QIAGEN

Downloadable drug response variant content

Enabling design of comprehensive pharmacogenomic panels and mapping of actionable variants to patient genomes

Sample to Insight

Advances in NGS have set the stage for gaining insight into the features of an individual's genome that may influence their response to a wide range of drugs, thus leading to more effective and safer treatments. Realization of this opportunity, however, relies on having access to information about known variants associated with drug response. Such information is prevalent in the published literature, but is difficult to query and apply in this form. QIAGEN's collection of manually curated drug response variants solves this challenge, enabling open use of the data for pharmacogenomics panel design and genome annotation.

Accurate genomic descriptions eliminate ambiguity

A key challenge in assembling actionable variant annotation is to accurately identify and describe the DNA change. Pharmacogenetic effects are complex and are often described to varying degrees of detail in the published literature. Studies may refer to a variant by a common name such as CYP2D6*1 with no specific description of the DNA alteration – a practice that is common for star and HLA alleles. QIAGEN's curated variants are described by their genomic location and sequence with both hg19 and hg38 reference genomes supported. For each curated observation the phenotype is described relative to the most specific genotype description of the variant that is supported by the data. As illustrated in table 1, one study may describe drug response at the level of an allele while another study may describe it at the level of a genotype or even a haplotype composed of multiple sites of variation. Supplementary linkage disequilibrium scores identify additional variants in the region that may have the potential to contribute to the observed phenotypes.

Structured phenotype data supports rich context and evidence

Four categories of information are captured for every genotype-phenotype observation: the variant or set of variants involved, the drug that was administered, the observed response to the drug and the source of the observation – the PubMed ID of the curated reference or the curated FDA or EMA drug label. Additional layers of information are collected when present to provide additional context including the disease being treated, the patient sampling considered (counts of cases and controls), statistical measurements (p-value, odds ratio, confidence interval, relative risk, hazard ratio), patient demographics (age, sex, ethnicity, geography) as well as details of the drug treatment (dosage, number of courses) and quantitative and qualitative attributes of the phenotype. An example entry is shown in table 2.

Download access gives full freedom to operate

Having direct access to curated data is critical for bioinformatics analysis. QIAGENS's drug response variant content is made available for direct download as tab-delimited text files (.tsv format) for easy parsing and integration into internal or 3rd party pipelines and tools. Both hg19 and hg38 genomes are supported with the data delivered via three files optimized for unambiguous presentation: SNPS and Indels, Haplotypes, and Linkage Disequilibrium. Want to see an example of the file formats? Download sample files at the following URLs:

- SNPs and Indels
- Haplotypes
- Linkage Disequilibrium

Variant	Disease	Drug Treatment	Genotype	Phenotype	Phenotype details	p-value	Reference
rs1045642	Epilepsy	Carbamazepine, Phenobarbital, Pheytoin	C	Typical response rate	Frequency of corresponding allele was 41% among responders and 55% among non-responders	0.042	25121365
			T	Increased response rate	Frequency of corresponding allele was 59% among responders and 45% among non-responders		
rs1128503	BCR-ABL positive chronic myelogenous leukemia	Imatinib	C/C	Typical resistance to drug	Corresponding genotypes were 12% resistant and 37% sensitive	0.007	20204543
			C/T	Increased resistance to drug	Corresponding genotypes were 28% resistant and 44% sensitive		
			T/T	Highly increased resistance to drug	Corresponding genotypes were 60% resistant and 18.5% sensitive		
rs1128503 rs2032582 rs1045642	Acute myeloid leukemia	MAV and MAMAC protocol	C/T-G/T-C/T	Typical overall survival	34.7% of patients survived >4yrs	<0.05	12208746
			C/C-G/G-C/C	Decreased overall survival	21.5% of patients survived >4yrs		

Table 1. Examples of differing levels of genotype description

PubMed ID	24083708
Drug(s)	Cisplatin, Dactinomycin, Doxorubicin, Methotrexate, Vincristine
Genotype	T/T
Phenotype	Decreased response rate
Phenotype details	Out of 44 subjects with corresponding genotype, 18 subjects showed good tumor response
Disease treated	Osteosarcoma
Sex	Mixed
Age	9-48
Sample size	208
Cases	44
Source used for genotyping	Retrospective study
Study design	530
Treatment	Sample consists of osteosarcoma patients who were treated preoperatively with intravenous 25-30 mg/m(2) of adriamycin for three courses and one day, 14 mg/m(2) methotrexate for four courses and one day, and intra-arterial 35 mg/m(2) of cisplatin for three courses and three days. However, the adjuvant chemotherapy after surgery included 10 g/m(2) methotrexate for one day, and alternate cycles of 0.45 mg/m(2) cisplatin or actinomycin D and 1.5 mg/m(2) vincristine for one day. The adjuvant chemotherapy was used for at most 48 weeks.
OR	2.46
CI	1.21 - 5.74
Statistical measurement	Significance is based on logistic regression analysis

Table 2. Sample entry for rs1128503, Chr7:87550285

Statistics

Variants	17,721
Genotype-phenotype observations	139,451
Genes	7,027
Drugs	1,387
Diseases	530
References	6,867

The 17,721 variants are distributed across the following major disease areas:

Cardiovascular Diseases	1793
Digestive System Diseases	1379
Hemic and Lymphatic Diseases	1259
Immune System Diseases	5788
Mental Disorders	2725
Musculoskeletal Diseases	3381
Cancer	5714
Nervous System Diseases	1058
Skin and Connective Tissue Diseases	4476

Observations are categorized by the following types of evidence:

Molecular and Cellular Functional Assays	3190
Pharmacokinetics	29831
Pharmacodynamics and Drug Response	87423
Clinical Outcome	19044