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## LETTER


*Nature Genetics* **12**, 445 - 447 (1996)  
doi:10.1038/ng0496-445**A homozygous mutation in the endothelin-3 gene associated with a combined Waardenburg type 2 and Hirschsprung phenotype (Shah-Waardenburg syndrome)**Robert M.W. Hofstra<sup>1</sup>, Jan Osinga<sup>1</sup>, Gita Tan-Sindhunata<sup>1</sup>, Ying Wu<sup>1</sup>, Erik-J. Kamsteeg<sup>1</sup>, Rein P. Stulp<sup>1</sup>, Conny van Ravenswaaij-Arts<sup>2</sup>, Daniëlle Majoor-Krakauer<sup>3</sup>, Misha Angrist<sup>4</sup>, Aravinda Chakravarti<sup>4</sup>, Carel Meijers<sup>5</sup> & Charles H.C.M. Buys<sup>1, 6</sup><sup>1</sup>Department of Medical Genetics, University of Groningen, Ant. Deusinglaan 4, 9713 AW, Groningen, The Netherlands.<sup>2</sup>Department of Clinical Genetics, University of Nijmegen, The Netherlands.<sup>3</sup>Department of Clinical Genetics, Erasmus University Rotterdam, The Netherlands.<sup>4</sup>Department of Genetics, Center for Human Genetics, Case Western Reserve University, Cleveland, Ohio, USA.<sup>5</sup>Institute of Paediatric Surgery/Cell Biology and Genetics, Erasmus University Rotterdam, The Netherlands.<sup>6</sup>Correspondence should be addressed to C.H.C.M.B.

**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<sup>1-2</sup>, which codes for a receptor tyrosine kinase, and in *EDNRB*<sup>3</sup> 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*)<sup>4</sup>, 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<sup>5</sup>). 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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