Reduced Penetrance in Hereditary Movement Disorders

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Abstract

The number of genes identified as relevant for human diseases has substantially increased in recent years. This is mostly due to the advent and increased application of next-generation sequencing (NGS). An unexpected outcome of these major sequencing efforts was the identification of a surprisingly large number of carriers of an allegedly pathogenic mutation who eventually did not develop the disease in question. This phenomenon is commonly referred to as ‘reduced penetrance’.

Formally, ‘penetrance’ is defined as the conditional probability of being affected with disease X given a specific genotype. While penetrance relates to the proportion of a population actually expressing the phenotype in the context of a given genetic variant, ‘expressivity’ describes the extent to which the phenotype is expressed. In this respect, it needs to be acknowledged that ‘reduced penetrance’ is an evolving concept and in the current literature is less often used in the sense of all-or-none phenomenon than originally defined. Specifically, in conjunction with disease traits, penetrance is typically age-dependent and may border on ‘variable expressivity’ in cases of late or subtle disease manifestations or endophenotypes. Reduced penetrance is a conundrum well-documented in hereditary diseases where it initially emerged from case and family studies of monogenic disorders. However, the scope of this phenomenon appears to have been substantially underestimated and, in light of a generalized preoccupation with disease susceptibility, the concepts of protection against disease or delay of its onset age have thus far been largely neglected within the genomic research community.

One of the remarkable discoveries of the 1000 Genomes Project in 2010 was that each person carries an average of 50-100 variants previously implicated in inherited diseases. Large-scale NGS efforts, such as the 1000 Genomes Project and ExAC, allow at an unprecedented scale to assess penetrance of putatively pathogenic mutations and gene variants from the reverse perspective - based on large numbers of presumably non-diseased individuals - and to discover protective alleles. This concept offers the possibility to specifically test for modifier genes and protective alleles among at-risk individuals and to study the efficacy of therapeutics based on the so-called ‘genetics of health’.

Delineating and understanding the mechanisms underlying reduced penetrance of mutations otherwise known to cause movement disorders has a particularly high imperative given that the phenomenon of reduced penetrance may be viewed as a means of ‘endogenous’ disease protection, e.g. by significantly delaying or even preventing the development of the implied disorders. Intriguingly, elucidating the cause(s) of reduced penetrance in these and other conditions may directly contribute to a more personalized medicine even in the absence of a complete understanding of the disease mechanism itself. For instance, it is still unclear how mutations in the SGCE gene lead to the development of myoclonus-
dystonia. However, our discovery that SGCE is maternally imprinted - explaining why mutations are non-penetrant when transmitted through the mother - has enabled specific counseling of SGCE mutation carriers for more than a decade. Another striking example is that of DYT1 dystonia, in which a non-synonymous polymorphism, i.e. p.D216H (rs1801968), in TOR1A reduces the penetrance of the otherwise pathogenic TOR1A GAG deletion to 3% when present in trans to the mutated allele.

The aforementioned cases of movement disorders with a single, discernable genetic or epigenetic factor explaining the appearance of reduced penetrance not only underline the translational potential of such findings but also demonstrate that they can be discovered using relatively small sample sizes. For instance, imprinting of SGCE as the cause of reduced penetrance in myoclonus-dystonia was found based on only two families. Likewise, the penetrance-modifying effect of p.D216H on the TOR1A GAG deletion was discovered using less than 250 mutation carriers and less than 200 controls. Notwithstanding, it is likely that in many cases the drivers of reduced penetrance will be more difficult to identify, e.g. due to smaller effect sizes and/or interactions between different factors. For example, penetrance may also be influenced by ethnicity, as demonstrated for the PD gene LRRK2 showing markedly different penetrance rates of the autosomally transmitted p.G2019S mutation in Tunisian vs. Norwegian carriers. Another interesting example is XDP, which is caused by the same gene defect on the X chromosome in all affected individuals. Despite this identical cause, a broad, age-related penetrance and wide variability in disease expression is observed in mutation carriers, with ages of onset ranging from 12 to 64 years, implying the existence of yet undiscovered genetic or epigenetic factors modifying the eventual phenotype. When trying to dissect the determinants of these differences, a ‘renaissance’ of the study of monogenic or oligogenic conditions seems warranted and particularly powerful when combined with genomics and other ‘omics’ approaches, such as transcriptomics or proteomics.

Although the mechanisms by which the vast majority of the >3,000 genome-wide association study (GWAS) loci currently known to be associated with common diseases – including 28 well-established risk loci for PD - exert their pathogenic (or protective) effects are still mostly unknown, recent technological advances now provide unprecedented opportunities to elucidate these effects. Large public databases, such as the ENCODE project data or genome-wide 3D proximity maps of the human genome (e.g. 3D/virtual 4C genome browser (http://promoter.bx.psu.edu/hi-c/virtual4c.php) and HiC databases (http://hic.umassmed.edu)), provide unique resources of extensive functional genomic data that will help to close this knowledge gap. In addition, recent developments and improvements of new technologies (e.g. chromatin conformation capture assays) now also allow identifying specific interactions of selected genomic regions with other loci opening up new avenues of research to investigate the pathogenic as well as the protective functions of non-coding variants in or close to disease-associated genes.

It is the aim of the ProtectMove Consortium (DFG-sponsored Research Unit FOR2488; www.protect-move.de; starting date: December 2016) to elucidate mechanisms of reduced penetrance and endogenous disease protection in hereditary movement disorders.