COMMENTARY

The Search for Apnea Genes

Commentary on Thakre et al. Lack of Association of the APOE ε4 Allele with the Risk of Obstructive Sleep Apnea: Meta-Analysis and Meta-Regression. Sleep 2009;32:1507-1511.

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EVER SINCE THE FIRST DESCRIPTION OVER 30 YEARS AGO OF A FAMILY WITH MULTIPLE CASES OF OBSTRUCTIVE SLEEP APNEA (OSA),[1] INVESTIGATORS have attempted to identify genes predisposing to this disease. The variant that has garnered the most attention thus far has been the ε4 haplotype of the apolipoprotein E (APOE) gene, already recognized as a risk factor for Alzheimer disease. In this issue of *SLEEP*, Thakre and colleagues perform a meta-analysis summarizing the evidence for an association between APOE ε4 and OSA.[2] Combining data from 8 cohorts and over 6500 individuals, the authors conclude the evidence is poor that the ε4 haplotype increases OSA risk. It has been argued that the OSA - APOE ε4 relationship is strongest in younger populations and wanes with age.[3] Performing a meta-regression on age, Thakre et al were unable to find support for this contention.[2] However, with only 8 studies, some with very wide age ranges, the power to detect a relationship was likely poor.

How the APOE gene, which codes for a chylomicron component, might impact OSA risk is unclear. Might altered lipid levels somehow impact OSA risk? Might the neurofibrillary tangles and amyloid plaques found in Alzheimer disease occur in hypothalamic or brainstem regions relevant to regulating upper airway motor output or sleep/wake state? The answers to these questions are unknown because little research has been conducted to study OSA-related traits in APOE knockout mice or other relevant models.

Given the lack of a clear biological mechanism, the focus on APOE in OSA genetic research is surprising, particularly when compared to the effort spent on studying genes that have a stronger biologic basis for a role in OSA pathogenesis. Serotonergic genes would seem to be strong candidates given the known role of serotonin in modulating upper airway muscle tone, sleep/wake state, and appetite. Yet, a PubMed search cross-referencing "serotonin," "gene," and "obstructive sleep apnea" identifies just 5 studies, none with more than 300 cases, examining polymorphisms in only 3 genes involved with serotonin neurotransmission. Even worse, no published study has yet assessed the role of FTO, the strongest genetic risk factor for obesity,[4] in OSA pathogenesis.

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The Thakre et al meta-analysis highlights several important limitations in the APOE literature that likely generalize to the entire field of OSA genetics at present.[2] For example, despite a borderline P-value, the Egger's plot displayed in Figure 1B strongly suggests the presence of a selection bias in the studies identified for inclusion in this meta-analysis. Smaller studies tended to report more positive results than larger studies, suggesting small negative studies were excluded. Both a publication bias favoring positive results by journal editors and a time lag bias delaying the reporting of negative results by investigators can contribute to this problem.[5, 6] The growing push for repositories where results from genetic studies may be made readily available would help solve this problem by allowing easy access to both positive and negative results. Such a repository would also allow for a meta-analysis of individual level (rather than study level data),[7] providing greater power, for example, in assessing whether age acts as an effect modifier on the OSA - APOE relationship.

A second limitation is that most of the studies included in this meta-analysis only assessed ε4 haplotype status. Thus, whether or not another polymorphism in the APOE gene might cause OSA remains unknown. Linkage data from the Cleveland Family Study suggest a risk allele other than ε4 lies in or close to the APOE gene.[8] Findings from a small pediatric study using a tag single nucleotide polymorphism (SNP) approach to infer genotype status across all common polymorphisms in APOE support the presence of a risk allele that is not necessarily part of the ε4 haplotype.[9] This tag SNP approach is sorely needed in future OSA genetic studies to provide a more comprehensive assessment of candidate genes.

Another issue highlighted by this meta-analysis is that even with over 6,000 subjects, an odds ratio of 1.13 cannot be statistically distinguished from the null hypothesis.[2] This effect size is not unrealistic in complex disease genetics. For example, a polymorphism in the melatonin receptor 1B (MTNR1B) gene increases diabetes risk 1.09-fold.[10] Thakre et al perform a power calculation suggesting over 10,000 subjects would be required to reliably identify such an association.[2] These results underscore the need for collaboration across institutions. Success in identifying susceptibility genes for restless legs syndrome (RLS) and narcolepsy have relied on multinational collaborations.[11-13]

Based on their findings, Thakre et al call for genome-wide association studies (GWAS) in OSA.[2] Certainly, the relative lack of knowledge regarding the molecular basis underlying OSA suggests that GWAS, which does not require a priori bio-

logic knowledge, may be more productive than candidate gene studies. The success of GWAS at identifying associations that could never have been predicted from current understanding of pathogenesis in other diseases (e.g., BTBD9 and RLS or MTNR1B and diabetes),[10,11] demonstrates the utility of this study design. However, the substantial reduction in power that results from needing to account for the 1 million or more comparisons made in GWAS necessitates enormous sample sizes. Thus, a role continues to exist for smaller candidate gene studies, so long as a strong biologic rationale exists for selecting specific candidates.

Whatever the study design, it behooves researchers (and journal editors) to ensure future OSA genetic studies are adequately powered to identify meaningful effect sizes and have genotyped a sufficient set of SNPs to reliably identify an association with any common polymorphism in that gene. Genetic epidemiology has lived up to its promise in identifying the molecular basis for an increasing number of diseases. It is time for the OSA research community to demand genetic studies of the quality that our colleagues studying other sleep disorders have been able to perform. There are certainly enough patients with OSA being evaluated each night in sleep labs around the world to adequately power the needed studies.

DISCLOSURE STATEMENT

Dr. Patel has indicated no financial conflicts of interest.

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