nature genetics

Full spectrum genetics

Every instance of a variant in the human genome causing or correlated with a trait deserves to be databased and analyzed. As a consequence of rapidly evolving technology and strategies, more of the mutational spectrum of human disease is now accessible to research. Advised by our referees' progressively higher standards, we continue to select the most informative and useful results.

Detecting human gene variants has never been easier thanks to a growing portfolio of technology and analytical approaches, including but not limited to linkage, homozygosity mapping, case-control association, whole-genome genotyping, targeted resequencing and whole-exome sequencing with bioinformatic filtering. Many labs have for decades accumulated pedigrees, detailed phenotype information and DNA samples until these approaches finally became available. In consequence, we are seeing a welcome resurgence of work on monogenic disorders that were previously intractable to analysis. At the same time, we are noting an expansion of the intellectual framework in which disease caused by rare Mendelian variants is reported and interpreted. Rare heritable variants and very rare *de novo* variants act in the context of the haplotypic background of common variants upon which these mutations arise and within the context of particular genotypes.

Which Mendelian variants produce results suitable for publication in the journal? Our general principles are and have always been to select papers for review by the amount of new data and new ideas and the resource value contained within. Papers must meet current field-specific standards set by our latest benchmark papers and referee advice. Finally, we consider the value of the paper as a research tool, prioritizing those that will motivate larger numbers of scientists to do their research differently as a consequence. In principle it should be possible to find a phenotype for each of the tens of thousands of genetic elements in the human genome, but not all such results will be equally informative. However, if, say, 50 other labs will drop everything and instead use the results of your work, that paper is certainly suitable for this journal!

Although the premium that basic researchers place on novelty sometimes seems to demand a race to be first to identify a gene causing a disorder, we may reject the first identification of the minimum publishable number of mutations in a gene in favor of a more complete report of an allelic series, and we are more likely to send to review a more complete analysis with strong mechanistic insight explaining how variants in a gene result in altered phenotypes. Out of fairness, we do prefer to review and publish concurrent work in parallel, provided that each paper stands on its own as a sufficient conceptual advance, and we have a good record of doing just this. However, if each paper contains only the very minimal report of a mutation causing a disorder, there is a chance that we may reject the "first and worst" of the series and thereby be unable to consider similar but more complete papers that arrive on our desks a short time later. If, on the other hand, there is mechanistic investigation and further value to the paper, it is less likely to be rejected solely for reasons of editorial consistency.

Fortunately there are many other excellent journals in the field of genetics and genomics, including some also published by NPG, such as the *European Journal of Human Genetics*, *Genetics in Medicine* and *Journal of Human Genetics*. Although we do not presume to make editorial policy for other journals, we think the minimum criteria for a report of a monogenic human disorder are fairly consistent, mainly because the same referees review for and advise a range of journals. We, for example, look for well-documented phenotyping together with a gene identification supported by linkage, statistically significant association or bioinformatic filtering. All genes within a linkage interval should be considered or sequenced systematically. Gene identification should be confirmed by more than one mutation in more than one pedigree, and the variants considered causal should include nonsense, splicing, frameshift or deleterious missense variants. The variants reported should be appropriate to the proposed mode of inheritance: dominant, recessive, either *de novo* or segregating. A well-planned paper is appropriately skeptical, devoting equal resequencing effort to cases and controls to ensure an ascertainment free from bias and carrying out a full investigation of other candidates and known variants in the same population.

This journal is unlikely to send to review manuscripts that report findings from a single case or family, or reports where the disease is extremely rare and does not overlap phenotypically with more common diseases or where the disease or related diseases are already well understood mechanistically. We are unlikely to consider human disorders for which there are published results from an animal model with the same mechanism or for which the gene identified is another component of an existing or well-studied pathway. Finally, some organs, such as sensory ones, are more sensitive to nonspecific genetic disruption than others, without a new mechanism being elucidated by each additional mutation. There are a large number of mutations in different genes that result in blindness, deafness and intellectual disability. All are interesting, but not all are mechanistically informative, and we may therefore set a higher bar for papers in these areas.

Instead, we are more likely to select from papers that meet the above basic criteria and will prioritize for review those that present a new fundamental biological insight, identify new pathways in a disease that is not well understood, offer an insight into a genetic or environmental component or mechanism of common disease or identify oligogenic or novel genetic mechanisms. In addition, as the journal is relatively mature in its 20th year, translational utility is an important strategic consideration. We are interested in results from a monogenic disorder that advance translation to a preclinical trial or work that reports pharmacogenetic findings that make an economic difference or change clinical outcomes. ■