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NATIONAL CLINICAL AUDIT DATA DECODES THE GENETIC ARCHITECTURE OF DEVELOPMENTAL DYSPLASIA OF THE HIP

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Abstract:

Purpose: Developmental dysplasia of the hip (DDH) is a heritable condition with an incidence of 3-6 per 1000 live births in the United Kingdom. DDH is characterised by abnormal development of the hip joint that results in pain, loss of function, and secondary osteoarthritis. We applied case identification using national clinical audit data and postal recruitment to conduct the first successful genome-wide study of the genetic architecture of DDH to better understand its biological aetiology.

Methods: We recruited 770 patients (639 female) with a history of DDH from the English National Joint Registry (NJR) and 3364 controls (3048 female) from UK Household Longitudinal Study (UKHLS) for the discovery cohort. All participants were of UK European ancestry. Genomic DNA was genotyped using the Illumina HumanCoreExome beadchip. Following quality control checks at the sample and genotype level, association analyses were conducted under an additive model. Identified independent signals were followed up in an independent replication cohort of 1129 (1004 female) children with DDH, recruited prospectively, and 4652 independent controls from the UKHLS.

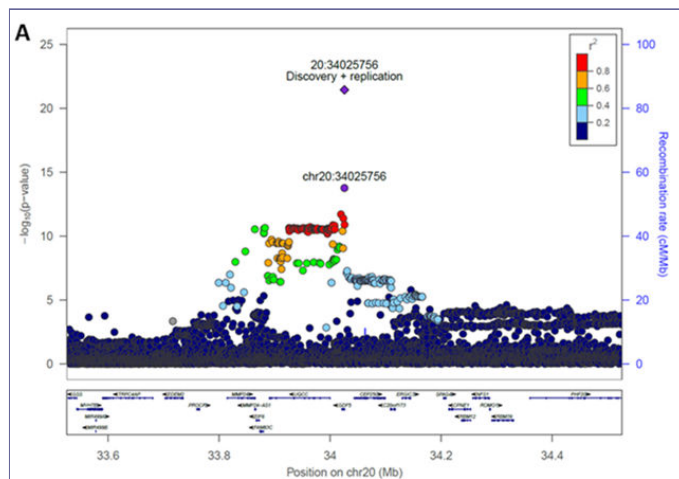
Finally, a meta-analysis of both cohorts was conducted. We defined genome-wide significance as $p < 5 \times 10^{-8}$. We estimated the heritability of DDH using genetic complex trait analysis (GCTA). To test for shared genetics of DDH with OA, we employed high-resolution polygenic risk scoring (with data from a previous GWAS of OA) by using evenly spaced p-value thresholds between 0.001 and 0.50.

Results: Using genome-wide single nucleotide polymorphism (SNP) data and GCTA analysis we find that common-frequency autosomal SNPs explain 55% ($\pm$ se=6%, $p < 0.0001$) of the liability-scale heritability of DDH. In the discovery case-control analysis we find 53 SNPs, comprising 25 independent signals, showed suggestive association with DDH at $p < 9 \times 10^{-5}$. Eleven correlated variants reached genome wide significance, with rs 143384 in the *GDF5* promoter as the lead variant (OR 1.57, 95% CI 1.3-1.77, $p = 1.72 \times 10^{-14}$). At replication, the rs143384 variant was also associated with DDH at genome-wide significance (OR=1.37, 95% CI 1.24 to 1.51, $p = 1.33 \times 10^{-10}$). Finally, at meta-analysis the rs143384 variant was associated with DDH with OR=1.44 (95% CI 1.34 to 1.56, $p = 3.55 \times 10^{-22}$, Figure A; regional association plot showing variants within *GDF5* locus and strength of association). We also identify two further replicating loci with suggestive association to DDH near the *NFIB* (rs4740554, OR 1.30 [95% CI 1.16-1.45], $p = 4.44 \times 10^{-6}$) and *LOXL4* (rs4919218, 1.19 [1.10-1.28] $p = 4.38 \times 10^{-6}$) genes. We identify *RETSAT* and *PDRG1* association with DDH through gene-based analysis ($p = 1.19 \times 10^{-6}$ and $p = 3.77 \times 10^{-6}$, respectively). To identify potential shared genetic aetiology and hence common biological pathways underpinning DDH and idiopathic hip OA we constructed polygenic risk scores using the arcOGEN dataset and tested their predictive potential in the DDH GWAS. We find no significant association between polygenic risk scores for hip OA and DDH.

Conclusions: Using the NJR as a proof-of-principle, we describe the genetic architecture of DDH and establish the first robust DDH genetic locus. Fine mapping of the 5'UTR of *GDF5* indicates rs143384 (rather than 143383) as the causal variant. We also demonstrate a robust and scalable national clinical audit-based recruitment strategy for genetic studies that is transferrable to other complex diseases.

Table 1:
Replicating
variants
associated
with DDH





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Category (Complete): Genetics and Genomics and Epigenetics

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