Genetic Testing Alters Care for Von Hippel-Lindau Syndrome Phenocopy

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A diagnosis of von Hippel-Lindau (VHL) can be made with clinical criteria or identification of a pathogenic variant (PV) or a variant likely pathogenic (VLP) in the *VHL* gene via germline genetic testing. Clinical and analytic sensitivity of germline testing in individuals with clinical diagnosis of VHL approaches 100%, and due to the rare and specific tumor spectrum, phenocopies are rare. Therefore, despite lifelong surveillance recommendations, patients with a long standing clinical diagnosis of VHL may not pursue molecular confirmation due to financial burden or other barriers.

Our proband, a 41-year-old male, presented to clinic due to an incidental renal cell mass subsequently diagnosed as clear cell renal cell carcinoma (RCC). His family history was significant for a clinical diagnosis of VHL in his mother due to multiple spinal hemangioblastomas, pancreatic cysts, and RCC. She had declined genetic testing previously due to out of pocket cost.

The proband underwent genetic testing primarily to provide information to his sister and her children. A 19 gene next generation sequencing (NGS) panel for hereditary RCC was performed and was negative. Due to the uninformative results, the patient's mother agreed to testing and underwent the same multigene panel. Her testing revealed a VLP in *VHL*, c.483_500dup18; NGS metrics were consistent with a germline call. Retesting of the proband's original peripheral blood sample, new blood specimen, and RCC tumor via Sanger sequencing were all negative for the familial VLP. An opthomalogical exam was performed to evaluate for retinal hemangioblastoma and was also normal.

This case highlights the role of genetic testing for individuals with long standing hereditary cancer syndromes. Specifically, our patient has been determined to be a phenocopy and without his mother's molecular result, would continue to undergo unnecessary and costly screening with potentially needless invasive interventions. This also created clarity and peace of mind for his unaffected sister who also tested negative for the family variant.