EDITORIAL

Novel insights into cancer predisposition genes

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Many Geneticists broadly divide genetics practice into rare conditions and genetic forms of cancer. In this issue we present a selection of papers covering a Spectrum of papers relevant to cancer genetics. Bon and colleagues under took a qualitative interview study of 21 Adolescents who had had genome sequencing for cancer predisposition [1]. These young people viewed genome sequencing positively but felt that they needed accessible information resources to be involved in decision-making and also that once they reached adulthood they should be reconsented before re-analysis of the genomic data occurred. Lynch syndrome is due to pathogenic variants in the mismatch repair genes and is associated with an increased risk of several cancers, most especially colorectal and endometrial. In this issue, a Norwegian group presents two families with clinical Lynch syndrome and immuno histological evidence of loss of mismatch repair proteins but no mismatch Gene variants on exome sequencing [2]. They used optical genome mapping along with long read sequencing to identify a small insertion in the MSH2 gene. In a Danish study, whole genome sequencing of undiagnosed colonic polyp families produced a meaningful diagnostic uplift [3]. This suggests that these technologies may be clinically useful to detect cryptic variants in these cancer predisposition genes. There is evidence to suggest that a very high proportion perhaps a size 95% of the syndrome patients are not diagnosed in the UK National Health Service. In 2017 guidelines reproduced suggesting that all clerical cancer should be assessed from mismatch repair deficiency. McRonald et al report the English diagnostic pathway for the syndrome and identify a very significant gap where only a minority of colorectal tumours are being screened for mismatch period deficiency [4]. Öfverholm and colleagues report a study in which clinicians by directly to relatives at risk of inheriting a cancer predisposition Gene [5]. Family views on the acceptability of this approach were somewhat mixed. McDevitt reports EMQN guidelines for best practice in genomic testing for breast and ovarian cancer [6].

Of course in this issue we also have important work on rare genetic conditions. Harms and colleagues report an ultra rare neural developmental condition was overgrowth of the gums possibly due to dysfunction of the endolysosomal system [7]. Hadar report variants in THBS2 as a cause of a medical condition resembling Ehlers-Danlos syndrome [8]. Human and mouse model evidence is presented in support of this novel disease-gene association. Exome and genome sequencing detection of single nucleotide variants is crucial for rare condition diagnosis. Detection of short tandem repeats using ExpansionHunter analysis of exome sequencing is reported in this issue to give a small diagnostic uplift [9]. Intellectual disability is a common medical condition within the umbrella of intellectual disability there are many hundreds of individually rare monogenic conditions. Urpa and colleagues report in a Finnish population that both rare and common genomic variants contribute to intellectual disability [10]. There may be differences in the pattern of genomic causation for mild and severe intellectual disability.

It is crucial to expand what is known about the phenotype of rare conditions to inform clinical management. Aqueduct stenosis is an unusual cause of hydrocephalus, only around 10 genes known to cause this condition. In this issue recessive variants in LIG4 are reported as a cause of prenatal hydrocephalus, and the associated neuropathological changes are described [11].

Exome or genome sequencing will identify many potential causal genetic variants in an individual. But the clinical significance of these may not be known at the time of initial assessment. Best practice is considered to be re-analysis of the initial data for undiagnosed patients cipro months or years later. Whether this should be done manually or in some automatic form has not been defined. An Australian study interviewed genetic staff to ascertain their views on how workflows should be established and what the practical challenges are to exome and genome reinterpretation [12]. In this issue there was also a scoping review of the Ethical legal and social implications of genomic test re-analysis. Several themes were identified including what professional is responsible for the analysis, consent and financial constraints [13]. Malakar et al Report a study of Australian health professionals which identifies that they feel that the patients should own their genomic data [14]. The implications for genomic data re analysis could be interpreted as being that the re- analysis procedure needs to be initiated by patients.

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AUTHOR CONTRIBUTIONS

AM conceived and wrote this article.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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