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Study matches infant stiff-joint syndromes to possible genetic origins

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A study led by the Translational Genomics Research Institute (TGen) has for the first time matched dozens of infantile diseases and syndromes involving muscle weakness and stiff joints to their likely genetic origins.

The study, in association with the University of British Columbia and BC Children's Hospital Vancouver, was published this month (May) in the *American Journal of Medical Genetics*. The study's goal is to better enable physicians and geneticists to advance new treatments that might help these children.

"It's amazing to us how diverse and complex the underlying genetics is for all of these diseases or syndromes," said Dr. Lisa Baumbach-Reardon, a TGen Associate Professor and the study's co-senior author. "A better understanding of disorders with contractures at birth and their associated genetics is critical for accurate diagnosis and optimal treatment."

The study describes over 50 of the more than 400 rare, but specific, disorders associated with multiple muscle contractures and stiff joints among newborns. They affect arms, legs, torsos and other parts of the body, often in combinations.

These more than 50 disorders are called "X-linked" syndromes, because the genes that cause them are on the X chromosome. Unaffected mothers can pass them on to their children, most often to their sons.

The study, or compilation of studies, identified 20 different genes associated with three categories of these more than 50 syndromes:

- One category represented more than 20 syndromes in which the responsible X-linked genes have been identified.
- A second category represented seven distinct reports consistent with X-linkage and present with contractures.
- A third category represented an additional 20 syndromes with reported contractures that are suspected to be X-linked.

"Clearly, there are many different causes of stiff joints in newborns," said Dr. Judith Hall, Emerita Professor in the Departments of Pediatrics and Medical Genetics at the University of British Columbia and BC Children's Hospital, and the study's other co-senior author.

"We wanted to bring together the clinical description of each of these syndromes, and match them to genes, the biochemistry of genes, and the cellular pathways, in order to identify potential therapies," said Dr. Hall, one of the world's leading experts in describing birth defects.

This ontology—or search of all medical literature—is believed to be the most comprehensive ever undertaking for these diseases.

Dr. Jesse Hunter, a TGen Research Assistant Professor and the study's lead author, said understanding how to potentially intervene and prevent stiff joints during pregnancy are fundamental.

"Contractures can develop at any age as a result of neuromuscular dysfunction, or limitation of movement, but muscle innervation and movement in utero is particularly critical for normal joint development," Dr. Hunter said.

The study, Review of X-Linked Syndromes with Arthrogryposis or Early

Contractures—Aid to Diagnosis and Pathway Identification, concludes: "It is our hope that with advances in clinical evaluation, next generation sequencing, and bioinformatics tools, that these syndromes will (all) have identifiable molecular etiologies (causes) in the near future."

Provided by The Translational Genomics Research Institute