Genome-Wide Linkage Analysis and Whole Exome Sequencing in a Large Multi-Generation Family Reveal Deleterious Mutations in Severely Affected Individuals with Developmental Dysplasia of the Hip

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Introduction: Developmental Dysplasia of the Hip (DDH) is characterized by incomplete formation of the acetabulum, suboptimal joint function, and accelerated wear of the articular cartilage resulting in arthritis. DDH affects 1 in 1000 newborns in the United States with well defined "pockets" of high prevalence in Japan, Italy and other Mediterranean countries. Although reasonably accurate for detecting gross forms of hip dysplasia, existing techniques fail to find milder forms of dysplasia. Undetected hip dysplasia is the leading cause of osteoarthritis of the hip in young individuals causing over 40% of cases in this age group.

Methods: A 72 member, four generation affected family has been recruited, DNA from its members retrieved. Genome-wide linkage analysis and whole exome sequencing were performed.

Results: Linkage analysis revealed a 2.61 Mb candidate region (38.7-41.31 Mb from the p term of chromosome 3) co-inherited by all affected members with a maximum LOD score of 3.31. Whole exome sequencing and analysis of this candidate region in four severely affected family members revealed one shared variant, rs3732378, which causes a threonine (polar) to methionine (non-polar) alteration at position 280 in the trans-membrane domain of CX3CR1. This variant was validated in all affected members of the family and obligate heterozygotes. Other possibly deleterious mutations shared by 4 severely affected members were found.

Discussion and Conclusion: This CX3CR1 variant is predicted to have a deleterious effect on its encoded protein which functions as a receptor for the ligand fractalkine. CX3CR1 mediates cellular adhesive and migratory functions and is known to be expressed in mesenchymal stem cells destined to become chondrocytes. A genetic risk factor that is very likely to be among the etiologic factors for the family in this study has been identified, laying the foundation for a predictive genetic test for newborns.