The Broad Implications of Developmental Dysplasia of the Hip (DDH)

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Developmental dysplasia of the hip (DDH) is a spectrum of abnormalities involving the hip joint, ranging from frank dislocation to only mildly inadequate acetabular coverage of the femoral head, called acetabular dysplasia. Using the Utah Population Database (UPDB), my co-investigators and I demonstrated a substantial familial predisposition to DDH, and thus a genetic component to DDH.1 The familial relative risk of DDH is extremely high. Comparing the relative risk of individuals related to a proband to control families, first degree relatives are 12.1 times more likely to have DDH (p<0.000001), siblings are 11.9 times more likely (p<0.000001), and cousins are 1.7 times more likely (p<0.04).

In a second paper also using the UPDB, we confirmed an increased risk of hip osteoarthritis in probands with DDH (RR 82.4 p=2e-16), and their grandparents (RR 1.33 p<0.000001), siblings are 11.9 times more likely (p<0.000001), and cousins are 1.7 times more likely (p<0.04).

In a third study further supported this possibility. In a follow-up of individuals whose DDH was treated by open reduction surgery, my co-investigators and I found acetabular dysplasia developed gradually in 20 percent (eight of 40) of the contralateral “normal” hips. None of these contralateral “normal” hips demonstrated any radiographic abnormalities until adolescence.

Acetabular dysplasia is typically asymptomatic in childhood and adolescence, but it predisposes to early osteoarthritis. Acetabular dysplasia has been attributed as the cause of hip osteoarthritis for a substantial number of adults who require THA. Genetic determinants in DDH may result in a familial risk for acetabular dysplasia in otherwise normal individuals. A better understanding of the full phenotype of DDH (acetabular dysplasia through frank dislocation) would elucidate the occurrence of acetabular dysplasia.

Using our DDH families from the UPDB and individuals in the long-term outcome study of open reduction surgery, we recruited uninvolved individuals who were first-degree family members of a proband. Our phenotyping methods included physical examination, functional questionnaires, and radiographs. With the physical examination, a Harris Hip Score (HHS) was assigned, and two validated outcome instruments, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the American Academy of Orthopedic Surgery (AAOS) Hip and Knee Outcomes Questionnaire, were completed to determine subtle functional changes. Anterior-posterior pelvic, frog leg pelvic, and false profile lateral radiographs were obtained, computerized CE angles were determined, and Severin scores were assigned. The Severin classification is a radiographic assessment of acetabular dysplasia, with a measurement of the center edge angle (CEA) <20 degrees considered abnormal. Our team has previously shown that using a specific computerized measurement system increases the accuracy of the CEA measurement and the Severin classification.3

We have enrolled and phenotyped 121 individuals from 20 DDH families. The 121 individuals include 34 probands and 87 “normal” family members. In addition to the phenotype analysis, all 121 study participants have had their DNA extracted from whole blood and saved for sequencing. On pelvic radiographs, 26 percent of the relatives, previously thought to be unaffected, had acetabular dysplasia, many with symptoms of hip osteoarthritis. The individuals were then divided into two outcome groups: those with normal hips (64) and those with acetabular dysplasia (23), and each outcome group was subdivided into individuals over and under age 30. The HHS, WOMAC, and AAOS Hip and Knee scores were compared in each subgroup. There was no difference in functional outcome scores in those under age 30 with or without acetabular dysplasia. Individuals over age 30 with acetabular dysplasia had worse WOMAC scores compared to individuals over age 30 with normal hips (p<0.023). The HHS and AAOS Hip and Knee scores were also worse in those with acetabular dysplasia, but the difference did not reach statistical significance. The phenotyping portion of the research was presented as a podium presentation at the 2013 POSNA Annual Meeting and has been submitted for publication consideration.
We are in the process of performing next-generation exome sequencing on select families based on the highest statistically significant FSIR values, most severe phenotype, number of individuals, and distance of relationship. We have a multidisciplinary team of clinical and molecular geneticists and orthopaedists to perform these studies (David Stevenson, MD; Reha M. Toydemir, PhD, MD; James Roach, MD; and Kristen Carroll, MD). We have a family within our phenotypic group that has two children with Stevenson-Carey syndrome. We have isolated the gene defect to the NAV1 gene. Using a zebrafish model, we have tested two of the three morpholinos to knockdown the gene NAV1 and have a reproducible zebrafish phenotype showing effects on the hindbrain/cerebellum; brain structure; small eyes; and dysmorphic muscle/skeletal development of the pectoral fin. We also have in situ zebrafish pictures at different stages of development for the NAV1 gene. The NAV1 morpholinos cause skeletal and muscular dysmorphism of the caudal zebrafish embryo, consistent with the gene’s predicted role in Stevenson-Carey syndrome. The most critical experiments, particularly the RT-PCR and rescue experiments, have not yet been performed, but are planned for the near future.

**Significance**

Future grant submissions include a March of Dimes application and a submission to the Arthritis Foundation. These potential future funds will permit phenotyping of a larger cohort of family members and obtaining more DNA for analysis. Our goal is to provide a basis for identification of DDH-related osteoarthritis.

**References**

