

profiles, mutation analysis showed a defect in TMEM165 resulting in a combined defect of N- and O-glycosylation.

### DEPTH OF THE RARE GENETIC DISEASES: STRATEGIES TO IDENTIFY THE REMAINING GENES AND DISEASES

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The number of rare genetic diseases is difficult to gauge precisely. An interrogation of Online Mendelian Inheritance in Man (OMIM), a catalogue of human genes and associated genetic diseases, and Orphanet, a comprehensive reference portal for rare diseases (including an inventory of such diseases), results in a best estimate of between 6,000 and 7,000 rare genetic diseases. However, the number of phenotypes that remain to be defined may be considerably higher. Work over the past 25 years has resulted in the identification of genes for ~4500 of the estimated 7,000 rare monogenic diseases; it was predicted that most of the remaining disease genes will be identified by the year 2020. This marked acceleration is the result of next-generation sequencing (NGS) and analysis. This presentation will examine the rapid maturation of rare-disease genetic analysis and successful strategies for gene identification. As we come closer to understanding the genetic aetiology of all rare diseases, it is likely that we will increasingly rediscover known genes and that the approach to completion of the disease compendium will be asymptotic and much more challenging than predicted.

### PHENOMICS AND ITS ROLE IN NEXT GENERATION SEQUENCING

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Medical research, in particular in the context of rare diseases, is becoming increasingly enabled by information technology. Perhaps more than any other field, the availability of low-cost whole genome sequencing is revolutionising the discovery of the aetiology of genetic disorders, and hence leading to new avenues to diagnostics and treatments. The analysis of phenotypic abnormalities provides a translational bridge from genome-scale biology to a patient-centred view on human disease pathogenesis. Detailed phenotype data, combined with increasing amounts of genomic data, have an enormous potential to accelerate the identification of disease aetiology, facilitate disorder stratification, inform prognosis and improve the understanding of health and disease. The acceleration of translational and clinical applications of genomic technologies relies on the harmonisation of phenomic information, including disorders and phenotype traits. This presentation provides an overview of the current state of the art in and challenges associated with the representation and acquisition of clinical phenotype data. Moreover, it discusses the steps required to apply human-centred and cross-species phenomics as a complementary technology to whole genome sequencing.

### HUNTING FOR THE SIGNATURES OF CANCER BY PLASMA DNA SEQUENCING

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Liquid biopsy refers to the analysis of DNA released by tumours into the circulation of patients for the detection, prognostication, selection of therapeutic targets or monitoring of malignancies. For example, regulatory approval has been granted for the detection of epidermal growth factor receptor mutations in plasma of patients with non-small cell lung cancers as a means to stratify therapy. However, the key challenge in the diagnostics of cancer is about its early detection. Given that cancers are highly heterogeneous, our group has been developing whole genome approaches to detect the signatures of cancer via a liquid biopsy. The rationale is to extract as much of the molecular information as possible from a plasma sample to catch a glimpse of the possible presence of cancer. Genome-wide approaches to detect tumour-associated copy number aberrations, molecular size profile, DNA methylation signatures and transcriptomic features from circulating nucleic acids have been developed. We have further developed an approach to pinpoint the anatomical location of malignancy, naming to determine a tissue map non-invasively. In summary, many facets of molecular information could be extracted from a liquid biopsy.

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### INCREASING DIAGNOSTIC YIELD OF GENOMIC SEQUENCING

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An accurate diagnosis is an integral component of patient care for patients with rare genetic disease. Recent advances in sequencing, in particular whole-exome sequencing (WES), are identifying the genetic basis of disease for 25–40% of patients. There are a variety of reasons why up to 75% of patients might be unsolved after WES, including incomplete coverage of the exome and genetic mutations elusive to the technology itself; some of these challenges can be addressed by pursuing additional genomic technologies. From our experience, however, there are a proportion of these cases in which the disease-causing variant is in fact within the WES data but for a variety of reasons there is insufficient evidence to support a definitive diagnosis. For some of these cases, performing WES on additional family members, including affected relatives or unaffected parents, may be useful. Importantly, a significant fraction of these unsolved families will have pathogenic mutations in novel disease genes; the FORGE and Care4Rare Canada projects have demonstrated that this occurs in more than ~20% of cases. This highlights the need for critical large-scale data sharing to solve more of these intractable families.