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Research offers novel insight into Hirschsprung's disease

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Defects in the protein Sox10, a transcription factor that regulates gene expression, may play a role in the development of post-operative GI dysfunction in Hirschsprung's disease patients, according to new research published in *Cellular and Molecular Gastroenterology and Hepatology*, the new basic science journal of the American Gastroenterological Association.

Hirschsprung's disease is a congenital disorder caused by the absence of ganglion cells in the colon, which causes problems with passing stool. Hirschsprung's disease is often treated with surgery to bypass or remove the diseased part of the colon. However, despite surgery, many patients still suffer from residual chronic constipation (5 to 33 percent of patients) and decreased bowel function. In addition, a substantial number of patients suffer from painful intestinal inflammation called colitis.

The researchers found that the Sox10Dom mutation, in a mouse model of Hirschsprung disease, disrupts the balance of cell types derived from neural progenitors and affects GI motility in the proximal, ganglionated intestine of adult animals. This is the first report identifying skewed differentiation of neural progenitors and altered GI motility in the small intestine of a Hirschsprung's disease mouse model.

"Our findings partially explain adverse outcomes in surgically treated Hirschsprung's disease patients," said study author E. Michelle Southard-Smith, PhD, associate professor, Department of Medicine, Vanderbilt University Medical Center. "We hope that our research will pave the

way for future studies and help clinicians better identify and treat Hirschsprung's disease patients at high risk for experiencing post-surgical GI dysfunction."

Different regions of the intestine in Sox10Dom mutant mice were found to have distinct abnormalities and GI transit assays revealed sex and age dependent effects. "These results suggest that timing and environment play a key role not only in differentiation of neural progenitors, but also ultimately in functional outcomes," added Melissa Musser, medical scientist training program student and first author on the study.

Because Hirschsprung's disease is a multigenic disorder, whereby an independent variant in any one of several genes can produce the absence of ganglion cells, these findings are potentially of broad relevance to other disorders of enteric neuronal development.

Future studies identifying similarities and disparities in outcomes between Hirschsprung's disease mutant models should help elucidate exactly when and where Hirschsprung's disease genes act within gene pathways.

"This research provides new understanding of processes required for development of nerves and associated cell types that might be impaired in diseases associated with defective enteric nervous system function," said Jerrold Turner, MD, PhD, AGAF, editor-in-chief of *Cellular and Molecular Gastroenterology and Hepatology*. "Continued research in this area will ultimately lead to improved diagnostic and therapeutic approaches for patients suffering from these debilitating conditions."

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More information: Musser, Melissa A., et al. Enteric Neuron Imbalance and Proximal Dysmotility in Ganglionated Intestine of the Sox10Dom/+ Hirschsprung Mouse Model, *Cellular and Molecular Gastroenterology and Hepatology* 2015: 1(1): 87-101, www.cmghjournal.org/article/S2 … (14)00003-4/abstract