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# Missense Mutation in Cancer in Correlation to Its Phenotype – VHL as a Model

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## 1. Introduction

Cancer is a complex genetic disease caused by abnormal alteration (mutations) in DNA sequences that leads to dysregulation of normal cellular processes thereby driving tumor growth. The study of such causal mutations is a central focus of cancer biology for two reasons; first is to reveal the molecular mechanisms of tumorigenesis, second is to provide insight in the development of novel therapeutic and diagnostic approaches. Although hundreds of genes are known to be mutated in cancers our understanding of mutational events in cancer cells remains incomplete (Futreal PA et al, 2004). This however has widely opened the field of cancer genomics studies which aims to provide new insights into the molecular mechanisms that lead to tumorigenesis.

As we are in the era of evidence-based molecular diagnosis, predictive testing, genetic counseling, gene-informed cancer risk assessment, and preventative and personalized medicine, therefore, studying the Mendelian genetics of the familial forms of cancer is one approach that can set up the basis for gene-informed risk assessment and management for the patient and family. Herein we selected a Mendelian genetics form of familial cancer such as hereditary tumor syndromic endocrine neoplasias caused by highly penetrant germline mutations leading to pheochromocytoma-paraganglioma syndromes. An example of such syndromes are autosomal dominant disorders; von Hippel-Lindau (VHL); Multiple endocrine neoplasia syndrome type 1 (MEN-1), loss-of-function germline mutations in the tumor suppressor gene MEN1 increase the risk of developing pituitary, parathyroid and pancreatic islet tumors, and less commonly thymic carcinoids, lipomas and benign adrenocortical tumors. In the case of multiple endocrine neoplasia type 2 (MEN 2), gain-of-function germline mutations clustered in specific codons of the RET proto-oncogene increase the risk of developing medullary thyroid carcinoma (MTC), pheochromocytoma and parathyroid tumors. PTEN mutations in Cowden syndrome (CS), associated with

breast, thyroid, and endometrial neoplasias. Identification and characterization of germline mutations in the predisposition genes of the great majority of these syndromes has empowered the clinical practice by the retrieved genetic information which guides medical management.

This review focuses specifically on the analysis of missense mutations in oncogenes and the tumor suppressor genes, though these genes can also be mutated through a variety of other mechanisms such as DNA amplification, translocation, and deletion. Unlike synonymous or silent mutations, which do not cause amino acid changes, missense mutations are non-synonymous amino acid substitutions that are typically caused by single-base nucleotide point mutations. However, many random missense mutations are not expected to alter protein function due to plasticity built into many amino acid residues.

## **2. Cancer and the "two hits" of Knudson's hypothesis**

Before proceeding into missense mutation in tumor suppressor gene we ought to introduce the "two hits" of Knudson's hypothesis. Alfred Knudson Jr in 1971 published his inspiring statistical analysis of the childhood cancer retinoblastoma where he found that retinoblastoma tend to be multifocal in familial cases and unifocal in sporadic presentation (Knudson A. G. Jr, 1971). Knudson postulated that patients with the familial form of the cancer would be born with one mutant allele and that all cells in that organ or tissue would be at risk, accounting for early onset and the multifocal nature of the disease. In contrast, sporadic tumors would develop only if a mutation occurred in both alleles within the same cell, and, as each event would be expected to occur with low frequency, most tumors would develop late in life and in a unifocal manner. His observations led him to propose a two-hit theory of carcinogenesis. The "two hits" of Knudson's hypothesis, which has proved true for many tumors, recognized that familial forms of cancer might hold the key to the identification of important regulatory elements known as tumor-suppressor genes (Ayerbes et al, 2008;).

## **3. Missense mutations in oncogenes and the tumor suppressor genes**

Using the second generation sequencing approaches provided detailed information on the frequency and position of single point mutations as well as structural aberrations of cancer genomes such as small insertions and deletions, focal copy number alterations, and genomic rearrangements (Wood LD et al, 2007;. Jones S et al, 2008; Greenman C et al, 2007; Sjoblom T et al, 2006; Pleasance ED et al 2010a,b; Cancer Genome Atlas Research Network, 2008). The findings show that the complexity of each cancer genome is far greater than expected and that extensive variations exist between different cancer types as well as between different tumor samples of the same cancer type. Several recent studies have used the Catalogue Of Somatic Mutations In Cancer (COSMIC) database to discriminate oncogenes and the tumor suppressor genes by using the difference in their mutation patterns in order to understand oncogenesis and diagnose cancers (Forbes SA et al, 2008; Stehr H et al, 2011; Liu H, 2011). Such investigations at the systems level are currently being performed for

many of oncogenes and the tumor suppressor genes as part of the Mutanom project (<http://www.mutanom.org>).

Stehr H *et al* study describes in a quantitative way, the opposing structural effects of cancer-associated missense mutations in oncogenes and tumor suppressors. Using COSMIC database (Forbes SA, 2008). Stehr H *et al* has assessed the effects of 1992 mutations cancer-associated mutations representing two common mechanisms through which tumorigenesis is initiated: via gain-of-function of oncogenes and loss-of-function of tumor suppressors (Vogelstein B *et al*, 1993). Then compared them to the effects of natural variants and randomized mutations. They focused on mechanisms of cancer mutations that have a consequence at the structural level. Another significant body of work has been published on consequences of mutations in a structural context (Ng PC, 2003, 2006; Ramensky V, *et al*, 2002; Wang Z *et al*, 2001; Karchin R *et al*, 2009). These studies differ in that either they focus on estimating the effects of individual mutations or they use different sets of disease mutations.

Studies of structural effects of mutations have found that disease mutations primarily occur in the protein core (Ramensky V, *et al*, 2002; Wang Z *et al*, 2001). This trend was confirmed only for the set of tumor suppressors. In contrast, core residues in oncogenes are significantly less often mutated than expected by chance. This is in agreement with Stehr H *et al* results for protein stability. Mutations located in the protein core are often destabilizing and result in loss-of-function. Thus, Stehr H *et al* data suggests that the loss-of-function of tumor suppressors is often caused by destabilization of the protein. They also suggested that specific mutations of functional sites that can either disable enzymatic activity and regulatory mechanisms or increase protein activity are often responsible for oncogene activation. Stehr H *et al* results show that the most frequently mutated types of functional sites in oncogenes are ATP and GTP binding sites and that the frequency of mutation is significantly higher than expected. This suggests that mutations of ATP and GTP binding sites are specific and common mechanisms of oncogene activation. Examples for such activating mutations near ATP binding sites have been described in the literature (Davies H *et al*, 2002; Shu HK *et al*, 1990, Jeffers M, *et al*, 1997).

Liu H *et al* investigated >120,000 mutation samples in 66 well-known tumor suppressor genes and oncogenes of the COSMIC database, and found a set of significant differences in mutation patterns (e.g., non-3n-indel, non-sense SNP and mutation hotspot) between them. They also developed indices to readily distinguish one from another and predict clearly the unknown oncogenesis genes as tumor suppressors (e.g., ASXL1, HNF1A and KDM6A) or oncogenes (e.g., FOXL2, MYD88 and TSHR). Based on their results, a third gene group was classified, which has a mutational pattern between tumor suppressors and oncogenes. The concept of the third gene group was thought to help in understanding gene function in different cancers or individual patients and to know the exact function of genes in oncogenesis.

#### **4. The clinical of VHL disease**

von Hippel-Lindau (VHL) disease (MIM 193300) is a dominantly inherited familial cancer syndrome. It is caused by mutations in the VHL tumor suppressor gene with an incidence of

1:31-36000 live births worldwide across all ethnic backgrounds, with similar prevalence in both genders (Maher *et al.*, 1991; Maher, *et al.* 2004). The prevalence however was shown to be higher in some population within the same ethnicity such as 1:39 000 in South-West Germany and 1:53 000 in Eastern England (Maher ER *et al.*, 1991; Neumann H *et al.*, 1991). VHL is characterized by marked age-dependent penetrance and phenotypic variability. The factors that affect the actual clinical expression and tumor formation, including age of onset, tissue and organ-specific lesions, severity of lesions, and recurrence, are unknown. VHL main clinical manifestations are:

#### **4.1. Hemangioplastoms**

Hemangioplastoms of the central nervous system (CNS) which are typically located in the cerebellum, but can also occur at the brainstem, spinal cord, and rarely, at the lumbosacral nerve roots and supratentorial (Neumann *et al.*, 1995). Retinal or CNS hemangioblastomas are often the earliest manifestations of VHL disease and the most common, occurring in up to 80% of patients (Maher *et al.*, 1990b; Melmon and Rosen, 1964; Weil *et al.*, 2003). VHL-associated cerebellar hemangioblastomas are diagnosed at a mean age of 29–33 years, much earlier than sporadic cerebellar hemangioblastomas (Hes *et al.*, 2000a, 2000b; Wanebo *et al.*, 2003). These lesions are rarely malignant, but enlargement or bleeding within the CNS can result in neurological damage and death (Pavesi *et al.*, 2008). A lower incidence of CNS hemangioblastomas has been documented in specific ethnic populations (12% Finland (Niemela M *et al.*, 1999); 5% German (Zbar B *et al.*, 1999). Patients with cerebellar haemangioblastomas typically present with symptoms of increased intracranial pressure and limb or truncal ataxia (depending on the precise location of the tumor). Wanebo *et al.* (2003) showed most CNS hemangioblastomas were associated with cysts that were often larger than other hemangioblastomas.

#### **4.2. Pheochromocytoma**

Pheochromocytomas are endocrine neoplasias with intra- or extra-adrenal gland lesions that appear histologically as an expansion of large chromaffin positive cells, derived from neural crest cells (Lee *et al.*, 2005). Seven to 18% of VHL patients are afflicted with pheochromocytomas (Crossey *et al.*, 1994a; Garcia *et al.*, 1997). The absence or present of this phenotype will type the VHL into type 1 or 2 (A,B,C), respectively (Woodward ER *et al.*, 1997; Hofstra RMW *et al.*, 1996). Untreated pheochromocytomas can result in hypertension and subsequent acute heart disease, brain edema, and stroke.

#### **4.3. Clear cell renal cell carcinoma (RCC)**

Clear cell renal cell carcinoma (RCC) occurs in up to 70% of patients with VHL and is a frequent cause of death. 70% of VHL patients have the risk of developing RCC by 60 years old (Maher *et al.*, 1990b, 1991; Whaley *et al.*, 1994), at an average age of 44 years versus the average age of 62 years, at which sporadic RCC develops in the general population ([http://www.umd.be/VHL/W\\_VHL/clinic.shtml](http://www.umd.be/VHL/W_VHL/clinic.shtml)). Renal cysts are common in VHL patients

as well; however, unlike the completely benign cysts in the general population, renal cysts in VHL patients might degenerate into RCC (Kaelin et al., 2004). However, it is unlikely that RCC in all VHL patients originates from cysts, or that all cysts will eventually become malignant. RCC often overproduces VEGF, and thus can be very vascular (Berse et al., 1992; Sato et al., 1994; Takahashi et al., 1994).

#### **4.4. Others clinical manifestations**

VHL patient can also have low-grade adenocarcinomas of the temporal bone, also known as endolymphatic sac tumors (ELST), pancreatic tumor, and epididymal or board ligament cystadenomas (Gruber et al., 1980; Neumann and Wiestler, 1991; Maher et al., 2004; Kaelin et al., 2007). ELST in VHL cases can be detected by MRI or CT imaging in up to 11% of patients (Manski TJ, et al., 1997). Although often asymptomatic, the most frequent clinical presentation is hearing loss (mean age 22 years), but tinnitus and vertigo also occur in many cases. In addition to the inherited risk for developing cancer, VHL patients develop cystic disease in various organs including the kidney, pancreas, and liver (Hough et al., 1994; Lubensky et al., 1998; Maher et al., 1990b; Maher, 2004).

Tumor growth commonly cycled between growth and quiescent phases. Patients with numerous tumors experienced growth and quiescent phases simultaneously, suggesting that a combination of acquired genetic lesions and hormonal activity influence tumor growth.

### **5. VHL clinical classification:**

Molecular genetic mutation and phenotypic clustering has allowed development of a clinical classification, although intra-familial variability is well recognized.

As mentioned previously VHL disease can be classified into VHL Type 1 or Type 2 depending on the phenotype. Type 1 describes those with typical VHL manifestations such as emangioblastomas and RCC, but does not include pheochromocytomas. Once a pheochromocytoma occurs the classification becomes Type 2. Type 2, accounting for 7–20% of VHL kindreds, is further subdivided into: (2A) pheochromocytomas and other typical VHL manifestations except RCC, (2B) the full spectrum of VHL disease including pheochromocytomas, RCC, and other typical VHL manifestation, and Type (2C) identifies those with familial risk of isolated pheochromocytoma (Gross D et al, 1996; Martin R, et al., 1998), although there are some kindreds without identified VHL mutation raising the possibility of another genetic locus (Woodward ER et al, 1997; Crossey et al., 1994b; Garcia et al., 1997; Mulvihill et al., 1997).

### **6. Morbidity and Mortality of VHL**

The morbidity of VHL disease depends on the organ system involved. For example, retinal hemangioblastomas can result in retinal detachment and/or blindness (Webster et al., 1999). Mortality is often due to either metastasis of RCC or complications of CNS

hemangioblastomas (Filling-Katz et al., 1991; Maher et al., 1990b; Neumann et al., 1992); however, due to improved screening guidelines, life expectancy of VHL patients has improved.

## 7. VHL gene and pVHL function

The human VHL gene is a 10-kb region located on the short arm of chromosome 3 (3p25.3) (Richards et al., 1993) and consists of 3 exons (Kuzmin et al., 1995; Latif et al., 1993a, 1993b): Exon1 spans codons 1–113, exon 2 spans codons 114–154, and exon 3 spans codons 155–213. Two protein products are encoded by VHL: a 30-kDa full-length protein (p30, 213 amino acids, NM\_000551.2 [variant 1 mRNA]) and a shorter protein product of 19-kDa (p19, 160 amino acids NM\_198156.1 [variant 2 mRNA]), which is generated by alternative translation initiation at an internal methionine at position 54 (Blankenship et al., 1999). Although evolutionary conservation of VHL sequence is very strong over most of the pVHL19 sequence, the first 53 amino acids included in pVHL30 are less well conserved and functional studies suggest that the two pVHL isoforms have equivalent effects (Woodward ER et al, 2000; Iliopoulos O et al, 1998). The VHL mRNA and protein is widely expressed in both fetal and adult tissues (Richards FM et al., 1996; Corless CL et al., 1997) and can be found in all multicellular organisms examined to date without known similarity to other proteins (van M et al., 2001). Remarkable progress has been made in elaborating the function of pVHL and the role its inactivation plays in the pathophysiology of this disorder, including dysregulation of angiogenesis and tumor formation.

Given the lack of primary sequence homology to other proteins, the function of pVHL has been derived from studying pVHL interactors and associated proteins. Roles in oxygen-dependent angiogenesis, tumorigenesis, fibronectin matrix assembly and cytoskeleton organization, cell cycle control and cellular differentiation have been proposed. The N-terminal acidic domain of VHLp30 contains eight repetitions of a five-residue acidic repeat, which are absent in VHLp19. Phosphorylation of this acidic domain participates in tumor suppression and this domain binds the Kinesin-2 adaptor KAP3, thus mediating microtubule-binding (Lolkema et al., 2005, 2007). This domain is also responsible for binding metastasis suppressor Nm23H2, a protein known to regulate dynamin-dependent endocytosis (Hsu et al., 2006). Further downstream, the  $\beta$ -sheet domain (residues 63–154) binds HIF0a subunits at residues 65–117 and the  $\alpha$ -helical domain (residues 155–192) binds the Elongin B and Elongin C (Elongin BC) complex at residues 158–184 (Feldman et al., 1999). Binding of pVHL to the Elongin BC is mediated by the chaperonin TRiC/ CCT. Elongin BC binding to pVHL requires TRiC, and VHL mutations causing defects in binding to Elongin BC are associated with VHL disease (Feldman et al., 1999). pVHL inactivation leads to an overexpression of hypoxia-inducible factor (HIF) and upregulation of its targets (vascular endothelial growth factor (VEGF), erythropoietin, transforming growth factor (TGF)-beta, alpha). Whether this is the sole etiologic factor causing characteristic VHL hemangioblastoma formation remains to be clarified. Evidence also suggests that pVHL inactivation alters fibronectin extracellular matrix formation, and that pVHL may participate in cellular differentiation and cell cycle control. Ongoing studies are directed at elaborating

the biologic consequences that these pathways play in the angiogenesis and tumor formation central to VHL. Additionally, VHL protein has functions that are independent of HIF-1alpha and HIF-2alpha and are thought to be important for its tumor-suppressor action, assembly of the extracellular matrix, control of microtubule dynamics, regulation of apoptosis, and possibly stabilization of TP53 proteins (Frew IJ and Krek W. 2007).

## 8. Molecular genetics of VHL disease

Germline mutations, including large deletions/rearrangements, in the *VHL* gene, linked to 3p25-p26, are etiologic for virtually all VHL disease (Latif, F. et al., 1993; Stolle, C. et al., 1998; Zbar, B. et al., 1996). These VHL germline mutations may be also detected in patients with autosomal dominant familial non-syndromic pheochromocytoma (Woodward ER et al., 1997; Neumann HP et al., 2002). Specific VHL missense mutations can cause an autosomal recessive form of polycythaemia without any evidence of VHL disease (AngSO et al., 2002; Gordeuk VR et al., 2004). Germ-line mutation confers genetic risk of tumor formation in concert with somatic second VHL allele loss or DNA methylation inactivation. However, somatic loss or inactivation of the wild-type *vhl* allele has been demonstrated in central nervous system (CNS) sporadic hemangioblastomas (Gnarra JR et al., 1994; Kanno H et al., 2000; Foster K et al., 1994; Herman JG et al 1994; Oberstrass J, et al., 1996; Tse J et al., 1997; Lee J-Y et al., 1998), in sporadic and VHL-associated renal cell carcinomas (RCCs) (Latif F et al, 1993; Shuin T et al., 1994; Phillips JL et al., 2001), pheochromocytoma (Bender BU et al., 2000; Linehan WM et al., 2001) and in endolymphatic sac tumors (ELSTs) (Vortmeyer AO et al., 2000).

More than 300 germline mutations have been identified in familial VHL. These occur throughout the coding region with only a few mutations appearing in multiple families (Zbar B et al., 1996; Beroud C et al., 1996). The new mutation rate has been estimated at between 3 and 20% (Latif F et al., 1993; Richard S et al., 1994; Schimke RN et al., 2000). Although decreased penetrance has been described (Maddock IF et al., 1994), comprehensive familial molecular data have not yet been reported to clarify this rate.

There has been limited correlation between specific mutation and phenotype, although some data on genotype-phenotype correlations have been reported (Neumann H et al., 1998; Hes F et al., 2000). Such correlations have revealed that certain missense mutations confer a high risk of pheochromocytoma (VHL type 1) whereas loss of pVHL through large deletions or nonsense-mediated decay appears to be incompatible with pheochromocytoma development (VHL type 2). [Chen et al., 1995; Cybulski et al., 2002; Glavac et al., 1996; Hes et al., 2000a, 2000b; Maher et al., 1996; Neumann and Bender, 1998; Ong et al., 2007; Zbar et al., 1996].

Interestingly, missense mutations causing amino acid changes on the surface of pVHL appear to have a higher risk for pheochromocytomas than missense mutations occurring deep within the protein; surface missense mutations also appear to have a higher risk for pheochromocytomas than deletions, nonsense, and frameshift mutations [Ong et al., 2007]. Thus, pheochromocytoma development appears to be related to an intact, but altered pVHL,



which has seeded the hypothesis that these mutations may induce gain-of-function possibly through a dominant negative effect [Hoffman et al., 2001; Lee et al., 2005; Maher and Kaelin, 1997; Stebbins et al., 1999]. Nordstrom-O'Brien et al., 2010, analyzed 1548 VHL families and provided a wealth of data for genotype-phenotype correlations. They found 52% had missense mutations most frequently occurred at codons 65, 76, 78, 98, splice mutations at codon 155, 158, 161, 162, and 167. 13% had frameshift, 11% had nonsense, 6% had in-frame deletions/ insertions, 11% had large/complete deletions, and 7% had splice mutations. Mutations that predict absence of functional protein (deletion, frame-shift, nonsense, and splice) are associated in 96-97% of cases with type 1 phenotype and show an increased risk of RCC (including type 2b cases). This suggests that expressed dysfunctional protein may be required for pheochromocytoma formation. Missense mutations are associated with type 2 phenotype (hemangioblastoma and pheochromocytoma +/- RCC) in 69-98% of cases (Stolle C et al., 1998; Chen F et al., 1995; Zbar B et al., 1996). While Nordstrom-O'Brien et al., found 83.5% of VHL Type 2 families mainly had missense mutations. However, this is not as high as some studies, reporting up to 96% of those with pheochromocytomas to have missense mutations (Zbar et al., 1996). Nordstrom-O'Brien et al., found low percentage of VHL Type 2 families (0.5-7%) had other types of mutation such as nonsense, frameshift, splice, in-frame deletion/insertions, and partial deletions. The small percentage of nonsense and partial deletions along with the absence of complete deletions supports theories that an intact though altered pVHL is associated with pheochromocytomas. Stratifying missense mutations into those that resulted in substitution of a surface amino acid and those that disrupted structural integrity demonstrated that surface amino acid substitutions conferred a higher pheochromocytoma risk (Ong KR et al., 2007). Although loss of heterozygosity has been reported in endolymphatic sac tumors (ELST) tumors (Kawahara N et al., 1999; Vortmeyer AO et al., 1997) no predominant mutation has been identified.

It may be difficult, however, to predict functional biologic consequences from specific point mutations without direct functional assays as reported in recent RCC *in-vitro* mutation panel studies.

The recent characterization of the VHL protein crystal structure might suggest possible functional consequences of specific mutations. If we focus on the structure of the pVHL we can predict the effect of the mutation on the functionality of the pVHL and therefore the phenotype resulted. Mutation-specific dysfunction may depend on protein destabilization, altered interactor binding at the various pVHP binding domains or potential alteration in binding to other factors involved in tumor suppressor/activator activity. pVHL has two domains: an amino-terminal domain rich in  $\beta$ -sheet (the  $\beta$ -domain) and a smaller carboxyterminal  $\alpha$ -helical domain (the  $\alpha$ -domain). A large portion of the  $\alpha$ -domain surface interacts with Elongin C, which binds to other members (e.g., Elongin B, Cul2, and Rbx1) of an SCF-like E3 ubiquitin-protein ligase complex as mentioned earlier. Obviously, loss of function VHL mutations prevents Elongin C binding and target ubiquitylation (Clifford et al., 2001). The  $\beta$ -domain on the other side has a macromolecular binding site targets the HIF-1 $\alpha$  and HIF-2 $\alpha$  regulatory subunits for proteasomal degradation. Whereas Type 1 and Type 2B mutations impair pVHL binding to Elongin C, Type 2A mutations map to the  $\beta$ -domain

HIF-binding site and do not affect the ability of pVHL to bind Elongin C (Clifford et al., 2001). Therefore, classifying missense substitutions according to their predicted effect on pVHL structure enhances the ability to predict pheochromocytoma risk (Ong KR et al., 2007)

Nordstrom-O'Brien et al 2010 suggested that increased identification of new mutations and new patients with previously described mutations gives momentum to the search for the exact role of pVHL in its normal and mutated form. Understanding such functions and its association with specific mutations allows for identification of disease risks in individual patients. Such insight will offer improved diagnostics, surveillance, and treatment of VHL patients (Nordstrom-O'Brien et al., 2010).

Ongoing delineation of clinical subtypes may allow for better genotype-phenotype correlations, prediction of clinical progression and molecular mutation-directed clinical management. There is significant intra-familial difference in clinical expressivity and as of yet limited knowledge about modifiers of this phenotypic variation (Webster AR, et al, 1998). Prediction of the clinical course in any one patient based on molecular data is therefore difficult.

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