Genetic Associations with Sleep Apnea in a Population of European Descent

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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: 27.3±5.9, OR: 1.14, $P < 0.05$
- 59 genome-wide significant hits (**Figure 1**)

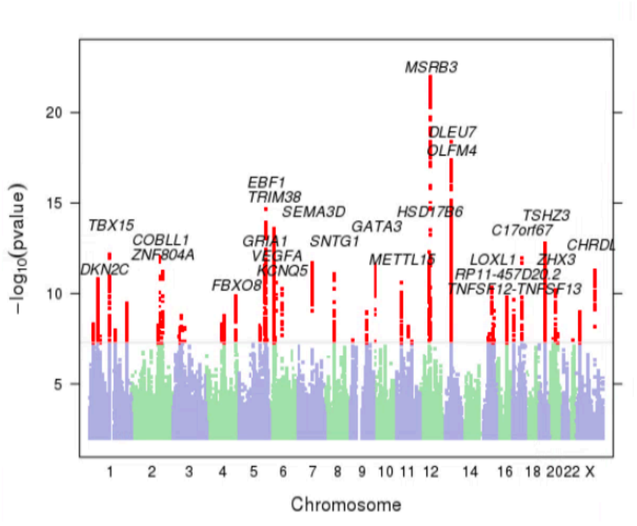

Figure 1. Manhattan plot of GWAS results

- Our most significant hit appeared to involve a structural variant on the X chromosome; While it was intriguing, we did not have the resources to explore it sufficiently to report on it at this time

Results (cont.)

- We identified the following hits:
  1. Lead SNP: rs2336715 (near *MSRB3*, OR: 0.96, $P = 1^* 10^{-22}$) (**Figure 2**)
     a. Located on Chr12
     b. *MSRB3*: previous GWAS suggested that it was related to snoring [UK Biobank], lung function [1] and FEV1/FVC ratio [2]

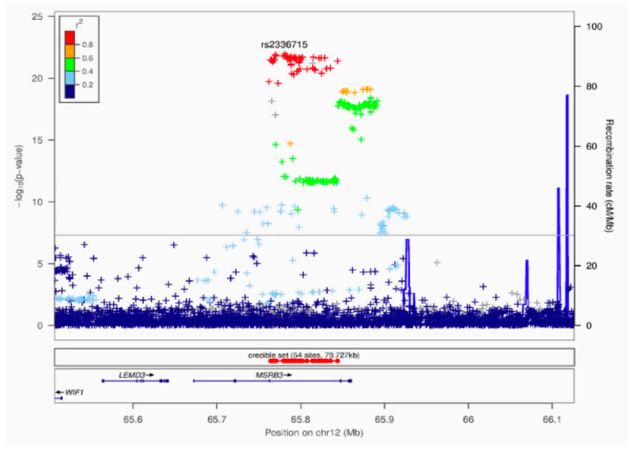

Figure 2. Regional association plot of the *MSRB3* locus

  2. Lead SNP: rs8105474 (near *TSHZ3*, OR: 0.62, $P = 1.7^* 10^{-13}$) (**Figure 3**)
     a. Located on Chr 9
     b. *TSHZ3*: expressed in multiple area of the brainstem involved in respiration, including pre-Bötzinge 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]

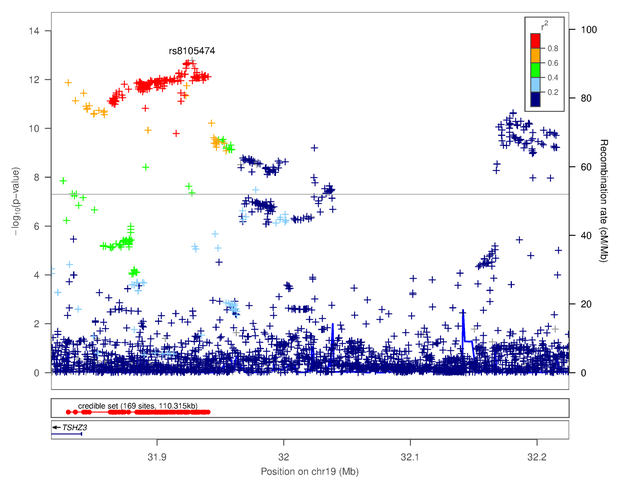

Figure 3. Regional association plot of the *TSHZ3* locus

  d. Conditional analysis in this GWAS: rs10415992 ($P = 3^*10^{-10}$) (**Figure 4**)

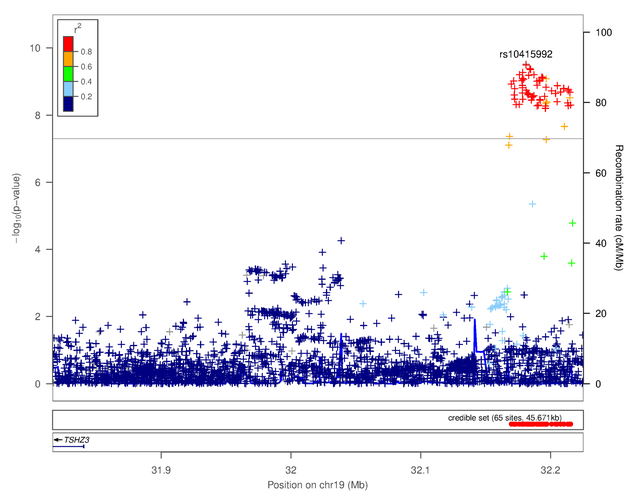

Figure 4. Regional association plot of the *TSHZ3* locus conditionally on rs8105474

Results (cont.)

- We also identified the following hits, which have been found in previous research:
  1. Sleep duration
     a. rs12594780 (*SEMA6D*, OR: 1.03, $P = 2.7^* 10^{-8}$)
     b. rs11030298 (*METTL15*, OR: 0.97, $P = 2.6^* 10^{-11}$)
  2. Snoring
     a. rs592333 (*DLEU1-[]-DLEU7*, OR: 1.04, $P = 4^* 10^{-19}$)
     b. rs2760194 (*GATA3*, OR: 1.04, $P = 2.4^* 10^{-12}$)
  3. Sleeplessness/insomnia
     a. rs2587359 (*OLFM4*, OR: 0.96, $P = 4.3^* 10^{-18}$)

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, $P = 1^* 10^{-8}$)
  b. rs6861421 (*GRIA1*, OR: 0.96, $P = 1^* 10^{-8}$)
- 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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1. Wain LV, et al. *Nat Genet,* 2017; 49(3): 416-425
2. Lutz, Sharon M. et al. *BMC Genetics*, 2015; 16: 1-11
3. Caubit X, et al. *J Neurosci*, 2010; 30(28): 9465-76.
4. Taghli-Lamallem O, et al. *Dev Biol,* 2007; 307: 142–151
5. Cade B, et al. *Am J Respir Crit Care Med*, 2016; 194(7): 886-897
6. Baik I, et al. *Sleep,* 2015; 38(7): 1137-1143