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Permalink

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Journal

Human Genetics, 87(2)

ISSN

0340-6717

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Publication Date

1991-06-01

DOI

10.1007/bf00204184

Peer reviewed

Von Hippel-Lindau (VHL) disease: distinct phenotypes suggest more than one mutant allele at the VHL locus

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Received November 13, 1990 / Revised January 4, 1991

Summary. As part of an attempt to locate the von Hippel-Lindau locus (VHL) on chromosome 3, we evaluated 41 families with von Hippel-Lindau disease from the United States and Canada. One large family was identified whose disease phenotype was distinct from typical VHL. The most common disease manifestation was pheochromocytoma occurring in 57% (27/47) of affected family members. Few (4/47) affected family members had symptomatic spinal or cerebellar hemangioblastomas; no affected family member had renal cell carcinoma (0/47) or pancreatic cysts (0/24). Previously, genetic analysis demonstrated that the disease manifestations in this family were linked to RAF1 and D3S18, markers shown to be linked to typical VHL. These results suggest that there are mutant alleles at the VHL locus associated with distinct tissue specificities.

Introduction

Von Hippel-Landau (VHL) disease is an autosomal dominant, multisystem neoplastic disorder characterized by variable expressivity. Individuals that inherit the disease gene may have no symptoms during their lifetimes or may develop tumors in one or more target organs: eye, brain and spinal cord, kidney, pancreas, adrenal gland and epididymis (Melmon and Rosen 1964; Maher et al. 1990; Glenn et al. 1990). There is no adequate explanation for the constellation of tissue types affected by neoplasia. If VHL families with different spectra of tumor formation could be identified, it might be possible

to correlate specific mutant alleles with particular neoplastic phenotypes.

Recent advances in molecular genetics, coupled with detailed information on the biology of VHL, provide the tools necessary to test for distinct clinical types of VHL. The VHL gene has been shown to be linked to RAF1, a locus on chromosome 3 (Seizinger et al. 1988; Vance et al. 1990; Hosoe et al. 1991). Recent studies suggest that VHL is located in a 6–8 centimorgan interval between RAF1 and D3S18 (Hosoe et al. 1991). The VHL gene appears to function as a tumor suppressor gene; the unmasking of the VHL gene by loss of the wild-type allele has been demonstrated in renal cell carcinomas associated with VHL (Tory et al. 1989).

The frequency of involvement of the kidney, brain, spinal cord, and adrenal gland in individuals affected with von Hippel-Lindau disease has been described. Renal cell carcinomas occur in 28%–45% of individuals affected with VHL (Horton et al. 1976; Glenn et al. 1990). Hemangioblastomas of the spinal cord or central nervous system occur in 61%–66% of individuals affected with VHL (Lamiell et al. 1989; Filling-Katz et al. 1989). Pheochromocytomas as the predominant disease manifestation occur in an occasional VHL family (Lamiell et al. 1989). We describe a large kindred in which pheochromocytomas were frequent, symptomatic hemangioblastomas were uncommon, and renal cell carcinomas were not observed. These disease manifestations mapped to the same locus as typical VHL.

Materials and methods

Clinical evaluation

We analyzed 475 descendants of families with von Hippel-Lindau disease: 105 individuals from family 9–14 (corresponds to families

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9 through 14 in Hosoe et al. 1991) and 370 individuals from the other VHL families. Families with a history of von Hippel-Lindau disease were identified from the literature, by other families with this health problem, and by ophthalmologists, urologists, medical geneticists, and neurosurgeons. Families with two or more affected members were included in this study.

Affection status was determined by medical examinations conducted at the National Institutes of Health (NIH), by review of medical records, and by review of genealogic records and written statements provided by family members. Determination of the frequency of retinal angiomas, symptomatic hemangioblastomas, renal cell carcinoma, and pheochromocytomas in affected family members was based on information obtained on living and deceased family members. For most affected individuals, determination of the site of tissue involvement was based on examination of medical records (death certificates, hospital summaries, and pathology reports) and written statements provided by family members. Determination of frequency of pancreatic cysts or masses was based on screening examinations conducted at the Clinical Center of the NIH.

We examined 180 asymptomatic family members and individuals in whom there was uncertainty about diagnosis at the Clinical Center of the NIH. Details of the examination for occult VHL have been described (Sinchai 1977; Choyke et al. 1990; Filling-Katz et al. 1989; Glenn et al. 1990). Family 9-14 has been described previously (Sharp and Platt 1971; Horton et al. 1976; Welch 1970; Hosoe et al. 1991). An asymptomatic member of a VHL family was considered affected if one or more of the following disease manifestations were present: retinal angioma, spinal or cerebellar hemangioblastoma, pheochromocytoma, multiple pancreatic cysts, epidymal cystadenoma, and renal cell carcinoma before age 60. An individual in family 9-14 who developed a unilateral renal cell carcinoma at 61 was classified as not affected; this individual had no other manifestation of VHL; no VHL lesions were detected in the individual's three adult children.

Results and discussion

In a previous study of 25 VHL families (Hosoe et al. 1991; Table 1), we found no evidence of genetic hetero-

Table 1. LOD scores from the von Hippel-Landau (VHL) family panel and from family 9-14^{a, b}

Family group	RAF1 (0.06) ^c	D3S18 (0.04) ^c
Family 9-14	7.23	6.86
VHL family panel	4.53	12.99

^a From Hosoe et al. 1991

^b No genetic heterogeneity was detected with the HOMOG program of Ott (1985)

^c Number within parentheses is the recombination fraction used for calculation of the maximum LOD scores

geneity but we did detect one large family with a unique pattern of tissue involvement. To test for disease heterogeneity, we compared the frequencies of disease manifestations in family 9-14 and a panel of VHL families (Table 2). The frequency of pheochromocytoma in family 9-14 was 57% (27/47); few family members had symptomatic spinal or cerebellar hemangioblastoma (4/47), and there was no affected family member with renal cell carcinoma (0/47) or pancreatic cysts or pancreatic masses (0/24). The VHL panel (with the exception of family 9-14) had an overall incidence of renal cell carcinoma of 37% (77/209 individuals), symptomatic spinal or central nervous system hemangioblastoma of 47% (98/209), pheochromocytoma of 1.9% (4/209), and pancreatic cysts or pancreatic masses of 85% (22/26). The observed differences were statistically significant ($P < 0.001$). There was no significant difference in the frequency of retinal angiomas ($P > 0.05$).

We looked for alternative explanations of the observed differences between family 9-14 and the panel of VHL families. To determine whether any affected member of family 9-14 had occult renal cell carcinomas, affected family members were invited to the NIH for screening examinations. Of 38 living, affected members of family 9-14, 26 were examined at NIH; no affected family member had evidence of occult renal cell carcinoma. The median age of affected members of family 9-14 screened at the NIH was 40 years. There were no differences in the median age of the affected family members in family 9-14 (39.5 years), of the affected family members in family 9-14 screened at the NIH (40 years), and the VHL panel (39 years). The frequency of renal cell carcinomas or renal tumors was 37% in the VHL family panel and 39% in affected members of the VHL panel screened at the NIH. The male female ratio was 1.5/1 in family 9-14 and 1/1 in the VHL panel.

Table 3 summarizes the observations in family 9-14 and compares the results to observations made by others (Atuk et al. 1979; Green et al. 1986; Lowden and Harris 1976). In each of the VHL families described in these reports, pheochromocytoma was the predominant disease manifestation and renal cell carcinoma was infrequent. The overall frequency of renal cell carcinoma in 112 members of the "VHL pheochromocytoma" families was about 2%. The overall frequency of pheochromocytoma was 61%.

Previously Glushien et al. (1953) suggested that pheochromocytoma be considered among the manifesta-

Table 2. Frequency of various manifestations of VHL in a family panel and in family 9-14

Manifestation	Family 9-14 ^a	Family panel ^a	P ^b
Retinal angiomas	22/47 (0.47)	86/209 (0.41)	0.58
Symptomatic hemangioblastomas	4/47 (0.09)	98/209 (0.47)	<0.0001
Renal cell carcinoma	0/47 (0.0)	77/209 (0.37)	<0.0001
Pheochromocytoma	27/47 (0.57)	4/209 (0.019)	<0.0001
Pancreatic cysts or masses	0/26 (0) ^c	22/ 26 (0.85) ^c	<0.0001

^a Number with manifestation/number affected with VHL

^b Results of two-tailed Chi-squared analysis

^c Number with manifestation/number affected with VHL that were screened at the Clinical Center of the National Institutes of Health

Table 3. Summary of VHL pheochromocytoma families described in the literature

	Atuk et al. (1979)	Green et al. (1986)	Glenn et al. (1990)	Lowden and Harris (1976)	Totals
Retinal angiomas	6/13	23/38	22/47	7/14	58/112
Hemangioblastomas	1/13	9/38	4/47	4/14	18/112
Renal cell carcinoma	0/13	1/38	0/47	1/14 ^a	2/112
Pheochromocytoma	12/13	20/38	27/47	12/14	69/112

^a "Malignant kidney tumor"

tions of VHL. Work presented in this report suggests that a distinct clinical subtype of VHL exists characterized by a high frequency of pheochromocytoma and low frequency or absence of renal cell carcinoma and pancreatic cysts. Recognition of this subtype has implications for prognosis and screening programs. Our work raises the possibility that VHL mutant alleles may produce a phenotype characterized by hereditary pheochromocytoma alone.

The clinical heterogeneity observed in von Hippel-Lindau disease is similar to that observed in other autosomal dominant, multisystem neoplastic disorders. Multiple endocrine neoplasia type 1 (Green et al. 1990), multiple endocrine neoplasia types 2a and 2b (Narod et al. 1989; Jackson et al. 1990), and hereditary polyposis (Leppert et al. 1990; Nakamura et al. 1988) are diseases in which distinct phenotypes have been linked to the same polymorphic DNA markers. At this time, it is not possible to determine whether distinct disease phenotypes that link to the same markers are caused by different mutant alleles at one locus (the simplest explanation) or adjacent mutant genes.

The VHL gene is considered to be a member of the family of tumor suppressor genes (Tory et al. 1989). Tumors are thought to be produced as a consequence of inactivation of both copies of these genes. It is difficult to envision a null allele producing two distinct phenotypes. Presumably the mutant alleles in VHL produce different defective proteins. The data suggest that one mutant allele at the VHL locus leads to uncontrolled growth of renal tubular epithelium while another mutant allele at this locus leads to uncontrolled growth of cells of the adrenal medulla.

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