Real-World Evidence Synthesis on the Sex-related Modifying Effects of GNAS SNPs on Development of Periprosthetic Osteolysis in Hip Arthroplasty

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INTRODUCTION

Although hip arthroplasty procedures tend to be performed more frequently among females, our previous study (*Clin Transl Sci 2020*) suggested that Periprosthetic Osteolysis (PO) is more frequent among males and that this male predominance may involve the sex-dependent role of rs7121 SNP in GNAS gene. In the current study, we identified GNAS locus SNPs linked to rs7121 by linkage disequilibrium (Ensembl) and further explored potential GNAS effects in the sex-related development of PO in hip arthroplasty.

METHODS

Genetic and epidemiologic information on hip arthroplasty (GNAS SNP genotypes and ICD9/10-based diagnoses/procedures, respectively) was derived from the NHGRI/NIH-supported eMERGE Network. Four sex-stratified cohorts with or without PO (CTRL_Male, CTRL_Female, PO_Male, PO_Female) were constructed for calculating allele frequencies in the rs7121-linked SNPs and analyzing comorbidities in relation to PO. Time-to-PO was calculated within the sex/ genotype stratified subgroups and assessed using Wilcoxon rank sum tests. HIVE platform and analytic tools were used for all GNAS SNP and comorbidity related analyses.

DISCUSSION / CONCLUSION

Supporting our previous results on potential PO biomarker role of rs7121 *(Clin Transl Sci 2020),* several rs7121-linked GNAS locus SNPs showed statistically significant allelic differences in the sex-stratified hip arthroplasty cohorts with vs. without PO. Rs3730168 in particular was identified as potential GNAS SNP biomarker with the most pronounced sex-dependent effects on PO development in hip arthroplasty. By leveraging time-to-PO measurements, we further demonstrated the sex-dependent role of genetic factors such as GNAS SNPs and their genotypes (including rs7121_CC vs. rs7121_TT) and haplotypes in development of PO (not shown). Our comorbidity analysis provided the epidemiological evidence that pointed at certain metabolic disorders as additional (non-genetic) modifying effects some of which could be traced back to potential GNAS effects.

In summary, this study reinforces the use of our framework for real-world evidence synthesis which allows to integrate pre-existing genetic and epidemiological data and illustrate:

- **the role of sexual dimorphism in PO;**
- ***in silico* discovery of sex-dependent PO biomarkers and modifying effects; and**
- **methodological approaches to development of cost/time-efficient Precision Medicine applications for informing the use of medical products in patient subpopulations.**

RESULTS

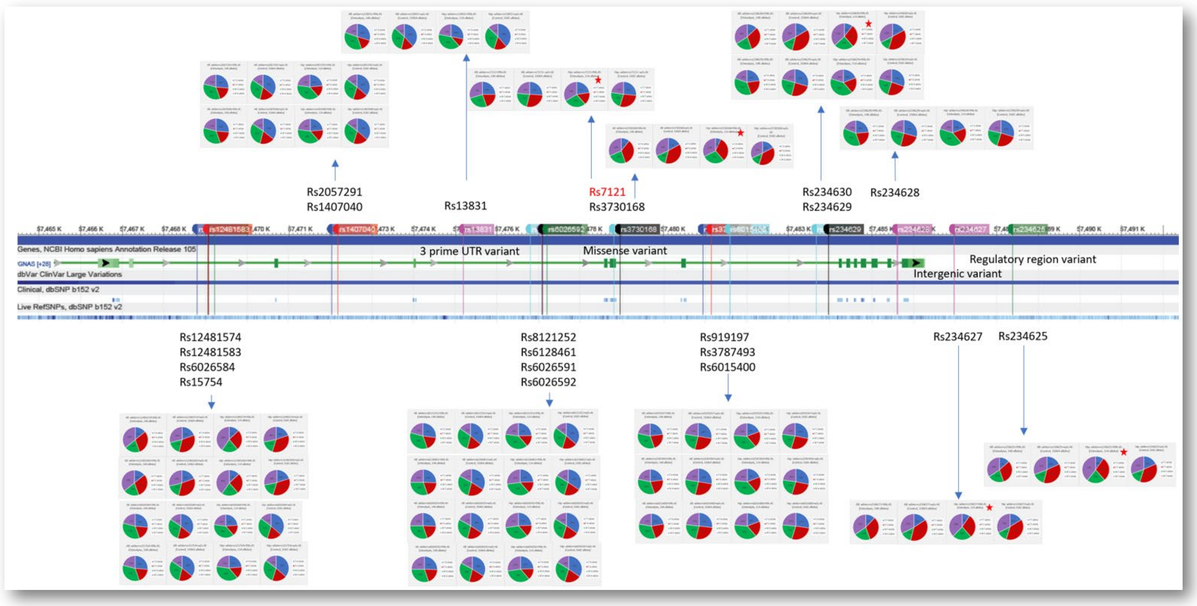

FIGURE 1. Distinct allele distribution for rs7121 and rs7121-linked GNAS SNPs in PO_Male vs. PO_Female cohorts. Each pie chart row represents one of the investigated GNAS SNPs; in each row, two pie charts on the left are based on All Arthroplasties, and two pie charts on the right are limited to Hip Arthroplasty.

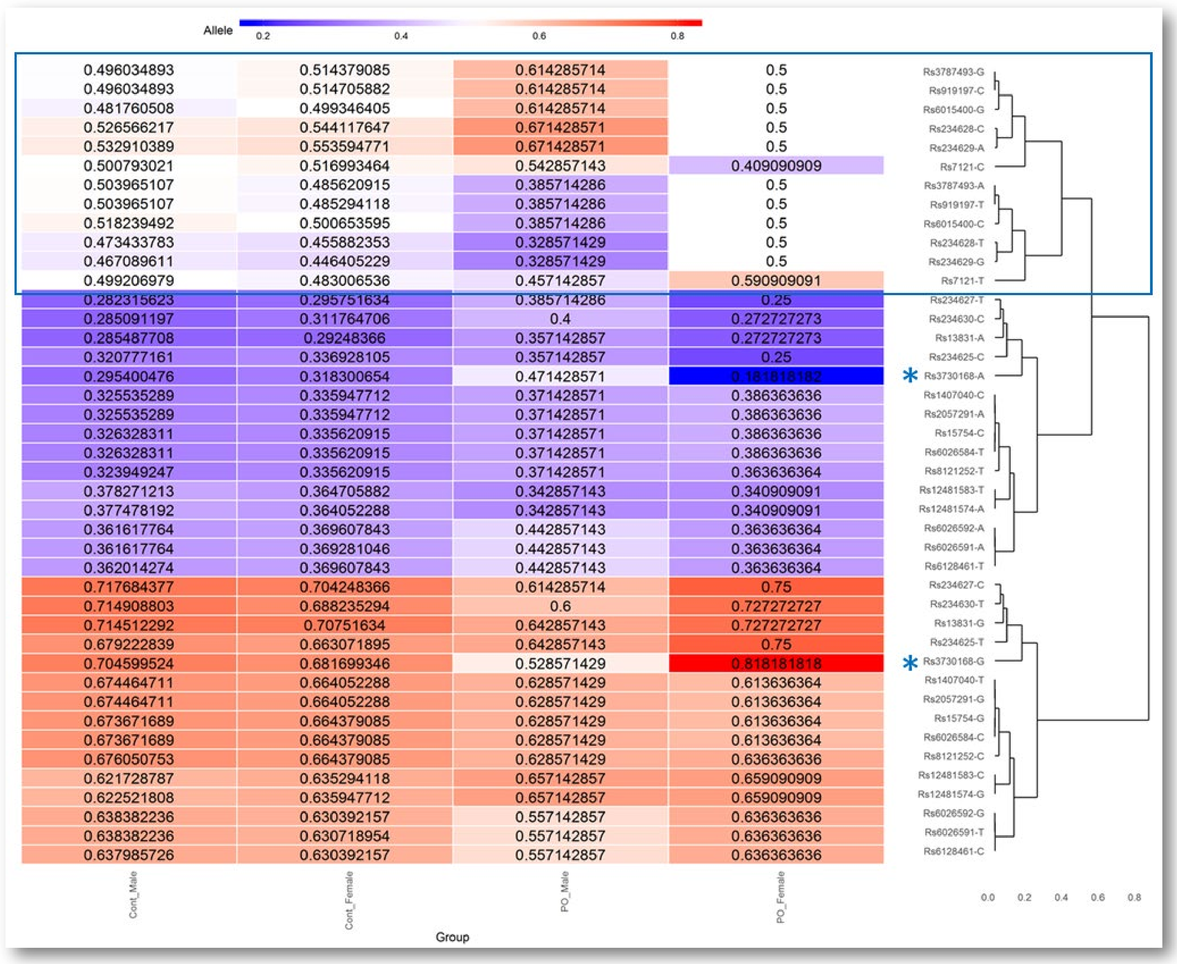

FIGURE 2. A heatmap with GNAS SNP allelic frequencies across the sex-stratified PO and Control cohorts reveals PO_Male specific cluster (*see the blue box*) and indicates the outlier role of rs3730168 *(see the asterisks)* in the sex-dependent GNAS effects on PO development. Allele frequencies for each SNP were calculated by dividing the counts for a specific allele by the total number of alleles within each hip arthroplasty group (CTRL_Male, CTRL_Female, PO_Male, PO_Female).

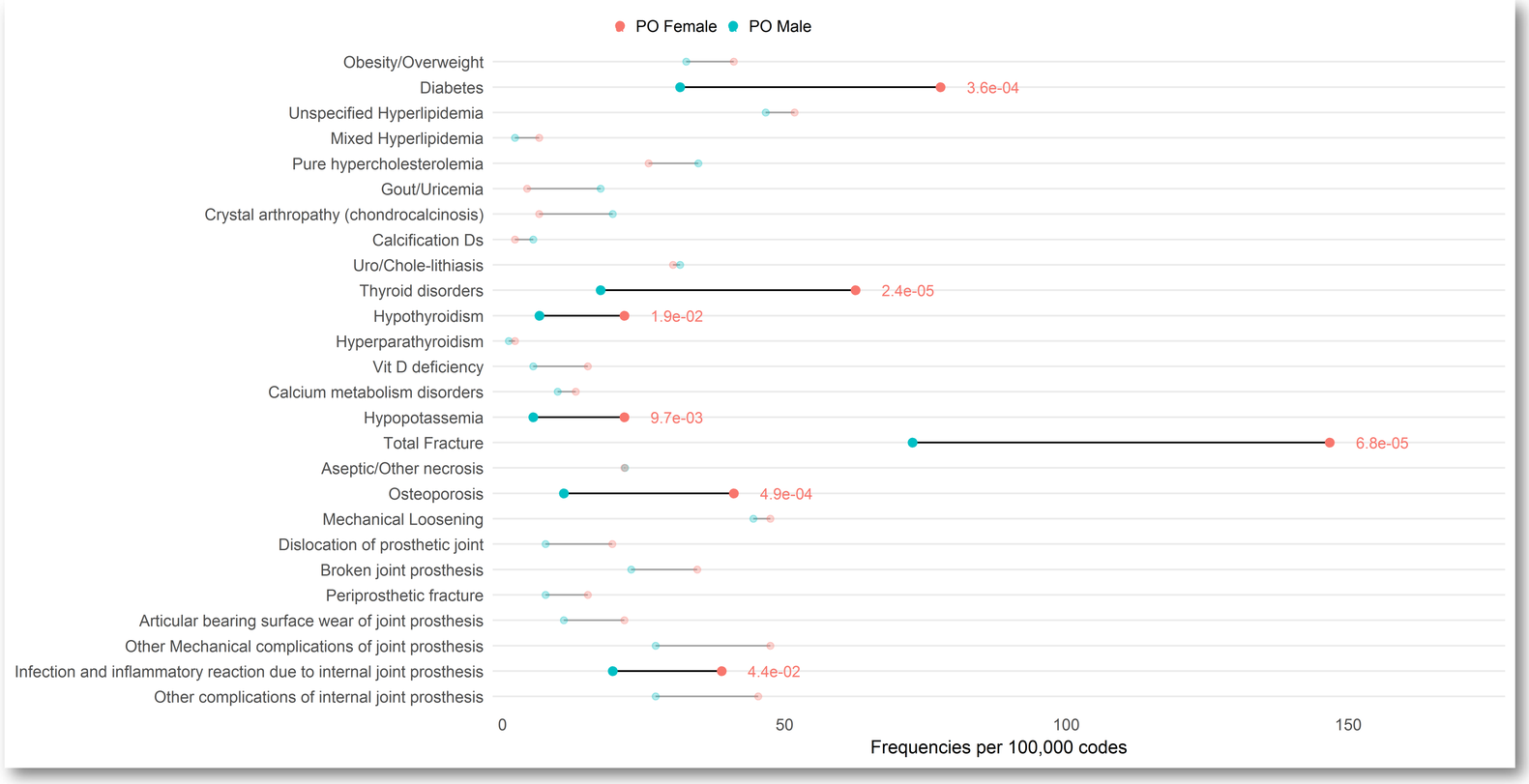

FIGURE 3. Comorbidity analysis reveals additional factors such as metabolism-related thyroid disorders and diabetes that may distinctly affect PO in males vs. females with hip arthroplasty. Frequencies of selected comorbidities were derived from ICD9/10 codes and normalized by the number of subjects within each constructed cohort. Statistical significance was assessed using two portion z-test and effect size measurements; PO_Male vs. PO_Female comparisons with statistically significant differences are shown in bold with respect p-values in red.

REFERENCES

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3. High-performance Integrated Virtual Environment (HIVE) (available at https://hive.fda.gov)

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