Introduction

• Sleep apnea, a sleep disorder, is characterized by uncontrollable pauses or repetitive periods of shallow breathing
• It affects approximately 3% to 7% adults, and is associated with increased risk for diabetes, cardiovascular conditions and premature mortality
• The genetic basis of sleep apnea is still not yet well understood, and research has been limited by the relatively small numbers of participants

Objective

To investigate associations between genetic risk loci, BMI, and risk of sleep apnea in individuals of European descent

Methods

Study Population
• Genotyped customers of European descent who were consented to 23andMe research

Outcomes
• “Have you ever been diagnosed with, or treated for, sleep apnea?”
• Self-reported sleep apnea (Yes/No)

Statistical Analyses
• Genome-wide association study (GWAS) using logistic regression, with sleep apnea as the dependent variable
• Covariates: age, sex, BMI, and ancestry-informative principal components (PC) 0-4
• Sex-stratified GWAS

Results

GWAS
• N = 1,477,352: 175,522 (Case), 1,301,830 (Control)
• Null model
  a. Age: 52±18.4, OR: 1.04, P<0.05
  b. Sex (female): 28.7%, OR: 0.49, P<0.05
  c. BMI: 27±5.9, OR: 1.14, P<0.05
• 59 genome-wide significant hits (Figure 1)

GWAS Results (cont.)
• We identified the following hits:
  1. Lead SNP: rs2336715 (near MSRB3, OR: 0.96, P = 1*10^-10) (Figure 2)
     a. Located on Chr 12
     b. MSRB3: previous GWAS suggested that it was related to snoring [UK Biobank], lung function [1] and FEV1/FVC ratio [2]
  2. Lead SNP: rs8105474 (near TSHZ3, OR: 0.62, P = 1.7*10^-12) (Figure 3)
     a. Located on Chr 9
     b. TSHZ3: expressed in multiple area of the brainstem involved in respiration, including pre-Bötzing complex (preBötC), embryonic parafacial respiratory group (e-pF), and cranial motoneurons that control upper airways
     c. TSHZ3: a key regulator of neonatal breathing behavior in mice; loss of function is embryonic lethal [3]; cofactor of HOX proteins in Drosophila [4]

Results (cont.)
• We also identified the following hits, which have been found in previous research:
  1. Sleep duration
     a. rs12594780 (SEMA4D, OR: 1.03, P = 2.7*10^-11)
     b. rs11030298 (METTL15, OR: 0.97, P = 2.6*10^-11)
  2. Snoring
     a. rs592333 (DLEU1-β-DLEU7, OR: 1.04, P = 4*10^-10)
     b. rs2760194 (GATA3, OR: 1.04, P = 2.4*10^-12)
  3. Sleeplessness/insomnia
     a. rs2587359 (OLFM4, OR: 0.96, P = 4.3*10^-10)

Sex-stratified GWAS
• Female
  a. 68,149 (Case), 729,369 (Control)
  b. 8 genome-wide significant hits
• Male
  a. 107,373 (Case), 572,462 (Control)
  b. 22 genome-wide significant hits
• Female & Combined
  a. rs9884482 (TET2, OR: 0.96, P = 1*10^-10)
  b. rs6861421 (GRIA1, OR: 0.96, P = 1*10^-10)
• Male & Combined
  a. rs2760194 (GATA3, OR: 1.04, P = 1*10^-11)

Discussions

Our Findings
• Our study is the largest sleep apnea GWAS study to date, and we identified 59 genome-level significant associations with sleep apnea in the population of European descent
• Multiple genes in associated regions had plausible sleep apnea related functions, including TSHZ3 and MSRB3

Potential Limitations
• Self-reported data
• Only focused on individuals of European descent: no consistent evidence of association for the top SNPs in other ethnic groups, including Hispanic [5] and Korean population [6]
• Only focused on sleep apnea: no consistent evidence of association for the top SNPs in other related traits, including obstructive sleep apnea (OSA) and apnea-hypopnea index (AHI) [5-6]

Conclusions
• Our findings highlighted sleep apnea susceptibility genes in individuals of European descent
• Further research in various ancestry groups is needed to evaluate these potential relationships in more detail

Acknowledgements & References

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