Constitution of a Brazilian National VHL Database

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Introduction: Von Hippel-Lindau (VHL) disease is an inheritable disorder caused by germline *VHL* gene mutations that predisposes individuals to multiple typical lesions lifetime. First characterization of VHL in Brazil was published in 2005 and it included 20 VHL families. The project lasted 12 years and gave access to genetic testing for all participants, from 1998 until 2010. After 2010, VHL testing started being offered in private laboratories for patients covered by their health insurance, but those dependent on the Brazilian public health system (SUS) (70% of population) did not. The aims of this study was to prospectively collect clinical (clinVHL) and molecular (mutVHL) characteristics of VHL families, and to determine the assess of VHL testing among the participants. Genetic counseling was offered for all participants, and they were oriented about the VHL clinical screening program they should follow during lifetime. Medical records, *VHL* gene mutational status, disease history, and imaging data of all VHL patients and asymptomatic carriers were collected over time in a structured database for analysis.

Results: A total of 61 unrelated Brazilian families were registered, including 140 individuals with VHL (55% were women, and 45% men), 132 of them with clinVHL (94.3%), and 8 were asymptomatic mutVHL carriers (5.71%). VHL testing was accessible for 101 clinVHL (72.1%), but 31 clinVHL patients (22,1%) were not tested. Patients in clinical screening had is a mean of 46.5 years (ranging from 12y to 86y). Thirty-five families (56.5%) were from the Southeast region, and 16 (25.8%) were from the South. A positive family history of VHL could be identified in 85.7% of probands. According with the familial phenotype, families were classified in: a) VHL type 1, 50 families (82.0%); b) type 2A, 7 families (11.5%); c) type 2B, 3 families (4.9%); and d) type 2C, 1 family (1.6%). Central nervous system hemangioblastoma (CHB) was the most common manifestation among clinVHL (94.3%), followed by multiple cysts of the kidneys and pancreas (PCT) (80.0%), retinal angiomas (RA) (36.4%), renal cell carcinoma (RCC) (22.9%) and pheochromocytoma (PHEO) (10.7%). Pathological variants (PV) on *VHL* gene (ACMG) were detected in 100% of clinVHL: missense were more prevalent (55.6%), followed by large deletions (24.4%), frameshift (8.9%), in-frame deletion (4.4%), nonsense mutations (4.4%), and splicing-site mutations (2.2%).

Conclusion: We constituted a prospective Brazilian National VHL database with organized collections of clinical and genetic information from VHL families and family members, which will be helpful to guide policies for VHL care and oncogenetics in Brazil.