Large Scale Analysis of Genetic and Phenotypic Characteristics in von Hippel-Lindau Disease

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Introduction: Von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome where individuals are predisposed to tumour development in the brain, adrenal gland, kidney and other organs. It is caused by deleterious mutations in the *VHL* tumor suppressor gene, although gene variants of unknown significance are regularly encountered in clinical practice. Standardized disease information has been difficult to collect due to the rarity and diversity of VHL patients.

Methods: A literature search from database inception to September 2019 identified over 4100 unique papers which were screened for germline genotype and phenotype data. Patient data was translated into standardized descriptions using HGVS gene variant nomenclature and Human Phenotype Ontology terms and has been uploaded onto an open-access database called Clinical Interpretations of Variants in Cancer (CIViC). Preliminary genotype-phenotype analyses have been conducted.

Results: We have curated data representing over 4000 patients and over 500 unique *VHL* mutation variants with associated phenotypes. Suspected hotspot mutations, preliminary associations between *VHL* mutation types and clinical manifestations, and potentially novel VHL disease classifications are discussed.

Discussion: The CIViC database is the largest accessible, international, and standardized source of clinically interpreted *VHL* gene mutations. It serves as an aggregate knowledge translation tool to facilitate information between clinicians, patients, and researchers about the pathogenicity of *VHL* mutations. Further, our analyses reveal novel genotype-phenotype associations to better predict the progression of VHL disease on a global-scale.