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# Two genetic variants in the *HIBCH* and *FTCDNL1* genes are associated with susceptibility to developmental dysplasia of the hips among the Han Chinese population of Southwest China

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## Abstract

**Background** Developmental dysplasia of the hip (DDH) is a common cause of childhood disability, and the incidence of DDH shows significant familial aggregation. As the genetic factors of DDH remain unknown, the correlation between five candidate single nucleotide polymorphisms (SNPs) and DDH was evaluated in the Han Chinese population of Southwest China.

**Methods** A case–control association study was conducted in 276 patients with DDH and 318 healthy controls. SNP genotyping in the case and control groups was performed by SNPshot and multiple PCR. SNPs were genotyped in the case and control groups by multiplex PCR. The relationship between DDH and candidate SNPs was evaluated using the  $\chi^2$  test.

**Results** The genotype distributions of rs291412 in *HIBCH* and rs769956 in *FTCDNL1* were different between the case and control groups ( $P < 0.05$ ). After genetic model analysis, logistic regression analysis revealed that the C allele of rs291412 had a protective effect on DDH (OR = 0.605,  $P = 0.010$ ) and that the G allele of rs769956 was a risk factor (OR = 2.939,  $P = 0.010$ ).

**Conclusion** These SNPs could be associated with susceptibility to DDH but larger population-based studies should confirm the current results.

**Keywords** Developmental dysplasia of the hip, *HIBCH*, *FTCDNL1*, Single-nucleotide polymorphism, Susceptibility

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## Background

Developmental dysplasia of the hip is a common hip joint deformity caused by incomplete acetabulum formation. This hip malformation changes the length of the hip muscle torque arm, the line of action, and the reaction force on the hip joint during walking [1, 2], resulting in higher than normal load and shear force in the joint. Clinical manifestations of this disease include dislocation, subluxation, acetabular dysplasia and hip instability [3, 4]. The overall prevalence of DDH is 1.52% in Chinese adults [5] and 1.7% in Chinese infants [6], with a high heritability of  $83.59\% \pm 4.90\%$  among siblings, and risk of the disease is at least twice as high in females than in males [7]. Mild DDH can heal itself in childhood, but if left uncorrected in infancy, DDH can lead to difficult rigid luxation of the femur head, leading to long spica casting treatments or surgical operations and further frequently leading to early total hip replacement [8, 9]. As the remodeling potential of the hip joint decreases with age, delayed treatment may result in increased surgical difficulty and frequency [10]; in general, additional surgery in adolescence requires less deformity correction after surgery for DDH in childhood [11]. Therefore, early diagnosis of DDH is crucial for its treatment and preventing complications [12]. At present, clinical diagnosis of DDH mainly relies on imaging methods [13], and the progress of related molecular diagnosis research is slow. Hence, it is necessary to study risk genes associated with DDH onset for early screening clinically.

The specific pathogenesis of DDH remains unknown. However, previous studies indicated that the formation of connective tissue, osteogenesis, chondrogenesis, cell growth, proliferation and differentiation during development may be involved [14, 15]. Moreover, the etiology of DDH is complex, and epidemiological studies have shown that genetic factors affect susceptibility [16, 17], presenting an autosomal dominant inheritance pattern in some families [18]. Accordingly, it is meaningful to consider genetic background while assessing the etiology of DDH formation.

## Methods

### Subjects

In this study, the subjects comprised 276 patients with DDH recruited from the Han Chinese population in Southwest China. Definitive diagnosis was made by two experienced orthopedic experts based on the results of physical examination and pelvic imaging. When clinical physical examination revealed one of the following positive signs, further imaging examination was performed: (1) asymmetrical dermatoglyphics of the bilateral thighs, buttocks, and perineum; (2) shorter lower limbs of the affected side and muscle strength lower than that of the healthy side; (3) hip discomfort or pain; (4) restricted hip abduction, with or without adduction deformity; (5)

abnormal gait with limping or duck-like gait; (6) positivity for one of the Allis sign, Ortolani sign, Barlow sign, Nelaton test or in the abduction test. A definitive diagnosis was made when the imaging examination showed any of the following: (1) B-ultrasonography for patients aged 0–6 months with angle A less than 60 degrees. (2) specific indicators measured by imaging for a patient over 6 months old, including ① the femoral head epiphysis located in the upper and lower lateral Perkin quadrant; ② acetabular index  $> 25^\circ$ ; ③ CE angle  $< 20^\circ$ ; ④ interrupted Shenton line; and ⑤ CT or MRI examination for elderly or adult patients showing poor acetabulum alignment, acetabulum coverage rate  $< 75\%$ , dislocation or subluxation. Patients with syndromic hip dislocation and other chronic diseases were excluded. The case group consisted of 65 males and 211 females, and the control group consisted of 318 individuals; those with congenital malformation, hereditary neuropathy, hip dislocation or family history of DDH were excluded. This study was approved by the ethics committee of 920th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army (2020-057-01), and informed consent was obtained from all participants and their families before enrollment in the trial.

### Site selection

This study prescreened candidate SNPs in the Han Chinese population in Southwest China based on Pool-seq and gene functional candidate strategies. Peripheral blood DNA from the 276 patients was extracted using Axygen® Axyprep Blood Genomic DNA Miniprep Kit following the manufacturer's instructions; the DNA was pooled at equal concentrations and subjected to Whole Exome Sequencing (WES) at 60X depth; the number of reads was obtained by sequencing, the WES were performed by the Beijing Novogene Corporation.

The pooled DNA were used to construct libraries using the Agilent SureSelect Human All Exon V6 kit. Subsequently, paired-end sequencing (PE150) was performed on the Illumina platform to generate FastQ files. After data cleaning and quality assessment, the reads were aligned to the human reference genome GRCh37/hg19 using BWA (Li et al., 2018). Qualified SNPs were called using SAMtools (Li et al., 2009) with specific criteria ( $QUAL \geq 20$ ;  $DP \geq 50$ ;  $MQ \geq 30$ ). Varcan2 [19] software was used to estimate SNP frequency in the case pool. Then, 1000 Genomes data for Asians were used as the control group, and the difference in locus frequency (1000G\_EAS) between the case group was compared by the chi-square test. SNPs ( $P < 0.0001$ ), with significantly different frequencies (case pool vs. East Asian population) in genes associated with DDH function selected as candidate sites.

## Genotyping

The five SNPs (rs4823187 A/C/G, rs2426300 A/C/T, rs10146692 A/G, rs291412 C/T, rs769956 A/G) genotyping was performed by the SNaPshot technology using PCR-A300 (Hangzhou Langi Scientific Instrument Co., LTD.), which is a multiplex PCR-based next generation sequencing based on a primer extension-based method for genotyping known SNP positions.

After obtaining written informed consent, 3 ml of peripheral blood was collected; genomic DNA was extracted from 300 ml peripheral blood using Axygen® Axyprep Blood Genomic DNA Miniprep Kit following the manufacturer's instructions. PCR primer design: Primer 5 was used to design multiple primers for specific amplification of candidate SNP sites. The primer sequences are shown in Table 1. The reaction was performed in a 15 µl volume consisting of 0.3 µl forward primer, 0.3 µl reverse primer, 1 µl DNA template, 7.5 µl PCR mix (Shanghai Yisheng Biotechnology Co., Ltd. ), and 5.9 µl ddH<sub>2</sub>O. The reaction conditions were as follows: predenaturation at 95°C for 5 min, 35 cycles of denaturation at 94°C for 20 s, annealing at 55°C for 20 s, and extension at 72°C for 40 s, and repair extension at 72°C for 10 min.

**PCR product purification:** The reaction was performed in a 7 µl mixture consisting of 3 µl PCR product, 0.2 µl ExoI, 0.8 µl FastAP, 0.7 µl ExoI buffer, and 2.3 µl ddH<sub>2</sub>O. Purification conditions: 37 °C for 15 min, 80 °C for 15 min. The above purification reagents were purchased from Fermentas, Canada. **Purified PCR product reaction:** The reaction was performed in a 6 µl mixture consisting of 2 µl purified PCR product, 1 µl SNAPSHOT mix (ABI, USA), extension primer 0.2 µl/strip, and 2.8 µl ddH<sub>2</sub>O. Reaction conditions: 94 °C for 10 s, 52 °C for 5 s, 60 °C for 30 s, for a total of 30 cycles. One microliter of the extension product was added to 9 µl HiDi (ABI, USA), denatured at 95 °C for 3 min, and immediately placed in an ice water bath. Next-generation sequencing of the PCR product was performed using a 3730 XL gene sequencer (ABI, USA). The original image data were converted to sequence reads by base calling and analyzed using GeneMarker software.

## Statistical analysis

SPSS (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Quantitative data are shown as the

mean ± standard deviation (SD). Comparisons between 2 groups were performed using Student's t test. The Hardy-Weinberg equilibrium (HWE) of the control group was evaluated by the chi-square test. The correlation between SNPs and DDH was evaluated. The relative risk of disease is expressed by the odds ratio (OR) and 95% confidence interval (95% CI). Bonferroni's correction was applied for multiple tests. All statistical tests were two-tailed, and  $P < 0.05$  was defined as statistically significant.

## Results

### Basic characteristics of the study subjects

A total of 609 subjects were recruited for this study, including 276 DDH patients and 318 healthy individuals. All patients with DDH were diagnosed by orthopedic experts according to their medical history, clinical symptoms and imaging results (hip X-ray, magnetic resonance imaging and ultrasound), including 67 males and 209 females. The control group was composed of 120 males and 213 females.

### Pool-Seq screen for candidate genes

WES with 60X depth were performed. 179.8 G data was obtained, and the Q30 of these data was 93.44. At last, the allele frequencies of total 14,535 SNPs were obtained. The SNP frequencies obtained through Pool-seq were compared to those from the East Asian population in the 1000 Genomes Project. A chi-square test was conducted to identify positive SNPs ( $P < 0.0001$ ).

SNPs were selected with the most significant  $P$ -values, while the genes in which these SNPs are located are functionally closely related to DDH. At last, the five candidate SNPs (rs4823187 in PARVB, rs2426300 in NFATC2, rs10146692 in DPF3, rs291412 in HIBCH, and rs769956 in FTCDNL1) were selected for genotyping in this study. Among them, the actin-binding protein encoded by PARVB plays a role in cytoskeletal tissue and cell adhesion and contains the calmodulin homologous domain for binding to actin filaments. NFATC2 is a member of the activated T nuclear factor (NFAT) family, which is related to inflammation and plays a central role in inducing gene transcription during the immune response. DPF3 encodes a member of the D4 protein family, which binds to acetylated histones acting as transcriptional regulators. The HIBCH gene encodes 3-hydroxyisobutyryl-CoA hydrolase. FTCDNL1 affects folate-binding

**Table 1** Primers for fluorescence quantitative polymerase chain reaction

Gene	SNP	Forward Primers	Reverse Primers
PARVB	rs4823187	CAGCGTGATTACCAGGGTCTC	TGCAGCTTTCAGAGGCTGCTC
NFATC2	rs2426300	GATAATTAGGACTTGGTGCA	CCTGGCTTGACAGACAGTCAC
DPF3	rs10146692	AGAGCTGAAGAGAAGCCCTG	GCGGCTCTGGCGGTGTGAAC
HIBCH	rs291412	CTGCCAGCCACGTGAAGATG	AGAGGTTTAATTGGCTCACAG
FTCDNL1	rs769956	GTATTCCTAGTGAGAACCAT	TCTAACAAAGCTGATCAGCA

**Table 2** Comparison of the gene frequency of 5 SNPs in DDH and healthy populations

Gene	SNP	Minor/Major	MAF (DDH) (%)	MAF (control)(%)	Allele P value	HWE-P
<i>PARVB</i>	rs4823187	(A + C)/G	0.197	0.228	0.201	0.866
<i>NFATC2</i>	rs2426300	(A + T)/C	0.293	0.253	0.119	0.316
<i>DPF3</i>	rs10146692	A/G	0.326	0.335	0.747	0.356
<i>HIBCH</i>	rs291412	C/T	0.489	0.550	0.035	0.767
<i>FTCDNL1</i>	rs769956	A/G	0.245	0.187	0.016	0.248

**Table 3** Gene frequency comparison and genetic model analyses of 2 positive SNPs in the DDH and control populations

Gene(SNP)	Genotype	Casefreq	Controfreq	OR(95% CI)	P value
<i>HIBCH</i>	C/C	0.268	0.299	0.782(0.622–0.983)	
rs291412	C/T	0.442	0.503		
	T/T	0.290	0.198		
Dominant	MM + MN	0.710	0.799	0.605(0.414–0.884)	0.010
	NN	0.290	0.201		
Recessive	MM	0.268	0.285	0.860(0.601–1.231)	0.414
	MN + NN	0.732	0.715		
<i>FTCDNL1</i>	A/A	0.069	0.025	1.407(1.065–1.858)	
rs769956	A/G	0.351	0.324		
	G/G	0.580	0.651		
Dominant	MM + MN	0.420	0.378	1.352(0.970–1.885)	0.076
	NN	0.580	0.622		
Recessive	MM	0.069	0.027	2.939(1.266–6.823)	0.010
	MN + NN	0.931	0.973		

activity and transferase activity and is associated with osteoporosis. The above candidate SNPs were examined in 276 DDH patients and 318 healthy controls to identify genetic associations with DDH.

#### Distribution of genotypes and alleles

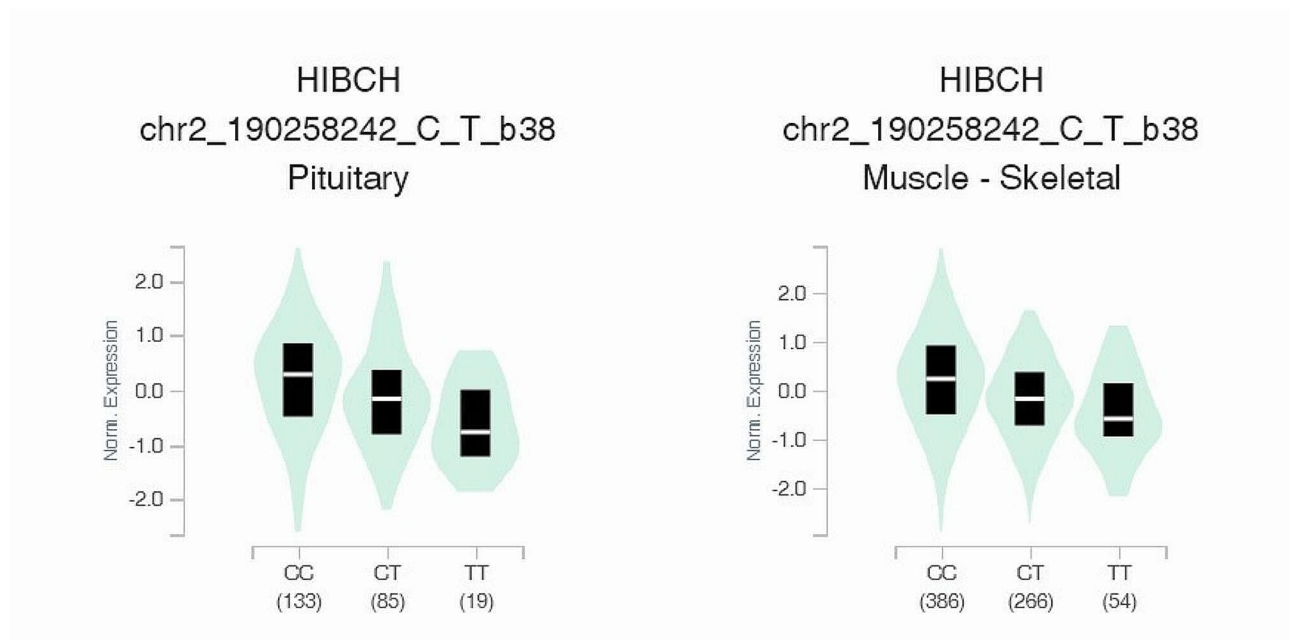
All five candidate SNPs conformed to Hardy-Weinberg equilibrium in the control and DDH groups ( $HWE-P > 0.05$ ; shown in Table 2), and the frequency of minor alleles was greater than 0.05, indicating that the frequency of each allele was genetically stable. The allele frequencies of the 5 SNPs in the control and DDH groups were compared using the chi-square test. It is worth noting that SNP rs4823187 in *PARVB* and SNP rs2426300 in *NFATC2* were found to be allele loci after SNPshot typing. We assumed these alleles with lower frequencies to be mutated in the population and combined their frequencies for chi-square analysis [20]. SNP rs291412 in *HIBCH* and SNP rs769956 in *FTCDNL1* showed differences between the DDH and control groups. In addition, the minor allele frequency (MAF) of rs4823187 in *PARVB*, rs10146692 in *DPF3* and rs291412 in *HIBCH* was statistically lower in the case group than in the control group, though the MAF of rs2426300 in *NFATC2* and rs769956 in *FTCDNL1* was higher. Although the positive results of SNP rs291412 in *HIBCH* and SNP rs769956 in *FTCDNL1* disappeared after multiple tests

and Bonferroni correction, these two variants are probably related to the genetic susceptibility of DDH.

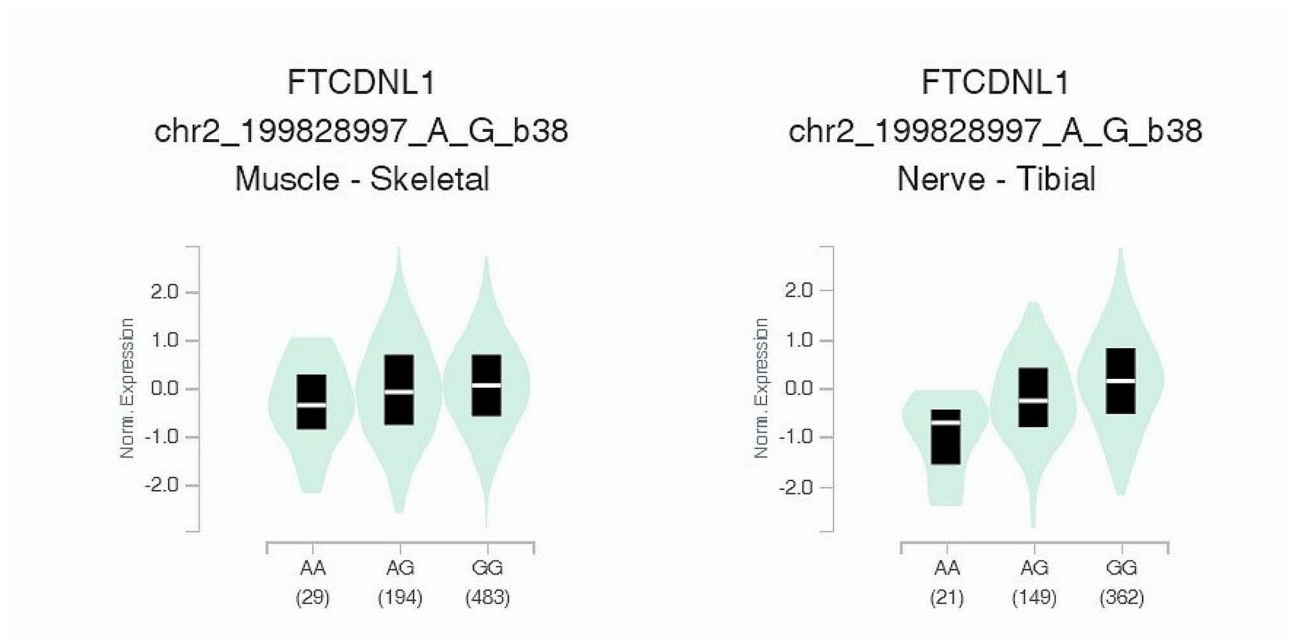
#### Analyses of the genetic model of the correlation between 5 candidate SNPs and DDH

The association between the above 2 SNPs and risk of DDH was evaluated using the assumption of various genetic models with low-frequency allele M: the dominant model, MM + MN vs. NN (as long as the M allele is carried, the disease risk is influenced), and the recessive model, MM vs. MN + NN (it is necessary to carry two M at the same time to influence the risk of carriers). According to the above hypothesis, the correlation between rs291412, rs769956 and genetic susceptibility to DDH was evaluated using the chi-square test, and the results are shown in Table 3. Under the hypothesis of the dominant model, SNP rs291412 in *HIBCH* showed significant differences between the DDH and control groups ( $OR = 0.605$ ,  $P = 0.010$ ), indicating that the rare genotype of *HIBCH* rs291412 has a protective effect against DDH. However, under the hypothesis of the recessive model, SNP rs769956 in *FTCDNL1* showed significant differences between the DDH and control groups ( $OR = 2.939$ ,  $P = 0.010$ ), indicating that the common genotype of *FTCDNL1* rs769956 is a risk factor for DDH.

The expression relationship between these two variants and their corresponding genes was explored in the eQTL database of GTEx (<https://www.gtexportal.org/>).



**Fig. 1** Differential expression levels of various allelic genotypes of SNP rs291412 in *HIBCH* in pituitary tissue and skeletal muscle tissue



**Fig. 2** Differential expression levels of various allelic genotypes of SNP rs769956 in *FTCDNL1* in skeletal muscle tissue and tibial nerve

The results revealed that the three genotypes of rs291412 significantly influence expression of the *HIBCH* gene in pituitary and skeletal muscle tissues (Fig. 1) but that the presence of the T allele leads to reduce expression in these tissues ( $P=1.2 \times 10^{-9}$ ;  $P=4.5 \times 10^{-12}$ ). The three genotypes of rs769956 also significantly influence expression of the *FTCDNL1* gene in tibial nerve tissue and skeletal muscle tissue (Fig. 2), whereas the presence of allele A reduces it ( $P=4.9 \times 10^{-7}$ ;  $P=6.4 \times 10^{-8}$ ).

## Discussion

In this case-control study, five candidate SNPs were pre-screened by pooled sequencing, and the link to genetic susceptibility to DDH was investigated in these candidate SNPs (rs4823187 in actin-related *PARVB*, rs2426300 in T-cell-related *NFATC2*, rs10146692 in transcription-regulating factor-related *DPF3*, rs291412 in *HIBCH* encoding 3-hydroxyisobutyryl coenzyme A hydrolase, rs769956 in folate binding activity-related *FTCDNL1*). The results

showed that the genetic variant rs291412 in *HIBCH* and rs769956 in *FTCDNLI* can significantly reduce the risk of DDH onset.

DDH is a common disorder in children, and its risk increases with the presence of various factors, such as mechanical constraints in the uterus and abnormal position in the last three months, but it is also related to the postnatal environment and genetic susceptibility [21–25]. To reveal the genetic background of DDH, some candidate genes (including *WISP-2* [26], *CX3CR1* [27], and *TXNDC3* [28]) responsible for susceptibility to DDH have been detected by molecular analysis and sequencing technology. However, in this study, differences in the above genes in the control and DDH groups were not revealed by pooled sequencing, which may be related to different genetic backgrounds. As data from 1000 Genomes for Asians were used as controls in preliminary screening of candidate sites, we speculate that these DDH gene results may be difficult to replicate in different populations. This may be caused by different geographical regions or different environments and lifestyles among races or ethnic groups; this study only explored susceptibility genes for DDH in the Han population.

The *HIBCH* gene (containing 17 exons) is located at chromosome 2q32.2 and encodes HIBYL-CoA and  $\beta$ -hydroxypropionyl-CoA hydrolase. Mutations in this gene are associated with 3-hydroxyisobutyl-CoA hydrolase deficiency and accumulation of metabolic intermediates of valine. The *HIBCH* gene is widely expressed in human tissues such as the kidney, heart and skeletal muscle [29], and its alternative splicing results in multiple transcript variants. *HIBCH* deficiency is a rare autosomal recessive hereditary neurodegenerative disease characterized by a continuous decline in psychomotor ability, which can be clinically observed in young children with developmental delay, hypotonia, neurological degeneration and seizures [30–32]. The results of this study showed a significant association of SNP rs29141 in *HIBCH* with the DDH phenotype in the Han population of Southwest China, which suggests an increased risk for people carrying the minor allele of this SNP ( $P=0.035$ ). However, statistical significance was lost after Bonferroni correction, which indicates that the significant association of this SNP may lead to the first type of statistical error during simultaneous analysis of multiple SNPs. Nevertheless, considering the genetic heterogeneity of DDH and the small possibility of multiple DDH patients carrying the same susceptibility mutation, we believe that such sites with  $P$  values on the margin of statistical positivity are worthy of further attention. Furthermore, we verified the hypothesis of *HIBCH* gene polymorphism and susceptibility to isolated DDH. In the general population, low-frequency alleles are considered to be derived from mutations. *HIBCH* rs291412 is associated with susceptibility to DDH in the

Han population of Southwest China, suggesting that the rare allele of *HIBCH* rs291412 (C allele) has a protective effect on susceptibility to DDH (OR=0.605,  $P=0.010$ ).

Forminotransferase cyclodeaminase N-terminal-like gene (*FTCDNLI*), located at chromosome 2q33.1, is widely expressed in various tissues, including bone. Mutations in this gene have been significantly associated with susceptibility to osteoporosis [33], which has also been verified in the Taiwan DDH population [34]. The results of this study showed a significant association of SNP rs769956 in *FTCDNLI* with an increased risk of DDH in the Han population of Southwest China, suggesting that individuals carrying the common allele of *FTCDNLI* rs769956 (G allele) have a potential risk factor (OR=2.939,  $P=0.010$ ).

In addition, after querying the expression relationship of *HIBCH* rs291412 and *FTCDNLI* rs769956 in the eQTL database of GTEx, we found that different genotypes of *HIBCH* rs291412 and *FTCDNLI* rs769956 showed significant differences in expression in skeletal muscle. The pathogenesis of DDH is related to slow and stable accumulation of toxic methylacryl-coA in mitochondria, as well as to rapid and intensive accumulation under conditions of insufficient energy, such as exercise or fever [35]. The most common pathophysiology from DDH to osteoarthritis is femoral bone malformation [36], and the mechanism by which DDH produces a destructive load on skeletal muscle is also related to abnormal skeletal muscle geometry and function [37]. The study of Sacha et al. [38] showed that the absence of *HIBCH* would lead to the absence of respiratory enzymes in skeletal muscle, resulting in hypotonia. This evidence suggests that differential expression of *HIBCH* and *FTCDNLI* may lead to changes in skeletal muscle morphology and function, which may be related to the pathogenesis of DDH.

In summary, DDH is a complex muscle-joint disease, and we speculated that the pathological changes in muscles caused by DDH are related to deficiency of *HIBCH* and *FTCDNLI*, as well as to heterogeneity in the genetic background. Therefore, association analysis of susceptibility to DDH in different populations should be further investigated. This study is the first to suggest the relationship between *HIBCH*, *FTCDNLI* and susceptibility to DDH.

## Conclusion

This study shows for the first time the association of SNP rs291412 in *HIBCH* and SNP rs769956 in *FTCDNLI* with the risk of DDH, suggesting that these sites are potential genetic susceptibility markers of DDH in the Chinese population.

Although the mechanisms by which *HIBCH* and *FTCDNLI* cause DDH are largely unknown, these findings provide new insight into the complex genetic

structure of DDH and may have some significance for the identification of high-risk individuals and genetic counseling.

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#### Author contributions

Conceptualization: XHM, YTW, HS, CL; Data curation: YR, YQX, HS, CL; Formal analysis: YR, YQX, HS, CL; Funding acquisition: CL; Writing - original draft: XHM, YTW; Writing - review and editing: all authors.

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#### Data availability

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

This study was approved by the ethics committee of 920th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army (2020-057-01), and informed consent was obtained from all participants and their families before enrollment in the trial.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare no competing interests.

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