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Developmental dysplasia of the hip: a systematic literature review of the genes related with its occurrence

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- Developmental dysplasia of the hip (DDH) is one of the most prevalent congenital malformations. It has a wide spectrum of anatomical abnormalities of the hip joint and is characterized by mild or incomplete formation of the acetabulum leading to laxity of the joint capsule, secondary deformity of the proximal femur and irreducible hip dislocation. It is the leading cause of early hip osteoarthritis in young individuals.
- Both genetic and environmental factors have been proposed to play an important role in the pathogenesis of DDH. A high prevalence is present in Asian, Caucasian, Mediterranean and American populations, with females being more frequently affected. We evaluated a variety of genetic studies indexed in the PubMed database.
- Several susceptive genes, including WISP3, PAPPA2, HOXB9, HOXD9, GDF5, TGF Beta 1, CX3CR1, UQCC, COL1A1, TbX4 and ASPN have been identified as being associated with the development of DDH. Moreover, genetic association has also been reported between hip dysplasia and other comorbidities. Even though genetic components are a crucial part in the aetiology of DDH, several DDH susceptibility genes need further investigation.
- The purpose of this review is to present current literature evidence regarding genes responsible for DDH development.

Keywords: developmental dysplasia of the hip; genes; congenital malformation

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Introduction

Developmental dysplasia of the hip (DDH), also known by the preceding term congenital dislocation of the hip (CDH), is one of the most prevalent congenital malformations.[1,2] DDH has a wide spectrum of anatomical abnormalities of the hip joint and is characterized by mild or incomplete formation of the acetabulum, leading to laxity of the joint capsule, secondary deformity of the proximal femur and irreducible hip dislocation.[3] The leading cause of osteoarthritis of the hip in young individuals is undetected hip dysplasia.[4] Variability in phenotypic presentation is observed in DDH-affected patients.[1,5] Genetic and environmental factors are both involved in the pathogenesis of DDH.[1,4] Breech presentation, oligohydramnios, female gender, large birth weight and primiparity may play a role in the occurrence of DDH.[2] The condition may often affect multiple individuals in a single family through generations and a 12-fold increase of DDH among first-degree relatives of those affected by the disorder has been noticed. A large Chinese cohort study proved that there is a high sibling recurrent risk of DDH in the Asian population, with female siblings having double the risk in comparison with male siblings.[6] Several studies have reported multiple genes to be associated with DDH. This underlines the evidence of a genetic cause as the dominant factor in the development of DDH.(1,4,5)

An incidence of 1.0–1.5 cases per 1000 live births has been reported.[4] DDH presents high prevalence in Asian, Caucasian, Mediterranean and American populations;[4] and females are more frequently involved with a sex-ratio of 4–10:1.[7]

Table 1. Genes related to developmental dysplasia of the hip (DDH) in studies

Type of study	Gene	Number	Population	Polymorphisms (SNPs)
Case-control[1]	WISP3	386 patients with DDH and 558 healthy controls	Han Chinese	rs69306665 rs1022313, rs1230345, rs17073268 rs10456877
Familial study[2]	CX3CR1	4 DDH, 4 healthy controls	Saudi family	rs3732379
Case-control[7]	CX3CR1	689 DDH, 689 healthy controls	Han Chinese	rs3732378 rs3732379
Familial study[4]	CX3CR1	4 affected, 71 members	Utah family, USA	rs3732378
Case-control GWAS[10]	20q11.22 UQCC GDF5	386 DDH, 558 controls	Han Chinese	12 including rs6060373
Case-control[10]	UQCC	755 cases, 944 controls	Han Chinese	rs6060373
Case-control[3]	TGFB1 locus29 IL6 locus-572	OA secondary to DDH ($n = 68$) and controls, patients with OA unrelated to DDH ($n = 152$)	Caucasians of European descent	rs1800470 rs1800796
Case-control[11]	GDF5	192 patients, 192 healthy	Female Han Chinese	rs224332 rs224333
Case-control[17]	PAPPA2	697 subjects, 707 controls	Han Chinese	rs726252
Case-control[19]	HOXB9	460 DDH cases and 562 control	Han Chinese	rs2303486 rs8844
Case-control[20]	COL1A1 Gene Promoter	154 unrelated female patients and 180 matched healthy female children	Han Chinese	T-139C C-106T C-35T
Case-control[16]	PAPPA2	310 unrelated patients and 487 healthy	Han Chinese	rs726252
Case-control[12]	GDF5	960 children (338 patients and 622 healthy)	Han Chinese	rs143383
Case-control[14]	GDF5	239 unrelated DDH patients and 239 healthy controls	Caucasians (Brittany, France)	rs143383 rs143384(possible)
Case-control[21]	Tbx4	505 radiology-confirmed DDH and 551 healthy children	Chinese	rs3744448
Case-control[22]	ASPN	370 patients and 445 healthy controls	Han Chinese	D14 allele
Case-control[18]	HOXD9	209 patients and 173 healthy children	Female Han Chinese	rs711822
Preliminary[15]	TGFB1 locus29 IL6 locus-572	28 adult patients with DDH and secondary OA and 20 healthy	Europeans	
Familial study[25]	chromosome 17q21	18-member multigenerational family affected with DDH	Americans	4 Mb region extended from rs2597165 to rs996379

Note. GWAS, genome-wide association study.

Design

We evaluated case-control, cohort, familial studies and reviews on DDH-linked genetic analysis indexed in the PubMed database. Our search was in MeSH terms using: "developmental dysplasia of the hip"/congenital, genetics, genes.

Types of studies

Case-control studies have been carried out in which in a population of a few hundred sporadic DDH patients, a given variant is examined. Several candidate genes, including WISP3, PAPPA2, HOXB9, HOXD9, GDF5, TGF Beta 1, CX3CR1, UQCC, COL1A1, TbX4 and ASPN have been found in case-control studies and have been associated with the development of DDH. It has been shown that these genes play a role in cartilage formation and chondrocyte development.[1,5] Familial analysis was also used in the published literature in order to detect genetic factors with a strong impact on the occurrence of DDH. This approach involves taking into account data from large families with DDH-affected individuals. CX3CR1, HSPG2 and ATP2B4 genes have been highlighted by such studies so far.[2] Briefly, these candidate genes related with DDH are classified in Table 1.

Genes related to DDH occurrence

WISP3 gene

WNT1-inducible-signaling pathway protein 3 (WISP3) as a member of the CCN family regulates cell growth and differentiation. WISP3 was reported to be the gene responsible for the autosomal recessive skeletal disorder progressive pseudorheumatoid dysplasia (PPD) imposing hip joint damage characterized by continuous degeneration and loss of articular cartilage. WISP3 also has an important role in cartilage formation and chondrocyte development. Research has demonstrated the pathophysiology behind the above role of WISP3. WISP3 regulates the expression of type II collagen through the insulin-like growth factor (IGF) signalling pathway and restricts IGF1-mediated hypertrophic changes in chondrocytes. According to a case-control study, WISP3 was associated with DDH in a Han Chinese population.[1] In the association study between 386 DDH patients and 558 healthy controls, five SNPs – rs69306665 (upstream of WISP3), rs1022313 (WISP3), rs1230345 (WISP3), rs17073268 (WISP3) and rs10456877 (downstream of WISP3) – were identified for association with DDH, showing significant difference of allele frequencies with similar odds ratios and appear to be risk variants for DDH occurrence. SNP rs1230345 might participate in exon mutations of the WISP3 gene, which

would directly alter the function of encoded protein and thus cause disease phenotypes such as DDH. Concerning the additional haplotype analysis that was conducted between cases and controls, the frequencies of haplotypes GGCGG and AAAAA were statistically significantly different. Specifically, GGCGG haplotype was associated with a higher risk of DDH, which implied that GGCGG haplotype might be a biomarker for DDH.[1]

CX3CR1

The CX3CR1 gene has a double role as it encodes CX3CL1's receptor which is expressed in innate immunity cells and thus gets involved in the inflammation process. Secondly, CX3CR1 participates in differentiation of mesenchymal stem cells towards chondrocytes. So, a misexpression of this gene may lead to the abnormal formation of the acetabular cartilage.[7] A linkage analysis and whole-exome sequencing of four affected individuals from a large, multi-generational family in the USA demonstrated CX3CR1 as a potentially responsible gene of DDH occurrence.[4] Whole-exome sequencing revealed a candidate region on chromosome 3p22.2 and variant rs3732378 of CX3CR1 shared by all affected individuals, implying that it was the putative pathogenic gene of DDH. This Utah family showed transmission of DDH through four generations with an autosomal dominant mode of inheritance and incomplete penetrance. Because of the problem of unknown, incomplete penetrance, not all unaffected individuals will also be free of the disease allele.[4,7] A case-control association study, inspired by the previous genome-wide linkage analysis, was conducted to explore the correlation between CX3CR1 and sporadic DDH.[7] Two SNPs of CX3CR1, rs3732378, and rs3732379, were genotyped in 689 DDH patients and 689 controls. For both variants, significant differences were observed in both genotype and allele distributions between DDH and control groups, suggesting that CX3CR1 was a disease-causing gene for DDH. The rs3732378 and rs3732379 polymorphisms are considered risk factors for DDH. The reason they are considered to be risk factors instead of disease-causing SNPs is that rs3732379 polymorphism changes the polarity of amino acids from polar to non-polar, which affects the encoded protein.[7] Sanger sequencing of already-known genes, whole-genome SNP genotyping and exome sequencing were performed to identify underlying genetic defects in a Saudi family with four individuals having DDH. The genes sequenced included CX3CR1, ASPN, HOXB9, HOXD9, DKK1, GDF5, PAPPA2, TGF Beta 1 and UFSP2. Sanger sequencing of all known genes did not identify any pathogenic variants except variant rs3732379 in CX3CR1. This represents a different variant of the same candidate gene responsible for the occurrence of DDH that had been detected in the previously reported Utah family. However, this variant was not present in one of the affected children in the Saudi family and therefore did not segregate with DDH in this family. Also, in contrast to the variant detected in the Utah family the variant detected here did not appear to have a functional effect on the protein, or to alter a conserved residue. Finally, the high frequency of this variant in the general population, indicates that this variant cannot be highly penetrant, although it might be a modifier of the DDH phenotype, similarly to the suggested effect of the CX3CR1 variant reported in the Utah family.[7,8] Homozygosity mapping used for genotype data analyses identified two shared homozygous regions on chromosome 15q13.3 and chromosome 19p13.2. Copy Number Variation (CNV) analysis revealed a shared copy number gain on chromosome 6p21.32 in all affected individuals. Partial gain of this region has also been found in unaffected members of this family. Exome data did not detect any candidate sequence variant.[2]

UQCC

The Ubiquinol-cytochrome c reductase complex chaperone (UQCC) gene physiologically encodes a zinc-binding protein, repressed by fibroblast growth factor (FGF2), which plays a role with several other genes in the morphogenesis and growth of the skeleton. Moreover, it is expressed in differentiating chondrocytes and as a result is very important for chondrogenesis. The first genome-wide association study (GWAS) demonstrated that common variants of UQCC are associated with DDH in the Han Chinese population. Specifically, rs6060373 was chosen for a replication study instead of 11 other SNPs in UQCC as the most dominant locus, because of its greater diagnostic value and a case-control analysis was conducted. rs6060373 appeared to be a risk variant for DDH occurrence. UQCC is identified as a target gene of FGF2, which plays a vital role in chondrogenesis. So UQCC, repressed by FGF2, is likely to be involved in the regulation of skeletal development and chondrogenesis by FGF2.[8]

TGFB

The superfamily of TGF Beta proteins, especially growth differentiation factor 5 (GDF5) and asporin (ASPN), seems to be strongly correlated with the occurrence of DDH as proved by numerous studies.[3] Interleukin 6 (IL-6) is a cytokine of paramount importance in the regulation of inflammatory processes. According to a study, increased levels of IL-6 lead to increased levels of TGF Beta 1, proving that there is an interaction in secretion of these two cytokines.[9]

Specifically, a case-control study in which cases were patients with OA secondary to DDH and controls were patients with OA unrelated to DDH was conducted to clarify the hypothesis that TGF Beta 1 and IL6 SNPs are associated specifically with DDH, because it was unclear

whether the evaluated SNPs were associated primarily with OA or DDH.[9] Both TGF Beta 1 and IL-6 have been implicated in the pathophysiology of OA. An association between TGF Beta 1 29 T → C transition (rs1800470) and IL-6 572G → C transversion (rs1800796) with DDH, and also a possibility of TGF Beta 1 and IL-6 interaction in DDH pathogenesis and particularly their combination was found. In populations in Europe, rs1800470 is considered to be a risk factor for aseptic loosening of the total hip arthroplasty. TGF Beta 1 and IL-6 are both pro-inflammatory cytokines that are involved in the development of the musculoskeletal system, bone remodelling as well as fibrous, bone and cartilage tissue development.[9] Transition to homozygosity (C/C) at TGF Beta 1 signal sequence locus 29 was around 2.4 times more likely in cases than in controls and transversion at IL-6 promoter locus -572 was around 6.4 times more likely in cases than in controls.[3]

Growth differentiation factor 5 (GDF5) belongs to the transforming growth factor (TGF)-beta superfamily of proteins.[10] GDF5, known also as cartilage-derived morphogenic protein 1 (CDMP1), is an important regulator of cartilage by stimulating the development, growth and maturation of cartilage. A functional SNP in the 5′-untranslated region of GDF5 (rs143383) has been reported to be associated with DDH. The findings of an association study in a female Chinese population indicate that GDF5 may be a candidate gene for DDH occurrence, based on an association between two SNPs, rs224332 and rs224333, of GDF5 and DDH development. Both SNPs were located in the same intron of GDF5. For SNP rs224332, the C allele had the higher frequency in patients and the CC genotype frequency was significantly higher than the other two genotypes. Respectively for rs224333, the G allele and the GG genotype were significantly higher. Also, C and G alleles are associated with DDH occurrence and their frequency is high in all populations and in Asian population database, according to the database of the 1000 Genomes Project.[10] A previous case-control study performed on a Han Chinese population with DDH reported for the first time the correlation between the GDF5 gene and DDH.[11,12] A later investigation proved for the first time that positive correlation between GDF5 polymorphisms is present not only in Chinese but also in Caucasians, while suggesting another SNP (rs143384) for further investigation.[12,13] A limited sample case-control study in Croatia supported the association of IL-6 promoter and TGF Beta 1 signal sequence polymorphisms and appearance of DDH and adult osteoarthritis.[12,14]

PAPPA2

Pregnancy-associated plasma protein-A2 gene (PAPPA2) encodes a novel metalloproteinase pregnancy-associated plasma protein-A2 which may play roles in foetal development. The SNP rs726252 located in the region of 5th intron of PAPPA2 on chromosome 1q25.2a is another gene implicated in the pathogenesis of DDH. PAPPA2 is known for its importance in the development of the foetus and normal postnatal growth while it is a protease. During embryonic, foetal and infantile growth periods, insulin-like growth factors (IGFs) tend to have a vital contribution in the normal development of bone, cartilage, fibroblast and skeletal muscles. Six IGF binding proteins (IGFBPs 1–6) are responsible for the bioavailability of IGFs, which is achieved via proteolysis of IGFBPs. PAPPA2 is a protease that can cleave IGFBPs during pregnancy and lead to an increase of IGF bioavailability. A former genome-wide linkage scan in a four-generation Chinese family and a case-control association study in a Han Chinese population demonstrated that there is a notable correlation between PAPPA2 and development of DDH.[12,15] A following case-control study was conducted investigating whether the SNP rs726252 was associated with DDH. In the comparison between 697 DDH subjects and 707 control subjects any significant difference in genotype distribution or allele frequency between cases and controls was not detected and thus, rs726252 in PAPPA2 was found to have no association with susceptibility to DDH in the Han Chinese population. However, the association between the PAPPA2 gene and DDH is debatable.[16]

HOX

The homeobox (HOX) genes are a group of 39 related genes that encode well-conserved transcription factors which are involved in vertebrate skeleton development. HOX genes are separated into four clusters: HOXA–D. HOXD genes form a cluster of nine genes (HOXD1,3,4,8–13) at 2q24.1-q33.1 loci. This gene cluster plays a determinant role, especially 5' HOXD gene (paralogous groups 9–13), in skeletal and limb morphogenesis. The HOXD9 gene specifically, regulates not only muscle cell growth and differentiation, but also the differentiation of mesenchymal cells into new bone and cartilage that may affect the acetabular shape, the ossification groove development and the position of the femoral head. In this way, the HOXD9 gene might be part of the aetiology of DDH development.[17] A case-control study was conducted in a female Han Chinese population to investigate the association of HOXD9 with DDH development. The investigators isolated genomic DNA from peripheral blood leucocytes from blood samples of both patient and healthy control groups. The patients group included people with unilateral or bilateral DDH. Thus, two SNPs were chosen and after a comparison between the two groups only one showed significant difference. Specifically, this study established the association between one tag SNP (rs711819) settled at the promoter region of HOXD9 gene with DDH in a female Han Chinese population, regardless of whether it was unilateral or bilateral. However, the authors suggest a

future investigation with larger sample size and different populations to confirm the HOXD9 gene and DDH development association.[17] A study examined the role of the HOXB9 gene, which is involved in limb development, on chromosome 17 in DDH patients from a Han Chinese population and indicated that the SNP rs2303486 may be associated with severity of DDH.[18] Although the relation between this variant and DDH occurrence and severity is well established through the above studies, the exact pathogenic mechanism has not been identified.

COL1A1

The COL1A1 gene encodes collagen protein type 1. A case-control study sequenced the COL1A1 gene promoter for detection of variations and demonstrated it as a new candidate gene responsible for DDH. Three variations in the COL1A1 gene promoter were detected among ten patients, which shows that the higher rate of total variations contributed to DDH occurrence. Follow-up studies are needed to highlight the pathogenic mechanisms that lead to DDH occurrence.[19]

T-box

Genes of the T-box family, which were first identified in mice and later in the human genome, participate in axial development. Particularly the Tbx4 gene in humans, with 27857 bp in size, located on the 17q21-q22 chromosome, is a crucial regulator for the hindlimb outgrowth and its identification during vertebrate foetal development. Thus, an alteration of the nucleotide sequence of this gene may result in abnormal skeletal formation. Taking into account the role of the Tbx4 gene in limb development, a case-control study on a Chinese children population with unilateral and bilateral DDH was performed. The investigators concluded that rs3744448 SNP located in exons of the Tbx4 gene is related with DDH only in the dominant model of male subjects.[12,20]

ASPN

Asporin (ASPN), an extracellular matrix protein of the small leucine-rich repeat proteins family (SLRPs), is known to participate in bone formation. For this reason it is of interest to investigators of the development of DDH. A case-control study, including patients and controls of both sexes, on a Han Chinese population indicated a correlation between the D repeat polymorphism of the asporin (ASPN) gene and DDH. This gene encodes an extracellular matrix (ECM) cartilage protein, ASPN, that is a member of the small leucine-rich repeat proteins family. TGF Beta 1 is a regulator for the perichondrial and fibroblast cells in tendons. Former studies have proven that ASPN can bind to TGF Beta 1 and prevent its interaction with the TGF Beta type II receptor following up the inhibition of TGF Beta/Smad signaling and induced chondrogenesis. In this way, perichondrium-dependent skeletal development, such as that of tendons and ligaments, is inhibited. BMP2 (bone morphogenetic protein 2) is a TGF Beta family member which participates in differentiation and proliferation of perichondrial cells and osteoblasts. ASPN can also bind to BMP2 and inhibit BMP2/Smad signaling. A polymorphism in an aspartic acid (D) repeat of ASPN, which was initially associated with osteoarthritis, the D14 allele indicated stronger inhibition of TGF Beta 1 activity than the other alleles. Thus, inhibition of TGF Beta/Smad and BMP2/Smad signaling may lead to delay of skeletal components development, and reduction of multipulation of fibroblast cells in tendons and fascia, which loosen around the hip joint and make it more plausible to dislocate.[12,21]

DDH and other comorbidities

Studies have proven that some genes contribute to other musculoskeletal diseases beyond DDH. Specifically, an editorial sustains that polymorphisms at ASPN D-repeat (D14 allele) and mutations at GDF5 genes (rs143383) are responsible not only for DDH but also lumbar-disc degeneration as well as knee osteoarthritis.[22] Mutations in humans settled on the GDF5 gene lead to a wide variety of skeletal abnormalities such as acromesomelic dysplasia Hunter-Thompson or Grebe type, Grebe-type chondrodysplasia,[23] brachydactyly type C and osteochondrodysplasia. Grebe-type chondrodysplasia is an acromelic shortness syndrome caused by a mutation of the GDF5 gene on the 20q11.22 chromosome.[23] Genes' expression depends on both genetic and environmental factors and thus carriers of the same mutation may not have the same phenotype.[24] It is remarkable that in some patients with the above-mentioned syndromes DDH coexists.[11–13] According to a single-centre study hip dysplasia is associated with osteogenesis imperfecta (OI), a heritable skeletal disorder that is usually due to mutation in one of the two genes, COL1A1 and COL1A2, that code for collagen type I a-chains. This study described the association of hip dysplasia with collagen type 1 C-propeptide mutation. Presence of a C-propeptide mutation appears to be a risk factor for hip dysplasia (80%).[25] An association has also been reported between hip dysplasia and disorders associated with ligamentous laxity, such as Down syndrome, Ehlers-Danlos syndrome, Larsen syndrome, Marfan syndrome and OI.[25]

Discussion

Familial genetic studies, genome-wide screening and linkage studies have demonstrated that familial DDH is inherited as an autosomal dominant disorder mapped to chromosome 4q35, and two further locations of interest have been located at chromosome 13q22 and at

chromosome 17q21.[3] An 18-member multigenerational family with DDH in the USA participated in a case-control study, which was awarded with the Otto Aufranc Award in 2010. Isolated DNA from buccal swabs and blood specimens was submitted to a total genome scanning using GeneChip Mapping 250K Assay (Affymetrix, Santa Clara, California). As a result, the investigators managed to map the mutated gene for DDH at a region 4 Mb in size on chromosome 17q21. To be more specific, the maximum logarithm of the odds (LOD) score of 1.82 was found at SNP rs16949053, located 45,844,439 bp from the p-term of chromosome 17. The region of positive LOD score (which favours the presence of linkage) is extended from rs2597165 to rs996379 for 4 Mb approximately. So, the disease-associated polymorphisms are settled in this limited area. Besides this, pedigree analysis of this family revealed the autosomal-dominant transmission trait of DDH while rejecting the X-linked inheritance hypothesis.[12,26] We suggest that molecular studies on DDH families might highlight the underlying genetic factors for DDH occurrence.

To sum up, alterations in WISP3 and CX3CR1 genes lead to abnormal cartilage formation and chondrocyte development. WISP3's GGCGG haplotype might be a biomarker for DDH, which would be very useful for DDH diagnosis. Alterations in UQCC, HOX, and T-box genes are responsible for abnormal chondogenesis and skeleton development. HOX's SNP rs2303486 on chromosome 7 and T-box's SNP rs3744448 have been identified as being associated with DDH. PAPPA2 is a protease with a crucial role in the development of bone and cartilage, so possible mutations are associated with DDH. Regarding the TGFB genes family, abnormal interaction of IL-6 and TGF Beta 1 leads to abnormal fibrous, bone, cartilage tissue formation. A positive correlation between GDF5 polymorphisms and DDH has already been proven. GDF5's SNP rs143384 needs further investigation as a possible variant for DDH occurrence.

All of the above-mentioned genes have been proven to be responsible for the development of DDH encode factors that participate in inflammation, hindlimb outgrowth, as well as the formation of bone, cartilage, ligaments and other skeletal components. It is assumed that aetiopathologically, a mutogenesis or misexpression of these genes results in the production of pathological products that contribute in development of DDH.

DDH is a complex disorder and it is accepted that genetic components play a crucial part in the aetiology of DDH. A specific pathophysiologic pathway for the development of DDH has not yet been described. Several DDH susceptibility genes were discovered by studies in Chinese and Caucasian populations. However, the genetic basis of DDH remains largely unknown and researchers suggest further investigations in bigger sample studies and in DDH families.[8] We suggest further genomic approached studies on already identified and newly discovered genes associated with DDH occurrence, in order to achieve a better understanding of the genetics and pathogenic mechanisms of DDH.

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