Letter to the Editor

Recurrence of Hirschsprung disease due to maternal mosaicism of a novel RET gene mutation

To the Editor:

Hirschsprung disease (HSCR, MIM 142623) or aganglionic megacolon is the most frequent genetic cause of congenital intestinal obstruction. The tyrosine kinase receptor gene RET is the major gene implicated in isolated non-syndromic HSCR, with both rare coding sequence mutations and/or a frequent variant located in an enhancer element predisposing to the disease (1, 2). Inactivating RET mutations, scattered throughout the gene, are identified in about 50% of familial cases, where long-segment HSCR (L-HSCR) is also more frequent. RET mutations are inherited in an autosomal dominant fashion with incomplete and sex-dependent penetrance. We report a family with recurrence of L-HSCR in two siblings due to a novel RET mosaic mutation in the unaffected mother. To our knowledge, this mechanism has not been reported yet in isolated HSCR.

Following an uneventful pregnancy, a female baby was born to healthy unrelated parents with no other family history of note. She presented in the neonatal period with intestinal obstruction. Physical examination was otherwise unremarkable. She was diagnosed with L-HSCR, requiring early enterostomy and definitive surgery by the end of her first year of life. Five years later, a subsequent pregnancy resulted in a male newborn, also with L-HSCR and very similar clinical presentation. In view of the family history, RET mutation analysis was arranged at their local hospital, identifying a heterozygous alteration in intron 14 (c.2608-24G>A) in both children and their unaffected mother. This variant had previously been described in a patient with HSCR and not observed in 150 unaffected control individuals (3), and was considered at the time as pathogenic.

This family was subsequently referred to us for assessment and genetic counselling. We were aware of the results of the previous genetic investigations. However, Fitze et al. (4) had identified the same allelic variation in heterozygosity in 37.7% of control subjects, and our laboratory had also identified the same variant in a few individuals without HSCR in whom RET mutation analysis had been requested for other indications. So we questioned the pathogenicity of this change and repeated the complete RET mutation analysis by polymerase chain reaction and direct sequencing of all coding exons and flanking intronic fragments. We identified in both siblings a heterozygous alteration (c.987dupT) in exon 5 of the gene, which predicts the truncation of the protein (p.F329FsX24), and is therefore pathogenic. This mutation has not been previously reported in the literature. The study in the mother identified the same mutation, but the electropherographic signal intensity of the mutant allele was low, suggesting a mosaic mutation (Fig. 1). The same result was also obtained when the analysis was carried out in genomic DNA from buccal cells. The pyrosequencing assay was not able to detect the level of mosaicism (data not shown).

Phenotypically normal individuals may transmit several gametes that are clonal descendents of a single progenitor cell in which a de novo mutation occurred during their early development (5). Somatic or germ-line (also called gonadal) mosaicism in a parent may result in more than one affected children, in a pattern that mimics autosomal recessive inheritance (6). In this family the mother with somatic mosaicism for the RET mutation showed no manifestations of HSCR, whereas her children, who carried the mutation in their germ line, showed full-blown manifestations of HSCR. We are not aware of any other cases of somatic mosaicism for RET mutations reported in isolated HSCR familial cases. As the somatic mosaic mutation in the mother was detected by a widely used standard method (direct sequencing), we wonder whether this is a truly unique family or whether the true frequency of somatic and germ-line mosaicism is underestimated in HSCR. On the basis of these findings, we would recommend that germ-line or somatic mosaicism should be specifically looked for in families with recurrence of HSCR in the offspring of unaffected parents.

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Fig. 1. Pedigree showing Hirschsprung disease (HSCR) family with two affected children. Direct sequencing of genomic DNA shows the segregation of the de novo mutation (c.987dupT, p.F329FfsX24), in exon 5 of RET, observed in heterozygosis in both affected children. This mutation leads to the interruption of the normal frame. In the mother’s sequence from peripheral blood DNA the double sequence with a small mutant peak is evident, indicating mosaicism. The same image was obtained in the sequence of her buccal DNA (data not shown). Dashed line indicates the double sequence after the mutation. Neither of the maternal grandparents are carriers of the mutation.

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