GEN Biotechnology
Volume 3, Number 3, 2024

DOI: 10.1089/genbio.2024.0022

GEN Biotechnology

VIEWS & NEWS

Risky Business: Human Genetics Improves Drug Development Success

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A new study in* Nature *by Matt Nelson and colleagues, updating work published 9 years ago, provides compelling evidence that human genetics is key to improving drug development success rates.

Drug development is a risky and expensive business. Less than one out of ten drugs that enter clinical development succeed. An analysis by Biotechnology Innovation Organization (BIO) of data on 9,704 drug programs from 1,779 companies between 2011–2020 found that the odds of a drug candidate successfully transitioning from phase I to II, III and finally regulatory approval was a meager 7.9%.[1] Such a poor success rate forces drug developers to cast a wide net, improving their odds of landing on at least one successful drug that will offset the cost of all the failures. As a result, the cost of successfully developing a new drug has ballooned into the range of billions of dollars, which includes the costs involved in the development of many failed drugs.[2] With such a precarious business model, any refinement in the drug development processes that can improve the success rate even by a few points is highly valued.

Drugs fail mainly for two reasons: lack of efficacy and adverse effects.[3] Preclinical animal models often fail to recapitulate the human physiology, resulting in poor efficacy or unexpected adverse effects during the clinical trials.[4] Of course, the most accurate animal models to study human disease are humans themselves.

Human genetics can help study drug efficacy and adverse effects of certain drugs before conducting expensive clinical trials. For example, a drug targeting protein X designed for the treatment of disease A is more likely to succeed, if there is evidence that a naturally occurring genetic variant in the gene encoding X is associated with disease A in the general population.

A proof of concept of this hypothesis was first described in 2015 by an industrial research team led by Matt Nelson, who was then leading statistical genetics at GSK.[5] Through a systematic analysis of phase transition success rates of drug programs extracted from a commercial pharma database, Nelson et al. reported that drug-indication pairs with genetic evidence in the literature (i.e., a genetic association linking the drug target gene to its disease indication) were twice as likely to succeed than those without. These findings meant that by including human genetics evidence in the decision-making process to prioritize drug programs for clinical trials, a drug company could double their success rate from the base rate of 10% to 20%. The Nelson et al. article has had a significant impact on the drug development field over the past decade, inspiring many companies to invest in human genetics.[6]

Recently, Nelson (now the CEO of Genscience) and colleagues published in *Nature* a revision to their 2015 report that further refines the impact of human genetics on clinical success.[7] In the new analysis, Minikel et al. extracted information on nearly 30,000 drug-indication pairs from a proprietary database. For 7.3% of these drug-indication pairs, the authors were able to identify human genetic evidence linking the drug targets with their disease indications based on either common (Open Targets database, Genome-wide association studies (GWAS) catalog etc.) or rare variants (Online Mendelian Inheritance in Man (OMIM)).[8–10] Across all phases of clinical development, the authors found more drug-indication pairs with genetic support compared with their earlier analysis, which is to be expected as the human genetics literature has grown since 2015.

Raising the Odds

In the revised analysis, the authors find that the odds of a successful transition from phase I to regulatory approval for drug programs with genetic evidence is 2.6-fold higher compared with those without (Fig. 1). This is a 30% increase in effect size compared with their 2015 analysis, thanks to the expanded human genetics databases. The revised analysis suggests that continued investment in human genetics research will further improve the power of human genetic evidence to predict drug programs' success.

Interestingly, almost 93% of the extracted drug-indication pairs did not have supporting evidence in the human genetics literature. However, absence of evidence does not mean evidence of absence. The reason that many of these drug-indication pairs did not show genetic support may be because related genetic studies have not been conducted yet or were conducted in small sample sizes. Hence, such pairs may eventually change groups when new genetic evidences surface, thereby further increasing the effect

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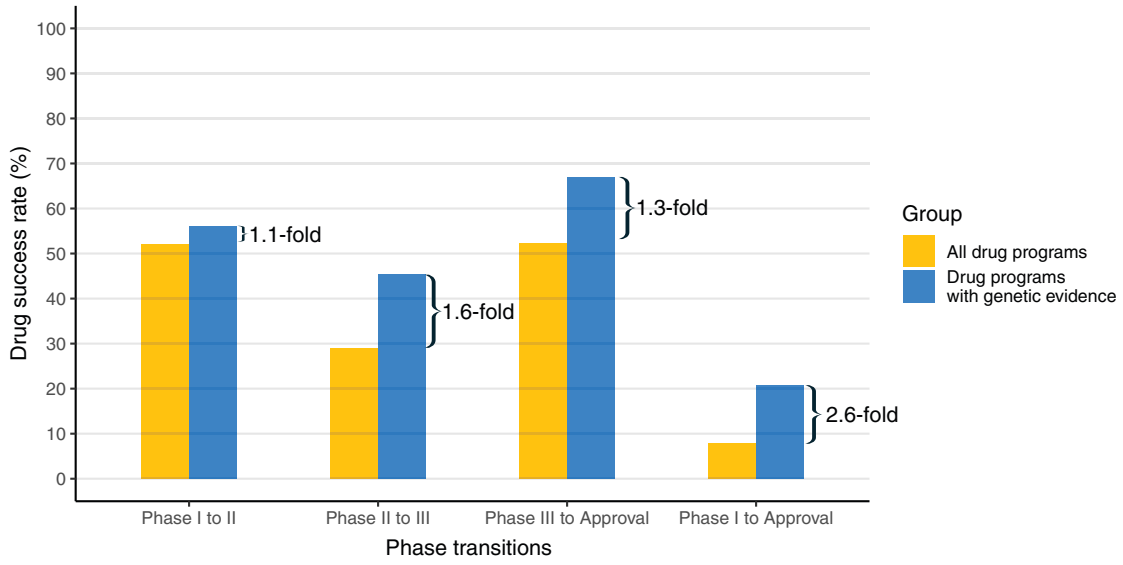

FIG. 1. Comparisons of phase transition success rates of drug programs with and without genetic support.
Base success rates are based on data from the 2011–2020 report of new clinical development success rates by BIO.[1] The phase III to approval rate was calculated by multiplying phase III to New Drug Application (NDA)/Biologic License Application (BLA) by NDA/BLA to approval. The Phase 1 to approval rate was calculated by multiplying across all rates (phase I to II, phase II to III and phase III to approval). The success rates of drug programs with genetic support are based on relative success (rs) estimates from Minikel et al.[7] The success rates are calculated by multiplying base rate by relative success estimates shown in text.

size of association of human genetic evidence with drug success.

The authors also studied the value of genetic support to improve drug success across different groups of drugs stratified by various criteria such as database resource (Open Targets vs. OMIM), minor allele frequency (MAF), genetic effect size, year of publication etc. Through these stratified analyses, the authors address one of the popular criticisms in the GWAS field—the value of common variant associations with small effect sizes to drug development. Interestingly, in doing so, the authors also end up highlighting a key challenge of using common variants to map genes to traits.[11]

Nelson and colleagues show the increase in success rate in drugs with genetic support is statistically indistinguishable across different strata of MAF bins or effect size bins. Thus, both the common variants with small effect sizes and rare variants with large effect sizes seem to predict drug success similarly. However, when comparing Open Targets and OMIM databases, the authors found a larger effect size for the latter. They attributed this difference mainly to the current challenges in confidently assigning causal genes to common variants identified by GWAS.[12]

Unlike rare coding variants, which directly pinpoint causal genes, common noncoding variants (the majority of GWAS-identified variants are noncoding) do not pinpoint causal genes. Open Targets maps genes to GWAS variants using multiple layers of evidence such as physical distance, expression quantitative loci association, and epigenetic annotations. It calculates a locus to gene mapping (L2G) score, reflecting the confidence in the gene assignment.[8] When stratified according to different ranges of L2G score, the authors find drug-indication pairs with genetic support with higher L2G score had larger effect sizes compared that with lower L2G score, highlighting the impact of accurate knowledge of causal gene in drug success prediction.

Cautionary Tale

While the revised estimates strengthen the much-appreciated impact of human genetics on clinical success, the authors caution against concluding that identification of an association between gene and disease implies that the gene is a good drug target. This is certainly not the case. Today, GWAS are typically performed using hundreds of thousands of samples, spewing out hundreds if not thousands of associations. Identifying which of these associations hold good drug targets remains an unsolved challenge. The authors' analysis addresses the likelihood of success of a drug program with genetic support, not the likelihood of a gene with a disease association to become a successful drug target.

Minikel et al.'s work should be interpreted in the light of few limitations such as hindsight and selection biases. Both their present and the past analyses were retrospective in nature, where they draw reasons on past successes. Many factors could have influenced why successful programs often had supporting genetic findings in the literature, for example, publication bias.[13]

Successful drug targets or their indications may have been the ones that were popularly studied, hence there is a high likelihood that there is a supporting published genetic study. A prospective study employing a randomized controlled trial would be an ideal approach but unrealistic. However, real world experiences of

drug companies implementing genetics-based drug target prioritization should come to light in the near future. Hopefully, such experiences will offer further confirmation on the true impact of human genetics on clinical success.

Author Disclosure Statement

The author is an employee of Regeneron Pharmaceuticals, Inc., a commercial biotechnology company.

Funding Information

No funding was received for this work.

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