the group showed that the genomic sections they had identified could explain 50% of the variation in height.

Hence, the missing heritability of height has been found. Further genetic studies in people of European ancestry will not contribute any more information — 'saturation' has been achieved for this trait in this ancestry group. This astonishing result will now motivate efforts to achieve saturation for other traits and diseases. Once achieved, attention might shift more widely to the momentous task of identifying the genes that underlie these associations, and inferring mechanisms for some of them.

Efforts to achieve saturation for complex diseases will face challenges. Height is a relatively stable trait that can be measured easily and reliably. By contrast, it can be difficult to determine how to measure outcomes for complex diseases such as major depressive disorder. Low disease prevalence can make it hard to generate large-enough sample sizes, and some diseases might be affected by more genes than is the case for height[11]. But concerted international efforts to overcome these challenges are a likely outcome of Yengo and colleagues' work.

It is important to acknowledge, as the authors do, that saturation is currently limited to only one ancestral group. Yengo *et al.* used existing data sets, in which diversity is limited. Out of the 5.4 million samples that were included in the study, 4 million were from participants of European ancestry; fewer than 78,000 were from those of South Asian ancestry.

There is also a lack of geographical diversity. Among the studies contributing data from participants of African descent, to the best of my knowledge, only one is from the African continent, with the rest coming from the diaspora. This single study, conducted in Nigeria, had 1,188 participants, implying that only 0.4% of the participants of African descent included in the GWAS were from Africa. The genetic and linguistic diversity of Africa is immense[4,12,13]. Although participants from the African diaspora add valuable data, these groups do not capture Africa's diversity.

Thus, this study, like other GWAS, did not comprehensively cover human genetic variation[14]. Some of the genetic variants associated with height will have been missed. Yengo *et al.* showed that, for participants of African ancestry from the United States and the United Kingdom, the identified genetic variants could explain only 5–12% of variation in height (in comparison to 40% in people of European ancestry). This is in line with other research demonstrating that GWAS based on people of European descent can less accurately predict gene–trait relationships in other groups[15]. Moreover, a study published earlier this year demonstrated that, across different sub-Saharan African populations, the performance of genetic scores generated from GWAS of African Americans varied widely[16], suggesting that environment, as well as ancestry, can affect genetic associations. Understanding how environmental factors might affect gene–trait relationships[17] will require more global diversity in genetic research.

Yengo *et al.* have demonstrated that it is possible to achieve saturation for complex traits. Now, ancestrally, ethnically, globally and socio-economically diverse samples are needed to reap the full benefits of GWAS.

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1. Yengo, L. *et al. Nature* **610**, 704–712 (2022).
2. Barton, A. R., Hujoel, M. L. A., Mukamel, R. E., Sherman, M. A. & Loh, P.-R. *Am. J. Hum. Genet.* **109**, 1298–1307 (2022).
3. Klein, R. J. *et al. Science* **308**, 385–389 (2005).
4. The Wellcome Trust Case Control Consortium. *Nature* **447**, 661–678 (2007).
5. *Nature* **456**, 18–21 (2008).
6. Visscher, P. M. *et al. Am. J. Hum. Genet.* **101**, 5–22 (2017).
7. Manolio, T. A. *et al. Nature* **461**, 747–753 (2009).
8. Loos, R. J. F. *Nature Commun.* **11**, 5900 (2020).
9. Shi, H., Kichaev, G. & Pasaniuc, B. *Am. J. Hum. Genet.* **99**, 139–153 (2016).
10. Yengo, L. *et al. Hum. Mol. Genet.* **27**, 3641–3649 (2018).
11. Zhang, Y., Qi, G., Park, J.-H. & Chatterjee, N. *Nature Genet.* **50**, 1318–1326 (2018).
12. Zeggini, E. & Morris, A. (eds) *Assessing Rare Variation in Complex Traits: Design and Analysis of Genetic Studies* (Springer, 2015).
13. Fan, S., Hansen, M. E. B., Lo, Y. & Tishkoff, S. A. *Science* **354**, 54–59 (2016).
14. Fatumo, S. *et al. Nature Med.* **28**, 243–250 (2022).
15. Martin, A. R. *et al. Nature Genet.* **51**, 584–591 (2019).
16. Kamiza, A. B. *et al. Nature Med.* **28**, 1163–1166 (2022).
17. Giannakopoulou, O. *et al. JAMA Psychiatry* **78**, 1258–1269 (2021).

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Chemical synthesis

A leap forward in the quest for general catalysts

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Truly general chemical reactions work well regardless of the structural features and functional groups in the starting molecule. A new screening protocol speeds up the identification of such reactions in the field of asymmetric catalysis. **See p.680**

Whether a newly developed chemical reaction finds its way into the chemist's toolbox for synthesis depends on various factors, such as the convenience of the experimental set-up and the toxicity of the reagents and by-products. Most importantly, an ideal reaction should be general — it must generate the expected products reliably for a wide range of previously unused substrate molecules. However, the generality of a reaction typically becomes apparent only after it has been used reproducibly in a variety of syntheses. On page 680, Wagen *et al.*[1] present a protocol for screening reactions that might accelerate the development of general catalytic methods for asymmetric synthesis, the field of chemistry that aims to make single mirror-image isomers of organic compounds.

Synthetic chemists strive to make complex molecules in the most efficient manner. Methods are therefore constantly being developed to enable the formation of previously unattainable chemical bonds and to prepare products in high yields. A subfield of chemical synthesis deals with a more intricate problem. Some molecules possess a property called chirality, which means that they can form as two possible isomers that are mirror images of each other. These isomers — known as enantiomers — have the same physical properties, but behave very differently when placed in chiral environments, such as the binding pockets of proteins in our bodies. In the case of pharmaceutical compounds, only one of the enantiomers might have the desired biological activity; in the worst-case scenario, the other enantiomer is harmful[2].

Medicinal chemists therefore need to be able to make enantiopure compounds — that is, single enantiomers — for biological testing. This is not straightforward, because most reactions generate chiral molecules as a one-to-one mixture of enantiomers. Enantiopure compounds can sometimes be made by starting a chemical synthesis from a single-enantiomer building block found in nature — most biomolecules, such as amino acids and sugars, are produced as single enantiomers. However, this approach is restricted by the limited set of enantiopure compounds found in biological systems[3].

Another strategy, known as asymmetric catalysis, is to use a chiral, enantiopure catalyst to transform a substrate into a chiral product that exists predominantly in one mirror-image

version. Such a reaction must provide the product not only in usefully high yields, but also with high enantioselectivity — a property that quantifies the distribution of the two enantiomers in the product. Most asymmetric-catalytic transformations are not highly enantioselective when first attempted, and require substantial optimization to identify the ideal catalyst and reaction conditions.

The conventional optimization process involves testing numerous catalysts under various conditions using a model substrate — a moderately complex reactant molecule that is expected to undergo the desired reaction smoothly. Once high enantioselectivity is achieved with the model substrate, the optimized catalyst and conditions are tested using more-complicated molecules, to explore the generality of the reaction.

This approach is inherently problematic, because it can overlook catalytic systems that work well for molecular classes other than the one represented by the model substrate. Another issue is that the ideal catalyst for the model might not work for other substrates. A huge number of individual experiments would be required to screen every possible combination of catalysts and substrates, which is neither a time- nor a resource-efficient strategy. The main hurdle in the development of general synthetic reactions is thus to find a way of extracting maximum data at an early stage from as few experiments as possible.

In 1998, a method known as multi-substrate screening was devised as a possible solution[4]. In this approach, a set of achiral substrates is reacted catalytically in the same vessel to give a set of chiral products (Fig. 1a); these are analysed simultaneously to determine the enantioselectivity of the individual reactions using, for example, high-performance liquid chromatography (HPLC). The total number of experiments required to obtain information for all of the substrates is therefore considerably reduced, compared with the conventional strategy.

However, as the authors of that paper acknowledged[4], only about five to ten substrates could be analysed simultaneously, to minimize the risk of the peaks for the products overlapping in the HPLC experiments and thereby preventing an accurate analysis. Only a few research groups have adopted multi-substrate screening for the discovery of asymmetric catalytic reactions (see, for example, refs 5, 6), most probably because of the difficulty in identifying an analytical method that overcomes this problem.

Wagen *et al.* now report a new multi-substrate screening procedure (Fig. 1b). Instead of pooling substrates into one reaction vessel, reactions with different substrates were run individually and the products were combined before analysis, which was carried out using a method called supercritical fluid chromatography–mass spectrometry (SFC–MS). In this technique, the products are detected not only from their peaks in a chromatography analysis, but also by their molecular mass. This is crucial to success, because similar compounds that have overlapping peaks can still be analysed simultaneously as long as they differ in their molecular mass. Furthermore, the authors describe a computational peak-fitting model that enables accurate analysis of overlapping enantiomer peaks.

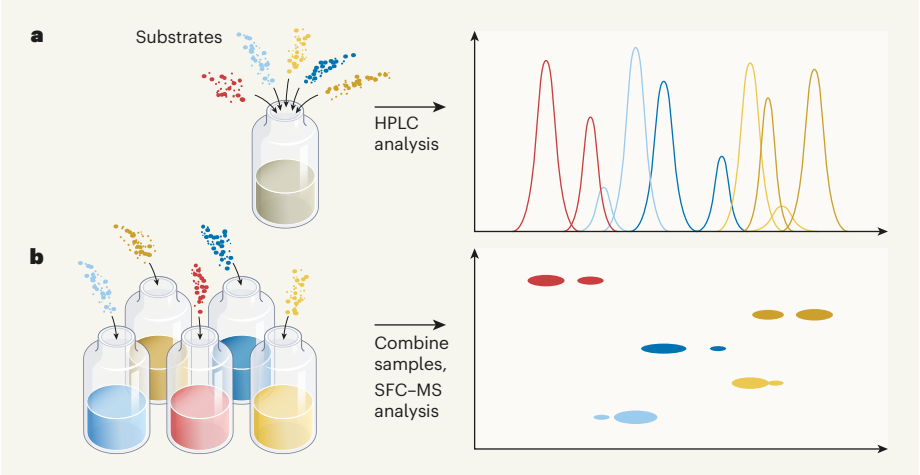

Figure 1 | Protocols for multi-substrate screening of asymmetric catalytic reactions. In the field of asymmetric catalysis, a catalyst is used to promote reactions that transform substrates into single mirror-image isomers (enantiomers) of products, rather than mixtures of enantiomers. **a**, A method known as multi-substrate screening[4] has been used to identify catalysts and reaction conditions that are optimal for a wide range of substrates. A mixture of substrates is reacted in the same reaction vessel, and the resulting products are analysed using, for example, high-performance liquid chromatography (HPLC); pairs of peaks represent the enantiomers formed from each substrate. However, the peaks can overlap, preventing an analysis of the ratio of enantiomers formed. **b**, Wagen *et al.*[1] carried out individual reactions of sets of substrates that were selected to maximize molecular diversity, then combined the products and analysed them using supercritical fluid chromatography–mass spectrometry (SFC–MS) — this provides a 2D plot that separates peaks that would overlap in an HPLC analysis. This protocol could accelerate the search for truly general asymmetric-catalytic reactions.

As a proof of principle, Wagen *et al.* investigated a known asymmetric-catalytic chemical reaction that can be used to make medicinally interesting natural products known as tetrahydro-β-carbolines. Impressively, the authors demonstrated that the most general catalysts and reaction conditions could be identified quickly for a set of 14 substrates, which had been selected to maximize the structural diversity represented in the screening set. The study revealed that the reactions of electron-rich substrates benefit from the use of certain solvents — something that could have been overlooked in a conventional study focusing on a single substrate that was not electron-rich.

Multi-substrate screening holds great promise for the rapid, resource-efficient development of general synthetic methods by substantially reducing the number of screening experiments needed. However, the benefits will be reaped only if the method is widely adopted by chemists. This, in turn, means that the analytical methods used must be reliable, cheap and simple. Given advances in analytical instrumentation[7,8] in the past few years, the present study is a leap in that direction.

The next step should be to refine the method to conduct multiple experiments in a single reaction vessel. If this can be achieved, then Wagen and colleagues' method opens the door to a future in which the time-limiting factor in asymmetric-catalysis research is not the screening and analysis of reaction conditions, but the rational design and optimization of catalytic platforms.

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1. Wagen, C. C., McMinn, S. E., Kwan, E. E. & Jacobsen, E. N. *Nature* **610**, 680–686 (2022).
2. Crossley, R. *Tetrahedron* **48**, 8155–8178 (1992).
3. Nugent, W. A., Rajanbabu, T. V. & Burk, M. J. *Science* **259**, 479–483 (1993).
4. Gao, X. & Kagan, H. B. *Chirality* **10**, 120–124 (1998).
5. Kim, H. *et al. Nature Commun.* **10**, 770 (2019).
6. Duursma, A., Minnaard, A. J. & Feringa, B. L. *Tetrahedron* **58**, 5773–5778 (2002).
7. Bu, X., Regalado, E. L., Hamilton, S. E. & Welch, C. J. *Trends Anal. Chem.* **82**, 22–34 (2016).
8. Korch, K. M. *et al. ACS Catal.* **12**, 6737–6745 (2022).

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