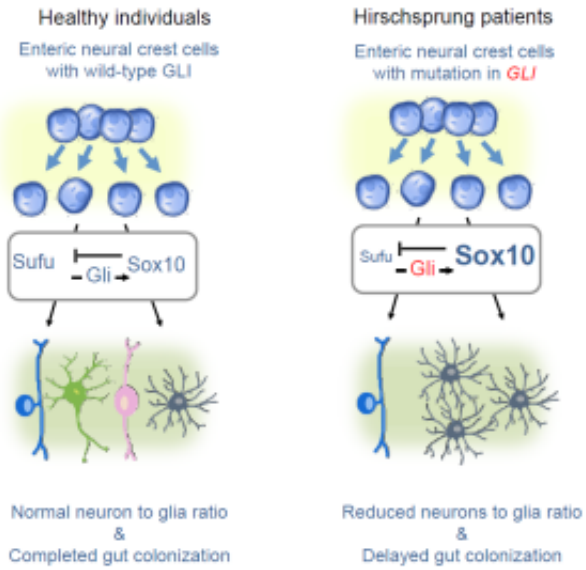
GLI mutations in patients with Hirschsprung disease

Hirschsprung (HSCR) disease (congenital megacolon) is one of the more common birth defects. It is a global problem but is particularly prevalent in Asia, affecting 1 in 3000 babies. These babies suffer from severe constipation and intestinal obstruction because nerve cells which co-ordinate bowel movement are absent. The reasons for the absence of nerve cells in the bowel are unclear, and therefore treatment remains unsatisfactory.



Babies born with HSCR disease will die unless the portion of the bowel with no nerve cells is surgically removed. In Hong Kong, over 120 affected babies have been operated in the last ten years. Nevertheless, the functional outcome of surgery is variable and a significant number of patients still suffer from life-long complications, ranging from intractable constipation, incontinence, enterocolitis to devastating short bowel syndrome, leading to not only tremendous psychosocial impact on the patients, but also a heavy financial burden to the health care system.

HSCR disease is attributed to a failure in formation of nerve cells in the intestine. During development, neural stem cells in the bowel receive varied signals from their environment and differentiate into a wide-range of nerve cells, which subsequently form a neural network to control the bowel movement. At least two types of cells are present in the bowel, the functional nerve cells (neurons) and the nerve-supporting cells (glia). This ratio of neurons and glia cells has to be precisely regulated, in order to establish a functional network. DNA changes in the genes implicated in this process may disturb the formation of functional neural network, leading to HSCR disease.

Li Ka Shing Faculty of Medicine, The University of Hong Kong (HKU) has conducted a genetic screen to identify disease-causing DNA changes and established experimental mouse models to

investigate the mechanisms underlying and how these DNA changes cause HSCR disease. The study identified specific DNA changes in *GLI1*, *GLI2* or *GLI3* genes that all result in increased GLI protein activity, leading to increased *SOX10* expression. In mouse, at the early stage of the development, majority of the gut is colonized by neurons and only very few glia can be detected. Functionally, GLI and SOX10 work coordinately with another GLI regulator, namely SUFU to form a regulatory loop to control formation of nerve cells versus nerve-supporting cells and gut colonization. If the mice carry abnormal GLI proteins resulted from loss of SUFU, the mice show premature formation of glia, accompanied by an obvious delay of gut colonization. The situation is similar to the patient with HSCR disease. Thus, mutations in *GLI* will interrupt the SUFU-GLI-SOX10 regulatory network and disrupt the formation of the nerve cells and their subsequent gut colonization, resulting in absence of nerve cells at the distal end of the colon as seen in HSCR patients. The novel finding provides important breakthrough for understanding the pathology of this genetic disease.

Collectively, HKU researchers have identified several novel *GLI* mutations in HSCR patients. With the functional data, the study directly demonstrated for the first time the coordination of SUFU-GLI-SOX10 gene in formation of nerve cells and nerve-supporting cells in the bowel and that its perturbation leads to HSCR in mouse and human.

Publication

Identification of GLI Mutations in Patients With Hirschsprung Disease That Disrupt Enteric Nervous System Development in Mice.
Liu JA, Lai FP1, Gui HS, Sham MH, Tam PK, Garcia-Barcelo MM, Hui CC, Ngan ES
Gastroenterology. 2015 Aug 7