Osteoarthritis and Cartilage Open 6 (2024) 100424

Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131

COL11A1 is associated with developmental dysplasia of the hip and secondary osteoarthritis in the HUNT study

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ARTICLE INFO

Handling Editor: Professor H Madry

Keywords:
Developmental dysplasia of the hip
Genetic
Hip dysplasia
COL11A1
HUNT

ABSTRACT

Objective: Developmental dysplasia of the hip (DDH) is a congenital condition affecting 2–3% of all infants. DDH increases the risk of osteoarthritis, is the cause of 30 % of all total hip arthroplasties (THAs) in adults <40 years of age and can result in loss of life quality. Our aim was to explore the genetic background of DDH in order to improve diagnosis, management and longterm outcome.

Design: We used the large, ongoing, longitudinal Trøndelag Health Study (HUNT) database. Case definition was based on ICD-9/-10 diagnoses of DDH, or osteoarthritis secondary to DDH. Analyses were performed using SAIGE software, with covariates including sex, batch, birth year and principal components. We included only single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) ≥ 0.01, $R^2 \geq 0.8$ and Hardy-Weinberg equilibrium (HWE) *P*-value ≥ 0.0001. Significance level was set at $p < 5 \times 10^{-8}$. Meta-analysis using data from DDH and primary osteoarthritis genome-wide association studies (GWASs) was done using METAL software. The study was approved by the regional ethical committee.

Results: Analysis included 69,500 individuals, of which 408 cases, and 8,531,386 SNPs. Two SNPs near *COL11A1* were significantly associated with DDH; rs713162 ($\beta = -0.43$, SE = 0.07, $p = 8.4 \times 10^{-9}$) and rs6577334 ($\beta = -0.43$, SE = 0.08, $p = 8.9 \times 10^{-9}$). COL11A1 has previously been associated with acetabular dysplasia and osteoarthritis. Meta-analysis supported previous GWAS findings of both DDH and primary osteoarthritis.

Conclusions: This large, genome-wide case-control study indicates an association between COL11A1 and DDH and is an important contribution to investigating the etiology of DDH, with further research needed.

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https://doi.org/10.1016/j.ocarto.2023.100424
Received 5 September 2023; Received in revised form 19 October 2023; Accepted 1 December 2023

1. Introduction

Developmental dysplasia of the hip (DDH) is a congenital disorder consisting of a shallow or dysplastic acetabulum, with or without a dislocatable or dislocated femoral head. The ultrasonographic prevalence of DDH in newborn children is 2–3%, and it is approximately five times more prevalent in females as compared to males [1,2]. Although the disorder is often classified as a pediatric one, it affects as many as 20 % of adults [3]. Even subtle DDH increases the risk of cartilage loss, leading to secondary hip osteoarthritis (OA) and a potential need for total hip arthroplasty (THA) at a young age [4]. Hip OA secondary to DDH is the major cause of THA in younger individuals and leads to a substantial reduction in quality of life [5,6].

The heritable aspect of DDH is well established, the relative risk (RR) of having DDH is 12.1 in first degree relatives of individuals with DDH, and the heritability estimated in epidemiological studies is as high as 84 %, with around 55 % explained by single nucleotide polymorphisms (SNPs) alone [7–9]. Familial DDH is one of the referral criteria for selective ultrasound screening of infants [10]. We have previously reviewed the genetics of DDH and highlighted the need for more genetic studies in this field (Jacobsen et al., 2023, under review). So far, only one well-powered (N = 8016) genome-wide association (GWA) study on DDH has been performed, revealing a genome-wide significant association at *GDF5* locus, a gene involved in the regulation of joint- and cartilage development [9]. However, this finding, together with a handful of candidate genes from small studies, explains less than 2 % of the estimated SNP based heritability of DDH [9].

The most common form of hip OA is primary/idiopathic OA, the genetics of which is more extensively studied than OA secondary to DDH [11]. The relationship between primary and secondary OA in terms of genetics is unclear, and although secondary OA has an altered morphology as an additional cause, it is believed that the two disorders could have some overlapping genetic risk factors. Hatzikotoulas et al. found some support of common genetic risk factors underlying in their study on DDH in the UK Biobank [9]. They used polygenic risk scores from primary OA in the arcoGEN and UK Biobank studies, which could only explain 0.05–0.35 % of the variance within the DDH cohort, which is quite low. However, using another method called LD-score regression (LDSC), there was a nominally significant genetic correlation between DDH and primary OA [9]. One of the challenges of studying DDH and OA secondary to DDH is the difficulty of available data sets. Thus, looking at common genetic risk factors for primary OA can contribute to our knowledge of DDH and secondary OA. In this study, we aim to investigate the genetics of DDH and OA secondary to DDH in a Norwegian cohort (The Trøndelag Health Study; HUNT) of 69,500 individuals.

2. Method

2.1. Study population

This study utilized the sample collected within HUNT (The Trøndelag Health Study). The HUNT study and its genotyping have been thoroughly described elsewhere [12,13]. Briefly, the HUNT study is a collection of several population-based health studies from the former county of Nord-Trøndelag (now merged into Trøndelag) in Norway. The study has been carried out over more than 30 years, with four major data collection waves (HUNT1-4) so far, including quality controlled genotypic data for 69,500 individuals in HUNT2 and 3 [14]. Case/control definitions were based on available ICD-9 and ICD-10 diagnoses from the Norwegian Patient Registry which contains reported diagnoses from hospital records from 2008 onwards. The diagnoses were made by doctors based on current and previous findings from inpatient and outpatient visits to the hospital, where radiological modalities are commonly used to assist DDH and secondary OA diagnostics. Individuals were included as cases if they had at least one of the DDH diagnoses (all Q65 codes from ICD-10 and the 754.3 code from ICD-9) and/or a diagnosis of secondary osteoarthritis due to DDH (M16.2 and M16.3 from ICD-10 and 715.25 from ICD-9). Individuals with post-traumatic arthrosis (M16.4 and M16.5) were excluded from both case- and control groups. Controls, thus, included all remaining participants who did not meet the case criteria and were not removed due to exclusion criteria.

2.2. Genotyping, imputation and quality control

The HUNT sample has been genotyped using three different versions of the Illumina HumanCoreExome array. Quality control including imputation using MiniMac3 and population stratification assessment is described elsewhere [12,14,15].

2.3. Statistical analyses

Genome-wide association (GWA) testing was performed using SAIGE version 0.44.5, with the covariates being sex, genotyping batch, birth year and the first eight principal components (calculated by projecting the full HUNT sample into the space of the principal components of unrelated HUNT sample) [15,16]. The LOCO (leave-one-chromosme-out) option was set as TRUE for autosomal chromosomes, and logistical regression using dosages was chosen as analysis type. We restricted results further to include only single nucleotide polymorphisms (SNPs) with Minor Allele Frequency (MAF) ≥ 0.01, imputation quality $R^2 \geq 0.8$ and Hardy-Weinberg Equilibrium (HWE) test $P \geq 0.0001$ in controls. To identify genome-wide significant SNPs, we applied the standard threshold of $P = 5.00 \times 10^{-8}$.

Functional relevance of the findings was assessed in FUMA using both the SNP2GENE and GENE2FUNC options, and including the MAGMA gene-based tests, MAGMA gene set analysis and MAGMA tissue expression analysis (GTEx analysis), and analysis of overrepresentation of candidate genes in pre-defined gene sets [17]. For the MAGMA gene-based test, genome-wide significance was set at $P = 0.05/18620 = 2.685 \times 10^{-8}$ based on the number of genes tested, and for the gene set analysis, a Bonferroni corrected *P*-value of <0.05 was applied.

2.4. Meta-analysis of HUNT data with data from previous GWA studies on DDH and primary OA

To further explore the genetics of DDH in an increased sample size, we meta-analyzed our data with the freely available summary statistics from (1) a GWA study on DDH in a UK cohort (Hatzikotoulas et al.) and (2) another GWA study on primary OA in samples from UK and Iceland (Styrkarsdottir et al.) [9,11]. The meta-analyses were done in METAL software, combining the statistics in the inverse variance weighted manner [18]. The OA and DDH data were processed separately.

3. Results

After genotype quality control, 69,500 individuals and 8,531,386 SNPs were available for the analyses. Of these, 408 individuals fulfilled one or more criteria to be classified as a case. The distribution of ICD-9 and ICD-10 diagnoses can be found in Fig. 1 and Supplementary Table 1. The genomic inflation factor (lambda) was 0.9934 and the QQ-plot indicated good data quality (Fig. 2). Two SNPs on chromosome 1 passed the threshold of genome-wide significance, rs713162 ($\beta = -0.43$, SE = 0.07, $P = 8.4 \times 10^{-9}$) and rs6577334 ($\beta = -0.43$, SE = 0.08, $P = 8.9 \times 10^{-9}$), as indicated in the Manhattan plot (Fig. 3). Both SNPs are just downstream of *COL11A1* and lie within a large linkage disequilibrum (LD)-block that includes the gene itself (Fig. 4). Rs713162 is a genotyped SNP, and its association is supported by four other genotyped SNPs in the region, all revealing strong association (rs10782904, $P = 2.80 \times 10^{-7}$; rs3753841, $P = 3.47 \times 10^{-6}$; rs7524918, $P = 5.36 \times 10^{-6}$; rs12138977, $P = 7.32 \times 10^{-6}$).

We further explored the data by looking at regions with significance threshold of $P = 1.00 \times 10^{-5}$. In addition to *COL11A1*, further 15 loci

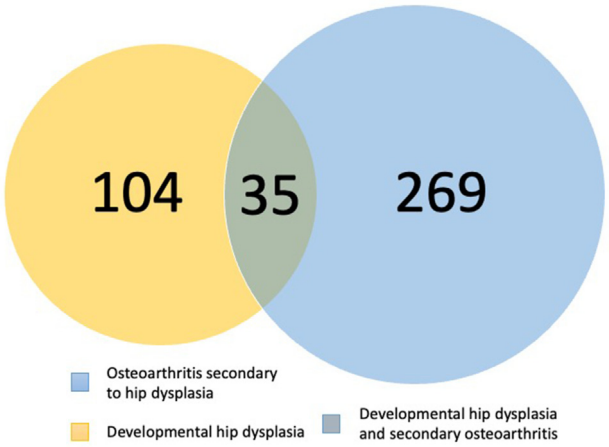

Fig. 1. Distribution of the various diagnoses from the International Classification of Disease version 9 and 10 (ICD-9 and ICD-10) diagnoses encompassing developmental dysplasia of the hip (DDH) and osteoarthritis (OA) secondary to DDH. 104 individuals had DDH as their only diagnosis, 269 had secondary OA as their only diagnosis, whereas 35 individuals had both a diagnosis of DDH and a diagnosis of secondary OA in the national patient registry. For a more detailed overview, see Supplementary Table 1.

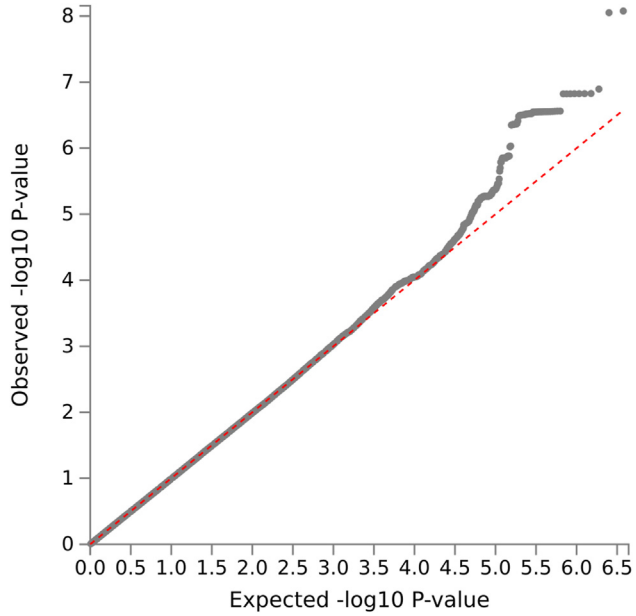

Fig. 2. Quantile-quantile plot (qq-plot) for the SAIGE genome-wide single nucleotide polymorphism (SNP) analysis.

were identified. Among these, several regions have previously been reported to be associated with skeletal phenotypes. An overview of these regions is presented in Table 1. We included all variants at these 16 loci in functional analysis in FUMA [17]. No tests, apart from the *COL11A1* gene test, were significantly associated with our phenotype in any of the tests using FUMA. In the publicly available gene expression data, within FUMA, we note several genes with high expression in fibroblasts (PTS: 4.96, POMGNT2: 4.71, CENPW:4.42) (Supplementary Figure 1). However, there is a lack of other joint related tissues in the databases, where expression analysis would be highly relevant to DDH.

The meta-analysis with the data from a GWA study on DDH showed the strongest association in *GDF5* at rs143384 with a combined *P*-value of 1.85×10^{-12} and same direction of effect in both studies. In meta-analysis with the data from a GWA study on primary OA, several of the previous findings were supported by our data. Notably, both studies revealed genome-wide significant associations in *COL11A1* locus, resulting in a combined *P*-value of 4.23×10^{-15} at rs2126643. Further details are available in Supplementary Tables 2 and 3.

4. Discussion

In this study, we investigated genetic factors underlying DDH and secondary OA due to DDH in a large population cohort. We found genome-wide significant association of DDH and secondary OA with SNPs in *COL11A1 locus*. Our results also support findings from a previous GWA studies on DDH as well as primary OA. Our study is one of the largest GWA studies on DDH performed to date, including 69,500 individuals.

COL11A1 encodes one of the trimers forming collagen type XI, a heterotrimer consisting of three alpha-chains where the other two are encoded by *COL11A2* and *COL2A1*. Type XI collagen is extruded into the extracellular matrix (ECM) and regulates the diameter of cartilage collagen fibrils. It is not abundant in amount but has a key regulatory role in the architecture of cartilage collagen and the binding of proteoglycans to collagen fibrils [19]. *COL11A1* has up to eight different isoforms that are differentially expressed temporally and spatially, with alternative splicing of the N-propeptide [20,21]. Transcripts are expressed in cartilage, retina and bones of the inner ear, giving rise to different phenotypes in syndromes involving *COL11A1* mutations [21]. These syndromes include fibrochondrogenesis, Stickler type 2 and Marshall syndrome, all of which have skeletal dysplasia as a major feature [22,23]. Among these dysplasias is also hip dysplasia, with patients receiving THA at a young age (30–40 years of age) [23].

A similar phenotype to fibrochondrogenesis is seen in mice with knock-down or knock-out of *Col11a1* [20]. Changes to *Col11a1* affect maturation of chondrocytes, the thickness of collagen fibrils and result in increased rate of collagen type II degradation, possibly increasing the risk of any type of OA [24,25]. Holyoak et al. showed that the development of OA in *Col11a1* knock-down mice was load independent and, thus, possibly a risk factor for OA independent of body mass index (BMI) [26]. *COL11A1* is part of an ECM protein network associated with OA and is also involved in cartilage formation in both OA and healthy individuals and is differentially expressed in OA cartilage compared to the healthy one [27,28]. *COL11A1* is in the same Wnt/beta-catenin signaling pathway as *GDF5,* a well-established OA and DDH candidate gene [29].

An analysis of genetic and radiological data from the Rotterdam Study found an association between a *COL11A1* gene variant and center-edge angle of the acetabulum, a diagnostic measure of DDH ($\beta = 0.444$, $P = 3.4 \times 10^{-4}$) [30,31]. Baird et al. found several *COL11A1* variants to be associated with hip shape in the ALSPAC study, the strongest being rs10047217 ($P = 3.00 \times 10^{-06}$) [32]. Several studies have found associations between various *COL11A1* variants and primary OA, including a large international GWAS in over 800,000 individuals (rs11164653, OR 0.92, $P = 2.77 \times 10^{-18}$) [11,33–36]. These findings suggest that *COL11A1* plays a role in both hip morphology and progression from DDH to secondary OA. *COL11A1* has also been reported to be associated with other OA-related traits, such as height, bone size and degenerative intervertebral lumbar disc disease [19,31,37–43].

Our study supports findings from previous GWA studies on DDH, strengthening the role of *GDF5* in DDH [9]. It also supports the link between primary and secondary OA, strengthening the role of *COL11A1* in these disorders [11]. This is interesting, as Hatzikotoulas et al. found very little overlap between DDH and OA in their study using polygenic risk score and some overlap using LD score regression ($rg = 0.5839$, s. e. $= 0.2068$, $P = 0.0047$). Hogervorst et al. introduced the concept of cartilotype and morphotype in terms of DDH, separating genetic risk factors into factors that affect joint morphology and factors influencing cartilage robustness [44]. This cartilage robustness includes cartilage development, metabolism and stress response as well as other factors affecting the joint cartilage. Based on this hypothesis, it is likely that primary OA, DDH and secondary OA will have some overlap in terms of genetic risk

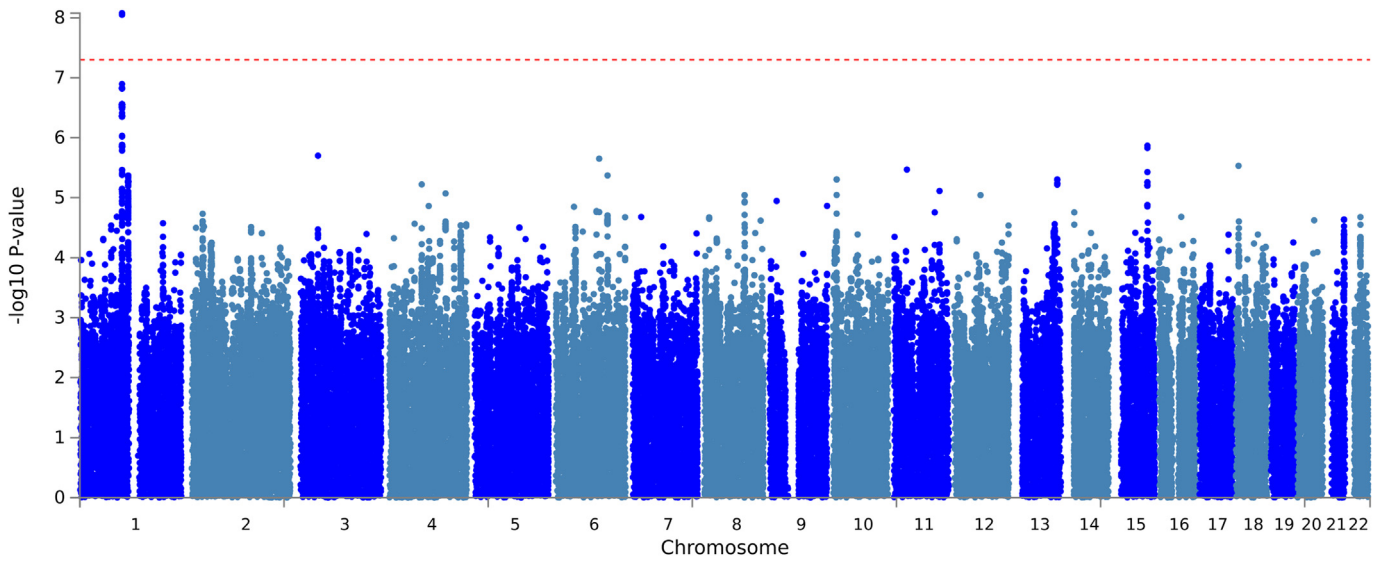

Fig. 3. Manhattan plot for the SAIGE genome-wide single nucleotide polymorphism (SNP) analysis. The -log10 *P*-value is plotted according to the SNP chromosome position along the X-axis. The dotted red line indicates the threshold for genome-wide significance. A locus on chromosome 1 surpasses this threshold.

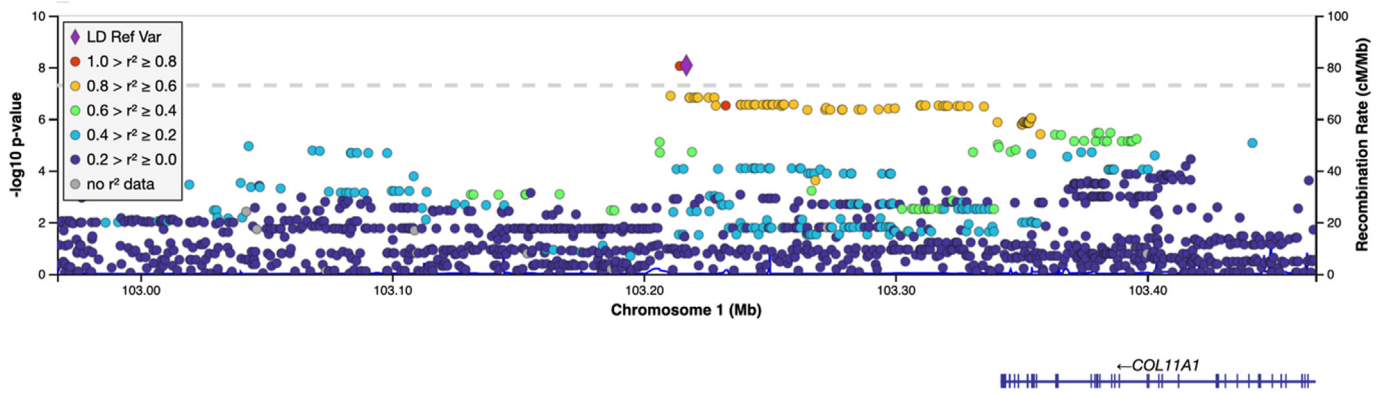

Fig. 4. Regional Locus Zoom plot of the locus on chromosome 1 with a genome-wide significant association between rs713162 and developmental dysplasia of the hip. The grey dashed line indicates the genome-wide significance threshold. Colors indicate r^2 value as indicated in the legend. The locus include the 3′ end and downstream region of *COL11A1*.

Table 1
Overview of regions with P < 1e-5, including genes in the region and the top SNP associated.

Locus	Chromosome	Region	rsID	*P*-value	N SNPs	N SNPs <10-5	Gene(s)
1	1	103113416–103464210	rs713162	8.40E-09	131	102	COL11A1
2	1	118279908–118357635	rs1837043	4.27E-06	92	83	PNRC2P1
3	3	42894986–43149580	rs62247064	1.99E-06	4	4	ACKR2,KRBOX1,CYP8B1, GASK1A,POMGNT2
4	4	79344554–79880156	rs149588309	6.01E-06	10	8	FRAS1,ANXA3,BMP2K, PAQR3
5	4	137901143–137966103	rs115308354	8.51E-06	23	19	Intergenic
6	6	106157476–106172940	rs112312519	2.24E-06	3	1	Intergenic
7	6	126623947–126657472	rs7775748	4.26E-06	25	19	CENPW
8	8	99458623–99813818	rs111512514	9.11E-06	11	8	STK3
9	10	9066923–9155598	rs2146602	4.96E-06	93	73	Intergenic
10	11	32227180–32227180	rs117908576	3.40E-06	1	1	Intergenic
11	11	112052673–112244015	rs147346096	7.72E-06	4	2	SDHD,TEX12, BCO2, PTS
12	12	64132915–64157495	rs144898894	9.07E-06	3	1	SRGAP1
13	13	94098659–94098659	rs1052976954	9.30E-06	1	1	GPC6
14	13	105245059–105274114	rs1434344	4.95E-06	18	15	Intergenic
15	15	84207325–84253965	rs72760364	1.36E-06	14	12	SH3GL3
16	18	6445880–6449931	rs1365304	2.94E-06	11	7	Intergenic

factors, but also some differences.

One might speculate that two subgroups of DDH exist. One group would respond adequately to early, non-surgical treatment in early childhood, and would not develop subsequent, secondary OA after skeletal maturity. Another group would demonstrate residual dysplasia at skeletal maturity, and develop secondary OA. This latter subgroup might share genetic risk factors with primary OA to a higher extent than the first subgroup. Findings in our sample, which contains a large number of individuals with DDH and secondary OA, supports this hypothesis. We found a higher overlap of risk factors between a sample of primary OA and our sample, than for a sample of individuals with DDH without secondary OA.

Our main finding in this study is related to *COL11A1*, a gene important for cartilage formation and function [19]. Thus, this finding more likely has implications for our understanding of the hip cartilotype than the morphotype. On the other hand, our secondary finding supporting the role of *GDF5* in DDH implicates both cartilotype and morphotype, as *GDF5* is expressed at the time of joint formation as well as during cartilage development [9].

There are several limitations to our study. A major limitation is the validity of the diagnoses. HUNT diagnoses are based on clinicians' registration in the hospital patient records, without any information on radiological validation. Our group has previously shown that Norwegian orthopedic surgeons reporting to the Norwegian Arthroplasty Registry (NAR) have a correctly reported diagnosis of osteoarthritis secondary to DDH in 88 % of cases when pelvic radiographs are used for validation [3]. As the data in this study is based on diagnoses from the National Patient Registry (NPR), also supplied by Norwegian orthopedic surgeons, we can assume a similar diagnostic and reporting precision. From clinical experience, we find that it is more likely that secondary osteoarthritis due to DDH is erroneously coded as primary osteoarthritis, especially in borderline cases, and this is supported by our previous work [3]. Another limitation is that the NPR only started registering patient identifiable data in 2008, implying that individuals with DDH/secondary osteoarthritis who have not been seen at the hospital in relation to these diagnoses since 2008 will not be correctly registered. As the controls are recruited from the general HUNT cohort, and thus not screened for DDH or secondary osteoarthritis, it is likely that some cases are misclassified as controls.

Another limitation is the large discrepancy in case/control numbers. Although we address this by using the SAIGE software specifically designed for use in such situations, there is still a risk of type I error due to the small number of cases. Another drawback in the use of SAIGE is that it limits our possibilities for further analyses such as heritability, due to the use of penalized quasi-likelihood in order to reduce computation time which would cause a bias when using certain SNP heritability calculation methods [15].

Although batch and principal components were included in the analyses, the fact that the cohort has been genotyped over some time using three different array versions is not optimal as there might still be residual bias.

The fact that the associated locus is supported by several independently genotyped SNPs strengthens our confidence in the results. In terms of functional analyses, a major limitation is that publicly available datasets do not contain cell lines such as chondrocytes or other cells expected to be involved in joint formation or homeostasis of the cartilage, making the interpretation of these analyses challenging.

Here, we present one of the largest GWA studies on DDH and secondary OA to date. Genetic studies of phenotypes requiring complex diagnostics such as imaging can be challenging, as large population cohorts often lack detailed phenotype data. In this study, we observed genome-wide significant associations with SNPs in *COL11A1,* a strong candidate gene previously associated with cartilage function, skeletal development and osteoarthritis [11,19,27–29,32].

As DDH is treatable with minimally invasive measures at a young age, an early diagnosis can possibly prevent the need for invasive surgery, including THA at a later age. Elucidating the pathogenesis of DDH is an important part of enabling early, specific diagnoses. As such, further studies on the genetics of DDH in well characterized samples are needed.

Author contributions

KKJ and SB did the statistical analyses, QC and interpretation of the data. KKJ and LBL drafted the manuscript. All authors contributed to the design and patient selection criteria, as well as critical review and revision of the paper.

Role of funding source

This study was funded by Helse Førde and Helse Vest.
TZ was supported by R37MH107649-07S1 and 5R01MH12485.

Declaration of competing interest

All authors report no competing interests.

Acknowledgments

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The genotyping was financed by the National Institute of health (NIH), University of Michigan, The Norwegian Research council, and Central Norway Regional Health Authority and the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The genotype quality control and imputation has been conducted by the K.G. Jebsen center for genetic epidemiology, Department of public health and nursing, Faculty of medicine and health sciences, Norwegian University of Science and Technology (NTNU).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2023.100424.

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