VIEWPOINT

2021 at *European Journal of Human Genetics*: the year in review

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In Scotland, Hogmanay (the last day of the "auld" [old] year) is a time for celebrating the year gone by, and the year to come. What better time to look back on the research highlights from EJHG in 2021?

We begin, as we should, in January 2021. Many nations are now developing genetic screening for carriage of autosomal recessive conditions. Kirk [1] et al. describe the Australian approach to selecting which genes to include. Their approach could help guide others undertaking similar programs. Genetic testing techniques continue to evolve, with many arguing that genome sequencing will have superior diagnostic performance to exome sequencing. Bauer and colleagues [2] describe a clinical series of over 1000 people who had clinical whole genome sequencing. They provide evidence that genome sequencing may be a useful second line test after a negative exome. However, our published correspondence indicated that not everyone agrees on this.

In Spring, the February and March issues continued to provide green shoots. Agnostic genomic tests have revolutionised diagnosis of rare diseases. Such techniques are now being utilised in prenatal testing [3]. Much work remains to be done to refine the use of prenatal exome and genome sequencing. For example, should variants of uncertain significance or variants that cause adult onset diseases be reported? Gene agnostic techniques are also being applied in screening for carriage of recessive diseases. This can be of particular importance for consanguineous families. Mor-Shaked [4] and colleagues demonstrate that 10% of consanguineous couples are carriers for more than one autosomal recessive condition. This has clear clinical implications.

Genetic clinicians are clear on the clinical benefits of genomic technologies, but measuring objective utility can be problematic. A scoping review suggests that diagnostic accuracy is the most common method to assess utility of genetic tests [5]. However, patients and families may see broader utility in genomic tests.

One of the most exciting aspects of genetic research is identifying novel genomic causes of human disease. Several were published in *EJHG* in 2021. Danial-Farran et al. identified homozygous COCH variants as a novel cause of deafness [6]. Shadur and colleagues identified variants in GIMAP6 as a novel immunodeficiency [7]. *SLC30A5* bi-allelic variants were reported in May as a cause of neonatal cardiomyopathy [8]. Identifying new genes directly improve diagnostics and disseminating such work is a key task for a genetics journal.

What can case reports and case series teach us about rare genetic diseases? *EJHG* seeks to publish case reports which go into greater depth, rather than merely describing a patient with a rare diagnosis. For example, Webb [9] and colleagues describe how using phenotypic information from a murine model helped them to identify KCNJ16 variants as a cause of a human metabolic condition. In the report of a new patient affected by WNT2B variant [10], the authors added to our understanding of the gene by examining the expression of the transcript in human tissues. Reports describing novel clinical features which influence management are also welcome.

None of these publications would have been in EJHG were it not for the hard work of our section editors, editorial board, reviewers, editorial assistant in Sheffield and publishing staff. My thanks. It is fitting that I leave the last word(s) of the "auld year" to our Section Editors and editorial board: what were their favourite papers in 2021?

Felicity Boardman (Warwick) picked the paper by de Graaf et al. on the prevalence of Down syndrome in Europe [11]. This paper demonstrates the reduction in prevalence of Down's Syndrome in Europe 2011–2015 which can be directly attributed to prenatal testing and selective termination. This paper is important as, by showing variation between countries, it demonstrates the significance of social and cultural factors involved in reproductive decision-making and prenatal testing use, by demonstrating their aggregate effect.

Zoltan Kutalik (Lausanne) selected Ruotosalainen's paper on a novel GWAS analysis. There are many multi-trait association methods, but most are not amenable to simple summary statistics-based follow-up analysis. Ruotsalainen [12] et al. offers a solution to this via canonical correlation analysis, which creates an optimal univariate Linear Combination Phenotype. They apply their method to 12 highly correlated inflammatory biomarkers in a Finnish population-based study and reveal and interpret many novel associations.

Alberto Piazza (Turin) highlights the paper on the genetic architecture of Norway [13]. The main finding of this study is that despite Norway's long maritime history and as a former Danish territory, the region closest to mainland Europe in the south appears to have been an isolated region in Norway, highlighting the open sea as a barrier to gene flow into Norway.

Yves Sznajer (UCLouvain), Eaaswarkhanth Muthukrishnan (Abu Dhabi) and Zerin Hyder (Manchester) felt the special issue on SOLVE-RD was of special interest [14, 15]. The SOLVE-RD project involves a very large cohort of rare disease patients, being well powered to identify novel genetic variants and characterise phenotypes. The results of this project will be directly relevant to clinical practice.

Orsetta Zuffardi (Pavia) identified the paper on recessive inheritance of genes previously associated with dominant disease as being clinically important [16]. The concept of dominant inheritance (a single allelic variant) is being questioned, and missense variants of the other allele, even the common ones whether they are coding or not rather than regulatory, modulate the final phenotype. The next step is "Clinical genetics-it's polygenic": not only variants of the other allele but also those of the interacting genes will allow us to frame the penetrance and expressiveness of the original dominant mutation with obvious relapses in therapeutic approaches.

Dr Patrick Benusiglio (Paris) found a paper on DNA extraction from paraffin-embedded tumour tissue of use [17]. Germline genetic testing for cancer susceptibility is most informative when done on affected individuals. In this paper, Bennet et al. show that when all affected cases are deceased, NGS cancer gene panels can be performed utilising DNA extracted from formalin-fixed-paraffin-

embedded (FFPE) tumour tissue. Overall success rate was 78%, with direct surveillance and risk-reduction implications for unaffected relatives.

Reuben Pengelly (Southampton) emphasises the importance of LOVD [18]. As more and more large-scale projects generate genomic data, it becomes increasingly essential to have joined up, standardised data sharing platforms. This new version of the oft used LOVD facilitates this in a distributed yet centralisable manner, encouraging open data sharing.

Andrew Walley (London) and Claire Morgan (Swansea) highlight the van der Schoot paper on unsolicited exome findings [19]. With a low frequency of unsolicited findings (0.58%) it is clear that thousands of individuals need to be included to give useful results, and this study has managed to do this. They demonstrate that the ACMG59 list is too narrow, and give examples of categories where reporting findings is important but not covered by ACMG59.

Rengyun Liu (Sun Yat-Sen University) found the paper on genomic testing in young people with cancer useful. By performing a whole-exome sequencing in 160 unselected children with cancer and their parents, Wagener et al. [20] reported the frequency and inheritance pattern of cancer-related germline variants, and revealed that identification of the children with genetic cancer susceptibility may be more complex than expected.

Both Belinda McClaren and Erin Turbitt(Sydney) found Boardman and Clark's [21] paper on what constitutes a serious genetic condition a useful read. It is a methodologically robust mixed-methods study, providing a timely and important cue to action for the perspectives and experiences of those who have genetic conditions and their family members to prioritise in framing the language used to describe genetic conditions.

Elizabeth Bhoj (Philadelphia) selected Viuff et al's study of Turner syndrome [22]. This paper was very clear in identifying a gap in what we know about Turner syndrome and performing a well-designed systematic study to fill this. It provides important information for clinical management of Turner syndrome.

Andrew Lindsay (Dublin) picked the ESHG position statement on biobanking [23]. This policy paper clearly articulates and formalises the opposition of the European Society of Human Genetics to the potential abuses and misuses of genetic information that is now routinely being collected by a number of governments and organisations. The ESHG outline steps that can be taken by institutions, journals and life science companies to help prevent or minimise the effect of these abuses.

We would like to thank our Section Editors, Editorial Board members, publishing staff and peer reviewers for their hard work —in the face of a pandemic—during 2021.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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