LETTER

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A homozygous mutation in the endothelin-3 gene associated with a combined Waardenburg type 2 and Hirschsprung phenotype (Shah-Waardenburg syndrome)

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Hirschsprung disease (HSCR) or colonic agan-glionosis is a congenital disorder characterized by an absence of intramural ganglia along variable lengths of the colon resulting in intestinal obstruction. The incidence of HSCR is 1 in 5,000 live births. Mutations in the *RET* gene[1–2], which codes for a receptor tyrosine kinase, and in *EDNRB*[3] which codes for the endothelin-B receptor, have been shown to be associated with HSCR in humans. The lethal-spotted mouse which has pigment abnormalities, but also colonic aganglionosis, carries a mutation in the gene coding for endothelin 3 (*Edn3*)[4], the ligand for the receptor protein encoded by *EDNRB*. Here, we describe a mutation of the human gene for endothelin 3 (*EDN3*), homozygously present in a patient with a combined Waardenburg syndrome type 2 (WS2) and HSCR phenotype (Shah-Waardenburg syndrome[5]). The mutation, Cys159Phe, in exon 3 in the ET-3-like domain of *EDN3*, presumably affects the proteolytic processing of the preproendothelin to the mature peptide *EDN3*. The patient's parents were first cousins. A previous child in this family had been diagnosed with a similar combination of HSCR, depigmentation and deafness. Depigmentation and deafness were present in other relatives. Moreover, we present a further indication for the involvement of *EDNRB* in HSCR by reporting a novel mutation detected in one of 40 unselected HSCR patients.

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