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Biopsychosocial clusters based on genetic risk scores for chronic post-surgical pain in children undergoing spine fusion

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Background: Poor control of postoperative pain (PoP) and childhood anxiety sensitivity (CASI), are associated with chronic postsurgical pain (CPSP). They have high heritable risk and likely, common underlying genetic processes.

Hypothesis: We hypothesized that genetic risk could predict phenotype clusters. This would allow *a priori* risk stratification to enable personalized preventive/therapeutic measures.

Methods: Systematic literature review for known genes associated with phenotypes (PoP, CPSP, CASI), was followed by computational modeling to identify novel candidate genes. We prospectively recruited 171 children undergoing spinal fusion under standard anesthesia/pain protocols, assessed CASI and pain scores immediately after and 6-12 months post-surgery. Blood samples were analyzed using Omni5M arrays. Association analyses of phenotypes with ranked deciles of candidate gene variants (against 10,000 matched control gene sets) was followed by gene set enrichment analyses. Genetic risk scores were developed to predict phenotypes, and hierarchical cluster analysis used to determine genotype-phenotype clusters.

Results: The cohort (14.5±1.8 years, 75% female) had CASI scores of 28.5±8.5 and pain scores of 2.2±2.5 at 6-12 months. After adjusting for covariates, compared to control sets, there was enrichment of SNP associations in 10th-50th decile gene sets ($p < 0.05$) for CASI, 50-80% deciles for PoP, and training set for CPSP ($p < 0.001$; Benjamini-Hochberg correction). Common and unique biological processes enriched by significant SNP sets were identified for each phenotype. Genetic risk scores were predictive of phenotypes ($p < 0.05$) and 5 phenotype-genotype clusters were identified.

Discussion: Integrated biopsychosocial factor clusters for CPSP were identified. They need validation in other surgical cohorts.