Genetics of Pheochromocytomas and Paragangliomas

An Overview on the Recently Implicated Genes *MERTK, MET, Fibroblast Growth Factor Receptor 1*, and *H3F3A*

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KEYWORDS

• Pheochromocytomas • Paragangliomas • MERTK • MET • c-MET • H3F3A • FGFR1 • Exome

KEY POINTS

- Pheochromocytomas and paragangliomas (PPGLs) are among the most hereditable tumors occurring in humans.
- A sole germline mutation in one of the many known susceptibility genes is identified and the cause of approximately 50% of patients with PPGL independently of a clear familial history of PPGLs.
- Two previously unrecognized PPGL syndromes were characterized both clinically and genetically: PPGL-giant cell tumor of the bone caused by the H3 histone family member 3A (*H3F3A*) G34W hotspot mosaic mutation and non-*RET* PPGL-medullary thyroid carcinoma caused by MER proto-oncogene, tyrosine kinase (*MERTK*) germline mutation.

REVIEW OUTLINE

Pheochromocytomas and paragangliomas (PPGLs) are neural crest-derived tumors rising on the adrenal medulla and extra-adrenal gland, respectively. Our knowledge of the molecular pathogenesis of PPGLs has greatly expanded in the recent years because of genomic investigation performed by several local groups and international

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consortiums. PPGLs are the most hereditable tumors known in humans with more than half of the cases, independent of family history of the disease, caused by a germline pathogenic mutation in one of the various susceptibility genes. In parallel to the analyses of germline susceptibility-associated variants, genomic studies could also focus on the tumor exclusively mutations and managed to decipher for the first time the somatic landscape of PPGLs. Although the mutation rates of PPGLs are one of the smallest among the sequenced tumors, several exciting findings have already been reported and many more are expected in the near future with the completion of other projects.

To date, there are at least 27 genes implicated in the molecular pathogenesis of PPGLs. The complete list and main information on these genes are shown in **Table 1**. Some of these genes are mutated exclusively on the germline and, therefore, are classic susceptibility genes; other genes are found mutated at the germline or somatic levels; in a third group only somatic mutations have been reported so far. Because of space limitation and the fact that genetics and genomics discoveries performed up to 2014 to 2015 were comprehensively reviewed elsewhere,[27,28] the current review focuses on very new findings and discusses the previously unrecognized role of *MERTK*, MET proto-oncogene, receptor tyrosine kinase (*MET*), *fibroblast growth factor (FGF) receptor 1* (*FGFR1*), and *H3F3A* genes in syndromic and nonsyndromic PPGLs. These 4 new genes were selected because, although their association with PPGLs is very recent, mounting evidence was generated that rapidly consolidated the prominence of these genes in the molecular cause of PPGLs.

MERTK PROTO-ONCOGENE MUTATIONS IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 2–LIKE PATIENTS AND PATIENTS WITH PHEOCHROMOCYTOMAS AND PARAGANGLIOMA

Recently, a rare multiple endocrine neoplasia type 2 (MEN2)–like 32-year-old patient diagnosed with medullary thyroid carcinoma (MTC), pheochromocytoma, and recurrent and metastatic paragangliomas carrying no germline mutation on exons 5, 8, 10, 11, and 13 to 16 of the *RET* proto-oncogene was comprehensively investigated. Genomic analysis confirmed the absence of mutation in the hotspot exons and entire coding region and splicing regions of the *RET* gene, and no mutation was observed in the remaining PPGL susceptibility genes or in the *estrogen receptor 2* (*ESR2*) gene, in which a frameshift variant has been reported in a young patient with MTC and in relatives with C cell hyperplasia.[29]

Whole-exome sequencing of this MEN2-like patient enables the discovery of the c.2273G>A p.R758H germline mutation on the tyrosine kinase (TK) domain of the *MERTK* receptor gene,[30] previously reported to play an oncogenic role in a variety of human cancers, mostly due to gene amplification.[31] RET and MERTK are both TK receptors that activate MAPK/ERK, PIK3CA, and AKT pathways. They have similarities and important differences (**Fig. 1**). The extracellular portion of RET is formed by 4 cadherin and a cysteine domains, whereas MERTK is formed by 2 immunoglobulin-like and fibronectin type III domains. Intracellular portions of TK receptors are usually more similar; however, some signature domains may be present, and sometimes define, specific TK receptor families. This situation is the case of the TK receptor family of MERTK that, along with *TYRO3* and *AXL*, forms the Tyro-3, Axl, and Mer (TAM) receptor family and is characterized by the unique KWIAIES motif in the TK domain.[31] The KWIAIES domain is also called the TAM-signature domain and defines the TAM TK receptor family.

Following the identification of the *MERTK* mutation in a MEN2-like patient, MERTK and RET protein sequences were carefully compared. Remarkably, it was found that