break junction, so that individual hydrogen atoms or molecules were captured between the tips of the electrodes, thereby establishing an electrical contact.

The resulting junctions constituted a single quantum-mechanical transport channel in which electrons could be transmitted from one electrode to the other with a probability that could be adjusted by varying the openness of the channel. This set-up provided an ideal test bed for exploring the properties of the so-far-overlooked noise contribution.

The authors observed a strong increase in electronic noise when they applied a temperature difference between the two electrodes, compared with when the electrodes were at the same temperature. The additional noise, which the authors call delta-T noise, scaled with the square of the temperature difference. It exhibited the same dependence on electrical conductance as shot noise (Fig. 1).

Shein Lumbroso and colleagues explained their finding using the quantum theory of charge transport, known as the Landauer theory[5], which has been developed in the past few decades. This theory incorporates both shot noise and thermal noise, and has been tested intensively down to the atomic and molecular scale[3]. It has been found to accurately describe many experimental observations obtained when working entirely in thermal equilibrium, or when applying small voltages. The authors took a closer look at the theory, and found that it includes a noise component that occurs when solely a temperature difference is applied across a junction: delta-T noise.

It is well established that an electric current can arise from a temperature difference in the absence of an applied voltage — a phenomenon called the Seebeck effect. However, delta-T noise is not the shot noise associated with this thermally induced current. The authors' results indicate that delta-T noise is larger than this shot noise, and has a different dependence on the temperature difference. Instead, the results suggest that delta-T noise arises from the discreteness of the charge carriers mediating the heat transport.

Because the Landauer theory is widely used, it is surprising that delta-T noise has not previously been observed. The importance of carefully considering all of the spatial temperature differences and resulting electric currents to understand the current flow in atomic and molecular contacts was pointed out in a 2013 paper[6], but implications for noise were not addressed.

Shein Lumbroso *et al.* found that the Landauer theory accurately describes all of the characteristic properties of delta-T noise. In this sense, their experiments are yet another beautiful demonstration of the theory. But the work also conveys a key message: careful design and rigorous analysis of experiments are required when studying any of the details of quantum transport.

The authors' discovery also has practical implications. In particular, quantum-transport experiments that are not entirely in thermal equilibrium could show strongly enhanced noise, which might be mistaken for noise arising from interactions between the charge carriers or from other subtle effects. Experimentalists who wonder about finding unexpectedly high noise in their electric-current measurements might wish to revisit their set-ups to search for unintentional temperature gradients. The most practical application of the authors' work is probably that the enhanced noise could be used to detect unwanted hotspots in electrical circuits.

For the future, researchers could explore the relationship between delta-T noise and shot noise that has a nonlinear dependence on applied voltage, which was observed earlier this year in high-voltage experiments on atomic junctions[7]. Such studies could also be expanded to more-complex quantum-transport experiments — for instance, those on artificial atoms called quantum dots. Because of the sensitivity of delta-T noise to the properties and interactions of charge carriers, the phenomenon might become a valuable tool in quantum-transport investigations. ■

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CANCER

Thousands of short cuts to genetic testing

Gene editing has now been used to introduce every possible single-nucleotide mutation into key protein-coding regions in the cancer-predisposition gene *BRCA1*, to identify the variants that are linked to cancer risk. **SEE ARTICLE P.217**

STEPHEN J. CHANOCK

For decades, cancer geneticists have been trying to understand which changes in the sequence of the *BRCA1* gene predispose affected individuals to developing breast or ovarian cancer. Extensive efforts have focused on interpreting the plethora of genetic variants in *BRCA1*, using clinical observations to determine whether this or that variant warrants patient counselling about options for medical intervention[1]. Generally, *BRCA1* variants are sorted into three categories[2,3]: benign variants, which cause no concern; deleterious variants, which can confer a high risk of cancer; and an unsettling intermediate known as variants of uncertain significance (VUS). Hardest to classify are variants that arise only rarely, of which there are thousands for *BRCA1*. Conventionally, genetic sleuthing has focused on families or populations within which certain mutations occurred at an unusually high frequency, exposing the effects of deleterious variants. But on page 217, Findlay *et al.*[4] report an innovative laboratory-based approach to assessing the effect of thousands of variants across protein-coding regions of *BRCA1*.

The BRCA1 protein is a key tumour suppressor, and is essential for a DNA-repair pathway called homology-directed repair. Mutations that prevent this function lead to the death of cultured human cells of a strain called HAP1 (ref. 5). Findlay and colleagues made clever use of this property of HAP1 cells to screen for deleterious *BRCA1* variants.

The authors used a gene-editing approach called CRISPR–Cas9 to accurately mutate each nucleotide in 13 crucial protein-coding regions (exons) of *BRCA1* into every other possible base, one nucleotide at a time — an exhaustive technique known as saturation genome editing (SGE). In each experiment, they edited 1 exon of *BRCA1* in 20 million HAP1 cells simultaneously. They left the cells to grow *in vitro* for 11 days, then sequenced the edited exon to gauge the frequency at which each variant was present in the cell population. From these data, they designated each variant as functional (if its frequency indicated that homology-directed repair was active in cells harbouring that variant), non-functional (if the frequency was lower than average, indicating that the variant led to cell death), or intermediate (Fig. 1).

Findlay *et al.* found that their results fit well with those obtained from a complementary assay designed to test whether homology-directed repair occurs normally in *BRCA1* mutant cells,

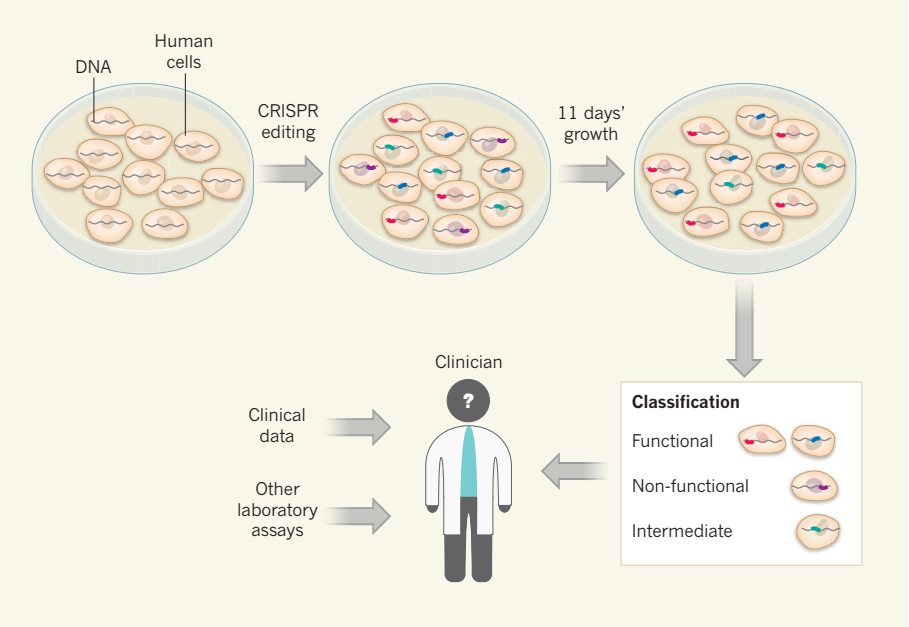

Figure 1 | Assaying how genetic variants affect BRCA1-protein function. Findlay *et al.*[4] grew human cells in culture. They used a gene-editing approach called CRISPR–Cas9 to modify the genomes of the cells in such a way that every possible single-nucleotide variation in a given protein-coding region (exon) of the *BRCA1* gene was present in some cells of the population. The edited cells were cultured for 11 days, and the exon was then sequenced (not shown) to determine the frequency of each variant in the population. Variants present at the expected frequency were classified as functional, meaning that the protein had no effect on BRCA1 function. Those present at lower-than-expected levels were designated as non-functional, because they had caused changes in BRCA1 that prevented normal cell growth. Variants in the middle of the range were designated as intermediate. This approach could be combined with other clinical data and with laboratory-based assays to enable accurate variant classification by clinicians, but how this should be done needs further discussion. (Adapted from Figure 1b of the paper[4].)

which is outlined in an accompanying paper in *The American Journal of Human Genetics*[6]. They also compared their results with an internationally recognized set of annotated *BRCA1* variants[7] designated as benign, deleterious or VUS on the basis of clinical data (or lack thereof, for many of the VUS). They found that their results, although not perfect, were strikingly accurate. Variants designated as non-functional in Findlay and colleagues' analysis generally corresponded with those annotated as deleterious in the database, and, reassuringly, nearly all functional variants corresponded with those annotated as benign.

The group therefore reasoned that its approach could be used to shed light on the many variants of the vexing VUS class, which keep clinicians up at night. The researchers provide evidence that some *BRCA1* VUS are non-functional — a subset that should be monitored carefully in the future. Finally, they provided insights into the extent to which variants in the sequences that flank exons can disrupt protein function, thus extending our ability to interpret more pieces of the genome.

The current study is remarkable for its scale, in that the method enables almost 4,000 possible *BRCA1* variants to be analysed in parallel. The next study should look at regions of *BRCA1* outside the 13 exons studied here, especially those that also harbour deleterious mutations and VUS. VUS are currently piling up, because the rate at which new patient sequences for *BRCA1* are being collected is greatly outstripping the accumulation of clinical information needed to classify variants. Findlay and colleagues' approach represents a potential game-changer for assessing VUS. But first, it will be crucial to collect further clinical data to validate the exciting findings of this paper.

If validated, the technique could prove to be a major advance over previous efforts to study the impact of VUS in the laboratory. Such efforts typically combined computational models with *in vitro* assays of, for example, protein–protein interactions or drug sensitivity. Over the past decade, these analyses have begun to be incorporated into annotation strategies. But the pace of change has been slow, and there is considerable disagreement over the weight that should be given to this type of evidence[8]. The scale of Findlay and colleagues' study, together with its apparent accuracy, bodes well for its future integration into the classification of *BRCA1* variants. It is likely that the findings will be incorporated into current efforts to annotate *BRCA1* variants[7] that are part of the international BRCA Challenge (http://brcaexchange.org).

"It is likely that the findings will be incorporated into current efforts to annotate BRCA1 variants."

But further thought is required to determine the best way to incorporate Findlay and colleagues' assay into variant classification. The backbone of genetic testing is the availability of sufficient clinical data to assign risk to a given variant[7,8]. The new assay should supplement, not supplant, these data. It might be tempting to make immediate use of the assay to interpret VUS identified during human genetic testing, particularly because SGE has been used successfully in the past to identify targets for drug development[9]. But *in vitro* data alone should not be used as the basis for medical advice — at least until the approach has been clinically validated.

Could Findlay and colleagues' approach be applied to analyse variants in the other 20,000 or so genes in the human genome? For cancer-predisposition genes (which number well over 100)[10], including the well-studied genes *BRCA2* and *TP53*, the answer is probably yes. For these genes, non-functional variants would be expected to alter cell growth in culture, enabling a modification of Findlay and colleagues' frequency assay to be used. The effort involved in developing such an assay for each gene is substantial, and will probably slow the immediate application of SGE for assessing VUS. But although developing these assays for all exons in cancer genes will take time and money, the dividends could be spectacular for cancer geneticists. Going forward, large SGE analyses of cancer genes should be made publicly available. It is plausible that SGE will lead to the identification of previously unknown cancer-predisposition genes that, in turn, astute clinicians will verify.

Findlay and co-workers' provocative paper should turn heads across disparate domains of genomics. It remains to be seen to what extent the authors' approach can be applied to all of these domains, or whether it will remain an exciting development restricted mainly to cancer. Either way, this study should help researchers to realize the promise of precision medicine[11]. ■

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