

Familial Predisposition to Developmental Dysplasia of the Hip

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Background: Developmental dysplasia of the hip (DDH) is a common birth defect and is thought to have genetic contributions to the phenotype. It is likely that DDH is genetically heterogeneous with environmental modifiers. The Utah Population Database (UPDB) is a computerized integration of pedigrees, vital statistics, and medical records representing over 6 million individuals, and is a unique resource providing the ability to search for familial factors beyond the nuclear family, decreasing the effect of a shared environment. The purpose of this study is to assess the degree of relationship between individuals with DDH.

Methods: Datasets were created from UPDB statewide birth certificates and from the University of Utah Health Sciences Center enterprise data warehouse using records for DDH and linked to the UPDB. Controls for the dataset were selected that matched cases on birth year and sex and 10 controls were selected per case. Statistics computed for each family were the number of descendants, the observed number of affected, the expected number of affected, *P* value, familial standardize incidence ratio, relative risks (RRs), and standard error. A kinship analysis tool was used to find pedigrees with excess DDH.

Results: The combined data resulted in 1649 distinct individuals with DDH. RR was significantly increased in first-degree relatives (RR = 12.1; *P* < 0.000001), siblings (RR = 11.9; *P* < 0.000001) and first cousins (RR = 1.7; *P* = 0.04). A total of 468 families were identified with at least 5 affected individuals in a family. These results were then filtered to only contain families that had a *P* value of less than 0.01. This resulted in 141 founders with anywhere between 4 and 30 affected living descendants with a *P* value of less than 0.01 with family sizes ranging from 594 to 44,819 descendants. A total of 28 founders had a familial standardize incidence ratio of greater than 5.0.

Conclusions: These data suggest a genetic contribution to DDH with a 12-fold increase in risk for first-degree relatives. Better

phenotypic characterization and classification will be critical for future genetic analyses.

Level of Evidence: Prognostic level II.

Key Words: developmental dysplasia of the hip, population database, familial predisposition, genetics

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Developmental dysplasia of the hip (DDH) is a disorder with a large spectrum of severity affecting the proximal femur and acetabulum. The soft tissue capsule of the hip joint is excessively lax and allows the femoral head to displace from the confines of the acetabulum. The displacement of the femoral head may be only partial, indicating a subluxation of the hip, or the displacement may be complete as in a dislocation.

The etiology of DDH is thought to be multifactorial.^{1–3} The reported incidence of DDH varies throughout the world, likely as a consequence of what is believed to be genetic susceptibility and differences in infant positioning in different cultures. In the United States, DDH occurs in approximately 1.5% of neonates.⁴ Reported risk factors include female sex, family history, breech presentation, multiple gestation, first pregnancy, high birth weight, and oligohydramnios.^{5–7} Increased incidences within families have been reported in various cohorts from different populations,^{2,8–11} suggesting a genetic contribution to the development of DDH.

To assess the contribution of relatedness to DDH, the Utah Population Database (UPDB), an electronic database that integrates pedigrees, vital statistics, and medical records, was used. This population-based approach is unique and avoids the common biases of ascertainment and recall associated with many population studies. The UPDB provides the ability to search for familial factors beyond the nuclear family, decreasing the effect of a shared environment, which likely plays a role in the development of DDH. Therefore, the use of the UPDB may provide a more accurate assessment of the genetic contribution to DDH.

METHODS

UPDB

The central component of the UPDB is an extensive set of Utah family histories, in which family members are

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linked to demographic and medical information. The UPDB contains information on over 6 million individuals, including the genealogies of the founders of Utah and their Utah descendants. These genealogic records originated as “Family Group Sheets” filled out by members of the Church of Jesus Christ of Latter-day Saints (LDS). Records were selected from the Family History Library maintained by the LDS Church, and the criterion for original selection was that one or more family members was born or died on the Mormon Pioneer Trail or in Utah. The purpose was to represent migrants to Utah and their Utah descendants. The genealogy records for early migrants and their families represent birth cohorts that date back to about 1760. Family group sheets have been linked across generations. Individuals are included in these data who have or do not have an affiliation to the LDS Church, and also individuals who lived in other states and countries. The genealogy records have been linked to other datasets, including Utah birth and death certificates, cancer records, driver license records, and the Social Security Death Index. Multiple sources of information are available in the UPDB for parents and their children; these include genealogy records and Utah birth certificates beginning in 1947. The UPDB is a dynamic database with annual electronic updates on vital events, and many families have as many as 11 generations.¹²

Beginning in 2003, patient records from the University of Utah Health Sciences Center Enterprise Data Warehouse have been linked to the UPDB. More than a million patient demographic records have been matched to a “person” record in the UPDB. Hospital records include pathology laboratory results, radiology results, pharmacy data, outpatient documentation, International Classification of Disease (ICD)-9 coded diagnosis, current procedural terminology data, birth certificates, and community clinic information.

Using these linked research resources, 2 datasets were created. The first dataset was identified from the University of Utah Health Sciences Center enterprise data warehouse using records for DDH with the ICD-9 code 754.3. The second dataset was created from UPDB statewide birth certificates using DDH with the ICD-9 code 754.3 for 1978 to 1988, and text fields from 1947 to 1969 and 1989 to 2005. No information was available from birth certificates from 1970 to 1977. Text fields from birth certificates were reviewed by the first and last author for inclusion. Individuals with records in both datasets (N = 39) were combined to identify distinct patients. Patients overlapping in both datasets were removed from the University of Utah Health Sciences Center dataset.

Birth certificates from patients and unaffected controls from both datasets were subsequently queried for selected variables (ie, gestation number, parity, birth weight, and breech presentation of the fetus). Patients and unaffected controls were grouped into categories of single gestation pregnancy versus multiple gestation pregnancy, first born versus subsequent birth order, breech presentation versus no breech presentation, and birth weight more

TABLE 1. Utah Birth Certificate Records With Developmental Dysplasia of the Hip

1947-1979	105
1980-1989	510
1990-1999	247
2000-2005	97
Total	959

Birth year from 1947 to 2005; data were not available from 1970 to 1977.

than 4.5 kg (exceptionally large birth weight) versus birth weight ≤ 4.5 kg. This study was approved by the Institutional Review Board at the University of Utah.

Statistical Analyses

Analytical tools available through the UPDB allowed for the familial analysis of DDH. These data and methods have been used in a number of studies in the past.¹³⁻¹⁵ Unaffected controls for the dataset were selected that matched cases on birth year and sex and 10 controls were selected per case and sampling was done without replacement. The relative risk (RR) by kinship class associated with family history of disease was determined through conditional logistic regression analysis using the above set of controls.¹⁶

A kinship analysis tool was used to find families with excess DDH.¹⁶ A sampling of statistics computed for each family included the number of descendants, the observed number of affected, the expected number of affected, *P* value, familial standardize incidence ratio, RRs, and standard error.¹⁶ The initial search set a requirement that there be at least 5 affected individuals in a family. Results were filtered to only contain families that had a *P* value of ≤ 0.01 .

RESULTS

Cases from each dataset are listed in Tables 1 and 2. The combined data consisted of 1649 distinct individuals with DDH, with a distribution of birth years between 1931 and 2005. A total of 1164/1649 (71%) of individuals with DDH were female whereas 485/1649 (29%) were male. RR for DDH was significantly increased in first-degree relatives (RR = 12.1; *P* < 0.000001) (Table 3). A subset of the first-degree relatives that were siblings also

TABLE 2. UUHSC Records With Developmental Dysplasia of the Hip*

1931-1979	115
1980-1989	101
1990-1999	251
2000-2005	223
(Total)	690

Birth year from 1931 to 2005.

*The individuals with developmental dysplasia of the hip included in the dataset from search of Utah Birth Certificate Records (see Table 1) are not included in this dataset from International Classification of Disease-9 codes from the University of Utah Health Sciences Center (UUHSC) enterprise data warehouse.

TABLE 3. Utah Population Database Kinship Analysis (Logistic Regression)

Relationship	Relative Risk	95% Confidence Interval	P
First-degree	12.13	7.78-18.93	< 0.000001
Siblings	11.85	7.24-19.37	< 0.000001
First cousins	1.74	1.04-2.91	0.035

had an 11-fold increase in RR for DDH (RR = 11.9; $P < 0.000001$). First cousins also had an increase in RR for DDH, although not as pronounced as first-degree relatives (RR = 1.7; $P = 0.04$).

Of the individuals with DDH, 41.5% (681/1640) were reported to be first born compared with 29.6% (4885/16,489) of controls [RR = 1.71; 95% confidence interval (CI) = 1.54-1.9; $P < 0.000001$]. Breech presentation was observed in 21.6% (355/1640) of individuals with DDH compared with 8.3% (1366/16,489) of controls (RR = 3.15; 95% CI = 2.76-3.59; $P < 0.000001$). Exceptionally large birth weight (> 4.5 kg) was reported in 1.3% (22/1640) of individuals with DDH compared with 1.0% (166/16,489) of controls (RR = 1.34; 95% CI = 0.86-2.09; $P = 0.2$). Of the individuals with DDH, 1.9% (31/1640) were reported to be part of a multiple gestation pregnancy compared with 2.4% (401/16,489) of controls (RR = 0.77; 95% CI = 0.54-1.11; $P = 0.16$).

With the requirement that there be at least 5 individuals with DDH affected in a family, our analysis resulted in a total of 468 families. When these results were filtered to only contain families that had a P value of ≤ 0.01 , a total of 141 founders with anywhere between 4 and 30 affected living descendants with family sizes ranging from 594 to 44,819 descendants were identified. A total of 28 founders had a familial standardize incidence ratio of greater than 5.0. An example of a selected pedigree is shown in Figure 1.

DISCUSSION

The data suggest a genetic contribution to DDH with a 12-fold increase in risk for first-degree relatives.

This is consistent with earlier reports from other populations, although methods for determining and reporting familial contribution varied. In these studies, the familial predisposition to DDH was primarily based on assessment of nuclear families of index cases identified through orthopaedic clinics.^{2,8-11} In the United Kingdom, 589 patients from 2 large orthopaedic clinics reported a 6% RR for an affected subsequent child if the parent already had one affected child.² One hospital in the United Kingdom showed that 3% of 1855 individuals screened with an ultrasound on account of a family history of DDH had DDH.¹¹ Another group of 1747 patients with DDH from Spain showed a greater incidence of DDH in patients with a family history of DDH.¹⁰ Investigators studied 2146 index cases from the Hungarian region in which orthopaedic treatment for DDH was given, and found a 4-fold to 8-fold increase in DDH in siblings and a 4-fold increase in the parents of individuals with DDH.⁸ To our knowledge, the only earlier study on familial relationships for DDH in the United States is from a group of 78 index cases, identified by contacting orthopaedic surgeons in Vermont and New York, in which 10/78 had an affected first-degree relative.⁹ The data reported herein confirm a familial predisposition to the development of DDH with a RR of 12 for first-degree relations.

The use of the UPDB allowed for the search of familial relatedness beyond the nuclear family, and several large families were identified in which their common ancestors may not have been observed in the clinical setting. It is possible that affected individuals within large pedigrees may not have known about affected family members outside the nuclear family. These large pedigrees in which the affected status of distant relatives may not have been recognized earlier will allow for future linkage studies.

Nonetheless, the etiology of DDH is likely multifactorial. Other reported risk factors (ie, breech presentation, parity) suggest that the baseline susceptibility is laxity of the hip joint at least in a subset of individuals.

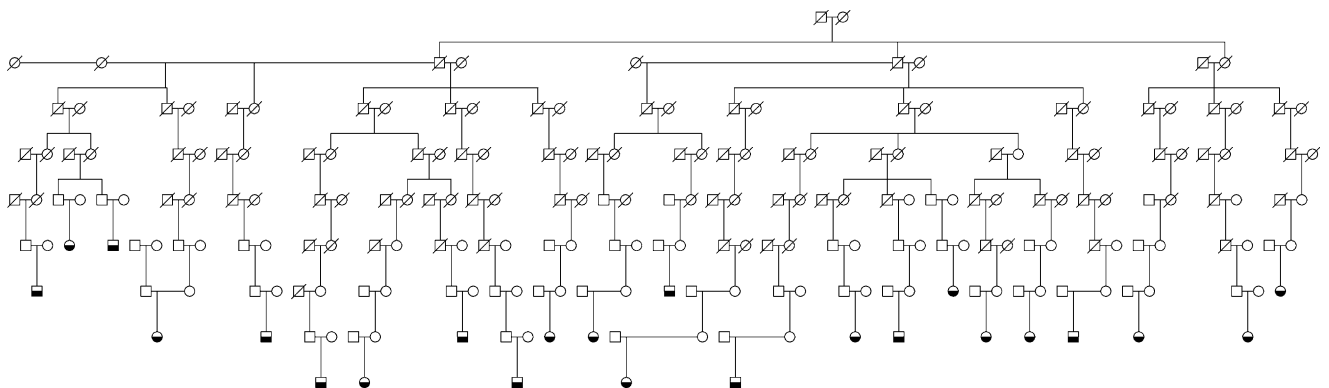


FIGURE 1. Sample pedigree of kindred with multiple members with developmental dysplasia of the hip (DDH). The pedigree has been trimmed for space and does not represent all family members within the pedigree highlighting the common ancestor of those known to be affected with DDH. The total number of descendants in this 9-generation pedigree is 22,196. Half-shaded circles or squares indicate known DDH-affected status.

Carter and Wilkinson¹⁷ reported joint laxity to be persistently increased on the basis of physical examination in a group of individuals with DDH, and Wynne-Davies² reported that joint laxity was increased in children with DDH, and that a higher proportion of neonates with DDH and their first-degree relatives had joint laxity than individuals with a later diagnosis of DDH. It is likely that in some individuals external forces during intrauterine development and postnatally act on the hips of susceptible individuals who harbor mutations in genes encoding proteins that lead to joint laxity resulting in DDH.

Some studies have proposed several different etiologic groups of DDH,^{2,17} and DDH has wide clinical variability with difficulty in determining what constitutes a dysplastic hip. One could have a dysplastic acetabulum without clinical dislocation of the hip, and potentially one could have a relatively normal obliquity of the superior acetabulum but extreme laxity leading to a subluxable hip. This leads one to think that DDH could be genetically heterogeneous, and the increased RRs could be secondary to a subset of individuals with the same genetic defect, whereas other genetic factors could lead to a different recurrence risk. The identification of specific disease-causing genes would provide insights into interventions for certain individuals with DDH. Individuals without clinical DDH have been reported to have subclinical acetabular dysplasia,² and it has been proposed that acetabular dysplasia can lead to osteoarthritis in later life.^{18–23} Identification of genes causing or predisposing to DDH will help in screening protocols of individuals at risk for these complications with the hope that early intervention will alleviate later complications.

One dataset was obtained through the University of Utah Health Sciences Center enterprise data warehouse and hence does not fully represent statewide data, which could introduce some bias. Individuals with DDH may have been diagnosed and treated at other hospitals and clinics. In addition, the data are limited to the accuracy of the physicians providing diagnostic codes, and the information contained within the database. A large amount of genealogic information within the UPDB allows for the compilation of extensive pedigrees, yet clinical data are not available on many older individuals within each pedigree. When one looks at a sample pedigree (Fig. 1), affected individuals in recent generations are shown but affected individuals are not prevalent in the older generations, although it is possible that many of these individuals were also affected. However, it may be difficult to assess the affected status of many deceased individuals because of lack of clinical data and age of individuals.

In summary, using a population-based database, there is a 12-fold increase in the RR for the development of DDH if one has a first-degree relative with DDH. Further studies will be needed to tease out the environmental and genetic contribution to this familial predisposition. Better phenotypic characterization and classification will be critical for future genetic analyses,

which will ultimately lead to a better understanding of the pathophysiology of DDH and potential insights into screening protocols and treatment.

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