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Primary Hip

Family History of Developmental Dysplasia of the Hip is a Risk Factor for the Progression of Hip Osteoarthritis

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ABSTRACT

Background: Developmental dysplasia of the hip (DDH) is considered to have genetic predisposition and presents many intrafamilial occurrences. However, there is no report that evaluates the effect of DDH family history on the progression after the onset of hip osteoarthritis (OA).
Methods: Medical interviews about detailed clinical information including family history were conducted on 298 consecutive patients who had undergone surgery for OA due to DDH. Clinical or radiographic items that are associated with the severity of DDH (total hip arthroplasty [THA], involvement of bilateral DDH, onset age of hip pain, and three radiological indices of DDH: center-edge angle, sharp angle, and acetabular roof obliquity) were collected and evaluated in multivariate analyses for their associations with DDH family history in a qualitative or quantitative manner. Survival time analyses for THA as the endpoint was also performed to evaluate the effects of DDH family history on the progression of OA.
Results: The DDH family history showed significant associations with bilateral involvement of DDH (odds ratio = 2.09 [95% confidence interval {CI} 1.05 to 4.16]; $P = .037$), early onset of hip pain ($P = .0065$), and radiological severity of DDH ($P = .016$). The DDH family history showed a significant association with undergoing THA (odds ratio = 2.25 [95% CI 1.09 to 4.66]; $P = .029$), further supported by the Cox regression analyses (hazards ratio = 1.56 [95% CI 1.15 to 2.11]; $P = .0044$).
Conclusion: A DDH family history is a risk factor for the progression of hip OA. Stronger genetic predisposition to DDH leads to faster onset and progression of hip OA.

The pathogenesis of developmental dysplasia of the hip (DDH) is highly affected by hypoplasia of the osteochondral tissue and the morphology of the soft tissue surrounding the hip joint; in DDH, the most common signs are acetabular dysplasia and a genetic laxity of the ligaments. It is known that DDH can lead to early hip osteoarthritis (OA), one of the leading causes of global disability [1–3] and accounts for about 80% of the cause of hip OA in Japan [4]. Since there are major direct and indirect costs attributable to arthritis for those who have disabling hip OA [5], it is critical to elucidate the pathogenesis of DDH.

Genetic components are associated with DDH in addition to acquired causative factors related to limb positioning, such as diapering, holding, and swaddling (a technique of covering babies with clothes on legs in extension and adduction) [6–8]. Other than the above, the reported risk factors of DDH include family history, female sex, breech presentation, multiple gestation, first pregnancy, high birth weight, and oligohydramnios [9–11]. In

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particular, regarding intrafamilial occurrence, the incidence of first-degree relative DDH patients was 12 times greater than that of people who did not have DDH relatives [12]. Increased incidences within families have also been reported in various cohorts from different ethnicities [13–17]. These suggest a genetic contribution to the development of DDH. While we should note that the absence of family history does not indicate a complete lack of a genetic basis in the subjects (due to the nature of polygenicity of complex traits), the presence of family history suggests stronger genetic components in the subjects [18]. Recent genetic studies of complex traits have revealed that genetic components contribute not only to development of diseases but also to severe progression of the diseases after onset [19]. Thus, detailed analyses of DDH progression (not restricting to its development) using the family history of DDH would provide the evidence of a genetic basis for DDH progression. There are few studies reporting the association of DDH family history with the progression and prognosis of hip OA [20], and stable view on this association has not been obtained.

Therefore, the purpose of this study was to investigate the impact of DDH family history on the progression of hip OA. As disease onset and progression often share genetic mechanisms [21], we assume that "population with DDH family history" are at higher risk of hip OA progression as well as of developing DDH than "population without family history of DDH," which have a weaker genetic basis.

Material and Methods

Subjects and Clinical Assessment

This study was approved by our institutional review board (number 840-02). A total of 298 consecutive Japanese outpatients who have undergone hip surgery including total hip arthroplasty (THA), periacetabular osteotomy, and Chiari pelvic osteotomy with proximal femoral osteotomy for OA secondary to DDH were included in this study. All subjects underwent the clinical assessment questionnaires performed by several orthopaedic surgeons affiliated with the hip disease research group. The questionnaire included DDH family history as well as age, sex, height, weight, body mass index (BMI), smoking history, onset age of hip pain, history of hip surgeries, surgical techniques, and age at surgery.

The Definition of DDH Family History

We conducted a patient survey on the family history of hip diseases up to the fourth degree of kinship (down to a cousin) of patients who had DDH. Orthopaedic surgeons filled out the survey by interviewing the patients who had DDH. All cases not clearly confirming their family history were assigned to the group without family history to avoid overestimation. Next, we excluded the history of diseases other than DDH from the family history of hip diseases. We carefully ruled out the family history of hip trauma or osteonecrosis of the femoral head from DDH family history. For example, the presence of a family member who had a history of treatment for femoral neck fracture does not mean that there is a DDH family history.

Radiographic Assessments

We measured the three radiological indices, references lateral center-edge (CE) angle, sharp angle, and acetabular roof obliquity (Tonnis angle), for the right and left hip joints separately using preoperative radiographs of each outpatient, and these data were included in the clinical information. In this study, we used sharp angle and acetabular roof obliquity as indicators reflecting the degree of acetabular dysplasia (the larger these angles, the more dysplastic) and CE angle as an indicator reflecting not only the degree of acetabular dysplasia but also subluxation (the smaller this angle is, the more subluxated the femoral head is).

The Definition of DDH

One hip was diagnosed as DDH when any one of the following three conditions was met: CE angle $\leq$20 °, sharp angle $\geq$45 °, and acetabular roof obliquity $\geq$15 °.

Demographics

There were 293 out of 298 consecutive subjects who completed the clinical assessment, and 287 out of these 293 subjects completed the radiographic assessment (287 subjects completed both the clinical and radiographic assessments). The number of individuals who had a DDH family history was 80 out of 293, about 27.3% of all cases, which is consistent with the previous study [22]. Of the 80 patients who had a DDH family history, 62 had one close relative with DDH history, 14 had 2 relatives, and 4 had 3 relatives (the maximum number of close relatives was three). All subjects were adults who had a mean age of 61 years (range, 25 to 90) in the group with DDH family history and 62 years (range, 16 to 89) in the group without DDH family history. One-tailed Student's *t*-tests were applied to compare the mean values of each continuous value between the two groups (Table 1).

Table 1
Demographics of the Subjects.

Characteristics	Total	Family History (+)	Family History (−)	*P* Value
Clinical assessment	293	80	213	
Number of close relatives with DDH history				
One		62		
Two		14		
Three		4		
Mean age in years (range)	62 (16 to 90)	61 (25 to 90)	62 (16 to 89)	.17
Sex				
Men	33	13	20	
Women	260	67	193	
Mean BMI (range)	23.6 (15.6 to 37.4)	23.7 (16.6 to 37.4)	23.5 (15.6 to 32.8)	.67
Smoking	49	18	31	
Radiological DDH				
Unilateral	73	13	60	
Right	41	9	32	
Left	32	4	28	
Bilateral	220	67	153	
Onset age of hip pain (y)	43.8 ± 16.0	41.5 ± 16.6	44.7 ± 15.7	.073
THA				
Total	212	63	149	
Age of primary THA (y)	60.2 ± 9.2	57.9 ± 9.0	61.1 ± 9.0	.010[a]
Follow-up time until primary THA (y)	14.1 ± 13.4	15.7 ± 15.3	13.8 ± 13.1	.72
Radiographic assessment	287	79	208	
CE angle				
Right	13.5 ± 11.1	12.1 ± 11.7	14.1 ± 10.8	.082
Left	10.2 ± 13.3	9.78 ± 10.8	10.4 ± 14.1	.36
Average	11.9 ± 9.4	10.9 ± 8.6	12.2 ± 9.7	.14
Sharp angle				
Right	47.7 ± 5.6	48.3 ± 5.6	47.5 ± 5.6	.16
Left	47.8 ± 7.2	48.7 ± 7.9	47.5 ± 6.9	.089
Average	47.8 ± 5.3	47.5 ± 5.0	48.5 ± 6.1	.077
Acetabular roof obliquity				
Right	20.8 ± 8.7	21.7 ± 7.8	21.0 ± 8.5	.24
Left	21.0 ± 8.8	21.1 ± 8.1	20.7 ± 8.9	.35
Average	21.2 ± 8.3	21.4 ± 6.4	20.8 ± 6.9	.25

All continuous values are given as the mean and standard deviation.
BMI, body mass index; DDH, developmental dysplasia of the hip; THA, total hip arthroplasty; CE angle, center-edge angle.
[a] *P* value <.05.

Data Analyses

There were 4 main analyses listed below that are performed using data from these 293 or 287 individuals. We used 1/10 values for age and onset age of hip pain to facilitate interpretation of effect sizes relative to the other variables. All statistical analyses were performed using R version 4.0.5, The R Foundation for Statistical Computing, Vienna, Austria.

Association of DDH Family History or the Number of Close Relatives Who Received THA and Bilateral Involvement of DDH

Given that THA is performed for advanced OA and that bilateral DDH more frequently causes hip OA than unilateral DDH, the association between these 2 items and DDH family history was analyzed. First, these 2 items were simply compared between groups divided by the presence or absence of DDH family history and then compared between groups based on the number of close relatives with DDH. Multiple regression analyses were performed with DDH family history or the number of close relatives as the main explanatory variable, and the presence or absence of THA and bilateral DDH were each set as binary objective variables. Logistic regression models were used, and age, sex, smoking history, and BMI were treated as potential confounding variables to control for in the analyses. The multicollinearity among covariates was confirmed using variance inflation factors and Pearson correlation coefficients.

Association Between DDH Family History or the Number of Close Relatives Who Have DDH Family History and Onset Age of Hip Pain

Assuming that young onset age reflects the severity of DDH as well as receiving THA and bilateral involvement, onset age was compared between/among groups according to DDH family history. First, onset age was simply compared between groups divided by the presence or absence of DDH family history and then compared between groups based on the number of close relatives who have DDH. The variables such as sex, BMI, and smoking history on onset age were first applied to regress and then the residuals calculated by the regression model were compared between the groups without family history (0 close relative), with family history, with one close relative, with two close relatives, and with three close relatives.

Association of DDH Family History With Radiological Indices in Both Hips

Multiple regression analyses were performed with family history as the main explanatory variable and radiological indices in both hips as the objective variable. Linear regression models were used, and age, sex, smoking history, and BMI were treated as potential confounding variables to control for in the analyses. The multicollinearity among covariates was confirmed using variance inflation factors and Pearson correlation coefficients.

As noted above, smaller CE angle and larger sharp angle or acetabular roof obliquity reflect more severe DDH. Noting whether the association between DDH family history and each angle was positively or negatively related to the development of severe DDH, a binomial test (background $P = .50$) was applied to test the consistency of the direction of the association with the development of severe DDH.

Association Between Follow-Up Period Until THA and DDH Family History

We defined the follow-up period as follows: "age at primary THA" - "onset age of hip pain" for patients receiving THA and "age" - "onset age of hip pain" for patients not receiving THA. Time to THA was estimated using Cox proportional hazards model (log-rank test and Cox regression). We set DDH family history as the main explanatory variable and onset age of hip pain as a covariate. Cox.zph function in R was used to confirm that the Cox proportional hazard assumptions were satisfied.

Table 2
Association of DDH Family History With the Presence of THA and Bilateral DDH.

Characteristics	Estimate (SE)	OR (95% CI)	*P* Value
THA	0.812 (0.371)	2.25 (1.09 to 4.66)	.029[a]
Bilaterality	0.735 (0.352)	2.09 (1.05 to 4.16)	.037[a]

Bilaterality, bilaterally affected (= 1) or not (= 0).
SE, standard error; OR, odds ratio; CI, confidence interval; DDH, developmental dysplasia of the hip; THA, total hip arthroplasty.
[a] *P* value <.05.

Results

We found a significant association between the DDH family history and bilateral DDH involvement (odds ratio [OR] = 2.09 [95% confidence interval {CI} 1.05 to 4.16]; $P = .037$, Table 2) and boundary associations (Supplementary Table 1).

We observed younger onset depending on inherited DDH-associated genetic architectures, as evidenced by the number of relatives with DDH ($P = .0065$, Figure 1 and Supplementary Table 2). Interestingly, subjects having three relatives affected by DDH showed age of onset 12.2 years younger on average than those who did not have a DDH family history.

While we did not observe statistical significance in associations with each radiographic index due to limited statistical power, the DDH family history was associated with a direction of severity across all of the three indices (Table 3). In addition, the DDH family history consistently showed associations with the severity of DDH on both sides (the three indices on right and left, binomial_$P = .016$).

A significant association between the DDH family history and whether the subjects who had DDH underwent THA surgery was observed (OR = 2.25 [95% CI 1.09 to 4.66]; $P = .029$, Table 2). Next, since DDH family history was associated with young onset age of hip pain, we addressed that the association between DDH family history and risk of undergoing THA could not be attributed to young onset age in subjects who had a DDH family history. As a result, we found that, even after taking into account the effect of onset age, DDH family history showed a significant association with increased risk on THA surgery (hazard ratio = 1.56 [95% CI 1.15 to 2.11]; $P = .0044$, Table 4).

Discussion

A number of intrafamilial occurrences of DDH have been reported [12,13,14,15,16,17], and it was well known that genetic predisposition was associated with its development, but there were few studies reporting the association of DDH family history with the progression of hip OA [20]. This was the first study to provide clear evidence that genetic predisposition of DDH was associated with the progression of hip OA. Based on clinical information obtained from nearly 300 consecutive patients who have DDH, to our knowledge, the largest number ever in the context of DDH family history, we tested relationships between genetic predisposition and hip OA progression by analyzing the association between DDH family history and clinical and radiographic parameters reflecting the severity of DDH. This consecutive sample collection enabled us to recruit samples in an unbiased manner. Actually, demographic

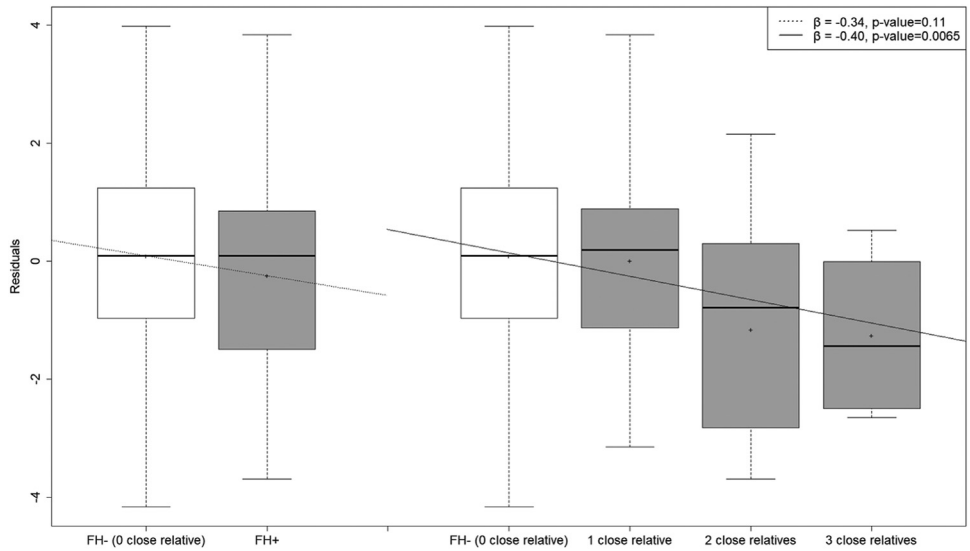

Fig. 1. This graph shows the residuals of onset age regressed out by variables (sex, BMI, smoking history) for groups. Groups are based on presence or intensity of family history. FH, family history; BMI, body mass index.

features and family history in the current data sets were well matched with the previous studies [22].

Multiple regression analyses using bilateral involvement showed that DDH family history had a positive association with OA progression, and analyses using onset age of hip pain as an index of severity showed that not only the presence or absence of DDH family history but also its intensity would affect the progression. It may not be so surprising that the mean age of the onset was three years younger in the group with DDH family history than in the group without DDH family history, but the age difference increases with the number of close relatives affected by DDH, and the group with three close relatives was on average more than 12 years younger than the group without DDH family history. This was an interesting finding because it supported that genetic factors are significantly involved in the progression from morphological characteristics of DDH to degenerative change of OA in a quantitative manner. Furthermore, focusing on the results of three radiographic indices, there were consistent associations of DDH family history with severe DDH. The two main pathologies of DDH were said to be dysplasia and joint laxity [1,2]. Sharp angle was an indicator of the degree of dysplasia, while CE angle was an indicator of the degree of subluxation as well as dysplasia. Therefore, the results were also reasonable in this viewpoint and suggest that genetic predisposition of DDH may be involved in both pathologies, namely, pelvic morphology and joint laxity.

Table 3
Association of DDH Family History With Left and Right Sides of Three Index Angles.

Characteristics	Estimate (SE)	*P* Value
CE angle		
Right	−2.17 (1.47)	.14
Left	−0.821 (1.77)	.64
Sharp angle		
Right	0.831 (0.741)	.26
Left	1.30 (0.946)	.17
Acetabular roof obliquity		
Right	0.997 (1.11)	.37
Left	0.535 (1.17)	.65

CE angle, center-edge angle; SE, standard error; OR, odds ratio; CI, confidence interval; DDH, developmental dysplasia of the hip.

Multiple regression analyses using THA showed that DDH family history had a positive association with OA severity. Furthermore, in the Cox regression analyses with the follow-up period from the time point of pain onset to that of THA as outcome, a significant association between family history of DDH and hazard increase was observed. This result indicated that when comparing patients who have a DDH family history with those who did not have a DDH family history and who have the same age of pain onset, the follow-up time to THA was shorter for the former, even accounting for onset age of DDH. Based on the results of these two analyses, we consider that genetic predisposition of DDH was a cause of not only the onset but also the exacerbation of hip OA.

There were several potential limitations to our study. The limitation can be caused by the interview-based detection of DDH family history. We might not evaluate family history for asymptomatic DDH that can be detected only by radiographs. Although familial occurrence of asymptomatic DDH has been reported [23], most of this study's evaluation items, such as age at THA and onset age, were events occurring after the onset of symptomatic hip OA. Therefore, family history in unrecognized asymptomatic DDH cases may not be precisely assessed. In addition, interview-based detection of DDH family history may not provide an accurate family history for some reason that differs from the asymptomatic cases, such as family history of adopted patients. However, we avoided overestimation by assigning all cases not clearly confirming their family history to the group without family history. As a result, the percentage of individuals who had DDH family history was 27.3%, which was comparable with the previous study [22], supporting a validity of the current data set. There was also the issue of sample size. In some regression analyses, especially those for radiographic items, the results did not meet the significance level, which indicated the necessity of further accumulation of DDH cases. While all results consistently point in a direction of DDH

Table 4
Association of DDH Family History With Follow-Up Time to THA.

Characteristics	Coefficients (SE)	HR (95% CI)	*P* Value
Family history	0.443 (0.156)	1.56 (1.15 to 2.11)	.0044[a]

SE, standard error; HR, hazard ratio; CI, confidence interval; DDH, developmental dysplasia of the hip; THA, total hip arthroplasty.
[a] *P* value <.05.

exacerbation, suggesting that the results were credible, further increases in sample size and replication studies were favorable.

Not a small number of genetic studies have highlighted the relationship between several candidate genes and the phenotype of DDH [24], and as is often the case with other complex diseases, many genetic variants may be involved in the pathogenesis of DDH. In this study, we demonstrated that the strength of genetic predisposition, as reflected in family history information, played a role in the etiology of DDH, which strongly supported the involvement of polygenicity in the etiology of DDH. However, the pathophysiological mechanisms supported by genetic associations remain unclear. Our next goal was to elucidate the specific genetic factors involved in the development of DDH and the exacerbation of DDH and OA. The results of this study were encouraging for our future genome-wide association study and suggest the possibility of detecting novel loci involved in the pathogenesis of DDH, in addition to disease susceptibility genes such as growth differentiation factor 5, which have been discussed in the previous genome-wide association studies [6,24].

Conclusions

Among patients who have hip OA, the presence of DDH family history was associated with parameters reflecting the progression of OA. A DDH family history is a risk factor for accelerated disease exacerbation in patients who have hip OA.

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Appendix

Supplementary Table 1
Association of the Number of Close Relatives With the Presence of THA and Bilateral DDH.

Characteristics	Estimate (SE)	OR (95% CI)	*P* Value
THA	0.476 (0.262)	1.61 (0.96 to 2.69)	.069
Bilaterality	0.542 (0.278)	1.72 (0.997 to 2.97)	.051

SE, standard error; OR, odds ratio; CI, confidence interval; DDH, developmental dysplasia of the hip; THA, total hip arthroplasty.

Supplementary Table 2
Association Between DDH Family History or the Number of Close Relatives With DDH History and Onset Age of Hip Pain.

Characteristics	Estimate (SE)	*P* Value
Family history	−0.337 (0.208)	.11
Number of close relatives	−0.396 (0.144)	.0065[a]

SE, standard error; OR, odds ratio; CI, confidence interval; DDH, developmental dysplasia of the hip.
[a] *P* value <.05.