VHL Family Forum

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Know Your Mutation!

by Berton Zbar, M.D., National Cancer Institute, Frederick, Maryland

In 1993, along with a large number of investigators, our team at the U.S. National Cancer Institute reported the finding of the gene that causes von Hippel-Lindau disease (VHL). The isolation of that gene was the beginning of a new era in which we can talk in much more specific ways about cancer[1] in families.

Until recently, the study of cancer in families was a matter of description by physicians interested in treating families with cancer. Like Drs. von Hippel and Lindau, there were many physicians who described the unusual occurrence of cancer affecting many members of the same family. With the revolution in genetic techniques, these families have become eagerly sought after in the same way I sought families with von Hippel-Lindau disease. Investigators all over the world look for families with cancer because they know that a remarkable amount of progress can be made once these families are found.

Cancer can occur as an inherited disease. There are at least fifty different varieties of cancer occurring as distinct inherited illnesses. Cancer susceptibility is not something that is general, it is extraordinarily specific. A family might inherit only kidney cancer, or it might inherit colon or breast or ovarian cancer. There is an eye cancer that runs in families—not VHL—which is known as *retinoblastoma*. These are examples of cancers occurring as a disease in families.

Sometimes the tumors occur as a single tumor type being inherited in a family, and other times there are very unusual situations where there is a predisposition to develop multiple types of tumors.

People who get kidney cancer on a sporadic[2] basis develop kidney cancer between the ages of 50 and 70, and develop a single tumor. People in kidney cancer families, on the other hand, develop multiple tumors. The tumors occur independently, and they occur in young people. This is one of the features of von Hippel-Lindau disease.

Continued on page 8

Research Progress With Your Help

It took donations from you and your friends, raffles, T-shirt sales, a Diamond Dig -- with your help, we have awarded $33,495 in research grants in the past twelve months. It's only a start, but *an excellent start! Let's do it again!*

With funding ***from you*** Dr. Diana Griffith of the Massachusetts General Hospital is determining the crystal structure of the healthy VHL protein. This will provide essential information toward developing a drug to emulate the function of the VHL protein and control or reverse tumor growth.

Using purified VHL protein supplied by Dr. Zbar's team at the National Cancer Institute in June, she has succeeded in making two different types of crystal forms of the VHL protein, one of which is shown in the inset picture. Here you see a shower of crystals, looking like a pile of needles. Each needle is a single crystal. Now begins the tedious process of mapping the crystal structure.

VHL protein crystals made by Griffith under a grant from VHLFA & the Murray Foundation.

A second grant award is announced on page 3. Three applications have so far been received for our 1997 research grants. *The number and size of the awards we can make depend on* ***You!***

Please contribute to the VHL Fund for Cancer Research.

Inside this issue!

Hearing Aid for VHL Patients with Bilateral Endolymphatic Sac Tumors

-- *Nicolaos Marangos, M.D., Gerd Kempermann, M.D., Hartmut P.H. Neumann, M.D.*[1]

A very rare tumor which grows in the inner ear, the endolymphatic sac tumor, can cause deafness in patients with VHL. A major difficulty with this type of deafness is that it cannot be treated with usual hearing aids, because these require that the structures of the inner ear be intact. However, in recent years a novel surgical strategy has been developed that enables doctors to restore hearing in patients with inner ear damage. Although deafness due to bilateral inner ear tumors appears to be very rare, we would like to inform the community of VHL patients about this promising therapeutic strategy.

Like waves on a lake, sound is waves of the air surrounding us. There is no sound in the vacuum of interstellar space. In order to hear, our ear has to convert the mechanical energy that underlies these waves into the excitation of nerves. The outer ear funnels the sound to the eardrum which seals the middle ear. Arriving sound makes the eardrum vibrate, and the delicate chain of the middle ear transfers these vibrations to the fluid filled cavities of the inner ear. Here the actual transformation takes place. Specialized receptor cells, the so-called hair-cells, convert the mechanical energy into an electrical impulse that travels along the auditory nerve to the brain, where the incoming information is decoded. From this anatomical structure the different types of deafness are easily understood. If the outer ear canal is blocked we do not hear well, but after removal of the obstacle hearing is fully restored because the essential structures are not damaged.

If the middle ear is damaged, the transformation of waves in the air to waves on the inner ear fluids is interrupted. Here, conventional hearing aids which amplify the incoming sound so that it directly affects the inner ear fluids can help the patients. In other cases a skillful surgeon can restore the chain of middle ear ossicles and thus reestablish the interrupted connection. However, if the inner ear is damaged none of these techniques will help, because it is the receptor cells themselves that are damaged.

In recent years a new technique has been developed which bypasses middle and even inner ear function. It enables patients with inner ear damage to understand speech without lipreading. A tiny microphone is permanently placed in the vicinity of the patient's ear and a surgically implanted cable runs past the middle and inner ear directly to the beginning of the auditory nerve. Neural excitation is basically an electrical excitation with an electric discharge traveling along the nerve and carrying the information. It is possible to stimulate a nerve directly with an electric current. An ingenious concept ensures that the correct nerve cells receive the correct bits of sound information. This device is called a "cochlear implant" because it is implanted in that part of the inner ear which is named the cochlea.

Patients with VHL in rare instances develop tumors of another inner ear structure, the endolymphatic sac. Because these endolymphatic sac tumors (ELST) grow so close to the cochlea, the hair cells are easily damaged. Surgical removal of the tumor can also destroy hair cells in the cochlea. However, the auditory nerve which travels from the cochlea to the brain usually remains intact. Therefore VHL patients who encounter deafness due to ELST are considered promising candidates for cochlear implantation. Even in those extremely rare situations where the tumors or the surgical procedure necessary to remove them did affect the auditory nerve, help might be possible. An even more intricate device has been developed which stimulates the nerve cells not at the site of the cochlea but directly in the brainstem, where the auditory nerve enters the brain. Although hearing with such a "brainstem implant" is rather coarse, the technique is promising and those patients that have been treated with it report that it is very useful for oral communication if combined with lipreading.

> "...the option of cochlear or brainstem implants should be considered and discussed before tumor surgery. . . The auditory nerve must be preserved during surgical removal of the tumor."

In cases of bilateral ELST causing deafness, the option of cochlear or brainstem implants should be considered and discussed before tumor surgery. Thorough examination can differentiate between damage to the receptor cells or the auditory nerve. The auditory nerve must be preserved during surgical removal of the tumor. In many cases it will then be possible to restore or retain hearing abilities.

1. Departments of Otolaryngology and Internal Medicine, University of Freiburg, Germany (NM and HPHN) and Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, California (GK)

References: G. Kempermann, HPH Neumann, R. Scheremet, B. Volk, W. Mann, J. Gilsbach, and R. Laszig, "Deafness due to Bilateral Endolymphatic Sac Tumors in a case of von Hippel-Lindau Syndrome." *Journal of Neurology, Neurosurgery, and Psychiatry* (1996) 61:318-320. ❑

Recent Insights into the Functions of the von Hippel-Lindau Protein

-- William G. Kaelin, Jr., M.D., Ph.D., Dana-Farber Cancer Institute, Boston, Massachusetts

Our group is specifically interested in how the normal von Hippel-Lindau protein (called pVHL for short) prevents tumor development. Every protein is made up of building blocks, called amino acids, hooked together in a particular sequence. The sequence of amino acids found in pVHL does not closely resemble the sequence of any known protein. Thus, the sequence of pVHL does not provide any immediate clues as to what job(s) it might perform.

We have already shown that reintroducing a normal version of pVHL into kidney cancer cells will prevent them from forming tumors in mice. To try to understand how pVHL might operate, we first immunized mice and rabbits with pVHL. These animals then generated antibodies which would bind specifically to pVHL. Using these antibodies we were able to identify pVHL in normal cells. Furthermore, we determined that pVHL "lives" primarily in a compartment of the cell known as the cytoplasm.

Just as you can tell a lot about a person from the company he or she keeps, so too you can learn a lot about a protein from the other proteins it bind with, or "talks to". Using our antibodies, we have determined that normal pVHL binds to about five other cellular proteins. Our group, as well as a group led by Dr. Richard Klausner, director of the U.S. National Cancer Institute, have shown that two of these proteins are proteins called elongin B and elongin C. When these two proteins bind to a third protein, called elongin A, they generate an enzyme which can "turn on" certain genes. pVHL competes with elongin A for binding to B and C, thereby inhibiting this enzyme activity.

These observations suggested that at least one pVHL job is to regulate which genes are "on" and "off" in a cell. Tumors which arise in VHL families contain many blood vessels and secrete factors, such as vascular endothelial growth factor (VEGF for short), which actually stimulate blood vessel formation. The genes which are the "blueprints" for these factors are normally "off" unless cells are deprived of oxygen. We have now shown that cells which lack pVHL are unable to turn off these genes. Similar observations have also been made by Marston Linehan's group an Dieter Marme's group. Thus, cells which have VHL mutations and lack a normal copy of pVHL behave as though they are deprived of oxygen even when they are not.

In the simplest view, inhibition of elongin, at least indirectly, inhibits the activation of these oxygen-regulated genes. Our laboratory is currently doing experiments to see if this is the case. Specifically, we are engineering cells so that we can selectively inhibit the elongin enzyme. We can then ask whether this is sufficient to turn off genes such as VEGF. If so, we can think about designing or developing drugs which will likewise inhibit the elongin enzyme. If we are lucky, these drugs might mimic the ability of pVHL to suppress tumor growth. In the meantime, several companies are developing drugs which will inhibit the ability of VEGF to induce blood vessel formation. It is expected that these drugs will go into clinical trials next year. The obvious hope is that these drugs will have an effect on the development and proliferation of tumors in VHL patients. ❑

We are pleased to award our
Second Research Grant
in partial support of a
research fellowship for
Dr. Othon Iliopoulos
of Dr. Kaelin's team,
whose exciting work in understanding
the function of the VHL protein
is reported here.

Thank You

I would like to express my sincere thanks to the von Hippel-Lindau Family Alliance for your recent contribution which will support the work being done by Dr. Othon Iliopoulos in my laboratory. As you know, Othon is continuing to try to determine how the protein produced by the von Hippel-Lindau gene prevents tumor formation. The long term goal of his work is to lay a solid foundation for the development of drugs which will, on one level, 'mimic' the activity of the von Hippel-Lindau protein and inhibit tumor growth.

I was extremely impressed, inspired, and moved by the many wonderful people I met during my trip to the Hawaii VHL meeting. Please extend an invitation for VHL Family Allliance members to come tour the laboratory and find our more about what we are doing. Short of that, please pass the word that we, along with many other members of the research community, are working hard to get us closer to the day when this disease can be eradicated.

With best wishes, William G. Kaelin, Jr., M.D.
Dana-Farber Cancer Institute, Boston, Mass.

Chapter Events

The Michigan Chapter had a booth at the Howell Mellon Festival, with a very prominent sign and an attendance of nearly 40,000 people. Lots of people picked up brochures, including a number of medical professionals. One county emergency response team requested a presentation on VHL. Many thanks to Fran M. for organizing our appearance there!

The Delaware Chapter had their annual Diamond Dig at a local fair. People paid $5 for one minute, or $1 for 15 seconds to look in the sandbox for the diamond or one of many cubic zirconia. Thanks to Melissa M. and J. J. Minster's Jewelers for making this annual event possible.

The British Affiliate met in London in November. Dr. Eamonn Maher of Birmingham Women's Hospital presented his research on the VHL gene, and he and Dr. Diana Wheeler of Wales talked about their Clinical Care Centers. Thanks to Hazel M., Tim and Benedict M. and Gillian H. for making the meeting possible.

The Irish Chapter of the British Affiliate met in Cork. Joyce Graff was there to give an introduction to VHL. Thanks to Gloria and Alan P., Margaret L. and Jimmy, and Maura and Bob H. for organizing the meeting.

The New York Chapter held their annual meeting in New York, with record attendance. Thanks to Altheada and Fred J. for organizing the meeting, and to Deborah, Evelyn, Rick, Jerome, Tena, Kathy, Steve, Stacy, Donna, Tom, Carrie and Bob for helping to make it one of the best ever.

The North Carolina Chapter met in Raleigh/Durham. Dr. Jeffery Vance spoke regarding the work of his group on the genetics of VHL, and the winner of the raffle was announced. Thanks to Audrey C., Louis W., and Susan M. for making it happen.

The Mid-South Chapters met in Jackson, Mississippi, with Dr. R. Hunt Bobo, neurosurgeon, speaking. They had 22 people in attendance. Thanks to Peggy and Don M. for organizing a great meeting.

The Arizona Chapter had its first Seminar December 4 in Phoenix, with guest speaker Dr. James M. Lamiell of San Antonio, Texas. Thanks to Pierre & Lisa B., and Micheline M., for arranging this meeting, which will be reported in the March issue. ❑

Success and Recognition

by Paul B., Quebec, Canada

When I volunteered to write something for the VHL newsletter, I figured it would be something easy to do since I was going to entertain you about someone I thought I knew well, me. I procrastinated until I had no choice and I found myself in a bind. I wanted to write something positive about VHL and I think I found it last week.

In life, we always face choices and challenges. With VHL, you can choose to be a victim and let VHL run your life and be depressed about it or you can be positive and meet it head on. Having the syndrome meant for me that I had to give up being a career man. Every time I seemed to do well in my career, an obstacle in the form of a brain operation, kidney removal, laser in the eyes or any number of monthly doctor appointments slowed me down.

The alternative is being a family man. My wife and kids profit from it. VHL is not an issue at home and even when I have an appointment (which is frequently) it is not a big deal, since I just go and they no longer notice it. I found a part time night job to allow for my day appointments. In return I find myself spending more time at home being able to do homework with my daughter and seeing her progress. She has math problems, and with this kind of lifestyle I can give her all the support she needs.

Last week, she finally understood her math. All of a sudden everything cleared up. It's a little thing, a minute detail, but I feel that my presence at home being able to help her made all the difference. She is in sixth grade going to High School next year. I want her to be successful and if I am there at her side, VHL is responsible. I can't be part of the rat race, my health won't allow it. I might as well make a difference close at home where the results are palpable.

In the end, we all want recognition. Whether it is at work, on the golf course or at home, we want to feel we make a difference. VHL is an obstacle to be dealt with and the Family Alliance is making every effort possible to help find a cure. My job is to live my life to the fullest within my limits. For the longest time, I felt guilty because I had no big job and no big income to go along with it. I finally found my peace. It wasn't a big thing, just math being understood. ❑

Key Contacts

VHLFA Patient support line, 9-9 Eastern U.S. time, +1-800-767-4VHL or +1-617-232-5946 or via E-mail to vhl@pipeline.com

VHL Tissue Bank, 24 hours a day, 1-800-847-1539.

VHL Registry and Research Committee: +1-703-759-7992 or vhlres@pipeline.com.

Clinical Care Committee: +1-708-687-7080 or fax to +1-617-232-5946 or vhlccc@pipeline.com

VHLFA Internet Web site: http://neurosurgery. mgh.harvard.edu/vhl-fa/

Miracles

by Kim Hasty, Fayetteville Observer-Times, *North Carolina*

Audrey C. likes to dress nicely anyway, but Sunday called for a little celebration. With the holidays this year had come some good news.

"My husband was so excited, he bought me *two* dresses," she said.

She opted for the red suit for church, the one with the gold buttons. Her gold jewelry added just the right touch.

"I gave my testimony," she said, "about the miracle of being healed."

Well, it isn't that she's completely healed of von Hippel-Lindau, the unusual disease that's plagued her for most of her adult life. But Audrey will take her good news in small batches, if that's how it must come.

Historically thought to be very rare, some research indicates that thousands of people may have VHL and not know it.

Audrey lost her right kidney and part of her left kidney to tumors. She had tumors removed from an eye and from her brain. The tumors used to occur about every ten years since she was first diagnosed 27 years ago, at the age of 32.

In recent years, the tumors have appeared more frequently. From time to time that has kept her from gardening, cleaning her house, and sometimes even prevented her from doing her beloved volunteer work with the Hospice in her local county. She has had surgery eight times.

She thought she was in for more surgery when tests indicated that she had three more tumors on her spinal cord and two on her brain. But she had further tests last week, and got the good news: the tumors either were not there, or they have disappeared.

Audrey calls it a miracle, though she knows that the miracle might last only until her next test.

"I was lying on the sofa one day, and I felt this warmth all over my body," she said. "I thought, 'Oh, someone must be praying for me.'"

So it was that she went to pick out her special holiday outfits. She looked her best Sunday. She does her best every day.

"People always say I look healthy," she said, "but I can't live an entirely normal life. Sometimes I feel like I have a monster inside me."

Hers is not an easy existence. Most people have never heard of VHL, and it is hard for them to comprehend. She is the North Carolina chair of the VHL Family Alliance. So far, she's found only 26 other people with VHL in North Carolina.

"It's important for people to have a support system, especially for a rare disease," Dr. James Zinser said. A family practitioner, Zinser never treated a person with the disease until he met Audrey. "Audrey is a very nice lady, and she's dealing with this as best she can."

At age 60, Audrey knows she has no guarantees for the future. "There are few miracles in medicine," said Dr. Carol Wadon, Audrey's neurosurgeon. "The incidence of recurrence of the tumors is high." Clifton has found that the best way for her to handle her disease is to try to help someone else.

"She is a really, really special volunteer," said Melissa Harris, hospice coordinator. "She's willing to do anything, and she's a very loving person. I'm sure her disease gets her down, but she always has a smile on her face.

More than anything, she'd love to find other people with VHL. She's constantly trying to educate people about VHL and expand the VHL Family Alliance. ❑

Mark your Calendar!

Bethesda Holiday Inn, Bethesda, Maryland
$109 per night, single or double
Hotel reservations must be made by March 28, 1997, to get this special conference rate.

Welcome Reception 6 pm Friday, May 2
Conference runs 8 AM Saturday, May 3
through 3 pm Sunday, May 4, 1997

Optional events:
Focus Conference on Stereotactic Radiosurgery & Hemangioblastoma, Friday, 12-5 PM
Meeting of VHLFA Board Members and Chapter Chairs, Friday, 9-12 AM

A discount is available off any published rate on *US Air* for our conference.

For reservations, call your local travel agent or
Jacki Hunsberger, CTC
a VHLFA member
Odyssey Travel, Box 840, Skippack, PA 19474
+1 (800) 972-3178, 9-5 Eastern time
Fax: +1 (610) 222-0520
Evening phone: +1 (610) 489-0896

1997 VHLFA Patient/ Provider Conference

-- *Melissa Minster, Conference Chair*

It's That Time Again!!!

Plans for the '97 VHLFA Patient/Provider Conference are under way. We are very excited that this conference will be held in Bethesda, Maryland, home of the National Institutes of Health and about 15 minutes from our nation's Capitol, with many sights to behold. If you've never been to Washington, D.C., plan to attend the 1997 conference, which will be held May 2-4, 1997.

Our preliminary plans for the conference include

- Treatment/management of the major manifestations of von Hippel-Lindau: angiomas of the eye, hemangioblastomas of the brain and spinal cord, endolymphatic sac tumors, pheochromocytomas, and renal cell carcinoma (kidney tumors).
- Insurance issues
- The effects of VHL on children in the family, how a child deals with having a parent or sibling with VHL, and with the fact that there is a genetic disorder in the family
- Alternative/complementary cancer therapies

On Friday, May 2, 12-5 pm, Dr. Edward Oldfield of the National Institutes of Neurological Disorders and stroke will host a Focus Conference on Stereotactic Radiosurgery (SR) for medical professionals. The day will focus on this method of treating brain tumors, and the pros and cons of using SR to treat the hemangioblastomas of VHL. Dr. Oldfield will report on the focus conference at the patient/ provider conference.

Please plan to join us in Bethesda, May 2-4, 1997, Friday evening through Sunday at 3 pm, for the 1997 VHL Patient/Provider Conference. You may want to plan some extra time to enjoy our nation's Capitol at night. Nothing is more spectacular. If it's history you love, there's no better plan than the many museums and historic buildings of D.C., featuring the Smithsonian, the National Gallery of Art, the National Archives, the Library of Congress, the U.S. Capitol, the White House, and Ford's Theater to name a few. Everyone should experience Washington, D.C., in their lifetimes, here's your chance! Join us for the '97 conference. We hope to see you there! ❑

> "Sending a patient to do battle with his disease without any training is like parachuting a soldier into the jungle without the benefit of survival training. -- *Michael Lerner, Ph.D., President, Commonweal, in a November 1990 address to the Annual Assembly of the National Coalition for Cancer Survivorship.*"

The VHL Athlete

Jennifer K. of Australia has been preparing herself over the last year for a tricky surgery on a hemangioblastoma at the second cervical vertebra (C2). She has been through other surgeries before, and was of course not looking forward to the experience, but knew she had to go through it to get beyond the current set of symptoms, the numbness and weakness and lack of coordination in her arms and hands.

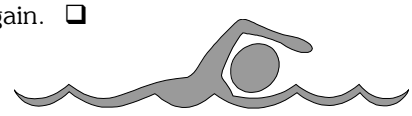
She looked for role models. She especially disliked the characterization in British parlance of a patient as a "sufferer". "Electing an operation is not choosing to suffer, it's choosing to go through a difficult, harrowing, even life-threatening experience in order to achieve a goal."

She noticed that marathon runners, or competitors in triathalons, also push themselves up to and beyond their physical limits. They endure pain, thirst, and suffering, all to win the prize, to compete sometimes more with themselves than with the others in the race.

In preparation for this surgery, she and her medical team took two important approaches. First, at Jennifer's request her medical team sought second opinions from neurosurgeons around the world. While they are excellent neurosurgeons in their own right, her team has limited experience with hemangioblastoma of the spinal cord, and were glad to confer with other physicians with greater experience with this tricky kind of tumor on the best ways to approach it.

Secondly, Jennifer herself trained for this event as if she were training for a sports event. She made sure her body was healthy and strong, tuned with vitamins and healthy natural foods, and that her mind was strong as well. Through meditation and guided imagery she pictured the surgery going well, the surgeons confident and successful, and her body helping to minimize bleeding and recover quickly. She used techniques from sports psychology.

On Sunday November 3 Jennifer and her surgical team ran their marathon. By evening Jennifer was awake, squeezed her husband Bruce's hand, and wiggled her toes. Everyone cheered, not only in Australia, but throughout the world. Our VHL Athlete had won the first event in her triathalon. There is still physical therapy to go, to recover the full use of her arm, but we are delighted to report that Jennifer and Bruce and their medical team are champions once again. ❑



Eddie's Story

by Linda G., Georgia

In June my wonderful husband and friend Eddie passed away at age 53. Perhaps his story can help others understand the importance of early detection.

His journey with VHL started at age 17. He was diagnosed with pheochromocytomas (pheos) on both his adrenal glands. One was removed then, the other at age 19. The doctors never mentioned VHL.

In 1985, his mother, Alva, was diagnosed with an angioma in her right eye. Her ophthalmologist was the first physician to tell our family about VHL. She was told to seek medical care immediately. She had renal cell carcinoma (RCC) in her right kidney and one pheo. Both were removed, and thankfully she is still doing well today in her 70's. How foolish we were not to begin to have Eddie checked then! Why didn't the doctors tell us what to do?

In 1992, Eddie was diagnosed with RCC in both kidneys. He had his right kidney and two-thirds of his left kidney removed. We were assured that he was going to be fine.

Eddie was a very proud man who lived life to the fullest. He worked hard to get his health back, but due to the extensive surgery and other complications there were many limitations. Eddie was no longer able to work, and applied for Social Security Disability. Lost paper work, mistakes by the government, and a series of rejections -- I watched as the government stripped away pieces of his pride. Family, friends, and outside sources were our saving grace, or we would have lost everything. Worst of all, there was no health care coverage while we fought this battle.

When, after two and a half years, his disability coverage was approved and health care coverage reinstated, the cancer had spread to his left lung.

He never gave up hope, he was an eternal optimist. He was always so positive that you had no choice but to believe he would beat it. He was a good person with so much to give. My children and I have received many cards and tributes letting us know how he touched their lives in so many positive ways.

Our biggest fear through all of this was our children. Would they have VHL? Three days before Eddie died we received a phone call telling us that they had found the alteration in Eddie's and his mother's VHL gene. It was the best news he could have received. He was happy to be leaving this "roadmap" for his children and others in his family. At least now they will be able to determine whether or not they carry the altered gene, and through early detection they will receive medical care to keep them well. ❑

Gifts that Endure

Funding for the VHL Family Alliance is provided by contributions from our members and friends. As we continue to build a valuable chain of information for patients, families, and physicians, private giving will be the key to our success.

Should you want to include a gift to the VHL Family Alliance in your will or other estate plans, the appropriate wording is, "I give and bequeath the sum of $____ to the VHL Family Alliance, a Massachusetts not-for-profit corporation," or "I give and bequeath ____ percent of my residuary estate to the VHL Family Alliance, a Massachusetts not-for-profit corporation." Another option is to create a charitable remainder trust.

Who does a charitable remainder trust benefit?

Someone who

- has a highly appreciated asset with a low basis
- wants to avoid the 28% capital gains taxes on the sale of the asset
- will benefit from a large income tax deduction
- may desire a guaranteed lifetime income
- desires to benefit the VHL Family Alliance and/or other charities
- desires to reduce his/her estate taxes.

How does the trust operate?

- the donor transfers an asset, preferably an appreciated asset, to a Charitable Remainder Trust
- the trustee or the Donor sells the asset
- the trustee invests the tax-free proceeds in income-producing assets
- the donor receives a stream of income for a term of years or over his or her lifetime
- at the donor's death (or sometimes after the death of donor's spouse and/or children), the remaining trust assets go to charity

What are the benefits to the donor?

- this trust avoids capital gains tax on the initial contributed asset. Charitable remainder trusts do not pay income taxes.
- it reduces current income taxes because of current charitable income tax deduction as the deduction can be carried forward for up to five years.
- it saves estate taxes because the asset transferred to the trust is removed from the donor's taxable estate
- the donor has a lifetime income
- the trust is usually exempt from the donor's creditors

What are the benefits to the family?

- a substantial charitable gift is made in recognition of the donor and his/her family
- income generated from the annual distribution can be used to pay life insurance premiums on the life of the donor which is held in an irrevocable trust and will pass free of estate taxes upon the donor's death
- a positive feeling that you are a true supporter of the VHL Family Alliance — an investment in our children's future.

For more information, call your attorney, or Tom Rodenberg, 816-229-2132. ❑

Know Your Mutation, *continued from page 1*

Any family group dealing with an inherited cancer needs to understand the basic characteristics of how their disease is inherited, what genes are, and what mutations are.

Pedigrees and inheritance

I'd like to start with an imaginary family, a family with thirteen children.

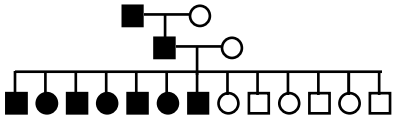


Figure 1: An Imaginary family with a dominant genetic characteristic

Pedigrees are the primary tool of people who study cancer in families. The traditional way of showing a pedigree is that at the top of the figure you have the grandparents, then the parents, and then the children. The squares indicate males, the circles females, and the black indicates that you are affected. And when you look at this illness you see that it started in the grandfather, it was transmitted to his son, and in this generation among the thirteen children half of the children develop the disease. This is the cardinal characteristic of von Hippel-Lindau disease, and it is the cardinal characteristic of virtually all of these fifty types of inherited cancer. You also can see by looking at the squares and circles that it affects men and women equally. There is no preference for men over women. This is an imaginary family. In a real family there would be some imbalance due to chance, just as there are not always an equal number of sons and daughters in a family even though the chance of having a boy or a girl is a 50-50 chance.

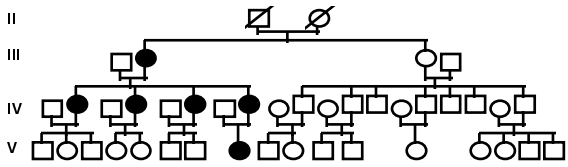


Fig. 2: A VHL family from Louisiana.

Figure 2 shows the pedigree of the first VHL family studied at NIH. It is a family from Louisiana. A urologist friend of Dr. Linehan was making rounds with Dr. Linehan at NIH, and mentioned his VHL family from Louisiana. Like I did with many of the families, I went to Louisiana, collected the samples, and eventually brought a number of the members of this family to NIH for study. What is striking about this family is that we have two sisters, one of whom is affected and one of whom is not. Each sister had many descendants. One sister is free of the disease gene. She cannot transmit it, and it will never run in this part of the pedigree. The affected sister, however, has four affected daughters, and one affected granddaughter. This was a particularly striking example of the transmission of this trait through the different branches of the family. So far we have studied more than 500 family members at NIH.

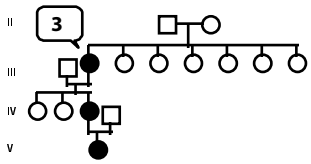


Fig. 3: VHL occurs de novo, and can now be inherited

Figure 3 illustrates a very unusual situation — or maybe not as unusual as we think. In the beginning when we looked for families with VHL we encountered situations in which just one family member had the illness. In the beginning of our work we did not study these families because for the kind of analysis we were doing, these families were not helpful. But later on we began to take samples from any individual with the illness. What is unusual about Figure 3 is that here we have a woman with six sisters. She is affected, she has an affected daughter, but her parents are not affected. Whenever you have this situation you wonder if maybe one of the parents has VHL and doesn't know it. In this situation, we were fortunate, both parents were alive. We brought them to NIH and examined them. They did not have the illness; none of the six sisters had the illness. When we found the gene we were able to demonstrate that this woman, whom we call "3," had a new mutation. This is an example of an inherited cancer appearing anew, afresh, *de novo,* for the first time in this line, in this genealogical tree. It first occurred in this woman, and can be passed to her descendants. The frequency of new mutations in VHL is calculated by Dr. Eamonn Maher to be 1 in 4.4 million live births.

We still do not understand clearly how new mutations occur. We can divide causes roughly into two categories: environmental factors over which we may have some control, and non-environmental factors over which we have no control. Cigarette smoking is an example of a *mutagen*, an agent which we know can cause genes to change, over which we may have some control.

Genetic Inheritance

I like to think of our genes as flowers on a Hawaiian lei or pearls on a string. They are like little isolated beads strung along a wire. Our chromosomes occur in different lengths, different lengths of pearls on a string. And all of these fifty different types of cancer start because one of these genes has become inactive. The structure of that gene is different from normal. There are two copies of each gene, one inherited from the mother and one from the father. One of these copies is inactive, as shown by the shaded bead in Figure 4.

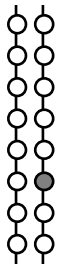


Fig. 4: one copy of the pair of chromosome 3's has an inactive copy of the VHL gene

When an individual in one of these families is born, every cell in their body has that little gray bead or that altered gene, and the evidence is strong that tumors occur only when other genes in that neighborhood do not function properly. In order for tumors to form in patients who have inherited cancers, you need to "inactivate" or "destroy" the function of both of the copies of that gene.

Finding the Gene.

Finding the VHL gene was like looking for one piece in a jigsaw puzzle, or looking for a single fish in the Pacific Ocean. We hunted it, from 1988 to 1993, by progressively shrinking the size of the ocean, the size of the container in which our fish lived, until it was so small it was obvious which fish we were looking for and we could pull it out.

The gene is a formula, like a recipe, with a variety of ingredients. If some ingredient is changed, or left out, or some other ingredient is added, we get a different result. Another way to think of the gene is as a simple sentence, such as *The cow jumped over the moon*. The genetic information, like a sentence, or like our string of beads, is made up of phrases. When we hear this complete sentence we have a picture of what happened in this children's story.

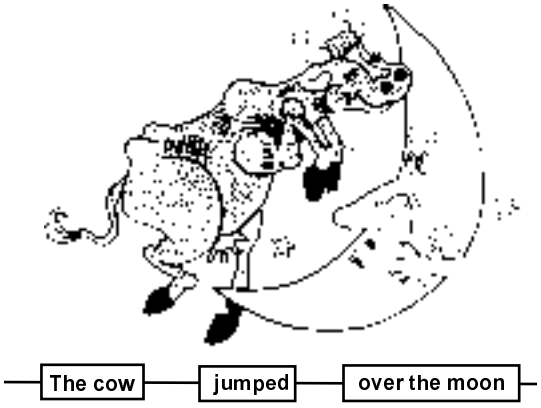


Fig. 5: The three exons of the VHL gene are assembled into one message

Sometimes genes are affected by what we call *Deletions*. One word or one part of the gene is missing, and then the message is not the way it should be. In this case (Figure 6) the moon is missing. Some 15-20% of mutations in VHL families are of this type. A piece of the genetic information has been physically removed. It's as if someone took a scissors and sliced it out, and it's no longer there.

Fig. 6: A Deletion mutation

Then we have something that we call an *Insertion*. In this situation, there is some additional information that doesn't belong. Again, this creates a message which is not the proper message, and there's trouble. This kind of mutation, an insertion, also causes a substantial percentage of VHL.

Fig. 7: An Insertion mutation

Fig. 8: A Missense mutation

Now let's make a very simple change, just one letter. By changing only one letter, we can change the entire meaning of the sentence.

Figure 8 shows what is called a *Missense* mutation. This is the kind of mutation which affects the Hawaii family. They have a missense mutation in a particular place, a single change that changes the message and leads to this illness. It's an incorrect amino acid. It's not something taken away or something inserted, it's something switched.

Different mutations, different illness

VHL does not simply provide a susceptibility to kidney cancer, there may be other tumors as well. We are only beginning to understand the relationship between the change in the gene and the tumors that result, but already there are a few clear distinctions. We are working toward being able to use the information we see in the genetic code itself to calculate an individual's risks of having particular kinds of tumors, so that we know better which areas to watch, and which areas do not need monitoring.

Perhaps the greatest advantage of the advances to date associated with the isolation of the VHL gene or any of the other genes that have been isolated and that are responsible for inherited cancers, is that you can do early diagnosis.

You can now do correct diagnosis in more families. Occasionally people are given the wrong diagnosis, because the symptoms might look very much like either of two conditions. In examining the DNA, however, the diagnosis becomes quite clear. In two cases, families were told they had VHL, but it proved not to be the case. In other cases, a family was told they had another inherited cancer, but through DNA diagnosis it was shown that in fact they had VHL. This kind of incorrect information, with all its consequences, is correctable now with DNA diagnosis. With the correct diagnosis, the family has better early warning information, and can more carefully manage their health.

The U.S. used to have an army recruiting poster showing Uncle Sam dressed in a tall hat with a flag

with his finger pointing, saying "Uncle Sam Wants You!" That image comes to mind as I say to the families that you should *Know Your Mutation*, because your mutation has consequences. The more we know about decoding this information, the more specific information we can give you for managing your health.

Where there are *Insertion* and *Deletion* mutations, we find kidney tumors, no adrenal tumors, and tumors in the back of the brain and in the eyes.

In the families under Dr. Neumann's care, whose origins are in the Black Forest region of Germany, with a mutation at codon[3] "505," we find few if any kidney cancers. They have adrenal tumors, few brain tumors, and eye tumors.

In families with a mutation at codon 712 we find kidney, brain, eye, and adrenal gland tumors.

The point is that the VHL that is produced by the 505 mutation, and the VHL that's produced by the 712 mutation, and the VHL that's produced by the insertion and deletion mutations, are not the same. When you know the particular mutation — where and what kind of mutation — you can begin to calculate risks. It's a little like handicapping horses. Based on a set of circumstances, you calculate the probability that a particular horse will win a race on this race track, with these weather conditions, and this jockey. Based on the look of the genetic code we are beginning to be able to calculate the possibility that someone with this particular gene may develop a particular kind of tumor. It's not a sure thing, there is still wide variability in VHL and probably some other environmental or genetic influences that we don't yet understand, but it's a start.

One of the things that the VHL Family Alliance can do is to help collect this information. We need more of it. In many cases, the numbers are too small to make good predictions. We have fairly good numbers of people with 505 and 712 mutations, but we need larger numbers of people with the other mutations. For example, it would be good if we could say with confidence that in a certain family we don't need to watch the kidneys because in families with this particular mutation they are not at any higher risk for kidney cancer than people in the general population. However we do not have sufficient data yet to trust ourselves to say that with certainty. It may be that we haven't seen it because the sample is too small, or because the people we have been watching are still too young. I invite centers with large families, or with large populations of people with one kind of mutation, to study the people under their care and help add to our understanding of that particular mutation.

It is also important to screen not only people with symptoms, but all members of VHL families. Dr. Hartmut Neumann in Germany found that when he screened whole families in Germany, as many as 60% of the people with the modified VHL gene did not have symptoms. Some of these were young and had not yet developed symptoms, but others were older and still had no symptoms. Learning more about people with very light cases of VHL will help us to better understand how to manage VHL for everyone.

It will not be enough in the future to say "I have VHL". It will be "I have VHL and I have a 505 mutation." Of course the physician is not going to know what you are talking about, but the physician is going to have to be educated also.

I should also mention that the mutations in the families are different than the ones which occur in sporadic kidney cancer — same gene, but different mutations. It is not really well understood why this is the case. This is one of the frontiers in VHL research. One thing we did was to collate all the mutations, the family mutations, and that information is going to be on the internet,[4] a list of 140-150 mutations and the kind of tumors that were associated with them. But that is one particular point in time. Since then more mutations have been discovered, more information about those families has accumulated, it is information which needs to be continually updated.

The Founder Effect

When Dr. Neumann was studying families with pheochromocytoma, Dr. Neumann noticed that most of his families in Germany with VHL had only eye and adrenal tumors and no brain tumors. Even before the finding of the gene, his team was predicting a strong grouping of symptoms by genetic characteristic. In 1994 Dr. Hiltrud Brauch, who is now in Hamburg, Germany, discovered that 14 of the families who had sent blood for testing had mutations at codon 505. Further study has shown a total of 18 German families, two Pennsylvania families, and one family in Switzerland, all with exactly the same mutation at codon 505. You can use genetic tools to show that these families, who think they are distinct, all come from one Founder, one individual more than 250 years ago, before the emigration to the United States.

Know Your Mutation

Kind of Mutation	Organs most commonly affected
Insertion/deletion	Eye, CNS, kidneys
712	Eye, CNS, kidneys, adrenals
505	Eye, adrenals

CNS = Central nervous system = brain & spinal cord

Note that screening of other organs should not be excluded, as the exact level of risk to other organs is not yet known. Other affects may occur later in life.

That person lived in a small village in the Black Forest region of Germany, about 80 km. north of Freiburg. Some of that individual's descendants emigrated to the United States in about 1720, and moved to Pennsylvania. The descendants of this individual for over 250 years have been having VHL. One of these families is the ideal for someone interested in genealogy, because when I visited them they handed me a book the size of a telephone book, which was their family history. This was one of the families studied by Dr. Robert Welch of Baltimore in his initial treatment of retinal angiomas by laser. That's another thread in this research, that the same families have been brought to medical attention repeatedly, and in different eras they have served to advance knowledge in different way. So this 505 mutation family in the 1970's was helpful in developing laser treatment for retinal angiomas. Later this family was used by another investigator to collect 50 individuals affected with VHL.[5] Then it was used by us in linkage analysis. And then it turns into the Founder Effect.[6] So the same family, the same mutation, is viewed over time with new techniques, and with new techniques comes more and more information.

The 712 mutation, by contrast, does not come from a single mutation. The 712 mutation is the commonest mutation in the gene. It appears again and again in different populations throughout the world. It's as if the gene has a weak spot in its structure and it gets injured at different times in different ways.

New Diagnostic Tools

It is still true that there are 20% of VHL families whose mutations have not been identified. But given time and new techniques we will hope that that will gradually decrease. With other inherited cancers like inherited colon cancer they have had a similar situation. They reached a plateau of about 75% of the families where they could find the mutations, and then they had to resort to a variety of sophisticated techniques to find other mutations. Some of the techniques they used have not yet been used in VHL disease — they are time consuming — but they will be in time.

VHL is a Hot Topic

Since the VHL gene was isolated in 1993, study of VHL has become a "hot topic." From the point of view of the VHL families this situation is desirable. VHL is no longer just a subject of interest to physicians or geneticists; now the entire medical community is interested in this gene for their own reasons. There are people who are very interested in the blood vessels that come in the tumors, and it looks like the VHL gene may be important in how blood vessels come into tumors. These people are

...to understand more about managing your health and to have a Very Happy Life.

in many countries; VHL research is now very much an international endeavor. One of my investigators has just written a paper about VHL in Chinese.

In research there are many bottlenecks. And when you get on the other side of the bottleneck you have a great expansion of a research area. The real significance of the gene isolation, is that it permits the diffusion and the expansion of research in a particular area.

Now I can talk with investigators and we can distribute reagents[7] of all sorts that are useful in VHL research that never could be distributed before because we didn't have them. And all the investigators throughout the world can work with these reagents and it's totally different now from a research perspective than it was in 1987 or 1988. It's a new kettle of fish, it's a new scene. I feel that this is in many ways a new journey.

It's a journey that started in 1987 and 1988. For me it was a wonderful journey because I got to travel throughout the United States and meet with so many of the wonderful people among the VHL families.

We have come a long way from those early pioneering days in VHL gene research. There are many more people involved, which is advancing progress at ever greater speeds and will bring ever increasing benefits to VHL families. But what has not changed is that we still need the VHL families themselves to participate in helping to amass enough information about their own and their families' experiences so that we can begin to make reliable risk calculations for future generations.

Based on an address delivered by Dr. Zbar in Honolulu, June 1996.

Notes: 1. While most tumors in VHL are not technically cancer, in that they are distinct tumors which do not metastasize or invade other tissues, VHL tumors in the kidney and some islet cell tumors of the pancreas can progress to cancer and can metastasize. VHL is therefore considered to be a hereditary cancer syndrome.

2. *Sporadic,* occasionally, at random.

3. *Codons* number sites along the length of a gene, providing a handy way to speak about the location of the change.

4. See http://www.ncifcrf.gov/kidney/

5. Horton, W.A. et al., Von Hippel-Lindau disease: Clinical and Pathological manifestations in nine families with 50 affected members. *Arch Intern Med* (1976) 136: 769-777.

6. Brauch, H, et al., Von Hippel-Lindau disease with pheochromocytoma in the Black Forest region in Germany: evidence for a founder effect. *Hum Genet* (1995) 95:551-556.

7. A *reagent* is a chemical which produces a specific reaction, and can therefore be used as a test. For example, a reagent which turns orange when it combines with the normal VHL gene or protein. ❑

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In Honor of . . .

...all our dear friends whose gifts help support VHL research, from Joyce Graff
...Dr. Larry Byers on his 80th birthday, by June & Harry Wilcox
...Dr. Peter Choyke, by Joyce Graff
...Peggy Graham on the birth of her grandson, Nathaniel.
...the Johnson family, by Genevieve & Van Wright
...Jennifer & Bruce Kingston, Australia, on Jennifer's successful spinal surgery
...the Kolinski family, by Cindy Loftis
...Jean Lima, by Becky & Peter Lima
...Christine Lydon on her birthday, by Mary Swanston
...Rachael Morgenstern on the birth of her grandson Michael, by the Marshalls
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...Cheryl Risser, successful spinal surgery
...Schneider family, by Karen Howell-Rice
...Virginia Schwarz, by Nathan Schwarz
...Stephen Stegner & Kathryn Eihn, by Harold & Marjorie Stegner
...Dr. McClellan Walther, by Joyce Graff
...Rebecca Wolyniec and her parents, Lisa and Randy, on the birth of her baby brother, Nathaniel Joseph, October 8

In Loving Memory of . . .

...Carrie Ater, by June & Harry Wilcox
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For their gifts and services . . .

...Casual Day at a law firm in Michigan
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...Dr. Jeffery Vance, for his talk in Raleigh
...Dr. Eamonn Maher for his talk in London
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... and members of the VHLFA

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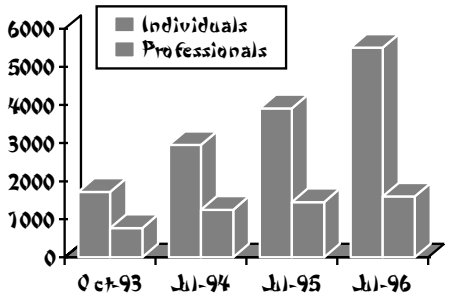
Reaching more people, Funding Research

Thanks to all of ***you***, the VHL Family Alliance was able this year to award two research grants, for a total of $33,495. We are excited and inspired by your outstanding support of these research funding efforts. ***Let's do it again this year!***

More than 6000 brochures have been distributed, and 400 new member packets have been sent out this year.

This year's operating expenses of $36,222 were up only 12%, even though the U.S. population served was up 19.6%, and the worldwide population served was up 40.7%. This is due to the hard work of a dedicated corps of volunteers in this and other countries. We are all volunteers. We pay no staff; we do not rent office space.



We are serving 41% more people than last year.

The budget for the coming year is $40,000, and our goal for research funding is $35,000. We can only spend what we have. The number and size of this year's research grants will depend on your generosity.

We need your help! As you will see on pages 1 and 7, we are already making a difference, spurring additional research on von Hippel-Lindau disease, bringing closer the day when there will be better non-surgical management of VHL.

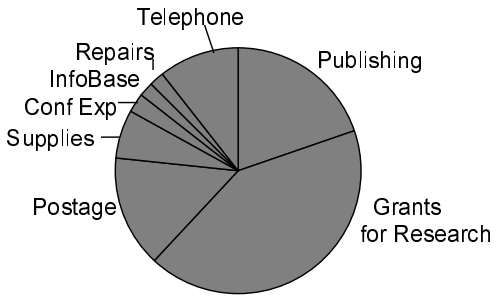
We realize that not everyone can contribute money, and we want to make sure that everyone has the information they need. This organization is not about money, it's about helping one another. We will always give our help and send literature to whoever needs it, regardless of their ability to pay.

If you can afford to give, please give a little extra for the person who can't. And if you can't afford to give at this time, perhaps you might suggest to a friend or relative that they contribute in your honor instead of buying you that holiday gift.

Last year more than 70% of the VHL families donated an average of $100 each. With 100% participation we can do even more this year. Those extra donations you send with your membership, the T-shirts and pins and cookbooks you buy, and the honor cards you send to your friends, all help to make this organization work.

If you value the 800 number, the Web service on the Internet, the Tissue Bank, the Clinical Care Centers and this newsletter . . . and want them to continue, please, please give what you can. Together we will find better management, and a cure for VHL. Be a *Leader* in promoting research -- *Who better than we to take the lead in this effort?*

We send love and blessings at this holiday season and always. -- VHLFA



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