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GENETIC DETERMINANTS OF CARDIOMETABOLIC AND PULMONARY TRAITS AND OBSTRUCTIVE SLEEP APNEA IN THE HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS

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Introduction: Obstructive sleep apnea (OSA) often co-occurs with other health outcomes. The respiratory event index (REI), often used to define OSA, is similarly correlated with several health phenotypes. Genetic data provide an opportunity to explain the nature of these associations.

Methods: We used data from the Hispanic Community Healthy Study/Study of Latinos (HCHS/SOL) to estimate genetic correlations (i.e., the correlation between phenotypes that is due to genetic effects) between OSA severity as measured by the REI and 56 anthropometric, glycemic, cardiometabolic, and pulmonary traits. Genetically-correlated traits (>0.2 and p-value<0.05) were carried forward for additional analysis. Using summary statistics from published genome-wide association studies (GWAS), we constructed Polygenic Risk Scores (PRSs) representing the genetic basis of each correlated trait and OSA, and studied their associations with the genetically-correlated traits, REI and OSA. OSA was defined as REI5. When a PRS for a correlated-trait was associated (p-value<0.05) with REI/OSA or vice versa, we used GWAS summary statistics to test causal relationships using Mendelian Randomization (MR) analysis. We further estimated correlated-trait PRS associations with REI and OSA in subgroups of individuals with and without obesity (BMI>30).

Results: The dataset included 11,155 participants (mean age: 46.2 (SD =13.8) years; 41.1% males) from the baseline HCHS/SOL exam who underwent home sleep apnea testing. 30.65% had OSA. 22 traits were genetically correlated with REI. Without BMI adjustment, the PRSs of BMI, waist-to-hip ratio (WHR), diastolic blood pressure (DBP), pulse pressure (PP), HbA1c, triglycerides (TG), FEV1/FVC and insomnia were significantly associated with REI/OSA. The associations of WHR, DBP, PP, HbA1c and insomnia PRSs and REI/OSA remained in BMI adjusted analysis. In obesity-stratified analysis, PRS of BMI, WHR and DBP were associated with REI/OSA in individuals with obesity, while PRSs of FEV1/FVC, HbA1c, insomnia, PP, TG, and WHR were associated with REI/OSA in individuals without obesity. MR analysis identified robust causal effect of increased BMI on OSA, and suggestive causal effects of WHR, DBP, and PP on OSA.

Conclusion: Our results support shared genetic basis of anthropometric traits, blood pressure traits, and insomnia with OSA, with potential differences in disease mechanisms in individuals with and without obesity.

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ENRICHMENT OF RAI1 GENETIC ABERRATIONS ASSOCIATED WITH SLEEP DISTURBANCES IN SMS, IN AUTISM SPECTRUM DISORDER

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Introduction: Autism Spectrum Disorder (ASD) comprises a complex of neurodevelopmental disorders primarily characterized by deficits in verbal communication, impaired social interactions and repetitive behaviors. The profound clinical heterogeneity of ASD poses challenges in diagnosis and treatment. Genetic studies have pointed to hundreds of presumptive causative or susceptibility variants in ASD, making it difficult to find common underlying pathogenic mechanisms and suggesting that multiple different genetic etiologies for ASDs influence a continuum of traits. Smith–Magenis syndrome is a rare genetic disorder that results from an interstitial deletion of 17p11.2 and, in rare cases, from a retinoic acid induced 1 (RAI1) gene variant. The prevalence is estimated to be 1/15,000–25,000. Haploinsufficiency of RAI1 is the primary cause of the neurobehavioral and metabolic phenotype in SMS. Individuals with SMS present with a distinct pattern of mild to moderate intellectual disability, delayed speech and language skills, distinctive craniofacial and skeletal abnormalities, behavioral disturbances, and, almost uniformly, significant sleep disturbances. Alterations in RAI1 copy number has been also linked to a number of neurodevelopmental disorders including ASD.

Methods: We conducted a large-scale association analysis of the ASD MSSNG whole genome sequencing data to elucidate the prevalence of RAI1 SNVs and CNVs in the ASD population. We accessed the MSSNG database hosting over 11,000 genomes (6080 probands) and queried both SNVs and CNVs.

Results: Specifically, we focused on the prevalence of the classic deletions, microdeletions of (exon 3) and of the causative variants. We report a single case of a classic deletion (17p11.2 critical region), and an additional 3 cases of microdeletions in exon 3. Moreover, we report 2 frameshift mutations and one splicing variant. Given that the frequency of SMS is 1 in 15000 in the general population, we observe a 2.5x enrichment of the major deletion (1 in 6080 samples) and a >5x enrichment of the frameshift variants (2 in 6080 samples). In a set of 6080 probands we also observed 54 unique missense variants in 84 individuals within exon 3 of RAI1 gene.

Conclusion: Both ASD patients and SMS patients suffer from sleep disturbances. In this population of individuals with ASD, we report here an enrichment of variants known to cause SMS. We estimate the enrichment to be at least 2.5-fold and potentially higher than 10-fold enrichment, considering the types of variants observed in the population. Currently, the prevailing theory is that there is an underlying circadian pathophysiology causing sleep disturbances in SMS associated with RAI1 haploinsufficiency, as these patients exhibit low overall melatonin concentrations and abnormal timing of peak plasma melatonin concentrations. This abnormal inverted circadian rhythm is estimated to occur in 95% of individuals with SMS. The sleep disturbance seen in individuals with SMS may be also the underlying mechanism in at least a subset of individuals with ASD, especially in those individuals with consequential variants in the RAI1 gene Further studies will help delineate the role of RAI1 variants in sleep physiology.

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