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Updates on the genetics and the clinical impacts on phaeochromocytoma and paraganglioma in the new era

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ABSTRACT

Genetic mutations of phaeochromocytoma (PCC) and paraganglioma (PGL) are mainly classified into two major clusters. Cluster 1 mutations are involved with the pseudo hypoxic pathway and comprised of *PHD2*, *VHL*, *SDHx*, *IDH*, *HIF2A*, *MDH2* and *FH* mutated PCC/PGL. Cluster 2 mutations are associated with abnormal activation of kinase signalling pathways and included mutations of *RET*, *NF1*, *KIF1Bβ*, *MAX* and *TMEM127*. In addition, *VHL*, *SDHx* (cluster 1 genes) and *RET*, *NF1* (cluster 2 genes) germline mutations are involved in the neuronal precursor cell pathway in the pathogeneses of PCC/PGL. Also, *GDNF*, *H-ras*, *K-ras*, *GNAS*, *CDKN2A* (*p16*), *p53*, *BAP1*, *BRCA1&2*, *ATRX* and *KMT2D* mutations have roles in the development of PCC/PGLs. Overall, known genetic mutations account for the pathogenesis of approximately 60% of PCC/PGLs. Genetic mutations, pathological parameters and biochemical markers are used for better prediction of the outcome of patients with this group of tumours. Immunohistochemistry and gene sequencing can ensure a more effective detection, prediction of malignant potential and treatment of PCC/PCLs.

1. Introduction

A neuroendocrine tumour that arises in the chromaffin cells in adrenal medulla is termed phaeochromocytoma (PCC). Extra-adrenal tumours arising from chromaffin cells are known as paraganglioma (PGL). PGL can occur in many different sites in the body and can be classified into sympathetic or parasympathetic depending on the type of paraganglia from which they originate (Lam and Chan, 1993a,b).

Incidence of PCC/PGL is around 2–5 patients per million per year. The collective incidence of PCC and PGL is about 1 per 100,000–300,000 in the general population where PCC is the most frequent tumour and PGL are much rarer (0.5 per million) (Kirmani and Young, 1993; Santos et al., 2014). The highest incidence of the tumours occurs between 30 and 50 years, with an almost equal gender affinity (Lam et al., 1993; Favia et al., 1998; Mannelli et al., 2009; Neumann et al., 2002). However, some studies have reported a slight preference for females (Goldstein et al., 1999; Melicow, 1977). Symptoms are produced due to excess catecholamine production in PCC and sympathetic PGL (Kirmani and Young, 1993).

As both PCC and PGL originate from chromaffin cells, the histological features of these tumours are similar. Occasionally, unusual histological patterns like composite tumours or oncocytic change are noted (Lam and Lo, 1999; Lam et al., 1998; Kasem and Lam, 2014). Although scoring systems based on morphology as well as clinical features have been proposed to assess malignant potential of these tumours (Thompson, 2002; Kimura et al., 2014), they have not been validated fully. Despite this, huge advances have been achieved in understanding the molecular pathogenesis of this group of lesions. Sporadic PCCs/PGLs are usually unicentric and unilateral while familial PCCs/PGLs are often multicentric and bilateral. Germline mutations and familial syndromes are known to be associated with 8–24% of sporadic phaeochromocytoma due to the advancement in genetics (Mannelli et al., 2009; Neumann et al., 2002). More recent studies have indicated, however, that up to 40% of cases could be attributed to germline mutations in a growing list of susceptibility genes having interconnecting pathways (Dahia, 2014)

Somatic mutations in inherited PCC/PGL genes can be detected in 25–30% of sporadic tumours. Also, somatic mutations in PCC/PGL can cause metastatic tumours in paediatric cases, and are mostly diagnosed before the age of 40 years (Luchetti et al., 2015). Overall, germline and somatic mutations in a known PCC/PGL gene are present in 60% of tumours (Favier et al., 2015).

The current study provides a comprehensive review of the genetic mutations reported in PCC/PGL and focuses on the newly discovered genes. It is anticipated that improved understanding of the pathogenesis in PCC/PCL may provide hints to aid the prediction of malignant potential and detecting novel molecular targets for therapy of this group of tumours.

2. Molecular genetics

2.1. Genetic pathways involved in PCC/PGL

Transcriptome studies show that many PCC/PGLs and their inherent genetic mutations can be classified into two major clusters depending on their gene expression profile (Dahia et al., 2005a).

Cluster1 or the angiogenic cluster genes are involved with the pseudo hypoxic pathway of tumour development and they are *PHD2*, *VHL*, *SDHx*, *IDH*, *HIF2A*, *MDH2* and *FH* mutated PCC/PGL (Dahia et al., 2005a). The molecular pathways of these genes and downstream targets are listed in Fig. 1. Favier et al. in 2012 reported that cluster 1 tumours showed a marked increase in vascularization and in the expression of vasoendothelial growth factor (VEGF) and its receptors (Favier and Gimenez-Roqueplo, 2012). VEGF proteins and receptors are the main factors in angiogenesis of cancers (Salajegheh et al., 2011, 2013). Also, increased VEGF expression was observed in both benign and malignant tumours from cluster 1 (Favier and Gimenez-Roqueplo, 2012). In addition, characterization of the methylation profiles has revealed that *SDHX* mutated tumours in cluster 1 display a hypermethylated phenotype (Letouzé et al., 2013).

Cluster 2 or kinase signalling cluster involve genetic mutations associated with abnormal activation of kinase signalling pathways such as *PI3Kinase/AKT*, and the *mTOR* pathway (Favier and Gimenez-Roqueplo, 2012). The molecular pathway of these genes and downstream targets are listed in Fig. 2.

The gene clusters are further subdivided based on transcription profiles. Cluster 1 can be divided into subcluster 1A and 1B. Cluster 1A contains PCC/PGL related to *SDHx* and *FH* while Cluster 1B contains tumours with HIF2A and *VHL* respectively (López-Jiménez et al., 2010). Cluster 2 can be divided into groups 2A, 2B, 2C and 2D. Group 2A comprises *RET*, *MAX*, *NF1* and *TMEM127* mutated tumours whereas groups 2B and 2C are sporadic tumours (Dahia et al., 2005a; Favier et al., 2009). Group 2D tumours are lacking known mutations related to PCC/PGL. The subdivisions of cluster 1 and 2 molecular pathways of these genes in PCC/PGL are listed in Fig. 3.

2.2. Cluster 1 genes

2.2.1. Elegans homolog of 1 (EGLN1)/Prolyl hydroxylase domain proteins (PHD2)

Hypoxia-inducible factors (HIFs) function as key players in the cell response to hypoxia. Prolyl hydroxylase domain proteins (PHDs) initiate the degradation of the HIF-α protein through its