EDITORIAL

Good genotype-phenotype relationships in rare disease are hard to find

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As the official journal of the *European Society of Human Genetics*, we open this month's issue with a piece introducing the Young Geneticists Network and ESHG-Young committee [1]. This explains who they are and what they hope to achieve.

Drawing robust genotype-phenotype correlations is vital for personalised medicine. In this issue, Forde et al. report a relatively mild neurofibromatosis type-1 phenotype associated with the c.2970_2972 3 base pair deletion [2]. Notably, a neurofibroma occurred in only one individual and none had gliomas. Such information is useful for clinical counselling and patient stratification in clinical trials. Identifying genotype-phenotype correlations in ultra-rare disease is often not possible. Dingemans et al. report 52 people affected by ZTTK-syndrome (*SON* variants), describing phenotypic variability even among people with the same *SON* variant [3]. Even if precise genotype-phenotype correlations cannot be identified, describing the clinical spectrum of rare diseases is important. Schröter and co-workers describe 10 new patients with *TUBA1A* variants [4]. They emphasise the clinical variability: from agenesis of the corpus callosum with autism to severe developmental epileptic encephalopathy. As with so many rare diseases, the explanation for this clinical heterogeneity is unknown.

From the above work, we can see that a single gene can be associated with significant phenotypic heterogeneity. Rarely the converse is true: a distinct phenotype linked to different genes. For example, Pallister–Hall syndrome (hypothalamic hamartoma, polydactyly) is most strongly associated with *GLI3* variants. However, Green et al. describe Pallister–Hall syndrome with bi-allelic *SMO* variants. This has clear implications for genetic diagnostics and gene panel approaches in people with Pallister–Hall syndrome and related phenotypes [5].

Clearly, polygenetic factors can explain some of the phenotypic variability seen in Mendelian diseases. Multi-locus inherited neoplasia allele syndrome (MINAS) is an example of this. Individuals can develop multiple neoplasms because they have pathogenic variants in multiple cancer genes [6]. In turn, polygenic risk, as measured by cancer-associated SNPs from Genome-Wide Association Studies (GWAS) has a role in modifying cancer risk. Dareng et al. demonstrate that polygenic risk scores for ovarian cancer are associated with ovarian cancer risk in the general population and penetrance of ovarian cancer in BRCA1/BRCA2 variant carriers [7]. A limitation of such polygenic risk scores is that they can be difficult to interpret; they do not tell an individual their absolute risk. Pain presents a method for converting polygenic risk scores into absolute risks [8]. Such statistical procedures could greatly enhance the clinical utility of polygenic risk scores.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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