Johns Hopkins University
McKusick-Nathans Institute of Genetic Medicine
Genetic Study of Hirschsprung Disease in Down syndrome

Our research study is investigating the genetic basis of Hirschsprung disease (HSCR). Hirschsprung disease is a congenital disorder caused by changes in the activity of gene(s) involved in the development of nerve cells in the colon. Normally, the walls of the colon are lined with nerve cells called ganglion cells. These cells are responsible for the wave-like contraction and relaxation necessary for passing stool. Babies with HSCR are born without these nerve cells along varying lengths of the colon. Stool cannot pass through the aganglionic (no nerve cells) segment of the colon, resulting in chronic constipation and often a functional obstruction. For most babies with HSCR, only the lower colon and rectum lack nerve cells (short segment disease). However, up to 20% of babies with HSCR have long segment disease, affecting a larger portion of the colon, and, in some cases affecting the entire colon. Although HSCR most often occurs as an isolated condition, approximately 30% of babies with HSCR have associated health concerns or genetic syndromes. The most common associated chromosome abnormality is Down syndrome; between 2-10% of babies with HSCR will also present with Down syndrome.

Most families in whom HSCR arises, have no prior family history of the disease. However, there are families in which multiple individuals are affected with HSCR. By studying many families with HSCR, we have observed patterns of inheritance that may be classified as dominant, recessive, or multigenic. The majority of HSCR cases appear to be multigenic, meaning multiple altered genes cooperate to result in disease. Affected individuals may have inherited, from one or both parents, subtle changes in more than one gene involved in HSCR. In the parents, these subtle changes do not cause disease. However, if a child inherits a specific combination of these changes, Hirschsprung disease will result.

Determining the genetics of HSCR is challenging. The goal of our research study has been to identify all the genes involved in HSCR and to understand this disorder at the genetic level. Although we have identified several genes thought to cause HSCR, we are currently investigating how these genes interact and we are searching for additional genes that may contribute to HSCR. In particular, we are investigating the association between Down syndrome and HSCR. Our previous studies have suggested that the 21q22 region may contain a modifier gene(s) for HSCR.

Eventually, with the knowledge of all genes involved in HSCR, we will not only be able to understand the inheritance patterns, but also better understand the variability within the disease and improve diagnosis and patient care. Furthermore, it will be possible to provide more accurate recurrence risks to family members.

Families interested in participating in our study are asked to complete a medical/family history questionnaire and submit blood samples from the affected family members and

their parents. Since this is a research study and our lab does not have CLIA-approval, we are not permitted to disclose results of any molecular testing to individual families nor to their providers. Participation in our study will hopefully lead to a better understanding of the genetics and, further down the road, improved diagnosis, treatment, and genetic counseling.

For more information, or to participate in our research study, please contact:

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