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Editorial

EDITORIAL

Progress in the genetics of restless legs syndrome: the path ahead in the era of whole-genome sequencing

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Restless legs syndrome (RLS) is a common neurological disorder characterized by an urge to move the legs, particularly in the evening and at night [1]. Epidemiological studies have shown that 5%–15% of European and North American populations suffer from RLS, whereas the prevalence is lower in most Asian populations, ranging from 1% to 3% [2]. Because of its high prevalence, RLS leads to an important social and economic impact by disrupting sleep, affecting work productivity and the quality of life.

Twin and familial aggregation studies have suggested that genetic factors contribute up to 70% of the risk of developing RLS [3, 4]. Linkage studies in multiplex families have identified several large genomic regions [5, 6], but to date, no definitive causal variant or gene has been identified based on this work. Genome-wide association studies (GWAS) have robustly identified many predisposing loci. A recent meta-analysis identified 22 RLS predisposing loci in individuals of European ancestry [6–8]. However, these variants only explain approximately 20% of the heritability [7]. Several small-scale hypothesis-based candidate gene studies were performed for RLS, none of which have been replicated in additional populations [5].

In this issue of *SLEEP*, Schormair et al. [9] analyzed previously reported RLS associations for replication in the International EU-RLS-GENE Consortium GWAS dataset that includes 6228 RLS cases and 10992 controls of European ancestry [7, 9]. They showed that candidate variants and genes identified in these small-scale hypothesis-based candidate gene studies were not validated in the EU-RLS-GENE dataset. Because the Schormair et al. study was sufficiently powered to detect these reported associations, the authors concluded that these previous reports were likely to be false-positive, and that future studies with larger sample sizes as well as stringent significance thresholds are needed to obtain reliable associations in RLS. This study confirms that small association studies are not suitable to identify common variants in RLS [10].

This negative study highlights the fact that the currently known variants account for only 20% of the RLS genetic risk, and so a large fraction of the heritability remains to be discovered [7]. Where is this missing heritability? One source may be intermediate frequency variants with moderate effect sizes. Another may be variants that remain difficult to find using technology used to date, such as repeat sequences and insertion/deletion variants. Third, the variants identified in the GWAS studies are likely not the biologically causative variants responsible for the signal. Finding these biologically active variants will allow a more precise measure of the contribution of these loci to the risk of developing RLS. The decreasing cost of next-generation sequencing will allow the generation of whole-genome sequencing data on large cohorts, enabling the search for all these possible sources for the missing heritability. Emerging technologies, such as long-read sequencing will also facilitate the detection of disease-related structural variants, such as large insertions, deletions, and repeat expansions.

Most large-scale RLS genetic studies included mainly patients of European ancestry [7, 8]. The genetic factors predisposing to RLS in other populations need to be studied. Some may be like those found in the European descent population, but surely other genetic factors are at play in these other population.

Finally, molecular studies aimed at understanding the biology of RLS, and the roles of the known loci in disease pathogenesis will define pathways critical to the disease. This knowledge can be used to better focus genetic studies and identify or validate new factors predisposing to RLS.

Taken together, although 15 years of genome-wide efforts identified several risk loci, whole-genome sequencing analysis, the inclusion of diverse populations, and biological studies will be essential to unravel the genetic mechanisms leading to RLS.

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