Pharmacogenomics is the study and application of the genetic determinants of drug response.

To date, clinical guidelines providing treatment recommendations are available for ~70 drugs whose response is associated with variation in one or more genes.

However importantly, this variation is almost exclusively limited to common variants (minor allele frequency (MAF) ≥ 1%).

The world-leading UK 100,000 Genomes Project1 offers the opportunity to further investigate variation in genes involved in drug pharmacokinetics (PK) or pharmacodynamics (PD) – hereafter termed ‘pharmacogenes’.

The aim of this study was to comprehensively identify and describe variation in pharmacogenes observed within the 100,000 Genomes Project, and to estimate the proportion of functional genomic variation attributable to rare variation.

In total, 195 pharmacogenes from 60,221 individuals were analysed (Figure 1).

2,164,677 variants were identified: 1,978,194 SNVs (91.4%) & 186,483 indels (8.6%).

Only 2.8% of identified variants were common; 94.0% of identified variants were very rare (MAF < 0.1%), and 3.2% rare (MAF < 1% but ≥ 0.1%) (Figure 2).

The majority of identified variants were intronic and classed as modifiers; 3% of identified variants were predicted to have a high (e.g. frameshift), moderate (e.g. missense) or low (e.g. synonymous) impact on gene function (Figure 3).

Of this 3% of variants, 58% were missense, 28% synonymous, and the majority of the remainder were high impact variants (Figure 3).

Importantly, the mean number of distinct high impact variants identified per gene varied across gene classes, ranging from 24.2 variants in transporter genes to 4.8 variants in genes related to neuropsychiatric drug targets (Figure 4, Table 1).

The fraction of predicted functional variation attributable to rare variants differed extensively between genes and, in over half of analysed pharmacogenes, rare variants accounted for all identified functional variation (Figure 5).

Overall on average, each participant carried 37 putatively functional variants within the analysed gene set, of which 4 variants (10.9%) were rare.

This study found that the majority of variants in pharmacogenes are very rare.

The prevalence of high impact variants differs between gene classes, plausibly reflecting the extent of evolutionary tolerance to perturbed gene function.

The overall proportion of putative functional variation attributable to rare variants was modest but not insignificant, given that ~80% of all adverse drug reactions are ‘type A’ reactions related to excessive on-target drug action where variation in drug PK and on-target PD are key.

Importantly, the impact of rare variation on drug response is predicted to differ notably between drugs, dependent on the extent of rare variation in genes relevant to each drug.

This study will be extended to determine the extent of variation in this gene set within the somatic genome.

References


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Figure 1. Study overview

Figure 2. Overall frequency of common & rare variants

Figure 3. An overview of variant types

Figure 4. Genomic variation in select gene classes

Figure 5. Functional variation attributable to common & rare variants in select gene classes

Table 1. Variation in the number of high impact variants by gene class

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<th>Gene class</th>
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<th>Pharmacodynamics</th>
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<tr>
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<td>Mean no. high impact variants per gene</td>
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Discussion

This study used whole genome sequencing to comprehensively identify and describe variation in pharmacogenes.

The prevalence of high impact variants differs between gene classes, plausibly reflecting the extent of evolutionary tolerance to perturbed gene function.

The overall proportion of putative functional variation attributable to rare variants was modest but not insignificant, given that ~80% of all adverse drug reactions are ‘type A’ reactions related to excessive on-target drug action where variation in drug PK and on-target PD are key.

Importantly, the impact of rare variation on drug response is predicted to differ notably between drugs, dependent on the extent of rare variation in genes relevant to each drug.

This study will be extended to determine the extent of variation in this gene set within the somatic genome.