

# Research Report

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## VHL Care in the New Millennium

As we approach the end of the year, the end of the century, the end of the millennium, we approach an awesome turning point in all our lives. I remember sitting with my grandmother watching television coverage of the astronauts first walking on the moon. We were fascinated. She turned to me and said, "Imagine! I remember Kittyhawk!" And I was awestruck too at the thought that in one lifetime science had taken us from Kittyhawk to the moon. In this century we have seen phenomenal advances in aerospace, in electronics, and in telecommunications.

We are standing here at the dawn of another new era. What will the next ten years bring? the next century? the next millennium? We pray that it will be a time of peace and healing for all people.

We are at the beginning of the era of genetic engineering in medicine. For VHL, our Kittyhawk occurred in 1993. We are experimenting with the technology, but we understand as aviators understood in the 1920's. There is still a great deal to do.

The Human Genome Project is ahead of schedule in mapping the human genome. We are now know some of the areas in the genome relevant to VHL, but we have only just begun to understand how to influence or control the intricate mechanisms involved.

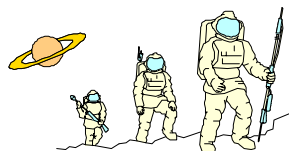
The three research projects we are funding this year help to understand the working of VHL in the cell. They also explore other genetic influences in the body that might making VHL more or less severe. By understanding some of these "modifier genes" we may discover other factors that we might use to modify the severity of the condition. As we learn, ideas emerge that pharmaceutical companies can follow to develop drug therapies.

When? It will take at least another four or five years to bring to market a drug to assist with VHL. Meanwhile there are many people in need of immediate help. Doctors around the world are engaged in experimentation to improve surgical techniques and reduce the risks and impact associated with surgery. Some of these advances are reported here.

Please help us to raise money again this year to fund innovative projects that will increase our chances of finding effective treatments for VHL in the New Millennium -- treatments that will halt tumor growth, stop their destructive power, and keep people healthy in the face of the risk factors of VHL.

We need every member of our VHL community of family and friends to work together to move this research forward. Last year under the leadership of Jay Platt we raised \$100,000. Let's do it again! We are especially grateful for the sponsorship this year of Sigma Phi Gamma Sorority. If each family would donate or help to raise only \$100 we would more than achieve our goal.

Our love and thanks and best wishes to all,  
Joyce Wilcox Graff,  
Founder Emeritus,  
VHL Family Alliance



## Helping One Person to an Early Diagnosis

by Toni Brunk, Cincinnati, Ohio

How many people know about VHL? Very few. This is why it is so urgent to raise funds so that you and others including doctors learn about this potentially debilitating disease.

VHL is von Hippel-Lindau syndrome, a genetic risk factor. Researchers project that VHL affects one in 32,000 people, meaning that thousands may be affected by VHL but not have the correct diagnosis. Without this diagnosis, they do not have the information they need to manage their health.

Twenty-five years ago, my husband suffered from severe headaches. After several physicians told him he had a sinus problem, he finally insisted on being put into the hospital for extensive tests. He was then diagnosed with brain tumors. After reviewing his family history, the neurologist diagnosed VHL. My husband succumbed to the VHL disease last year at the age of 62, after having four brain surgeries and removal of one kidney.

My husband's mother died at the age of 25; two brothers at the ages of 21 and 39, and presently the only living sibling is a sister who had brain surgery two years ago. We now know that all these family members struggled with VHL without diagnosis.

Over ten years ago, my son, due to recurring headaches, entered into testing. Since then he has had four brain surgeries and two Gamma Knife procedures. He presently lives with a brain tumor affecting his only hearing ear, and he has 21 tumors on his spine. Most of his time is spent in a wheelchair. He is only 38 years old.

All of my children and grandchildren have been tested for VHL. My son's 15-year-old daughter, my grandchild, has the VHL gene. Due to early testing and education, she could be a survivor.

Yes, found early, VHL is treatable. The key to successful treatment is early diagnosis and appropriate action. Delays in diagnosis can result in serious and permanent damage.

The VHL Family Alliance was organized in 1993 as a support group for patients, their families, their medical teams, and others. It is dedicated to improving diagnosis, to find ways of controlling tumor growth in VHL and other conditions, and to improve the quality of life for people with VHL.

Funds are desperately needed. How satisfying it would be if, through our donations, one person would be reached and saved from this potentially debilitating disease? The VHL Family Alliance is a small association with chapters throughout the United States and in many other countries of the world. It grows through volunteerism and donations. There is no Federal Funding. Our funds will be utilized to the fullest.

Sigma Phi Gamma is pleased to adopt the cause of von Hippel-Lindau disease for the first two years of the new millennium. We hope that you will assist in raising money for research in the application of breakthrough technologies to this difficult problem.



# 1999 Research Grants Awarded

The VHL Family Alliance and the Murray Foundation are pleased to announce the funding of three research grants, to advance research on von Hippel-Lindau disease, leading to better medical management and eventually a cure. The Murray Foundation will fund the project headed by Dr. Robert Burk of Albert Einstein College of Medicine in New York. The VHL Family Alliance will fund two projects. One is headed by Dr. Eamonn R. Maher of the University of Birmingham, England, one of the scientists who identified the VHL gene in 1993. The second is headed by Dr. Maria Czyzyk-Krzeska at the University of Cincinnati, Ohio. All three grants were favorably reviewed by the Alliance's Research Advisory Board, and recommended for funding. Thanks to the generosity of the members and friends of the VHL Family Alliance and of the Murray Foundation, all three projects are being funded.

**Dr. Eamonn R. Maher of Birmingham, England,** will study "Molecular Pathology of VHL disease". *Funding: \$20,000 from VHL Family Alliance.*

Investigations of the VHL protein have demonstrated that it has the ability to control levels of growth factors which promote growth of blood vessels. Maher's team proposes to investigate how this control occurs, and the relationship between mutations in the VHL gene, impairment of the VHL protein function, and the development of tumors. This should lead us toward new treatments for VHL disease.

"The identification of the VHL gene in 1993 provided an opportunity to understand how and why tumors develop in VHL disease. Investigations of the VHL protein have demonstrated that one important function is the ability to control levels of growth factors which promote growth of blood vessels. We have identified recently a mechanism by which growth factor levels can be controlled by the VHL protein, recently been reported in *Nature*.<sup>\*</sup> We propose to investigate how control of these growth factors is mediated and the significance for the development of tumors in VHL disease. A detailed understanding of the relationships between VHL mutations, impairment of VHL protein function and the development of tumors in VHL patients would enable a rational approach toward developing novel treatments for VHL disease." [\*Maxwell P, Wiesener M, Chang G-W, Clifford SC, Vaux E, Cockman M, Wykoff C, Pugh C, Maher ER, Ratcliffe PJ. "The von Hippel-Lindau gene product is necessary for oxygen-dependent proteolysis of hypoxia-inducible factor A subunits." *Nature* 399(1999):271-5]



## Did you know...

*That you can write in VHL Family Alliance as your preferred charity in a United Way donations drive?*

**Dr. Maria Czyzyk-Krzeska of Cincinnati, Ohio,** will be studying "VHL Function in Pheochromocytoma." *Funding: \$40,000 from VHL Family Alliance*

Pheochromocytomas, tumors of the adrenal gland, synthesize and release high concentrations of catecholamines – which in turn can cause sustained or episodic high blood pressure, potentially leading to heart attack or stroke. In this study we will investigate how disruption of normal VHL protein function (such as in the VHL disease) leads not only to pheochromocytoma tumor formation, but also to increased catecholamine synthesis, the major clinical feature of pheochromocytoma tumor.



"Pheochromocytomas, tumors derived from adrenal medulla chromaffin cells, are one of the major types of tumors occurring in von Hippel-Lindau neoplastic disease. While the frequency of pheochromocytoma in one large series of VHL patients vary from 7 to 20%, in some families 80-90% of members are affected, and in other families pheochromocytoma may be the only manifestation of the VHL disease. VHL disease-associated pheochromocytomas are linked to specific, usually missense, mutations in the VHL tumor-suppressor gene. Pheochromocytomas are usually non-malignant but in VHL disease they are often quite large, bilateral and recurrent. Clinically, the most serious, and potentially lethal, feature of pheochromocytomas is that they synthesize and release into the blood large amounts of neurotransmitters – catecholamines — resulting in either sustained or episodic hypertension. This increased catecholamine synthesis in pheochromocytoma results from augmented gene expression for tyrosine hydroxylase, the regulatory enzyme in catecholamine synthesis. We have recently discovered that wild type VHL protein is a strong repressor of the tyrosine hydroxylase gene. In this study we will investigate the molecular basis for the regulation of tyrosine hydroxylase gene expression by the VHL tumor suppressor protein. The major significance of our preliminary results is that VHL, the gene linked to pheochromocytoma tumors in VHL disease, is also a strong regulator of catecholamine synthesis. Disruption of normal VHL protein function, as in VHL disease, results not only in the pheochromocytoma tumor formation, but also in augmented catecholamine synthesis and release. These results will provide new and unique insights into the understanding of VHL function in the pheochromocytoma tumors and VHL disease."

## \$100,000 for Research in 1998 -- Let's do it again!

### What can you contribute? Every little bit helps!

This total includes lots of small and medium personal donations, gifts honoring special occasions, memorials, yard sales, raffles, benefit concerts, a walk-a-thon team and sponsorships, and several larger gifts from families and friends.

*Gifts of appreciated stock offer tax benefits to the donor as well as benefits to the Research Fund. Call to arrange transfer to the VHLFA account, 1-617-277-5667.*

**Dr. Robert Burk of Bronx, New York**, will be studying "VHLp18(MEA) protein". Funding: \$30,000 from the Murray Foundation, \$10,000 from VHL Family Alliance.

Dr. Burk and his colleagues have recently published a paper\* showing that within the length of the VHL gene, which is 24 kilodaltons (kDa) in length, there is an 18-kDa string which encodes a second distinct protein which seems to be the part most important for VHL disease. Introducing this protein, which is referred to as pVHL18(MEA), into renal cell carcinoma cells which do not contain normal VHL protein, results in a reduction in vascular endothelial growth factor (VEGF), the substance that promotes the growth of new blood vessels. Injecting renal tumors in mice with this protein caused their tumors to shrink.

The VHL protein (pVHL) is known to bind to certain other cellular proteins which are similar to certain proteins in yeast. This combination, like a set of gears, forms a "machine" which functions as a kind of "trash can" in the cell, removing and destroying cellular proteins that are no longer needed, halting processes at the appropriate time, and "cleaning up" proteins which may promote tumor formation (oncogenes). Our theory is that mutations in the VHL gene disrupt this process. The project will study where VHL proteins are found in the cell, and whether certain specific mutations in the VHL gene block this "clean-up" process.

"Inherited mutations in the von Hippel-Lindau (VHL) gene cause the familial cancer syndrome known as von Hippel-Lindau (VHL) disease. In order to understand how mutations in the VHL gene lead to the formation of tumors, it is important to determine the normal functions of the VHL gene and its protein products. It has been shown that VHL proteins bind to other cellular proteins which are similar to certain proteins in yeast. These yeast proteins are involved in the process of ubiquitin-mediated degradation, a process which functions as the "trash can" of the cell and has the potential to remove and destroy cellular proteins which may promote tumor formation (oncogenes). Therefore, based on the observation that VHL proteins bind to these possible "ubiquitination" proteins, our hypothesis is that VHL proteins are also involved in the process of ubiquitin-mediated degradation and that mutations in the VHL gene disrupt this process. To study this possibility, we will analyze the subcellular location of VHL proteins. It is likely that these regions are cellular sites at which ubiquitin-mediated degradation occurs. Furthermore, we will investigate whether certain specific mutations in the VHL gene hinder the ability of VHL proteins to either get to these ubiquitination sites or to function properly at these sites."

These results will provide new and unique insights into the understanding of VHL function in the pheochromocytoma tumors and VHL disease and potentially may lead to development of new treatments of these tumors.

\* Schoenfeld, Davidowitz, and Burk, "A second major native von Hippel-Lindau gene product, initiated from an internal translation start site, functions as a tumor suppressor." *Proc. Natl. Acad. Sci., USA*, 95:8817-8822 (1998).



# Virtual Slice Depth

## Lessening the Impact of Tests and Treatments

When they take an MRI, they talk about the "slice depth" of the images. Using modern imaging techniques, they are able to take pictures in a series of planes, a certain number of millimeters apart, as if they were slicing an orange and laying out the circles on the table for inspection. Before 1970, the majority of diagnoses of VHL were made by the pathologist in the autopsy, slicing up organs and finding tumors that were not found in time to help the patient. Today they can get pictures of very nearly the same quality without slicing the patient open.

This year has seen a number of advances in diagnostic imaging and surgical technique which will soon benefit people with VHL and many other conditions, lessening the stresses of diagnostic imaging and the toll of surgery.

*Laparoscopic surgery* to remove pheochromocytomas, tumors of the adrenal gland, are less prone to infection and complication, and usually have the patient out of the hospital and back to work much more rapidly.

*Harmonic ultrasound* is important not only because it helps the medical team determine the nature of a tumor, but because it may make it possible to do more screening with ultrasound rather than CT or MRI. This is important especially in parts of the world where ultrasound is more available and considerably cheaper.

New less expensive and more accurate *tests for pheochromocytoma* make it possible to rule out pheos in people with high blood pressure, and find more of the undiagnosed pheos in the general population. They also help to find pheos earlier in people with VHL, avoiding life-threatening risks and vascular damage.

Two experimental *treatments for kidney tumors* are under investigation. Neither is yet ready for general use, but they are exciting nonetheless. Cryotherapy for kidney tumors requires a surgical procedure, but treats the tumor with a freezing probe rather than completely removing it, doing less damage to the kidney. In another study, a very thin heating probe is inserted into the kidney with only a local anesthetic. The heat is used to "cook" the tumor in hopes of stunting its growth and destroying its ability to metastasize. We will hear more from these in the year 2000.

*Stereotactic Radiation* techniques continue to move forward, bringing the possibility of using this technology on tumors outside the brain. Most of these advances are for treatment of "hard tumors," rather than the hemangioblastomas of VHL. Because hemangioblastomas are very vascular, they react differently than hard tumors, making it difficult to predict how the tumor will respond. Many teams worldwide have now compiled a significant body of knowledge about stereotactic radiation and hemangioblastomas, helping to choose appropriate targets.

"It is worth all of the effort to do whatever I can for VHLFA. Your support has been appreciated more than I can ever say. I have never had the experience of belonging to such a "family" and I need to thank each and everyone of you for including me as such. I never knew what I wanted to be when I grew up, until I found VHLFA. I've never been so fulfilled as I am now, and I truly enjoy helping out at whatever I can." -- Maria Shipton, Communications Dir., Pennsylvania



## VHL in the 21st Century



Completing the 2,160 mile Appalachian Trail in January 1999, Jay Platt said that for him, it was like living with VHL. "People with VHL and their families must have perseverance and courage. We are challenged to manage this disease until all of us working together find the cure for VHL and cancer."

The Fourth Biennial Symposium on VHL, to be held in Rochester, Minnesota, in July 2000, co-sponsored by the Mayo Clinic, will focus on VHL Care in the New Millennium -- How will it be different? How can we use our new knowledge of genetics and the new technology to improve the course of VHL and similar disorders?

### Let's Cure VHL in the new Millennium

**Improve Diagnosis:** Let's find all those people with VHL who are struggling to find a diagnosis for all their mysterious symptoms.

**Improve Treatment:** Let's find improvements in imaging and surgical techniques that will make it easier to treat individual tumors and keep people healthy and productive.

**Improve Quality of Life:** By supporting one another, by keeping our spirits up, by focusing on the positive and creating real progress, we can live happier lives.

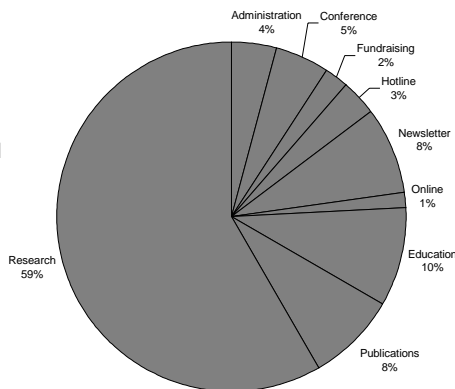
## Progress!

This year we reached ten more countries, and a thousand more people. We are now reaching more than 8700 people in 57 countries, up 15% over last year. At the same time, our operating budget is down 8% to \$56,534.

We pay no staff, we do not rent office space. The money we raise goes directly into programming and research. We are able to do this because of the hard work of a large number of dedicated volunteers in twelve countries around the world. Volunteers provide telephone and internet inquiry service, maintain our web site at [www.vhl.org](http://www.vhl.org), and provide outreach in their local areas.

The Murray Foundation grant to Dr. Burk enhanced our own research funding efforts and allowed funding of all three approved applications. Call or write for a list of special projects that need funding.

Total Revenue for Fiscal 1999 (ended June 30, 1998) was \$116,301. Of this, a total of \$71,000 was allocated to research funding.



## Remember VHLFA in Your Will

You can give hope to millions of people worldwide with VHL and other tumors by extending your support of VHL Family Alliance programs beyond your lifetime. Whether your legacy is large or small, you can support our programs of education, service, and research by remembering VHLFA in your will.

To make a bequest of cash or other property to VHLFA, your will (or supplemental codicil, if you do not wish to write a new will) should state:

"I give and bequeath to the VHL Family Alliance, Inc., a non-profit corporation, organized under the laws of the Commonwealth of Massachusetts, and having its principal office at 171 Clinton Road, Brookline, MA 02445, the sum of \$\_\_\_\_\_ or \_\_\_ percent of the rest, residue, and remainder of my estate to be used for general purposes of the organization."

A bequest to VHLFA is fully deductible for estate tax purposes. In addition, remembering VHLFA in your will is an important and personal way of providing hope to people with von Hippel-Lindau disease for generations to come. You may wish to learn more about other gift opportunities by consulting your attorney, accountant, and/or tax estate planning specialist, or simply write to VHLFA's Chairman of Development, 171 Clinton Road, Brookline, MA 02445, [info@vhl.org](mailto:info@vhl.org).

**Mail to: VHL Family Alliance, 171 Clinton Rd., Brookline, MA 02445**

Enclosed is my tax-deductible gift to support the:

☐ Fund for Cancer Research ☐ VHL Educational Programs

☐ Both Education and Research

☐ \$1000 ☐ \$500 ☐ \$100 ☐ \$50 ☐ \$25 ☐ \$\_\_\_\_\_

(Please make checks payable to VHL Family Alliance)

Name: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_

Zip/Postcode: \_\_\_\_\_ Country: \_\_\_\_\_

Tel: \_\_\_\_\_ Fax: \_\_\_\_\_

E-mail: \_\_\_\_\_

☐ Send quarterly newsletter ☐ Audio version needed

☐ My employer will match my donation. I have enclosed the necessary form.

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VHLFA is a non-profit organization. Our IRS Tax ID number is 04-3180414

My donation is ☐ In Honor of... ☐ In Memory of ... \_\_\_\_\_

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