EDITORIAL

Gene discovery for rare diseases

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Within Europe, a disease is classified as rare if it affects fewer than 1 in 2,000 people. Currently there are between 5,000 and 8,000 known rare diseases, while further novel syndromes are reported every month. There is wide variation in the numbers of people affected by each condition, with some conditions only known to affect a single family or person. However, while each of these disorders is individually rare, overall, rare disorders affect more than 5% of the population worldwide,[1,2] thus representing a significant medical problem. Few drug therapies exist for these diseases and investment in drug development by pharmaceutical companies for a rare disease is often not seen as economical, which leads to difficulties in providing suitable treatment options.

Rare genetic disorders can be caused by mutation of a single gene or multiple genes, or by large chromosomal rearrangements. Early diagnosis and treatment of these disorders, many of which are present at birth, can be a critical part of their successful clinical management. However, the genetic causes and definitive diagnostic criteria of a large number of these disorders are still unknown, making them unfamiliar to most clinicians. In addition, there can be significant clinical variability within a disease phenotype. In some cases this has resulted in genetically distinct disorders with overlapping clinical symptoms being erroneously grouped together. In other cases, variations in the presentation of a single disorder may result in subdivision of syndromes that are in fact a single entity. This means that obtaining a correct diagnosis is challenging and time-consuming, which exacerbates the problem of providing effective clinical management for affected individuals. Genetic characterisation of these disorders can be important for unequivocal diagnosis, and there is a pressing need for further research to identify the underlying genetic causes of uncharacterised rare diseases to inform patient care.

The large number of known rare disorders, together with the small number of people affected by each condition, often means that there is little research into their underlying causes. Traditionally, identification of pathogenic mutations has been achieved through the use of a variety

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of techniques, including chromosome mapping, Sanger sequencing and copy number analysis. More recently there has been a rapid increase in the number of whole-exome sequencing investigations, which has helped to accelerate the rate of identification of novel pathogenic mutations for rare diseases. As the cost of whole-genome sequencing decreases, it is becoming the new standard in gene discovery. This technology has the potential to enhance mutation discovery further, as it has the capacity to cover up to 100% of the genome sequence rather than the 1–2% obtained by exome sequencing,[3] thus allowing identification of mutations in non-protein-coding regulatory regions of the genome, and provides more comprehensive copy number information.

While whole-genome sequencing generates a large amount of genetic data, it also brings new challenges in data interpretation. There are increasing numbers of rare polymorphisms appearing on public online databases, obtained from large cohorts of anonymised individuals, either with a particular type of disease, or with no known disease. This can cause confusion when deciding whether a variant is clinically significant, particularly when trying to distinguish pathogenic low-penetrance variants from rare non-pathogenic polymorphisms without comprehensive clinical information. New programs and algorithms are being created to interpret copy number data, as well as non-exonic variants, and to make the data analysis pipeline more user friendly.

High-throughput sequencing efforts will enhance our ability to find the underlying causative variants of rare diseases and to delineate genotype–phenotype correlations, but collaboration is required to achieve this. This includes pooling of DNA samples from many institutions to increase the power of these studies, along with rapid high-throughput sequencing of those samples and large-scale bioinformatic data interpretation. One large-scale project aimed at identifying the causes of uncharacterised rare diseases is the 100,000 Genomes Project (http://www.genomicsengland.co.uk/the-100000-genomes-project/). Manchester is one of 11 sites across the country involved in the pilot study. The project has the overarching aim of integrating genomic data into the healthcare system to inform future clinical management decisions. An initial push for gene discovery will subsequently be translated into routine genomic diagnosis to allow faster, more accurate, diagnosis and improved medical care.

Identification of pathogenic mutations in genes that are involved in the same pathways as other known disease genes allows for the repurposing of existing drugs to expedite provision of effective drug therapies. This, in turn, will reduce the costs of developing medication for rare-disease patients. For diseases caused by mutations in genes without a known function, targeted drugs will take longer to develop, but their initial identification will provide the basis for future research to characterise them and to delineate the mechanism of pathogenicity so that novel drugs can be devel-

oped. In the meantime, clinicians need to be made aware of the collective prevalence of rare diseases and the importance of medical genetic research to improve future healthcare for these patients.

References

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