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), their parents (RR 2.22 p=0.0003), and their grandparents (RR 1.33 p=0.01).2 These parents and grandparents never had a diagnosis of DDH. We also found that those affected with DDH required total hip arthroplasty (THA) at a much higher rate than the control group (RR 1169 p<3.01e-8), and their grandparents also needed THA at a substantially higher rate than the control group of grandparents (RR2.06 p=0.01). Finding high rates of hip osteoarthritis and THA requirements in individuals whose hips were not affected by childhood DDH supported the likelihood that acetabular dysplasia occurred more frequently in families with a history of DDH.

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 Orthopaedic Surgeons (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 center edge angles (CEAs) were determined, and Severin scores were assigned. The Severin classification is a radiographic assessment of acetabular dysplasia, with a measurement of the 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

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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 knock down 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**


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**PEDIATRIC ORTHOPAEDIC FELLOWSHIP AT CHILDREN’S HOSPITAL OF PITTSBURGH**

Pediatric orthopaedic surgery enjoys a prominent place in the history of medicine in Pittsburgh. Albert B. Ferguson, MD, chair of orthopaedic surgery at UPMC from 1953 to 1986, and William F. Donaldson, MD, a former president of the American Academy of Orthopaedic Surgeons, were pioneers in the field of orthopaedic surgery. Dr. Ferguson focused on early surgical treatment of developmental dysplasia of the hip (DDH), and Dr. Donaldson specialized in spinal deformity surgery for children.

The Pediatric Orthopaedic Fellowship at Children’s Hospital of Pittsburgh of UPMC was approved by the Accreditation Council for Graduate Medical Education (ACGME) in 2012 and has subsequently had a fellow in training each year. Under the direction of James W. Roach, MD, the Division of Pediatric Orthopaedic Surgery offers a one year fellowship in pediatric orthopaedic surgery with board exposure to all pediatric orthopaedic conditions and diagnoses, including spinal deformity, trauma, and complex congenital abnormalities.

Fellows apply and are selected through the San Francisco Match process. An applicant must have completed an ACGME-accredited orthopaedic surgery residency and be able to obtain a Pennsylvania Medical License. The fellow participates in the care of pediatric orthopaedic patients at the Children’s Hospital of Pittsburgh and the associated pediatric orthopaedic clinics. Currently there are seven full-time pediatric orthopaedic surgeons attending at the Children’s Hospital of Pittsburgh, and the fellow works with all seven.

This fellowship includes a large volume of tertiary-level surgical reconstructions, as well as a wide exposure to the clinical management of complex pediatric orthopaedic conditions. With only one fellow accepted into the program each year, there is a significant focus on the training of this individual. The program contains an especially broad exposure to children with spine deformity, hip preservation requirements, trauma, and sports injuries. The fellow participates in the treatment of children at the Shriners Hospitals for Children — Erie Ambulatory Surgery Center and Outpatient Specialty Care Center. These patients often have complex, tertiary-level deformities and receive their hospital care at the Children’s Hospital of Pittsburgh. Opportunities and requirements for fellow participation also exist in resident education and research.
The Division of Pediatric Orthopaedic Surgery at Children’s Hospital of Pittsburgh of UPMC specializes in problems related to the musculoskeletal system, including inflammatory, congenital, developmental, neoplastic, and metabolic problems. Other areas of expertise include:

- Hip, knee, and foot problems
- Spine deformities
- Limb-length abnormalities
- Clinical management of complex pediatric orthopaedic conditions

Experts

Our pediatric orthopaedic surgery team, led by W. Timothy Ward, MD, offers several areas of subspecialty expertise, including:

- Spine Deformity Program
- Sports Medicine Program
- Hip Preservation Program
- Benedum Pediatric Trauma Program
- Cerebral Palsy Program

Research

Pediatric orthopaedic research at Children’s Hospital of Pittsburgh is focused on outcomes and clinical studies of pediatric orthopaedic conditions. Current projects include:

- Long-term follow-up of surgery for DDH
- Comparison of the outcome of non-operative treatment of scoliosis
- Coagulation abnormalities in spine surgery
- Rate of symptomatic misplaced pedicle screws
- Pulmonary compromise in early onset scoliosis
- ACL reconstruction in the skeletally immature

Pediatric Orthopaedic Surgery Studies

The Division of Pediatric Orthopaedic Surgery has a number of ongoing clinical studies that are enrolling patients. For more information on any of the studies below, please contact Joanne Londino, RN, at 412-692-5772.

- Adult Scoliosis Outcome Comparison Between an Untreated Group and a Surgical Group
  PI - W. Timothy Ward, MD
- BrAIST II: Minimum 2-Year Follow-up of BrAIST Cohort
  PI - W. Timothy Ward, MD
- Utility of Thromboelastography (TEG) in Adolescent Spinal Deformity Surgery
  PI – Patrick Bosch, MD
- Thoracic Malformation with Early Scoliosis: Effect of Serial VEPTR (Vertical Expandable Prosthetic Titanium Rib) Expansion
  Thoracoplasty on Lung Growth in Children
  PI – Ozgur Dede, MD, and Vincent F. Deeney, MD
- Clinical and Radiologic Outcomes of Anatomic Physeal-Sparing ACL Reconstruction Techniques in the Pediatric Population
  PI – Jan Grudziak, MD, PhD
- Infection Prevention Strategy in Spine Surgery for Cerebral Palsy
  PI – Ozgur Dede, MD
- Evaluating the Prevalence of von Willebrand Disease in a Cohort of Scoliosis Patients
  PI – Patrick Bosch, MD
- Does a Weekly Didactic Conference Improve Resident Performance in the Pediatric Domain of the Orthopaedic In-training Examination?
  PI – James Roach, MD
- Is There Value to Having Radiology Provide a Second Reading for Patients Seen in Orthopaedic Clinics?
  PI – James Roach, MD
- The Discoid Meniscus: Association with Osteochondral Defects and Other Pathology
  PI – Patrick Bosch, MD
- Outcomes of Displaced Fractures Managed With Closed Reduction by Orthopaedic Residents in the Emergency Department
  PI – James Roach, MD
- Management of Isolated Lateral Ankle Injuries with Benign Radiographic Findings in Young Children
  PI – Patrick Bosch, MD
- Clinical Decision Making in Early Wound Drainage Following Posterior Spine Surgery in Pediatric Patients
  PI – Ozgur Dede, MD
- Success of Screw Epiphysiodesis in Treating Limb-Length Discrepancy
  PI – Stephen Mendelson, MD
- MRI Characteristics in Little League Shoulder
  PI – Jan Grudziak, MD, PhD

UPMC Video Rounds

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**Developmental Hip Dysplasia in the Ambulatory Child**

James Roach, MD, explains that although surgical correction is often successful in treating dysplasia, it also carries long-term issues, including arthritis and an increased risk of ultimately requiring total hip replacement later in life.

**Confirming the Efficacy of Bracing for Scoliosis Treatment**

Patrick Bosch, MD, discusses the findings of the Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST), which revealed that bracing significantly decreased the progression of high-risk curves in patients with adolescent idiopathic scoliosis.

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W. Timothy Ward, MD, was published in the January 2015 edition of The Journal of Hand Surgery for his article “Hematoma block versus sedation for the reduction of distal radius fractures in children.”

Ozgur Dede, MD; James Roach, MD; and Patrick Bosch, MD, were recently published in the November 2014 issue of The Spine Journal for the article “Biomechanical comparison of ponte osteotomy and discectomy.”

Jan Grudziak, MD, PhD, recently published his article “The effectiveness of ambulatory continuous peripheral nerve blocks for postoperative pain management in children and adolescents” in the November 2014 issue of Pediatric Anesthesia.

Ozgur Dede, MD, published his article “Revision surgery for pediatric spine deformity: corrective osteotomies” in the October/November 2014 issue of the Journal of Pediatric Orthopaedics.

Ozgur Dede, MD, was published in the October 2014 edition of Orthopedic Clinics of North America for the article “Recent advances in the management of early onset scoliosis.”

Full citations for the above articles can be found on the National Institutes of Health’s PubMed.

ABOUT CHILDREN’S HOSPITAL OF PITTSBURGH OF UPMC

Children’s Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists.

Children’s is consistently recognized for its research and clinical achievements, including ranking seventh among children’s hospitals and schools of medicine (FY13) in NIH funding for pediatric research, and being named to the 2014-15 U.S. News & World Report Honor Roll of America’s Best Children’s Hospitals.