provides an example of antibodies that use binding domains that have intermediate affinities, highlighting the potential effect of affinity for maximizing the responses generated with agonist antibodies[8].

Christoph Wülfing is at the School of Cellular and Molecular Medicine, University of Bristol, Bristol BS8 1TD, UK. **Simon J. Dovedi** is in Oncology R&D, AstraZeneca, Cambridge CB21 6GH, UK. e-mails: christoph.wuelfing@bristol.ac.uk; simon.dovedi@astrazeneca.com

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Genetics

Contribution of rare variants to complex traits

Luke M. Evans & Pamela N. Romero Villela

An analysis of rare genetic variants reveals that they influence human traits through similar biological pathways to common ones. The work deepens our understanding of how this type of variant affects complex traits. **See p.492**

Our understanding of the genetic mutations that affect complex human traits — such as height, smoking-related behaviour or the risk of diabetes — has been vastly broadened by genome-wide association studies (GWASs). But such research has focused largely on associations between traits of interest and variants that are common in the human population. Rare variants pose challenges to GWASs, because they can be studied using only large samples and in-depth genetic information, and can be more strongly confounded by non-genetic factors than can common variants, increasing the chance of spurious findings[1]. Until now, therefore, researchers have been unable to assess accurately whether rare variants contribute substantially to complex traits. On page 492, Weiner *et al.*[2] introduce a new approach to address this question. They find that, although rare variants account for a much smaller proportion of heritability than do common variants, they act through the same genes and biological pathways.

GWASs can reveal the 'single nucleotide polymorphism (SNP) heritability' of a given trait — that is, the portion of variability in the trait that is attributable to genetic variation (with many small effects from individual common variants acting cumulatively). For example, data indicate that the SNP heritability for human height is around 50–60% among people of European descent[3]. GWAS data can be further analysed by partitioning how different functional categories — such as enhancer elements that regulate gene expression, or genes that are specifically expressed in connective tissues — contribute to this heritability[4], and assessing to what extent genes influence multiple traits (a phenomenon called genetic correlation)[5]. Such analyses can tell us much about the biology underlying the disease or trait being studied, from finding relevant molecular pathways and cell types to revealing the role of natural selection in shaping the trait.

Rare variants are often assessed through burden tests, which give each individual a burden score on the basis of how many rare, protein-altering variants that person carries in a gene. The burden score is then related to the risk of developing a given disease[6]. Burden tests can reveal the degree to which rare variants in each gene of interest alter disease risk, but Weiner *et al.* took a different tack, developing a genome-wide burden test. This test uses a statistical approach called a regression-based framework to estimate the total proportion of trait variance attributable to rare variants — a value that the authors called burden heritability.

The authors used their framework, named burden heritability regression (BHR), to analyse the contribution of rare variants to 22 complex traits, including height, alcohol consumption and cholesterol levels. They analysed nearly 400,000 exomes (the protein-encoding regions of the genome) from people whose data had been deposited in a large biomedical repository called the UK Biobank. They found that, on average, the burden heritability was only 1.3% — significantly less than SNP heritability (at a median of 13%). Most of this heritability was due to ultra-rare variants (those with frequencies of less than 0.001%) that prevent a gene from functioning.

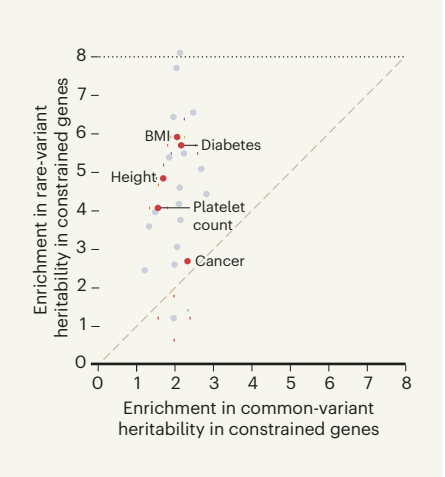

Figure 1 | How different types of genetic mutation contribute to complex traits. A combination of rare and common genetic variants act together to affect complex traits, such as height or risk of diabetes. Weiner *et al.*[2] developed a statistical analysis specifically to assess the total proportion of trait variance explained by rare protein-coding variants for 22 complex traits across the human genome. They found that, compared with common variants, rare variants associated with the 22 traits were more strongly enriched in evolutionarily constrained genes (in which mutations are more likely to prevent function than in less-constrained genes). Numbers indicate how much more of a trait's heritability is attributable to variants in constrained genes than expected on the basis of their frequency in the genome (nearly six times more for rare variants affecting body-mass index (BMI), for instance, and only about two times more for common variants affecting BMI). (Adapted from Fig. 4b of ref. 2.)

Next, Weiner and colleagues extended their analysis to partition the burden heritability into functional categories and to assess the genetic correlation between rare and common variants and between traits. They found that rare and common variation affect the same cell types and pathways. Furthermore, genetic correlations between traits are similar for both rare and common variants. However, the authors found that burden heritability is concentrated in fewer genes than is common-variant SNP heritability. Furthermore, these genes were more strongly evolutionarily constrained (less tolerant to disruption of function) than were those in which common variants cluster (Fig. 1). These findings suggest a fundamental difference between common and rare variation — the effects of common variants are spread throughout the genome, but rare variants that affect these traits are

concentrated in a limited number of genes.

BHR has several notable advantages over existing approaches to assessing heritability, functional partitioning and genetic correlation. First, it is computationally much more tractable and efficient than are existing methods. Second, it uses only summary statistics, not individual-level genetic data. Summary-based analyses have been transformative in complex-trait genetics[7], in part because they avoid privacy concerns for study participants and so can be shared more easily by researchers.

The method also seems to be largely robust against issues commonly seen in rare-variant genetic analyses, such as population stratification (in which some genetic variants are more common in some groups than in others, and thereby are erroneously found to be associated with a trait) and confounding environmental factors. As such, BHR seems to be a practical and robust method that can produce relatively unbiased estimates of the degree to which rare variation affects complex traits.

Weiner and colleagues' findings also come with caveats. For instance, the authors analysed only individuals of European ancestry, owing to sample-size limitations. Given that rare variants can be ancestry-specific[8], analysis of other ancestry groups is warranted. BHR assesses only protein-coding variants, but mutations in non-coding regions can have functional consequences, too[9]. BHR assumes that each gene acts independently, but interactions between genes carrying rare variants might also affect biological processes[10]. And the role of rare and common variation surely differs between different traits. What factors or evolutionary processes determine the contribution of rare or common variants to different traits, and why?

One more factor that could complicate the interpretation of the results is assortative mating — when individuals mate with others who have similar trait measurements, human height being a classic example[11]. Assortative mating is known to bias estimates of heritability and genetic correlation[12], and its impact on BHR-based estimates has yet to be fully evaluated.

Weiner and colleagues' study indicates that rare variants will contribute relatively little to heritability of disease at the population level. But these rare variants might still be valuable to consider when it comes to developing treatments. In support of this idea, the evolutionarily conserved genes in which rare-variant effects tend to cluster often encode proteins that can be targeted by drugs.

Although exciting, the potential of Weiner and colleagues' findings to translate to the clinic remains speculative for now. But there is no need to speculate over the importance of their work to basic biology — the authors have clarified some fundamental aspects of complex-trait genetics.

Luke M. Evans and **Pamela N. Romero Villela** are at the Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, Colorado 80303, USA. **L.M.E.** is also in the Department of Ecology and Evolutionary Biology, University of Colorado Boulder. and **P.N.R.V.** is also in the Department of Psychology and Neuroscience, University of Colorado Boulder.
e-mails: luke.m.evans@colorado.edu; pamela.romerovillela@colorado.edu

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Quantum physics

Quantum avalanches wipe out the effects of disorder

Lea F. Santos

Experiments on ultracold atoms reveal that disorder doesn't stop a quantum system of interacting particles from reaching thermal equilibrium. Instead, small thermalized regions ripple like an avalanche through the whole system.

When electrons move through a disordered material, they zigzag between imperfections. If there is enough disorder, the electrons can become trapped, inhibiting the material's ability to conduct electricity. This phenomenon is known as Anderson localization, and it was proved to be true for any strength of disorder in a one-dimensional system of wave-like particles, such as electrons[1], as long as they don't interact with one another. The picture changes when they do interact — a case known as many-body localization, which is still a subject of debate. Many-body localization arises only when the strength of the disorder is greater than that of the interactions. Even then, it has been proposed that small regions of weak disorder can accidentally appear and avalanche through the system to destroy the localization[2–7]. Writing in *Nature Physics*, Léonard *et al.*[8] demonstrate that this is indeed the case in a system in which ultracold rubidium atoms mimic particles moving through a disordered solid.

The experiment was performed in an optical lattice, which is a system that resembles a solid crystal. It is engineered by using intersecting laser beams to create a spatially periodic pattern of peaks and valleys in energy — the lattice potential — that traps ultracold atoms or molecules. This approach offers an ideal way of investigating complex phenomena, such as many-body localization, because interactions and disordered potentials can be introduced in a controlled manner.

Interactions are the main cause of complexity in many-body quantum systems. They drive such systems towards thermal equilibrium even if the systems are completely isolated from their surroundings[9,10]. But many-body localization offers a way of avoiding thermalization, because if the motion of the components of a system is restricted, then the system can't thermalize. Adding enough disorder to a system could therefore prevent thermalization by inhibiting the effectiveness of the interactions and ensuring localization. There is broad theoretical support for the idea that this holds in 1D systems, at least when the interactions act over short distances. But this general view is challenged by the results of Léonard and colleagues' experiments.

The disorder in such experiments is introduced by engineering a random potential at each lattice site. But this can result in the accidental appearance of small regions in which neighbouring lattice sites have nearly the same potential. In these regions, the interactions are not inhibited, so thermalization can occur. A thermal region of this kind serves as a 'thermalizing bath' to a neighbouring site, which, in turn, equilibrates with the thermal region and gets incorporated into it. The process is then repeated, and at each step the thermal region becomes larger and therefore more efficient at thermalizing its surroundings. This accelerated mechanism of delocalization is