Identification of Novel Genetic Markers for Risk of Pseudarthrosis after Spinal Fusion: A Genome-Wide Association Study

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INTRODUCTION:

Cervical spine instrumentation and fusion is performed for a variety of indications such as trauma, degenerative conditions, and deformity. However, despite significant improvements in surgical techniques and spinal instrumentation, pseudarthrosis remains a frequent issue, accounting for 25–40% of spinal revision surgeries. Identifying genetic risk factors for pseudarthrosis may lead to knowledge on underlying molecular mechanisms and the development of new treatments. Therefore, the purpose of the current study was to determine if there are specific genetic markers that influence risk of developing pseudarthrosis after spinal fusion.

METHODS:

Cases of pseudarthrosis after spinal fusion were identified through International Classification of Diseases, Tenth Revision (ICD-10) code M96.0 from the UK Biobank, a population-based prospective cohort of approximately 500,000 United Kingdom residents. Controls were patients without the diagnosis. Patient demographic data collected were age, gender, body mass index, and smoking pack years. Logistic regressions were used to test for genetic association of 784,256 typed and 7,304,261 imputed markers, while controlling for age, gender, body mass index, smoking pack years, and the top ten genetic principal components.

RESULTS:

A total of 389,413 participants were identified from the UK Biobank after control measures were performed, of which 259 were diagnosed with pseudarthrosis after spinal fusion. After controlling for demographics, comorbidities, and the top ten genetic principal components, two novel loci (chromosome 5, lead variant, rs10072892, odds ratio [OR]=1.64, 95% confidence interval [CI]=1.39-1.93 and chromosome 9, lead variant, rs1006009, OR=1.81, 95%CI=1.50-2.18 corresponding to the LOC105376270 gene) were significantly associated with pseudarthrosis after spinal fusion. Other genes located within 500 kilobases of these variants, which may contribute to the phenotype, included ADGRD2, PSMB7, NR5A1, NEK6, NR6A1, OLFML2A, WDR38, RPL35, ARPC5L, LHX2, and GOLGA1.

DISCUSSION AND CONCLUSION:

In this genome-wide association study, pseudarthrosis after spinal fusion was associated with variants corresponding to the LOC105376270 gene, which has not been previously identified and is currently uncharacterized. Validation of these results in additional populations as well as characterization of this gene may have significant impact on risk assessment and therapeutic strategies.

Figure 1: Manhattan plot of $-\log_{10}$ p-values for each association of a genetic variant with pseudarthrosis after spinal fusion in the UK Biobank by chromosome location

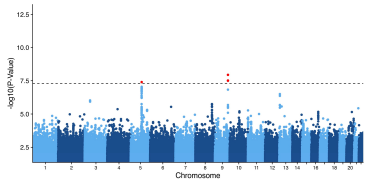

Figure 2: Q-Q plot comparing the observed p-values with the expected distribution of p-values for each association of a genetic variant with pseudarthrosis after spinal fusion in the UK Biobank

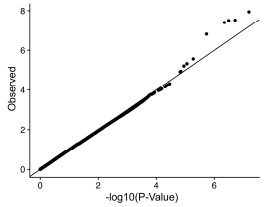

Table 1: Leading SNP Associations with Pseudarthrosis After Spinal Fusion in the UK Biobank

Pseudarthrosis After Spinal Fusion									
Chromosome	SNP	Gene	A0	A1	A1 Frequency	Info Score	OR	95% CI	p-value
9	rs1006009	LOC105376270	A	G	0.16	0.96	1.81	1.50 - 2.18	1.14E-08
9	rs201490347	LOC105376270	A	ATGT	0.16	0.99	1.77	1.47 - 2.13	1.04E-08
9	rs7863432	LOC105376270	T	C	0.16	0.98	1.77	1.47 - 2.13	1.16E-08
5	rs10072892	None	C	A	0.27	0.98	1.64	1.39 - 1.93	3.98E-08

SNP - Single nucleotide polymorphisms
OR - Odds ratio
CI - Confidence interval