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Cluster headache (CH) is a debilitating, fairly rare primary headache disorder that affects about 0.1% of the population.[1] It is characterized by strictly unilateral attacks lasting 15 to 180 minutes, occurring up to 8 times a day, often, repeatedly at the same time of the day, accompanied by at least one autonomic symptom ipsilateral to the pain or a sense of agitation, or both.[2] Treatment options have long been limited, but recent studies have provided new options.[3]

The pathophysiology of CH remains unclear. Yet, neurovascular processes involving the trigeminovascular system, trigeminal autonomic reflex, and posterior hypothalamus, including inflammation, are hypothesized.[4]

The tendency for CH to occur in multiple members of some families suggests that genetics could help in unraveling underlying disease mechanisms of CH. The aim of genetic studies is to identify genes and variants associated to a disease, interpret phenotype correlations, and glean insight about cells and molecular pathways that guide to meaningful follow-up experiments.

So far, genetics has not provided much insight into the biological mechanisms of CH. Familiar clustering and a substantially increased disease risk for first degree relatives of patients with CH up to 18 times higher than that in the general population have been reported. Even for second degree relatives, the risk seems to be somewhat elevated.[5] The existing evidence stimulates a hypothesis of polygenic predisposition. As in all complex diseases, the genetic predisposition does not act in isolation. Lifestyle and environmental risk and triggering factors include smoking, alcohol, stress, and use of nitroglycerin contribute as well.[6]

The rarity of the disease has made it difficult to collect sufficiently large samples for meaningful genetic studies. In most complex diseases, the polygenic nature and small effect of each associated variant requires samples of thousands or tens of thousands of cases and controls to provide sufficient power for genomewide association studies (GWAS). For a disease like CH, with a prevalence in the order of one in 1,000, the study design requires multisite collections and large international consortia. Thus, earlier genetic studies of CH have mostly been underpowered and have not resulted in findings that would robustly replicate.

In this issue of Annals, 2 papers by Harder et al[7] and O'Connor et al[8] demonstrate for the first time robust genetic associations to CH, using a classical case control GWAS design. This is the first evidence to demonstrate that there are genetic variants that contribute to CH predisposition. These studies lay the groundwork for developing even larger studies that would identify even more loci and stimulate follow-up functional experiments.

The 2 studies in this issue of Annals combined identify 7 genetic loci associated with CH. We are still in the early days of investigation, and the number of associated loci is still too low to allow identification of potential cellular pathways of functional significance in CH. However, there are some interesting aspects to highlight.

First, although the sample size in both studies is relatively small, they independently identified the same 4 loci. This is obviously a consequence of the slightly higher effect size of each variant (odds ratios between 1.31 and 1.54) than in many other complex diseases. In addition, 2 of the 3 additional loci identified in the joint analysis have odds ratios in the range of 1.24 to 1.87. It is early to interpret whether the slightly higher odds ratio reflects a more precisely defined phenotype compared to GWAS of many other complex traits, or whether they are a reflection of fewer, more strongly acting genetic variants. The former hypothesis is supported by the observation that about doubling of the sample size provided 3 more associated loci, indicating that increasing the sample size is likely to result in more associated loci with weaker effects.

Second, one of the questions has been how much overlap would there be in the genetic background of CH and other headache disorders, like migraine? Interestingly, 5 of the 7 identified genetic loci are only observed in CH, and do not overlap with other headache disorders. Two loci overlap with previously reported migraine loci, the locus on Chr 10 (rs 10786156), with PLCE1 as the

nearest gene and the locus on Chr 6 (rs2499799 and rs11153082) with FHL5 as the nearest gene. The FHL5 locus is one of the most robustly associated migraine loci, with little if any associations to other diseases. The lead variant rs10786156 is in the intron of the PLCE1 gene and is also associated to hypertension (https://www.finngen.fi/en/access_results). Functional consequences of intronic and intergenic variants, including their potential pleiotropic impact, should be interpreted with caution. The 2 papers[7,8] thus suggest that a large component of the genetic susceptibility is relatively specific to CH and a smaller component shared with other headache disorders, like migraine.

The number of loci is still small for meaningful pathway analyses. The authors report that genes nearest to the identified loci are expressed in the brain. Although this is in line with the clinical phenotype, as a very large fraction of human genes are expressed in the gene, this observation provides limited insight for the next steps. O'Connor et al[8] also suggest a relationship with immunological processes, the CREB pathway, and the circadian clock. The last of these is of interest considering the tendency for CHs to recur at the same time of day.

These 2 papers[7,8] turn the page in CH research. They bring CH research from the shadows to the center stage by providing, for the first time, hard biological evidence of a genetic component contributing to this disabling headache disorder. Yet, GWAS is only the first step. GWAS typically identify loci, not causal variants. The path from locus to variant and function requires extensive follow-up research. This is complicated by the fact that most GWAS lead variants are not coding variants but variants that are located in regulatory regions of the genome, and thus more challenging to study. The path from locus to variant and function is a major stream of basic medical research, although the need to tailor functional techniques limits high-throughput analysis and makes navigating this stream more difficult than identification of a single locus associated with a disorder. Yet, it appears that CH has become one on a growing list of diseases where there is a prospect that genetics and functional studies together can move the field forward.

Potential Conflict of Interest

The author declared no conflict of interest.

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