Real-World Epidemiologic and Genetic Evidence on Sexual Dimorphism and Sex-Dependent GNAS SNP Candidate Biomarkers for Periprosthetic Osteolysis in Hip vs. Other Arthroplasties

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Abstract

Background: Translational research on discovery of biomarkers for device-related adverse outcomes in patient subpopulations can enhance predictive evaluation of real-world device performance. Long-term outcomes of joint replacements, or arthroplasties, are affected by periprosthetic osteolysis (PO), which may lead to implant loosening and failure. Per our previous results, PO in hip arthroplasty shows sexual dimorphism associated with GNAS SNPs.

Objective: Following the reports on sex-dependent role of GNAS SNPs in hip arthroplasty-related PO, we explored PO sexual dimorphism in relation to GNAS SNPs in various arthroplasties.

Methods: Real-world data (RWD) from arthroplasty-related hospital discharge procedures from the Nationwide Inpatient Sample of the Agency for Healthcare Research & Quality (NIS/AHRQ 2010-2014) were used to analyze the PO occurrences in various arthroplasties. Arthroplasty-related PO occurrence in relation to GNAS SNPs was assessed using epidemiologic/genetic RWD from the eMERGE Network. Sex-stratified cohorts in relation to PO were constructed using arthroplasty/PO-related ICD codes in NIS/AHRQ and eMERGE datasets. SAS v.9.3 was used for assessing PO occurrences among sex-stratified NIS/AHRQ subgroups with arthroplasties. HIVE (High-performance Integrated Virtual Environment) was used for eMERGE data processing and SNP analysis.

Results: Per genetic eMERGE RWD, certain GNAS SNPs were identified as sex-dependent candidate biomarkers for PO in hip (but not other) arthroplasties. Per epidemiologic RWD from eMERGE and NIS/AHRQ datasets, male predominance was most pronounced in hip arthroplasty. A large-scale NIS/AHRQ analysis showed that the ratio of PO males compared to total males with arthroplasty decreased from 1.34 in hip arthroplasty to 1.26 and 1.15 in knee and other arthroplasties, respectively, providing possible explanation for the lack of associations with sex-dependent GNAS SNPs in non-hip arthroplasties.

Conclusion: The sex-dependent PO biomarker role of candidate GNAS SNPs is linked to the male predominance specific for hip arthroplasty. This finding underscores the need for sex-stratified approaches to identify risk predictors and emphasizes the guiding role of epidemiologic RWD in discovery of biomarkers that can inform the safe use of medical products in patient subpopulations.

Background & Rationale

PO is an arthroplasty-related Adverse Local Tissue Reaction (ALTR) which results from an inflammatory response induced by wear/ corrosion byproducts from joint replacements [1]. Our previous study [2] suggested that hip arthroplasty related PO is more frequent among males and this male predominance may involve the sex-dependent role of rs7121 SNP residing in the GNAS gene. In the current study, we explored potential PO biomarker role of the rs7121-linked GNAS locus SNPs in relation to the sexual dimorphism in patients with various arthroplasties.

Materials & Methods

Genetic and epidemiologic information on patients with arthroplasty (GNAS SNP genotypes and ICD9/10-based diagnoses/procedures, respectively) was mostly derived from the eMERGE Network. Ensembl-based linkage disequilibrium analysis [3] was used to identify the rs7121-linked GNAS locus SNPs. In-house HIVE platform and analytics [4, 5] were used to harbor the arthroplasty-related eMERGE data, and genetic profiles were parsed and indexed into HIVE's native NOSQL database from the original variant call format (VCF). The allelic frequencies in rs7121-linked GNAS SNPs were compared among the constructed sex-stratified cohorts with or without PO (Control_Male, Control_Female, PO_Male, PO_Female).

Data from the Nationwide Inpatient Sample of the Agency for Healthcare Research & Quality (NIS/AHRQ, 2010-2014) were also used for a retrospective analysis of the occurrence of PO among a total of 1,291,073 discharges with arthroplasties. SAS v.9.4 (Proc Logistic) was used for comparative analysis on PO among the sex/race-stratified cohorts with various arthroplasties. As a main limitation, the study results were based on unweighted number of cases (limited to in-patient events) and did not account for NIS sampling methodology over time.

REFERENCES

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Results and Discussion

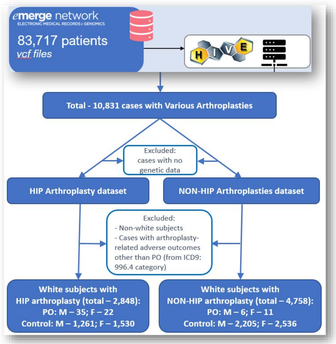


Figure 1. **Construction of the eMERGE-based cohorts with Hip and Non-Hip Arthroplasties.**
Per harmonized codes from the International Statistical Classification of Diseases and Related Health Problems (9th and 10th revisions: ICD-9/10), a total of 7,606 eMERGE cases with genetic data had various arthroplasties. The study sample was stratified by arthroplasty type and patient's sex. Due to scarcity of non-white subjects, race/ ethnicity-stratified analyses were prevented and both Hip and Non-Hip Arthroplasty datasets were limited to white subjects. Similar sex-stratified cohorts with different arthroplasties were created using NIS/AHRQ data (not shown).

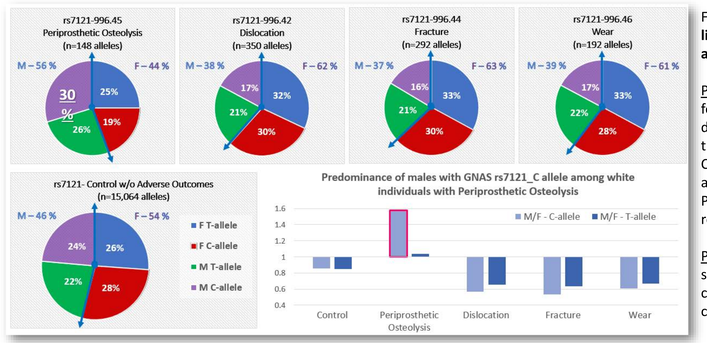
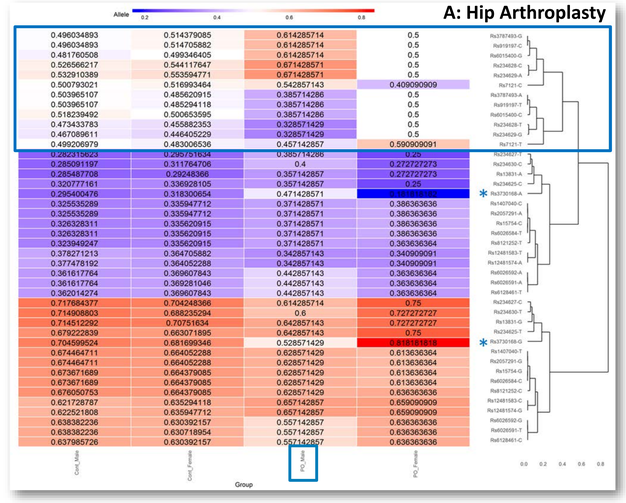


Figure 2. **Among white subjects with various arthroplasties, male predominance was limited to the rs7121-C allele carriers with PO but not with other arthroplasty-related adverse outcomes (eMERGE).**

Panel A: Among white subjects with various arthroplasties, female predominance was found in the control group with no adverse outcomes (54%) as well as subgroups with dislocation (62%), periprosthetic fracture (63%), and wear (61%). PO was identified as the only arthroplasty-related adverse outcome that showed male predominance (56%). Consistent with the previously shown predominance among PO males with hip arthroplasty [1], the rs7121-C allele was found more frequently among PO_Males vs. PO_Females with various arthroplasties (30% and 19%, respectively), but not among respective controls with no complications (24% and 28%, respectively).

Panel B: Possible rs7121/ sex-related co-modification in development of PO was further suggested by the male predominance among the C-allele carriers with PO (M/F=1.6), compared to the inverse M/F ratios in both C-allele and T-allele carriers with other complications.



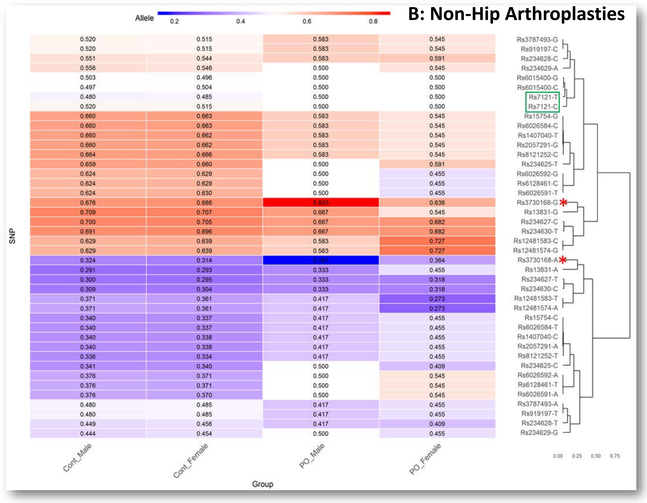


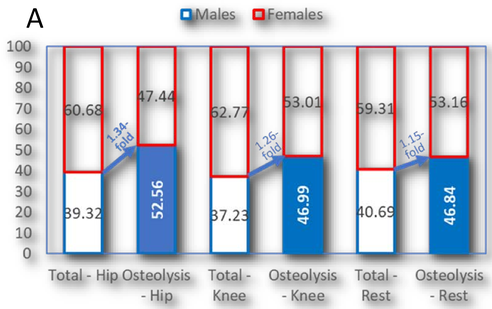
Figure 3. **Heatmaps of the rs7121 and rs7121-linked alleles in Hip versus Non-Hip arthroplasties reveal distinct PO-related patterns with the PO-Male specific GNAS SNP cluster limited to hip arthroplasty (eMERGE).**

Allelic 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 (Control_Male, Control_Female, PO_Male, PO_Female).

Panel A: The Hip Arthroplasty heatmap revealed the PO_Male specific GNAS SNP cluster (see the blue box) as well as indicated possible PO links for rs3730168 (see the asterisks). Among all tested SNPs, rs3730168 was identified as an outlier with the sex-dependent PO role, as shown by the inverse odds ratios in sex-stratified cohorts: a 2-fold increase of rs3730168 A-allele in PO_Males (OR=2.127; 95% CI: 1.278; 3.525; p=0.003) versus its borderline 2-fold decrease in PO_Females (OR=0.476; 95% CI: 0.190; 1.047; p=0.068), compared to respective controls with no PO. Statistically significant increases were also shown for some PO_Male cluster SNPs (rs234628-C, rs234629-A, and rs6015400-G).

Panel B: The Non-Hip arthroplasties heatmap lacked a PO-Male specific SNP cluster as well as showed a distinct allelic pattern for rs3730168. Further positive/ negative likelihood ratio analyses did not reveal any statistically significant trends for the tested GNAS SNPs in relation to PO in Non-Hip arthroplasties (not shown).

Thus, the male sex/ GNAS SNP co-dependent effects in development of PO were found in hip, but not non-hip, arthroplasties.



B

Periprosthetic Osteolysis	OR (95% CI) White Females vs. White Males
Hip Arthroplasty	**0.581 (0.539; 0.628)**
Knee Arthroplasty	**0.674 (0.607; 0.748)**
Rest Arthroplasty	0.790 (0.566; 1.103)

Figure 4. **Analysis of PO-related sexual dimorphism shows that the male predominance is mostly specific for subjects with hip arthroplasty (NIS/AHRQ).**

Panel A: Per our NIS/AHRQ-based analysis of PO occurrence (%) in the sex-stratified white subcohorts with different arthroplasties, the highest increase of males among PO subjects was detected in hip arthroplasty (1.34-fold) compared to knee and rest arthroplasties (1.26- and 1.15-fold, respectively). Delta-percentages for the males with PO compared to total males decreased from 13.24% in hip arthroplasty to 9.76% in knee arthroplasty and 6.15% in rest arthroplasties.

Panel B: Odds ratio analysis confirmed the highest PO-related male predominance among subjects with hip arthroplasty.

Thus, the PO-related male predominance presented possible explanation for the lack of associations between PO and GNAS SNPs in non-hip arthroplasties (see Figure 3), while suggesting its specific role in the sex/GNAS SNP co-dependent effects on PO in the hip arthroplasty.

Conclusion

- Overall, this study reinforces the use of our multidisciplinary evidence synthesis framework by consistently illustrating:
  - ✓ The role of sexual dimorphism in arthroplasty-related adverse outcomes;
  - ✓ The usability of pre-existing RWD for discovery of biomarkers predictive and/ or indicative of device-related adverse outcomes
- Further, *in silico* evidentiary approaches for integrating and analyzing healthcare RWD from different sources can be transferred for development of cost/time-efficient Precision Medicine applications to inform the use of various medical products.

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