TARGET VALIDATION

Genetic information adds supporting weight

> compounds whose target–indication pairs have genetic support are twofold more likely to reach approval

Selecting a target with genetic data supporting its role in a relevant disease could double the chance of a drug's success in clinical development, according to a recent paper in *Nature Genetics*.

The authors, including many from GlaxoSmithKline, started by identifying gene–trait combinations from genetic and drug databases. Data from the Online Mendelian Inheritance of Man (OMIM) and the Genome-Wide Association Studies Database (GWASdb; a publically available database that incorporates information from the US National Human Genome Research Institute GWAS Catalog and other sources) were matched with the most-specific medical subject heading terms applicable to identify 16,459 gene–trait combinations. The authors also generated 19,085 drug target–indication pairs using data from the commercially available Informa Pharmaprojects database.

Matt Herring/Alamy

The authors found that target genes for approved drugs were significantly enriched among genes associated with variations in human traits. This observation could imply that drug-responsive proteins tend to be encoded by genes that, when altered, can induce phenotypic changes.

The authors then tried to match these gene–trait and target–indication pairs to pinpoint drugs whose target genes have a genetic association tied to the same or a similar trait. Of 395 approved drug indications, 239 (61%) had at least one genetic association with a similar trait. Focusing on the 158 of these indications for which there were at least 5 genetic associations with a similar trait (suggesting good coverage of the trait in genome-wide studies), they found that of the 820 target genes for these indications, 67 (8.2%) also had a genetic association with a similar trait.

Notably, substantial variation was observed between indication types. For example, over 30% of target–indication pairs for musculoskeletal, metabolic or blood disorders had a genetic association with a similar trait, whereas little or no genetic support was found for drugs approved to treat diseases of the digestive system, the eye or cancer.

The authors hypothesized that if the existence of supporting genetic information is predictive of a drug's success, then the percentage of target–indication pairs with genetic support should increase with stages along the development pipeline. Indeed, for drugs that failed to progress beyond Phase I clinical trials, only 2.0% of drug targets had genetic support, and this fraction increased in a stepwise manner through Phase II (3.7%), Phase III (5.9%) and approval (8.2%). The authors estimate that compounds whose target–indication pairs have genetic support are twofold more likely to reach approval than those without genetic support; the overall approval rate for drugs that enter Phase I is less than 20%.

A genetic resource that integrates all known genetic associations to identify potential causal disease pathways could be an important tool for drug discovery and development. For example, using it to prioritize projects could help reduce attrition rates in clinical trials.

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ORIGINAL RESEARCH PAPER Nelson, M. R. *et al.* The support of human genetic evidence for approved drug indications. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3314 (2015)
FURTHER READING Plenge, R. M., Scolnick, E. M & Altshuler, D. Validating therapeutic targets through human genetics. *Nat. Rev. Drug Discov.* **12**, 581–594 (2013)