CellPress

Common Grounds for Family Maladies

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https://doi.org/10.1016/j.neuron.2018.05.006

Rare variants cause Mendelian family aggregation in subsets of common diseases, and common variants may contribute to rare diseases. In this issue of *Neuron*, Gormley et al. (2018) report that the common variant burden in familial migraine is larger than in migraine of the general population.

Genetic architecture of traits is a major subject of genetics since the reconciliation of Mendelism and Darwinism in the "Modern Synthesis" early in the 20th century. Prominent in that synthesis, Fisher (1918) showed how continuous variation may result from the combined effects of many discrete genetic loci. Using liability threshold or logistic models, traits and diseases can now be assigned to specific architectures with respect to the number, effect sizes, and interactions of contributing loci and environmental influences. The spectrum of possible architectures reaches from monogenic Mendelian disorders (such as CADASIL, a progressive vascular encephalopathy with migraine due to rare, fully penetrant autosomal-dominant mutations of *NOTCH3*) to common, multifactorial disorders (such as schizophrenia or typical migraine, where common variants at multiple gene loci contribute with small effects to the pathogenesis). The respective genetic architectures determine the inheritance risks. While a fully penetrant autosomal-dominant disorder has a recurrence risk in a child of R = 50%, declining by a factor of ½ for each degree of relationship, the recurrence risk of a polygenic disorder in a first-degree relative can be approximated by the square root of its prevalence, $R = P^{½}$, with the relative recurrence risk R/P declining with the power of ½ for each degree of relationship (Risch 1990, Young 1999). Thus, with a prevalence of 1 in 7, migraine occurs in children and grandchildren of a migraineur with probabilities of $(1/7)^{½} = 38\%$ and $(1/7)^{¾} = 23\%$, respectively. The prediction of 38% fits the observation of a 2- to 3-fold increased risk among first-degree relatives (Russell et al., 1993).

Familial occurrence patterns have been used to assess the genetic architecture of common disorders such as schizophrenia (P = 1/100) in which a single locus accounting for a large proportion of the familial aggregation appeared to be incompatible with the observed data (Risch 1990). However, small subsets of various common diseases, including cancers and neurological disorders, have been found to imply single-locus mutations with high penetrance; these include BRCA mutations in breast cancer, mismatch repair gene mutations in colon cancer, mutations of the amyloid precursor protein or the APP-processing presenilins in Alzheimer's disease, deletion at 22q11.2 in schizophrenia, and mutations of the ion channels CACNA1A, ATP1A2, and SCN1A in familial hemiplegic migraine (FHM). Moreover, disorders that convey strong selective pressure, such as autism spectrum disorder or intellectual disability, which can be regarded as common if they are not subdivided by their genetic origin, turned out to have a predominant etiological contribution of rare, frequently *de novo* mutations.

Hence, a basic differentiation of genetic architectures includes the schemes "rare disease—rare variants," "common disease—common variants," and "common disease—rare variants." The fourth possibility, "rare disease—common variants," has attracted growing interest in recent years. Brugada syndrome (BrS), for instance, a rare inherited arrhythmia with a prevalence of 0.05% predisposing to sudden cardiac death, has long been regarded as a typical instance of monogenic inheritance. However, a major relation to a rare causal variant with strong effect, almost always located in *SCN5A*, could only be established in 20% of BrS families. Moreover, the penetrance of the rare *SCN5A* variants in these families is incomplete, and family members may be affected without carrying the variant. A genome-wide association study (GWAS) of common variants in BrS patients indicated that another genetic architecture may be at work. Common variants at three risk loci (*SCN5A*, *SCN10A*, and *HEY2*) were found to have a surprisingly strong effect, with an estimated odds ratio of 21.5 in the presence of more than four versus fewer than two of the 3 × 2 risk alleles (Bezzina et al., 2013). While these variants were not sufficient to completely explain familial aggregation in BrS, accounting for 7% of the variance in disease susceptibility and occurring with more than four risk alleles in 1.5% of the population, their combined effect strength indicated that common variation may contribute much more than previously assumed to the pathogenesis of at least some rare disorders.

Incidentally, *HEY2*, encoding a NOTCH-dependent bHLH class transcription factor, was also among the 38 susceptibility loci identified in a large GWAS on migraine (Gormley et al., 2016). These loci were enriched for genes expressed in vascular and smooth muscle tissues, suggesting a vascular etiology of the common forms of migraine as opposed to ion-channel-associated monogenic forms of FHM. Of note, the *HEY2* effect was much weaker in migraine than in BrS. Nonetheless, Gormley et al. (2018, this issue) have now also observed that common variation contributes substantially to familial cases of migraine. Similarly to BrS, the search for rare

variants with strong effect on migraine had much less success than expected. Therefore, Gormley et al. (2018) performed a polygenic risk score (PRS) analysis based on the migraine GWAS data and determined the PRS levels in a large collection of familial migraine cases. PRS analysis detects the common polygenic burden, since GWAS has little sensitivity in case of rare variants. For all forms of migraine, they found that the PRS was significantly higher in familial cases than in cases recruited from the general population. Subtype analysis showed that the PRS enrichment was higher in migraine with typical aura and highest for hemiplegic migraine, where it explained 8.2% of the phenotypic variance in the familial cases. Indeed, for familial hemiplegic migraine, the authors found that 45% of the families carried a common variant burden that was in the highest quartile of the PRS distribution, while only 9% carried a pathogenic mutation in one of the three known FHM genes.

Gormley et al. (2018) based their migraine PRS analysis on GWAS data recalculated after exclusion of the Finnish subset and then compared the PRS levels in Finnish population cases versus Finnish family cases. This might raise concerns, since the variant distribution in the Finnish population deviates from non-Finnish Europeans. This deviation, caused by a population bottleneck in Finnish history, is large only for rare variants, however, while for common variants as included in the PRS analysis the difference is marginal (Chheda et al., 2017). Moreover, Gormley et al. (2018) tested the PRS method for bias by deriving PRS instruments from international GWAS on other traits (i.e., IQ and schizophrenia) and determining the corresponding PRS levels in Finnish migraine cases. Neither the population cases nor the family cases displayed any enrichment in that test, confirming the validity of the method.

How to follow up on the common causal variants? The majority of them seem to influence gene regulation. Thus, epigenetics comes into play. Hannon et al. (2017) recently showed that, both in whole blood and fetal brain, the significance profiles ("Manhattan plots") of the common variants acting on DNA methylation site cg05901451 in the 5′ untranslated region of *HEY2* are highly comparable to that of the migraine GWAS. At the *HEY2* locus, the same genetic signal seems to influence both DNA methylation and susceptibility to migraine, as well as, potentially, BrS. For another migraine GWAS locus (at chr 6p24, which is also associated with blood pressure and vascular traits, albeit with variable direction), Gupta et al. (2017) recently showed an effect on the expression of vasoactive endothelin 1, encoded by a gene 0.6 Mb from the causal variant. Interaction between variant and gene may involve a histone-acetylation-marked super-enhancer.

A generation ago, the then-available tools of molecular genetics allowed for discovery of rare monogenic causes in common diseases. Now, with big data genomics, the inverse perspective on the common polygenic burden in familial diseases has opened up. As Gormley et al. (2018) emphasize, their results in migraine are consistent with analogous findings in other common diseases such as dyslipidemia and Alzheimer's disease. Explicitly, however, they do not exclude the contribution of both common and rare variants to the genetic architecture. Allelic series of variants affecting the same gene with increasing effect size and declining allele frequency do exist, as in case of the BrS gene *SCN5A*, for instance. Rare variants may therefore undergo a revival, especially those whose effect sizes are not strong enough for a classical monogenic disorder but are much stronger than the average common susceptibility factor. As yet, these variants are notoriously difficult to identify because they are too rare for array-based GWAS and too weak for linkage analysis. Genome sequencing of large cohorts may soon provide some relief.

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