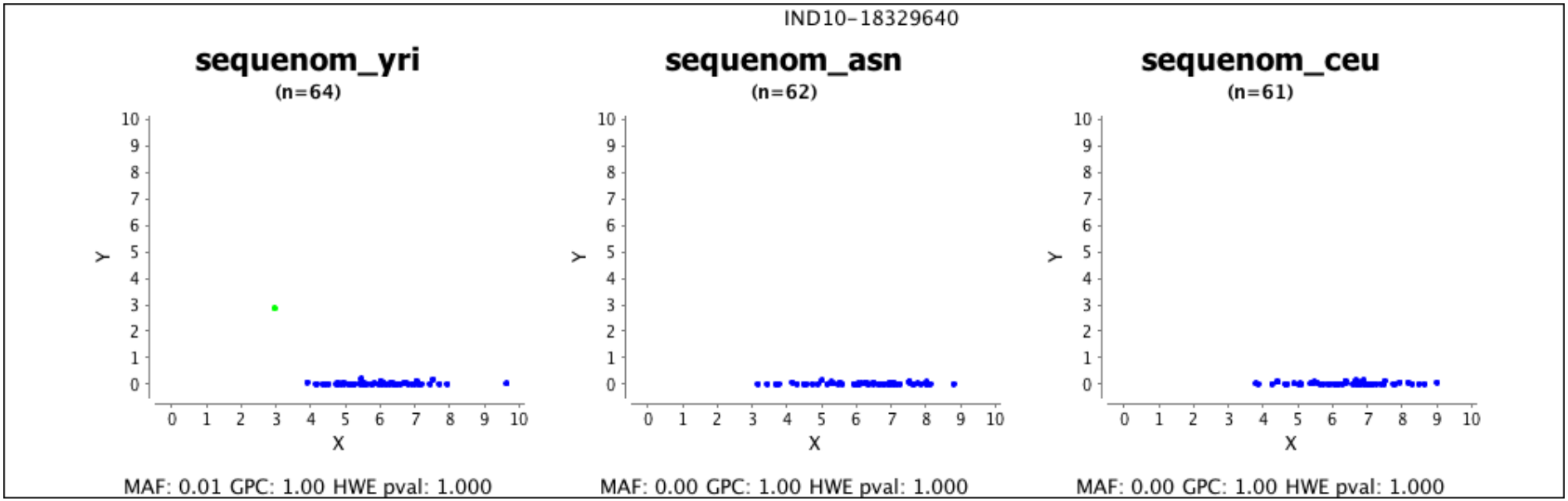

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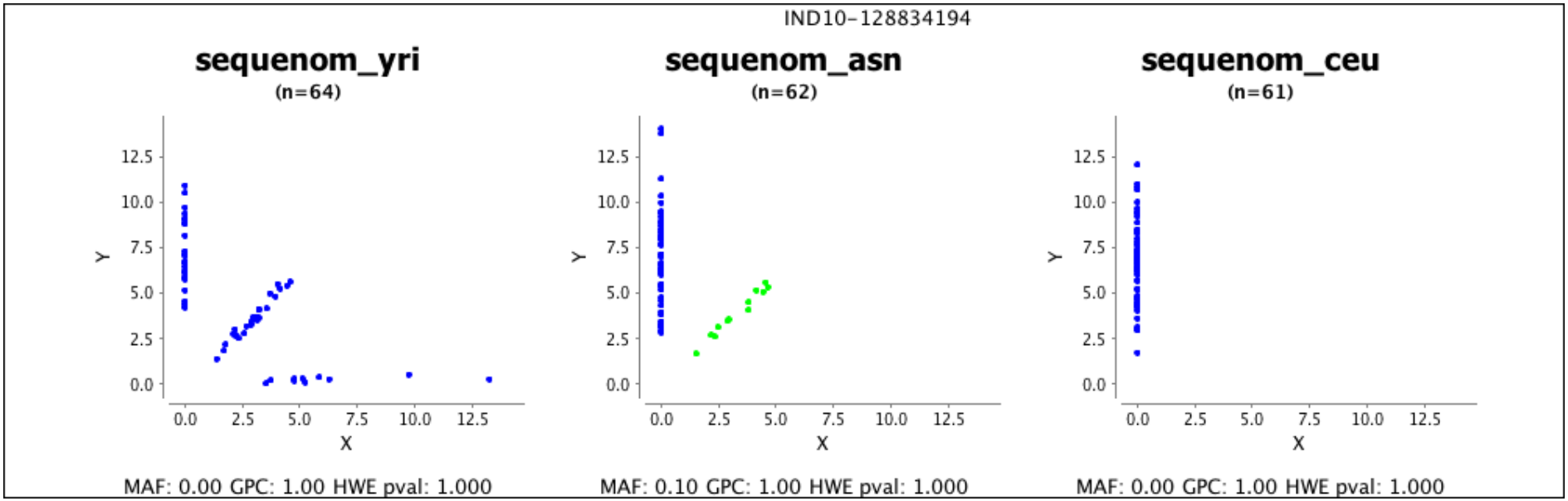

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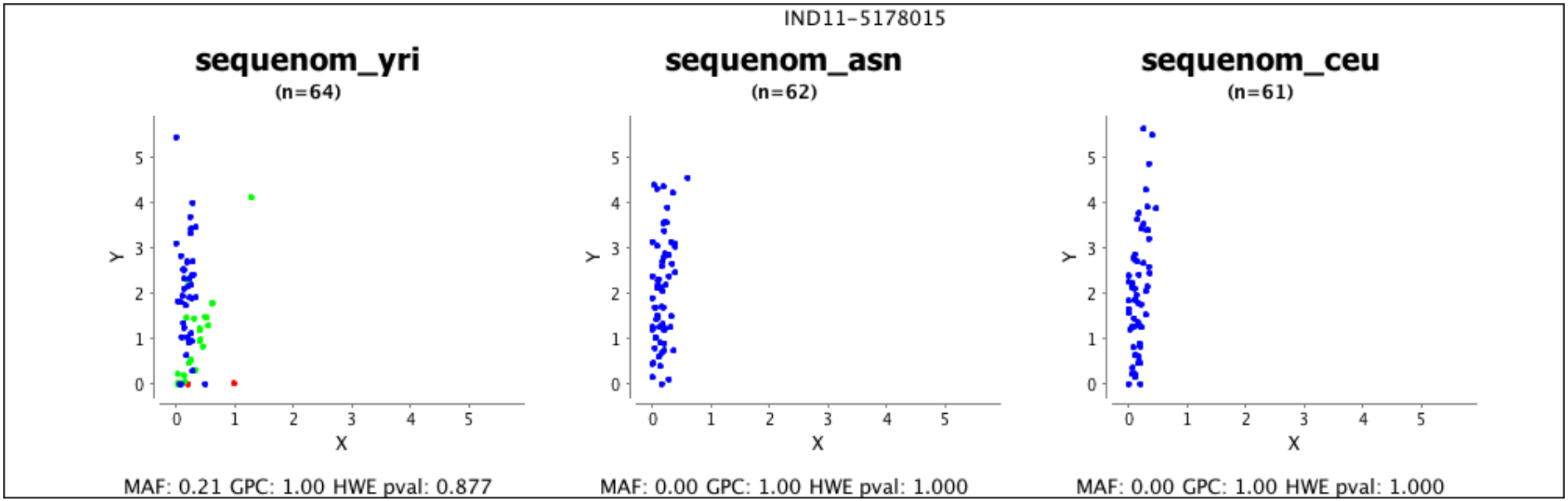
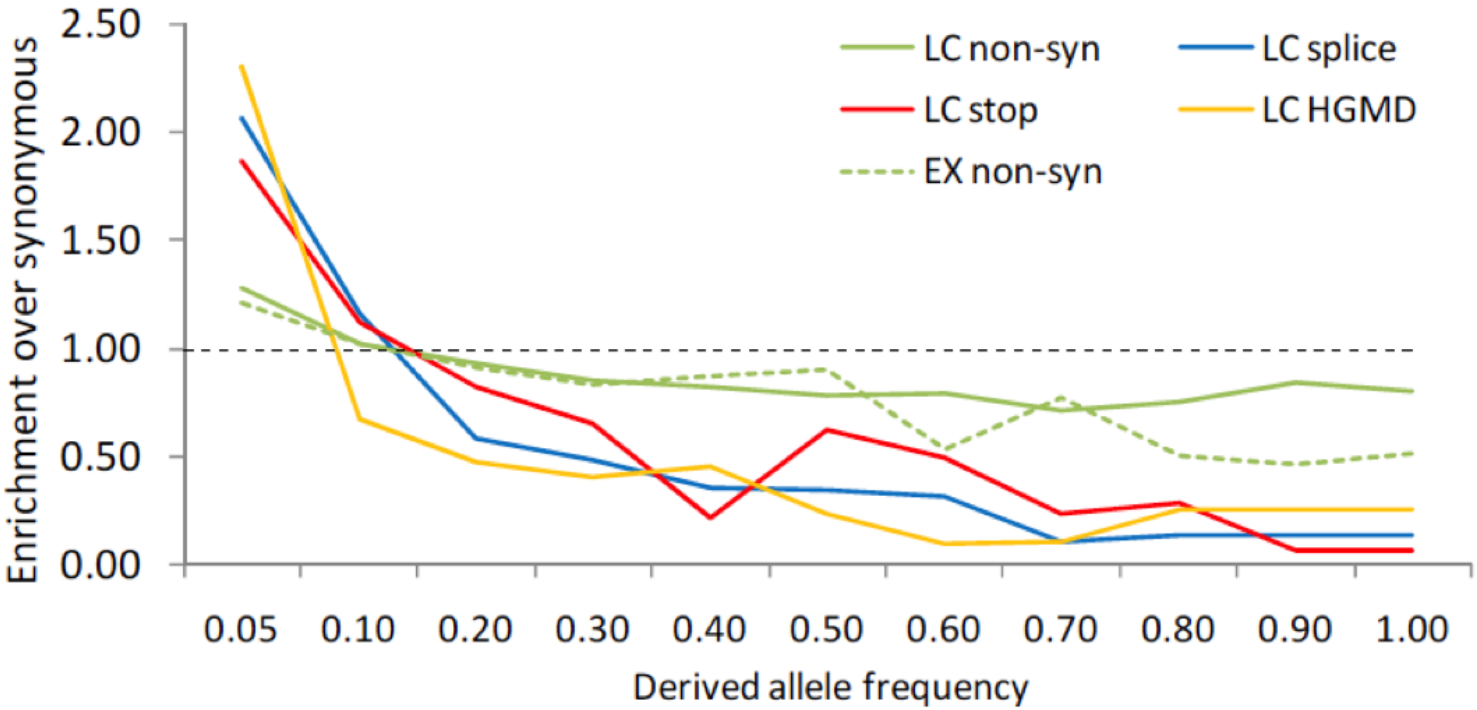


Functional annotation



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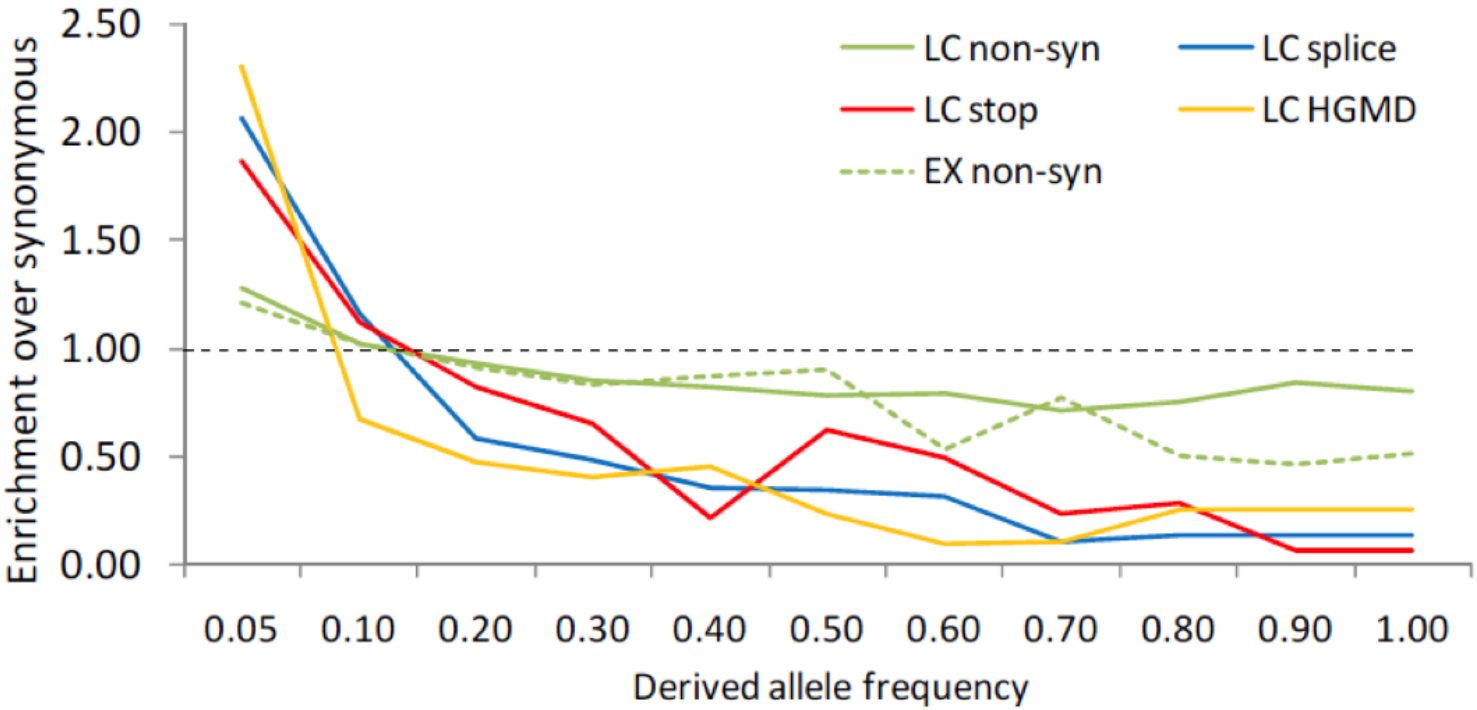

. . . $<$ 10% of GWAS hit SNPs have $r^2 > 0.9$ with a coding SNP

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- The project also enables the discovery and annotation of variants, standardization of files and development of genotyping products.
- Coming to grips with the subtleties of the data will take time and continue to evolve.

Thanks

1000 Genomes Project
Gonçalo Abecasis
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James Morris

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