

Supplementary Materials and Methods 1

Clinical questionnaire

The questionnaire included the following information: gender, age at diagnosis, clinical presentation (referring to the context in which the first suspicion of PPGL arose, classified as incidentaloma if after an imaging study or from a surgical procedure, and symptomatic if adrenergic or due to local mass symptoms), personal or familial history of signs or tumors of PPGL-related genetic diseases (medullary thyroid carcinoma, primary hyperparathyroidism, café-au-lait spots, neurofibromas, hemangioblastomas, gastro-entero-pancreatic tumors, cutaneous or uterine leiomyomas, renal cancer), findings from physical examination (weight, height, arterial tension, Marfanoid habitus, café-au-lait spots, neurofibromas, freckling), biochemistry studies (hemoglobin, hematocrit, calcium, phosphorus, urine calcium, vitamin 25-OH-D, thyrocalcitonin, chromogranin A, predominant biochemical secretion measured either by liquid chromatography with electrochemical detection or tandem mass spectrometry, depending on the center), results from imaging studies performed (including if optic fundus had been performed, and other signs found in image studies like hemangioblastomas or visceral cysts), tumor location, number of tumors, and metastatic behavior (defined as the presence of distant metastases in embryologically unrelated tissue, including lung, liver, bone or affected local and distant lymph nodes)[1, 2]. The time from the initial diagnosis or resection of the primary tumor used to classify metastases was 6 months, being ≤ 6 months for synchronous and >6 months for metachronous metastases [2]. Distant metastases were documented by imaging tests (computed tomography scan, magnetic resonance imaging, ^{123}I metaiodobenzylguanidine (MIBG), octreotide scintigraphy (Octreoscan) or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and pathological examination when possible [2]. Pathological confirmation of all metastatic lymph nodes was obtained. The questionnaire also collected data about surgical and nonsurgical treatments, follow-up visits with the results of the monitoring of biochemical and image test results. The family pedigree was also drawn.

- 1 Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nat Rev Cancer* 2014;**14**(2):108-19.
- 2 Jimenez C, Rohren E, Habra MA, *et al.* Current and future treatments for malignant pheochromocytoma and sympathetic paraganglioma. *Curr Oncol Rep* 2013;**15**(4):356-71.

Variant interpretation

Genetic variants found were classified as mutations or VUS according to information available in public databases. Their presence was checked in the Exome Aggregation Consortium (ExAC; <http://exac.broadinstitute.org/>); Catalogue of Somatic Mutations in Cancer (COSMIC; <http://cancer.sanger.ac.uk/cosmic>), the Single Nucleotide Polymorphism database (dbSNP; <http://www.ncbi.nlm.nih.gov/SNP/>), Leiden Open source Variation Database (LOVD; <http://chromium.lovd.nl/LOVD2/>), and the Universal Mutations Database for VHL mutations (UMD-VHL mutations; <http://umd.be/VHL/>). In silico analysis was performed using Sorting Intolerant From Tolerant (SIFT), Mutation Taster, Polyphen2, as well as tools able to predict splicing changes. Whether or not the variants had been previously reported was also taken into account.