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NEWS AND COMMENTARY

LINGO1 and Essential Tremor: linking the shakes

Linking LINGO1 to essential tremor

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Essential tremor (ET), one of the most common neurological conditions, is characterized by postural and action tremor.[1] The prevalence has been reported to be as high as 39 cases per 1000. As a family history of ET is frequently present among those affected, extensive efforts have been taken to identify the responsible genes. However, though linkage regions in chromosome 3q13 (ETM1), 2p22-p25 (ETM2) and 6p23 have been identified in Icelandic and North American families, the causative gene has yet to be unraveled.[2] The first genomewide association study (GWAS) in ET identified a sequence variant (rs9652490 G allele) of the *LINGO1* gene to be a risk factor in European and American populations.[3] This finding is exciting as the estimated population-attributable risk of the variant (20%) is relatively high and the effect appears to be driven primarily by a specific allele and not by the surrounding SNPs. Some skepticism remains as ET is widely recognized as a clinically heterogeneous condition and clinical diagnosis may not be always accurate.

Replication in independent cohorts and ethnicity remains the barometer for the validity of genetic association studies. Clark *et al*[4] conducted a replication study in a North American cohort and genotyped 15 SNPs in the *LINGO1* gene. Compared with most ET genetic studies, this study helps to provide additional insights primarily through a more robust methodology, whereby cases and controls were recruited as part of an ongoing epidemiological study, all of them were clinically well annotated, and the diagnostic criteria were applied uniformly through standardized screening and examination. Specifically, Clarke *et al* were able to evaluate subsets of 'definite', 'probable' or 'possible' cases and showed that the strength of association with rs9652490 was stronger in those with a more definitive diagnosis. They also alluded to the interesting observation that three other SNPs within a 2.3k haplotype (rs177008, rs13313467 and rs8028808) were associated with younger ET (age at onset <40 years) patients. The study by Clarke *et al*, together with the two currently available replication studies,[5,6] provides collaborative evidence that *LINGO1* rs9652490 is associated with ET. However, the varying strength of association with additional SNPs and the implication of different alleles of rs9652490 also suggest that this SNP may not be the functional variant but may be in linkage disequilibrium with unknown functional variants in the vicinity. Furthermore, the SNP is located in intron 3 and there is no clear evidence that it is predicted to alter splicing or affect protein function.

Based on current limited evidence, it is reasonable to be optimistic that elucidation of the link between *LINGO1* and ET is an important first step in genetic dissection of the condition. However, the current excitement has to be somewhat tempered with a reminder that initial observations linking *HS1-BP3* and *DRD3* gene variants to ET have not been consistently replicated. While we draw lessons from previous experiences, it is timely to highlight the potential pitfalls in dealing with genetics of complex disorders such as ET, and the unique problems specific to the condition, some of which have been exemplified in the GWAS study[3] and in the report by Clarke *et al*.[4]

Advances in technological genotyping platforms have improved the sensitivity of GWAS, and, with the lowering of financial cost, accessibility and feasibility, this will become less of an issue in most countries. However, it is important to recognize that the major limitation in genetic association studies in ET is a fundamental one. A case definition of ET is problematic without a biological or objective diagnostic marker. ET is essentially a clinical diagnosis and despite proposed diagnostic criteria by experts in the field, we do not know for certain whether ET is a single disorder or a disease syndrome with varied etiologies.[1] Some people with ET also have other associated movement disorders, while others progress to develop Parkinson's disease years after the initial ET diagnosis. Even limited post-mortem studies seem to suggest that the condition is likely to be heterogeneous. Most cases have cerebellar changes without Lewy bodies, whereas intriguingly some cases have brainstem Lewy bodies.[7] It is arguable whether the inclusion of the latter group would compound genetic association studies. One study showed that one in three patients with tremor have been wrongly diagnosed as having ET.[8] These problems are further exacerbated by the varying diagnostic criteria used by authors with varying degrees of expertise in managing this disorder.

Although most studies would suggest that at least 40−50% of their cohorts have a positive family history, many genetic association studies do not attempt to differentiate the familial from the sporadic group. For example, in the GWAS study,[3] familial and sporadic ET was either analyzed as a group or no information on the specific group of ET patients was provided. It would be interesting to determine how the overall effect size of the association will be affected if only familial or sporadic cases were examined. To compound the problem, many patients may not be aware of other family members with ET and their condition may remain undiagnosed. One study estimated the sensitivity of family history data given by ET patients to be around 40%.[9] This poses a challenge in clinical classification and can have an impact on the interpretation of large-scale population genetic studies in which family history may well be relevant.

The issue of age-dependent penetrance in ET is rarely highlighted. Similar to ET patients, many apparent healthy controls with essential tremor may not be aware of their tremor. Thus, in ET case–control studies, the controls should preferably be physically examined by an expert or subjected to standardized screening procedures, and their ages should preferably be similar or greater than those of ET patients. In the GWAS study[3] the 14 393 Icelandic controls were apparently not screened for ET, and in the two follow-up studies in Austria and Germany the median age of controls was about 20–25 years lesser than that of ET patients. It is unclear how these would have influenced the reported effect size difference.

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It is also interesting to highlight that genetic studies on ET in the literature (including the GWAS study) involved a relatively small number of ET cases. Thus, small effect size difference or rare at-risk variants may be missed. The current replication study by Clark *et al*[4] recruited 257 ET cases and the sample size was underpowered for many of the subset analyses. It is possible that there is a selection bias for the more severe cases that present to the tertiary centers and the investigators are only analyzing the 'tip of the iceberg'. The vast majority of ET patients in the community may well have a milder phenotype and are unlikely to participate in studies; thus, specific endo-phenotypes may be missed.

Despite these caveats, the positive replication of rs9652490 and the biological evidence that LINGO1 is involved in the regulation of neuronal survival and axonal regeneration warrant further efforts to evaluate this locus across different races and a multi-center collaborative effort to better define subsets of ET patients who are at greater risk and to explore the potential gene–environmental effects. Multiple approaches using different genetic methodologies are likely to be required to uncover additional variants or causative genes and susceptibility loci.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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