As the authors point out, users with a high tolerance to the risks involved might wish to avoid action, taking into account the possibility that a predicted marine heatwave might not occur. Those with lower risk tolerance might prefer to take action even when the probability of a marine heatwave occurring is low. The most suitable decision threshold will be user specific and will depend on balancing the cost of action with the cost of potential loss or damage in the case of inaction.

Aside from minimizing the effect of false positives and false negatives depending on a user's risk profile, there are other factors to consider when using such forecasts. Climate predictions are not perfect, and even if they are deemed to be skilful, they will sometimes be wrong. Consequently, users who strictly follow these predictions will make a wrong decision in some cases, but they should benefit in the longer term from receiving correct information more often than incorrect information. Users must therefore understand how accurate the predictions need to be to make them trustworthy enough to underpin decisions — as well as considering the critical forecast probability that should trigger action, on the basis of users' risk profiles. Both thresholds will probably differ between users.

Information from such predictions can be further optimized by identifying time periods or conditions (sometimes referred to as windows of opportunity) in which a prediction is regarded as more accurate than it is under other conditions[7]. Strategically targeting such periods when incorporating predictions into the decision-making process could further increase the predictions' usefulness. Jacox and colleagues' results suggest that the El Niño–Southern Oscillation modulates the forecasting skill of predictions, with marine heatwaves being more accurately predicted in large areas of the globe during the warm (El Niño) and cool (La Niña) phases of the oscillation, as opposed to during neutral phases.

There are also prospects for skilful predictions of marine heatwaves on longer timescales: previous studies have shown that climate forecasts for multiple years or even a decade can predict slowly varying ocean surface temperatures[8,9]. Marine-heatwave predictions could be further refined by taking the severity of events into account[10], because different heatwave intensities might have varied effects on users of the prediction, or require different actions to be taken.

In addition to improving the prediction systems further, future research should understand the specific needs of stakeholders in order to develop tailored forecast products that address these needs. This will further enhance the ability of predictions to aid decision-making — thereby increasing the resilience of communities that depend on marine resources.

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Psychiatric genetics

Origins of schizophrenia find common ground

Conrad O. Iyegbe & Paul F. O'Reilly

Two differing approaches that are used to study common and rare genetic causes of schizophrenia reveal convergent clues about the biology underlying this complex disorder. **See p.502 & p.509**

There has long been debate about whether the genetic component of complex disorders, such as schizophrenia, is attributable mainly to rare or common DNA variants[1]. Two studies in *Nature* now provide evidence for key roles of both types of variant. In the first study, Trubetskoy *et al.*[2] (page 502) identified hundreds of common genetic variants that each have a tiny influence on schizophrenia risk. By contrast, in the second, Singh *et al.*[3] (page 509) discovered a handful of rare variants, each of which have a large effect. Together, these studies show that common and rare genetic causes of illness might often disrupt the same biological processes that lead to disease.

Genome-wide association studies (GWASs), which analyse the differences in people's DNA to identify common variants linked to a disease or trait, are now so commonplace that practitioners don't flinch at studies of hundreds of thousands of people in which hundreds of genetic variants are associated with a disease. They know the drill: increase the sample size and the genetic hits will pour in. Even so, few scientific teams have such a finely tuned pipeline as the Psychiatric Genomics Consortium (whose members co-authored the first of the current papers), one that has produced a bounty of hits for 13 neuropsychiatric disorders[4–6].

Critics of GWASs — and there are plenty — point out that common genetic variants typically have minuscule effects on disease risk, and highlight the difficulty of deciphering biological effects from hundreds of risk variants of disparate function, scattered across the genome. But then, life probably didn't evolve for millions of years only to be decoded in the course of a five-year research grant. Judging from Trubetskoy and colleagues' current study, the patient, meticulous work of GWAS researchers is starting to reap rewards.

Trubetskoy *et al.* studied the genomes of 76,755 people with schizophrenia and 243,649 healthy control participants. Their analysis revealed 342 common genetic variants that can increase the risk of schizophrenia. Although each variant increases the risk by only a small amount (less than 5%), the many risk variants identified allowed the authors to gain insights into the biological processes that these variants modify.

In one key analysis, Trubetskoy *et al.* established the tissues and cell types in which the newly identified risk variants are most biologically active. Reassuringly, the genes are most highly expressed in brain tissue. Although this might seem obvious for schizophrenia, the consortium demonstrated that it is the increased size of its GWAS data sets — from big studies published in 2011 (ref. 7) and 2014 (ref. 8), to its massive one today — that has allowed these biological signatures to emerge from the tiny genetic effects involved. The consortium then further leveraged this power gain by zooming in to the cellular level, revealing the three neuronal-cell subtypes (pyramidal, medium spiny and granule) that are most closely associated with schizophrenia risk.

GWASs highlight regions of the genome that

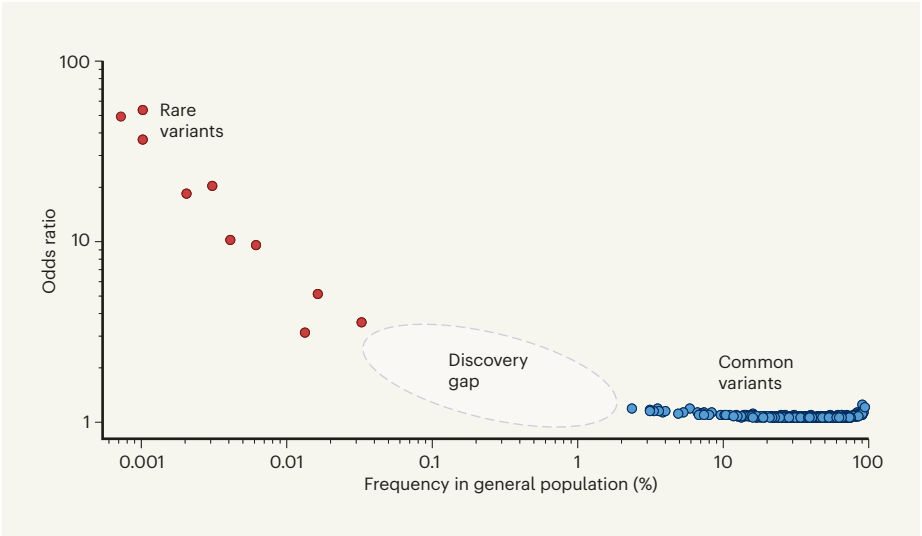

Figure 1 | Genetic variants associated with schizophrenia. Trubetskoy *et al.*[2] used genome-wide association studies (GWASs) to identify 342 common genetic variants that are each associated with a slightly increased risk of developing the disorder (blue; data from SI table 2 of ref. 2). By contrast, Singh *et al.*[3] used sequencing to study the protein-coding DNA sequences (exomes) of people with and without the disorder, identifying ten genes that harbour rare, protein-truncating variants with large effects on disease risk (red; data from Extended Data Table 1 of ref. 3). The two studies suggest that rare and common risk variants might often affect the same biological mechanisms (not shown). An approach that combines GWAS and sequencing could help to fill the 'discovery gap' between these two classes of risk variant, providing further insights into the biological pathways that can lead to schizophrenia. (Adapted from Fig. 6 of ref. 3.)

contain risk variants, but they do not tell us which genes are involved. The co-inheritance of adjacent DNA sequences over many generations leads to correlations between nearby genetic variants; in a GWAS, this generates disease associations for numerous genetic variants in the vicinity of one causal variant. This makes it challenging to decipher which are the causal variants and genes among an array of candidates. Therefore, Trubetskoy *et al.* embarked on an impressive 'gene prioritization' enterprise, using a combination of techniques to pinpoint 120 genes most likely to have causal roles in schizophrenia. These genes will be investigated by psychiatric geneticists for years to come.

In the companion paper, Singh *et al.* sequenced all of the protein-coding regions of the genomes (whole exomes) of 24,248 people with schizophrenia and 97,322 healthy control individuals. The goal of the study was to search for ultra-rare disruptive variants — those carried by five or fewer people in the cohort and likely to disrupt a protein's function — that have a large effect on schizophrenia risk. They compared the total number of ultra-rare, disruptive variants in the exomes of people with schizophrenia with that of the control participants.

In addition, they analysed the genomes of 3,402 family trios (which include a mother, a father and their offspring, who has schizophrenia). This type of analysis is helpful for identifying genetic variants produced by mutations that occurred in the offspring, as opposed to variants inherited from the parents. The authors found that these *de novo* mutations occurred significantly more often in 244 schizophrenia candidate genes than in other genes; candidate genes were identified in the comparison of participants with and without schizophrenia.

Integration of Singh and colleagues' two data sets revealed ten genes that were significantly associated with schizophrenia. One, *SETD1A* (which encodes an enzyme involved in gene regulation), has previously been implicated in schizophrenia[9]. Four others (*STAG1*, *FAM120A*, *GRIN2A* and *SP4*) were among the 120 genes picked out by Trubetskoy and colleagues' analysis. This hints that common and rare genetic variants might influence schizophrenia risk through shared biological processes.

Next, Singh *et al.* explored links between their ten genes and genes previously[10] associated with developmental delay and intellectual disability (DD/ID) disorders. Six genes were linked to both schizophrenia and DD/ID disorders, adding to previous evidence[9] of genetic overlap between these disorders. Differences in the mutations found in three of these genes (*GRIN2A*, *CACNA1G* and *TRIO*) draw attention to the diseases' biological distinctions — protein-truncating variants were linked to schizophrenia only, whereas less-damaging variants that modify the proteins' amino-acid sequences occurred in both schizophrenia and DD/ID disorders. Intriguingly, this suggests that the degree of damage to proteins that control neurodevelopment could contribute to which disorder a person might develop.

The theme of analysing the genetic overlap between neurodevelopmental disorders continues in a sequencing study by Palmer *et al.*[11] in *Nature Genetics*. Palmer and colleagues could not detect any gene associations specifically related to bipolar disorder in their data set of around 28,000 people with or without bipolar disorder. However, a subsequent meta-analysis that integrated their data set with that of Singh *et al.* revealed that a mutation in the gene *AKAP11* (which encodes an enzyme involved in cellular protein localization) is a risk factor for both bipolar disorder and schizophrenia.

Together, the current studies contribute to an emerging consensus that rare and common genetic risk factors for disease converge on many of the same biological mechanisms. For instance, they each reaffirm the functional importance of synapses — connections between neurons — in schizophrenia. The work also demonstrates how different study designs can support each other. In addition to the shared genes identified by both the GWAS and exome-sequencing approaches, a significant enrichment of rare, disruptive variants among the GWAS genes suggests that there are many more rare variants to be discovered.

Perhaps the logical next step would be to implement a design that combines both approaches. Once hundreds of genomic regions have been identified by GWASs, those regions could be subjected to targeted sequencing in much larger sample sizes than is possible using costly whole-genome or -exome sequencing. As well as pinpointing the causal genes driving the GWAS signals, this could help to address the 'discovery gap' that has not been filled by either approach (Fig. 1): identifying risk variants across the whole range of variant frequencies will help researchers to better understand how genes, and the variants that regulate them, work together in biological pathways and cause disease when perturbed. Another goal will be to distinguish pathways that are a direct risk for developing schizophrenia from those that drive behaviours that then modify the risk of developing disease[12]. This will, in turn, help to distinguish targets for drug development from targets for public-health intervention.

However, to uncover the full spectrum of risk variants, it will be essential to increase the diversity of participants in future studies of schizophrenia[13]. Large-scale genomic studies so far have mostly included people of European ancestry — future efforts should ensure that study populations are globally representative. This will also maximize opportunities for participating populations to profit equitably from the scientific and medical advances that occur as a result. Trubetskoy *et al.* and Singh *et al.* have begun to make progress in this direction, and numerous funding-agency

initiatives have emerged to support such efforts. Continuing to diversify in this way[14] will accelerate our understanding of how common and rare genetic variants combine with environmental factors to shape individual risk for mental illness.

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Evolution

Mutational clocks tick differently across species

Alexander N. Gorelick & Kamila Naxerova

Throughout life, cells accrue mutations. It now emerges that longer-lived animals acquire mutations at a slower rate than do short-lived species, potentially explaining why cancer risk does not increase with lifespan. **See p.517**

The animal kingdom comprises amazing diversity, ranging from small, short-lived animals to large, long-lived species. How does the risk of developing cancer manifest across these different life forms, and what are the molecular underpinnings of this? Cagan *et al.*[1] (page 517) and Vincze *et al.*[2] provide some answers.

How does cancer originate? To the best of our knowledge, it arises from a cell that has acquired a critical number of inauspicious genetic alterations. These abnormalities decouple it from the ordered cell society in which it resides, and enable a rogue existence that might eventually result in tumour formation.

If this classic model is accurate, then the probability that such a rogue cell will arise should scale with lifespan and with the number of cells in an organism's body. A blue whale has many more cells and lives much longer than does a mouse, so surely a whale is at higher risk of developing cancer than a mouse is. Strangely, this is not so. The surprising lack of association between body size, lifespan and cancer risk is named Peto's paradox[3], after epidemiologist Richard Peto, who mused about this in 1977.

The two latest reports provide new food for thought about this paradox. Vincze *et al.* prove Peto right through an analysis of mortality for 191 species in zoos, and confirm that animals with larger bodies or longer lives are not more likely to die of cancer than are smaller animals or animals with shorter lifespans. Cagan and colleagues study the mechanisms underlying Peto's paradox by investigating how rapidly cells in different animal species acquire mutations (Fig. 1). The authors conclude that cells in long-lived animals mutate much more slowly than do cells in short-lived species, providing a possible explanation for why cancer risk does not necessarily scale with lifespan.

Comparing genome-wide mutation rates across species is not a simple undertaking. Accurately measuring mutations in single cells poses substantial technical difficulties, and mutations in large populations of cells are hard to detect if the constituent cells are genetically diverse. Cagan *et al.* devised an inspired solution to this problem by choosing to sequence a particularly suitable cell population across 16 animal species. The authors focused on structures in the colon called crypts, which are tiny folds consisting of gut epithelial cells. These cells all have a common ancestral cell that existed a relatively short time ago compared with the species' lifespan. Therefore, sequencing genomes from crypts provides an excellent estimate of the number of

From the archive

Chemistry lessons with a historical twist, and conversations about mathematics come under the spotlight.

50 years ago

Teaching the History of Chemistry. Edited by George B. Kauffman — Those who hold almost any view of how, when, or whether the history of chemistry should be taught will find support for it in this volume, which consists of eighteen papers read at a symposium at a national meeting of the American Chemical Society ... Some urge separate courses in the history of chemistry, while others believe that chemistry will cease to seem colourless and over-factual when its presentation is enlivened with anecdotes and case-studies ... Attempts are made here ... to make us pursue ... the history of chemistry for its own sake and not because it is useful for something else.

From *Nature* 21 April 1972

100 years ago

Perhaps few well-known mathematicians have escaped an experience which would be amusing if it were not so exasperating. Mr. Brown (let us say) is introduced to Prof. Smith, who teaches mathematics at a provincial college. After the usual expression of pleasure at the introduction, Brown generally adds "Of course, although I haven't had the pleasure of *meeting* you before, I know you well by reputation." Then, without so much as pausing to take breath, he proceeds to explain that he was always a duffer in "maths" at school, and that he has now forgotten everything about the subject they tried to teach him as a boy. Now Brown doesn't act in this way to every celebrity ... Moreover, in making his lamentable confession, Brown shows no sign of regret or humiliation; on the contrary, a sort of satisfied look steals over his face, suggesting that he is glad to be free once and for all from the study of such a repulsive and useless subject ... One thing clear from Brown's attitude is that he evidently fears lest Smith should introduce some mathematical topic during the conversation. Of course this is the thing Smith is most unlikely to do.

From *Nature* 22 April 1922