Loss of Function *RET* Gene Variant and Cancer: Co-occurrence or an Association?

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Germline pathogenic variants (PVs) in the *RET* proto-oncogene (OMIM 164761) are associated with a diverse phenotype based on the type of PV. Gain-of-function (GOF) PVs are associated with the highly penetrant multiple endocrine neoplasia type 2 (MEN2-OMIM 171400), which are hallmarked by an increased risk for developing medullary thyroid cancer (MTC), pheochromocytoma, and parathyroid adenomas. Loss-of-function (LOF) *RET* PVs are associated with incompletely penetrant Hirschsprung's disease (HSCR OMIM 142623), which are pathologically characterized by the absence of enteric ganglia affecting the distal colon and clinically manifest as neonatal intestinal obstruction. Despite anecdotal reports of familial clustering of neoplasms in HSCR families, mostly MEN2-associated tumors [1,2], HSCR is not considered to be associated with an increased risk for developing cancer [3]. We report on a family with an unusual multigenerational solid tumor phenotype and severe HSCR phenotype with a LOF *RET* PV.

The study was approved by the Sheba ethics committee and each participant gave informed consent. DNA was extracted from leukocytes using a commercially available kit (Invitrogen™ PureLink™ Pro 96 Genomic DNA Purification Kit, Thermo-Fisher Scientific, Waltham, MA, USA). Multigene panel genotyping was conducted using the cancer panel of Invitae (https://www.invitae.com/en/providers/test-catalog/test-01101, San Francisco, CA, USA). Confirmatory sequence analyses were carried out for specific PV by Sanger sequencing.

PATIENT DESCRIPTION

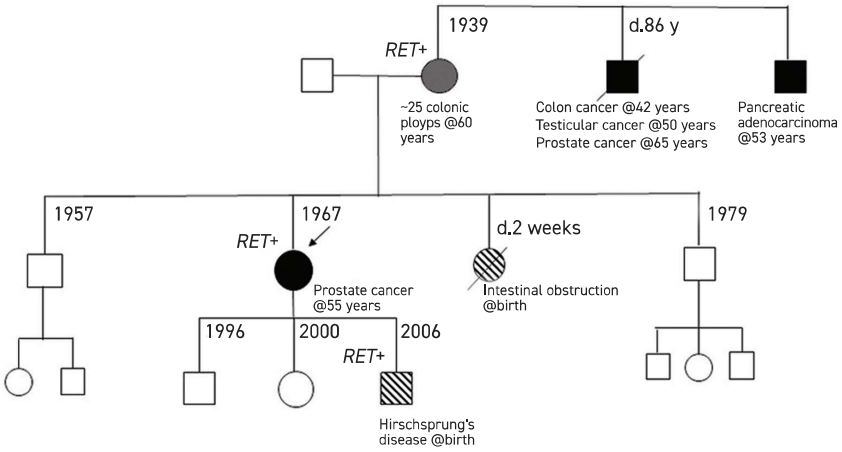
The proband, an Ashkenazi Jewish woman, was diagnosed with high grade pancreatic ductal adenocarcinoma at age 53 years. Her mother had approximately 25 colonic polyps diagnosed at about 60 years of age (mostly tubular adenomas with low-grade dysplasia). A maternal uncle had been diagnosed with colorectal cancer (CRC) at age 42 years, testicular cancer at age 50 years, and prostate cancer at age 65 years. Another maternal uncle was diagnosed with prostate cancer at age 55 years, and maternal grandmother was diagnosed with CRC at age 70 years. Notably, her son was diagnosed with Hirschsprung's disease at birth, and her sister died at 2 weeks of age because of intestinal obstruction [Figure 1]. A multigene cancer panel testing of Invitae. revealed a LOF PV in the *RET* proto-oncogene – c.1A>G; p.Ala2_Met255del; rs794728684 (SNP rs attribute is shown as it appears in SNPedia https://www.snpedia.com/index.php/Rs794728684). No other *bona fide* PV were detected in any of the other 83 genes genotyped using the Invitae platform. This *RET* PV was detected in the HSCR affected proband's son and her mother (born 1940). No other family members elected to participate in the current study.

COMMENT

This family reported displaying several unique features. The distinct and divergent HCSR phenotype of identical mutation carriers, ranging from a neonatal expression in the proband's offspring and presumably her sister, to no clinical features in her 82-year-old mother. These results correspond with previous studies that highlight the incomplete penetrance and the divergent expressivity of HSCR phenotype in identical *RET* PV carriers [4]. Given the putative contribution of modifier genes to this divergent phenotype it seems that this family, and clinically similar families, should be targeted for a subsequent genetic study to try and define the identity of these still elusive modifier genes by a comprehensive genetic analysis.

In addition, the unusual multigenerational clustering of cancers included those unrelated to the spectrum of endocrine-related neoplasms hallmarking MEN2, such as CRC, prostate, and pancreatic cancers. Germlines PV in the *RET* proto-oncogene have never been reported in individuals with a familial clustering of solid tumors as reported in this family. Yet, *RET* somatic abnormalities (e.g., GOF PV, altered expression, fusion proteins) have been reported in a variety of tumor types, including

Figure 1. The family pedigree shows the proband (arrow). Male (squares); females (circles). Deceased individuals are marked with a diagonal line across the symbol. Black squares/circles denote cases affected by cancer with the cancer type specified next to it. The grey circle denotes colonic polyps. Cross hatched symbols are used for individuals diagnosed with Hirschsprung's disease. RET+ denotes *RET* PSV carrier. PSV nomenclature is at the bottom left.



RET c.1A>G, p.Ala2_Met255del; rs794728684

non-small cell lung cancer (NSCLC), invasive breast cancers, pancreatic adenocarcinomas, colorectal adenocarcinoma, melanoma, small cell lung cancer, neuroblastoma, and small intestine neuroendocrine tumors [5]. Yet, our single case report does not prove causality, but simply describes an association between LOF *RET* PV and familial cancer clustering. Thus, the generalizability of these observations regarding the cancer clustering and *RET* LOF PV needs to be examined in a larger cohort of phenotypically similar families.

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A great deal of intelligence can be invested in ignorance when the need for illusion is deep.
Saul Bellow (1915–2005), writer, Nobel laureate

Capsule

Benefits of a grown-up microbiota

The intestinal microbiota modulates immune functions. However, whether the changes occurring in the composition of the microbiota during development affect the adult immune system remains to be verified. **Lubin** and associates created adult mice bearing preweaning microbiota and showed that the animals had an abnormal immune system with reduced numbers of regulatory T cells and immunoglobulin A. Importantly, the animals also showed increased susceptibility to *Salmonella* infections, indicating that changes in the microbiota during development are critical for the establishment of an effective immune system.

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