VHL Family Forum

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Q&A about DNA Testing

by Vicki Couch, Genetic Counselor, Mayo Clinic, Rochester, Minnesota. From her talk at the Symposium.

I was asked to organize my talk around the questions that are frequently asked of the people who staff the VHLFA hotline number. I would like to thank the 800 hotline volunteers for compiling this list of questions. Altheada Johnson, Eva Logan, Peggy Marshall, Barbara Redding

First I would like to do a quick review of some genetic concepts. We all have 46 chromosomes in every cell, and these contain all our genes. These are all in pairs, one chromosome in each pair comes from our mother, and the other from our father. And we each are estimated to have somewhere in the ballpark of 50,000 to 80,000 genes in total, so each chromosome has hundreds or even thousands of genes on its length, like beads on a string, lined up along the chromosome, next to one another. The function of genes is typically to produce a protein, or a protein sub-unit, that has some important cell function in the cell, that will affect its growth or activity in one way or another.

Sometimes when I'm talking with people there is some confusion. It sounds like we are discussing whether you have a gene or not. But in reality *we all have two copies of the VHL gene.* The question is whether you have a mutation in one copy of the gene or not – any change in the gene sequence that alters the information that the gene provides for production of the normal protein product. Some mutations in genes are "silent," meaning they don't seem to have any harmful effect on the function of the protein product and therefore don't have any impact on cell function and health. There are others that we think of as deleterious, having a harmful effect, and believed to be associated with disease. There are others still that we think of as leading to normal human variation — differences in eye color, hair color and so on, that make us a little bit different from each other. In fact, it is estimated that each of us has at least 10-15 harmful alterations in a variety of different genes, but most of us don't know what those genes are or what possible harmful effect those genes might have on us.

VHL is an autosomal dominant condition. That means that only one copy of the gene pair has the alteration in it. Each person has one copy from Mom and one copy from Dad. Similarly when we have children we pass only one copy in each of our gene pairs to a child. If a person has only one altered gene — one healthy copy and one altered copy — one of those two copies is passed to each child. That's the fifty-fifty chance of passing VHL to a child. It won't skip a generation, and suddenly appear in a grandchild. *It's either there or it's not.* It may appear to skip a generation — we may not have seen the effects for some reason — but it's there. Because VHL is on chromosome 3, which is not one of the sex chromosomes, it can be passed equally to male and female children.

VHL is in the category of tumor-suppressor genes that control the growth of specific kinds of cells. There is an increased chance of tumors when both copies of the VHL gene are inactivated or have mutations in a cell. People with VHL have inherited one altered copy of the VHL gene, and then at random, for reasons that we don't yet understand, in various tissue types the second copy of the gene may become inactivated and a tumor will appear.

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Another example is to think of this as brakes on a car. Most cars have two sets of brakes: front brakes and back brakes. If a person has inherited a mutation in a tumor-suppressor gene, one of those sets of brakes doesn't work. The second set does work, so the car can still stop. It's only when the second set of brakes is knocked out that the car can't stop.

Because a person with VHL is born with an alteration in every cell, we can see tumors in various tissues. But again we don't understand yet what these other causes are that explain why tumors occur in one tissue rather than another, or at one stage of life rather than another.

Myths

Someone who has two **unaffected children** might be led to believe that they no longer have to worry about VHL. "It hasn't happened twice, so it's not going to happen again." Not true. It's 50/50 every time, with each pregnancy. Just as in coin-flipping you can get two heads in a row, but it doesn't mean you won't get tails on the next flip.

Some people may believe that VHL only occurs in one **gender**, based on their own family experience. But this is a random occurrence. VHL occurs equally in males and females.

Some people believe that VHL only happens at later **stages of life**. Not true. Children can have issues from very young ages.

Conversely, if someone has **reached a certain age**, and haven't had symptoms, then they sometimes believe they must be in the clear. Not necessarily so. There are people who have been diagnosed for the first time in their 70's or 80's.

Some families believe that they will have only one of the **VHL issues**, but they may not have seen it yet in their relatives, but we don't yet have enough information to say with any certainty that there will be only certain aspects of VHL in a family, which is why we recommend screening for all.[1]

People sometimes say "she can't have VHL because she doesn't **resemble the side of the family** where the gene is." But those other traits have nothing to do with the gene for VHL, so we can't rely on those as a way of guessing who may or may not be affected.

If you've had **one clear screening**, we cannot say with any certainty that that will continue to be true. We have to continue screening regularly throughout a person's lifetime.

Seeing a genetics professional

Some people think they don't need to see a geneticist because they have already made their child-bearing decisions. Evaluating one's reproductive risks is the most common reason, but there are also other areas where genetics professionals may assist you in understanding and **coping with complicated medical and genetic information**, far beyond reproductive risks.

A genetic counseling session is an interactive process that often happens over a number of sessions. In addition to in-person visits there are often followup letters and phone calls, gene testing, summaries, and explanations.

Many people who call the hotline say, why do I need a genetics professional? Can't my ophthalmologist or neurosurgeon submit the test? But a specialist is usually focused on the issues in their sub-specialty. The genetics professional can **take the broader view** and tie all the pieces together, and explain why all these various organs may need to be evaluated, and help you understand much of this complex information. While the primary purpose is not to evaluate reproductive risks, that is certainly a topic that can be explored, including providing test information during a pregnancy or discussing other approaches to having children to determine whether their child will have VHL or not. Another very important aspect of genetic counseling is to help the family cope with having a chronic genetic condition, making sure that over the years answers are provided and the right specialists are involved in a person's care. In many of the clinical care centers (CCCs), including the one here at the Mayo Clinic, it is the genetics department that coordinates care among the various specialists for people with VHL and other multi-system genetic conditions.

People who call the hotline want to know how to **find a genetic counselor**, how do I find someone. In the US and Canada the certification is provided through the American Board of Genetic counseling, and the geneticists are certified through the American Board of Medical Genetics. Genetic counseling is most often available in teaching hospitals, associated with the department of pediatrics or obstetrics. A list is maintained on the internet by the National Society of Genetic Counselors (http://www.nsgc.org/).

People often ask who is going to **pay for genetic counseling**. Some insurance policies do cover genetic counseling and even genetic testing, but we have to evaluate it policy by policy. You can read your own policy or call the insurance carrier to determine the answer to the question. In most other countries, payment is not an issue. We have heard at this meeting about the registries maintained in many other countries with more centralized health care systems — France, Poland, Japan — where the genetics professionals will assist you in determining who else in your family tree might be at risk.

Often the hotline is asked, what is the **role of a genetic counselor** in a CCC? The CCC's are institutions across the world that have volunteered to provide comprehensive services for VHL onsite, including genetic services. The genetic counselor can also help with coordinating appointments, making your visit as streamlined as possible, coordinating genetic

testing, counseling with the practical issues that come up, and the emotional issues -- the fears and anxieties in the family.

Screening

When we think about screening of organs, **who should be screened?** Everyone who is at risk for VHL should be screened, including brothers and sisters and children of a person with VHL, and others identified in the pedigree: parents, aunt, uncles, and cousins.

Who should have DNA testing? Anyone who wants to clarify their personal risks for VHL. Sometimes people would prefer to go forward with clinical screening every year and would rather not know for sure whether they have the gene or not. It's something that should be carefully thought through in advance. No one should be forced to have the test "It's an easy blood test, just go for it!" But there are emotional issues, and each person has to be ready to hear the results.

What if I start this process, and then I **change my mind**? Do I have to know my result? No, it is your right *not* to know as well. If the lab has completed the testing we can't tell them to destroy the results — the results will exist, but you don't have to accept the result. It doesn't have to be shared with you until you are ready to learn that information.

Some people want to know what's the best approach to **learning the result**: letter, phone call, or meeting. Our preference is to arrange an in-person visit to discuss the test results, and the implications of that information for their children and other family members. People almost always have other questions. It is important to make sure that the information is well understood, and to keep that avenue of information open for future questions.

Testing Children

At what age is it right to test a minor for VHL mutations? I don't think there is a single right answer for this. We need to begin screening at an early age. If it were me, I would want to know whether there is a mutation or not, so I know whether to do this screening or not. But in other families this may not be the right answer, so this has to be individualized.

Should I **share the results** of genetic testing with my child and at what age? Again I think this has to be individualized to the family and the child. Clearly by the age of junior high school the child is clearly going to know that there is VHL in the family, and there is no reason to hide this information from them. They need to be undergoing screening, so they are going to know that something is going on. The gene result will probably help to clarify things for them, as long as it is explained in an age-appropriate way, and again this is a place where the genetic counselor can help.

Am I being a **responsible parent** by delaying gene testing? It has got to be a family's decision, but if genetic testing is delayed I hope the parents will follow through with the screening. That untested child has to be considered at risk, and we have to continue the screening.

Communications

People have asked how to **prepare for genetic testing**. It is important to work this through with a genetics professional, to think through the implications not only for yourself but for others in the family. Sometimes people have surprisingly strong emotional reactions to the result – surprising even to themselves. "I came into this visit thinking I knew what the answer was going to be, and you've told me the opposite, and it's just blown me out of the water." Other people say, "Well, it's what I thought I was going to hear, but it's impacting me more than I had expected."

What responsibility do we have toward **other family members** if we do test positive for VHL? In the medical community there is a clearly recognized "duty to warn." If someone comes in for VHL evaluation and has never had genetic counseling and doesn't realize that others in the family may also be at risk for VHL, the genetic counselor has a responsibility to explain that to the patient. I think the patient has that same kind of moral duty toward their family members, to provide them with information to obtain the best health care they can.

What responsibility do I have to **notify my ex-spouse** about testing for our children? Again it needs to be individualized for the particular family. I would hope that both parents are still involved in the raising of their children, and both need to know the medical situation of their children.

Can the results of DNA testing be kept out of my **medical record**? And if so, how? I can tell you our policy here at Mayo, which is that any gene test result used for medical purposes and shared with the patient and physicians, will go into the medical record. That information needs to be available to all the people providing care for that person. Some institutions have in the past kept that information out of the medical chart, in order to keep it from being available to the insurance company or employer. Could this now become a "pre-existing condition" and something that would not be covered under the insurance policy? We would each need to check the fine print in the insurance policy. But it is becoming increasingly difficult to withhold this information from the insurance carrier, and there are more and better legal protections against abuse. In the case of someone who does carry the mutation, this information should become justification for the relatively expensive screening that it takes to manage this person's health. This also helps them to avoid costly screening if they do not carry the gene.

You will undoubtedly have more questions that are unique to your own situation. The most important thing is to keep open the channel of information

between you and a genetics professional so that as questions arise you can get the answers that you and your family need.

1. In fact one of the families who attended the conference had always believed that they only got brain and spinal cord issues. For three generations, that was all they had experienced. But in the course of the meeting they realized that the mysterious symptoms their 17-year-old daughter was experiencing were probably a pheochromocytoma. Testing showed that this was the case, and surgeons removed a pheo the size of a lemon.

From the Mailbag:

Dear VHLFA: I had asked my neurologist about DNA testing for VHL over a year ago. He told me there were only a few labs in the country that did this test. At the time they supposedly sent the sample to a lab in Boston. A year later I was still waiting for the results. Every time I called the doctor, he said the results were not back yet.

In April of this year, we drew the blood again. This time I had to sign a consent form and fill out forms about my family. The blood was sent to the University of Pennsylvania Medical Center and I received the results in about two weeks. My neurologist called to tell me the results were negative and I received a followup letter from the lab explaining the results. I was able to tell my father that I do not have the VHL gene and his grandchildren will need no testing before he passed away from VHL complications on May 1. My older brother passed away from the disease in 1978 at the age of 25.

-- Debra R., Connecticut

Response: We are sorry to hear of your father's passing, but delighted to hear that you and your children tested negative. The labs at the University of Pennsylvania and the University of Padua in Italy have the highest reliability ratings for VHL in the world.

There are two changes we would recommend to others seeking DNA testing:

(1) Submit samples to a clinical lab, not a research lab. The lab in Boston is a university research lab that does not promise a particular turn-around time. At this point you can obtain DNA testing for VHL from a clinical lab that provides the same kind of timely service that a doctor would expect from a Complete Blood Count or other routine clinical test. Debra subsequently received the results from Boston University, 14 months after submission.

(2) Submit samples through a geneticist. While you have a relationship with the neurologist (or neurosurgeon or urologist) and those physicians are certainly very skilled professionals in their own specialties, they are probably not best equipped to explain to you the details of what the results actually mean to you and your family. The letter from the lab has the scientific details, but there will be other questions that they and the lab are not staffed to answer.

Having been through this with a large number of families, our best advice is that you meet with a genetics professional (geneticist or genetic counselor) before submitting the samples. Unlike a simple blood test, there are emotional and insurance implications surrounding DNA testing which a genetics professional is better prepared to deal with. (For example: it's a good idea to make sure you or your child have a life insurance policy before doing a DNA test so that you can truthfully say that you have not tested positive for VHL.)

Look for a genetics professional associated with the departments of pediatrics or obstetrics, and inquire about someone who specializes in hereditary cancer syndromes. Someone with this specialty will be able to work with you through your questions about the inheritance of VHL.

Ask the Experts

Question: I read somewhere that when you have scans done with gadolinium, the brain and spine should be done on separate occasions. Is that true?

I have a memory from one of the lectures we had at the meeting that timing was essential when you use contrast!

A year ago they scanned my spine and brain at the same session, and they found two tumors in the spine, but nothing in the brain. From what I´ve read and from the lectures I understand that you "invariably" get brain tumors if you have spinal tumors. I´m worried that maybe they missed something!

Shall I ask for a new brainscan, do you think?

Answer: We often do the spine and brain at the same time. Because of the normal blood brain barrier the contrast "sticks around" longer in the brain and spine than in the rest of the body. As a result there is a longer window of opportunity to scan. That is not to say that a huge amount of time can elapse between the spine and the brain after contrast. We try to scan both within 15 minutes of injection.

Regarding the spine/brain lesion question. It is quite possible to have just spine and no brain lesions. It's not the most common but it does occur. If there was a big delay between the spine and the brain scans after contrast very tiny (2-3mm) lesions might be harder to see. But they should not be symptomatic.

For abdominal imaging, speed is much more important because the contrast is not contained by the blood brain barrier and leaks out much faster. That's why rapid scanning is much more important in the abdomen.

-- Peter L. Choyke, M.D., Diagnostic Radiology Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland

Information is Power to Protect

By Emily P., Minnesota

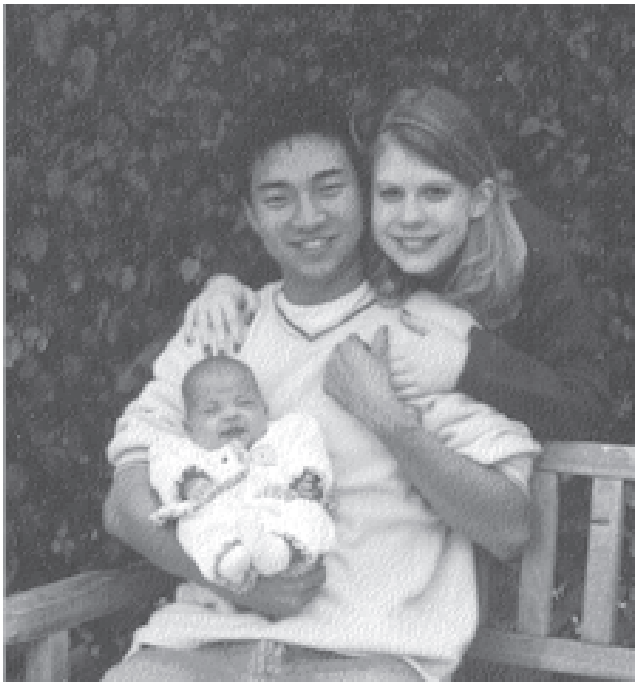
In the month of July, my mother MaryBeth and Aunt Laurie west to the VHL conference in Rochester, Minnesota, where they gained a lot of information about VHL. MaryBeth has VHL, and their mother died of VHL at a young age. All the people in our family who have VHL have had only brain tumors. I had been tested in the past for brain tumors, but I never had DNA testing to look for the gene.

Sitting in the meetings, hearing the many warnings about the importance of checking pregnant women for pheochromocytoma, MaryBeth began to wonder about my pregnancy. I was seven months pregnant. I felt sick every day and had been in bed for the past two months. They said my blood pressure was high, and the medication they gave me did not seem to affect it. We thought it would be a good idea to visit my family physician and talk to him about this.

He thought it would be a good idea to perform an ultrasound since there was unusually little movement from my baby. Also he ordered a 24-hour urine test to check for a pheo. After doing the ultrasound there was concern for my baby's health. He said that there was slow head growth and a very low level of amniotic fluid surrounding the baby. He referred me to another center for a more extensive ultrasound. The results were the same, and they ordered more tests.

My blood pressure was dangerously high, 199/149. The doctors were unable to stabilize my blood pressure, and increasingly worried about the baby as well. They did an MRI of my chest and abdomen, and found that I had a pheochromocytoma, a tumor on my adrenal gland which secretes adrenaline into my body, causing the elevated blood pressure. This tumor began to explain all my symptoms of illness. The pregnancy might have spurred the growth of this tumor, causing increasing problems. They kept me in the hospital a few days and decided to deliver the baby within the next two weeks. My condition became more dangerous. They transferred me to Intensive Care, did another ultrasound, and decided to deliver the baby as soon as possible for fear of my own and the baby's health. I was rushed down for emergency surgery to deliver my baby and to remove the tumor.

The surgery went well and I had a 3 lb 15 oz baby girl, whom we named Hanna. The next few days after surgery things were still not looking good. The baby was in good health and was doing well. But blood clots had developed in my lungs, and some additional complications. After another day and many prayers, things began to get better for me.



Emily, Eric, and baby Hanna.

I truly believe that God helped my baby and me survive through the tough times, and I hope that He can be of help with many others with VHL.

What Laurie learned: We are so very grateful for the VHL Family Alliance and the meeting in Minnesota, and for Joyce's "VHL 101" class. At least three times we were reminded that everyone with VHL should be checked for a pheo before any surgery, before or during pregnancy, and before labor and delivery. We finally heard it, and used that information to protect Emily and Hanna.

Our family always felt that we only got brain tumors. We never knew of anyone in the family who had anything else. My mother died of a brain hemorrhage during her fourth pregnancy, and we always thought that too was a brain tumor. Now that we know more about pheos, however, we realize that that was much more likely a stroke brought on by a pheo, so frighteningly like Emily's experience.

Our family wants to thank everyone for sharing their stories, Dr. Michels and the VHL Board of Directors for providing us with the valuable information that saved Emily's life, and will help keep her and her sister monitored and safe. Our family has been through a great emotionally stressful ordeal in the past few months, and we sure appreciate the support and help we have received. Thank you so much!

— Laurie D., Minnesota

The VHL Family Alliance would like all gynecologists and obstetricians to know the importance of testing for a pheochromocytoma in all cases of uncontrolled high blood pressure in pregnancy. Pheos may be rare, but they can be deadly. And among people at risk for VHL, they are not rare. *Take the time, get the test, be safe.*

It's all in your Head

I have lived with VHL for many years. I lost my left eye. I had extreme pain in that eye but I am not sure I could say it was directly related to the VHL angiomas in the eye or the side eye complications that they caused. I also had pain after a kidney surgery -- much of this was due to the way things were healing and went away over time. I know everyone is different though.

One thing that I do know…. Pain is never imagined, it is very real to the patient -- what ever the cause. I went through literally hell a few years ago feeling pain in my back and legs. I was told in an indirect way by a couple of doctors that the pain was in my head. Unfortunately I believed it for a while. I later found out that I had a tumor in the spinal cord with an associated cyst. This was diagnosed by a Neurologist who realized that VHL could manifest itself this way and sent me for an MRI. I guess my point is -- never let any one say the pain is not real. Even if it is panic related, it still hurts and I am sure there are things that can be done to assist in that.

-- Elizabeth B., Alabama

Genetic Discrimination -- in reverse!

Is anyone aware of cases where people were covered at lower rates or were given coverage based on a negative test result?

At an insurance conference recently we heard about a woman who had been given an expensive policy because of family history. A mutation was found in the family, she tested negative, and she was able to argue with the insurance company for a new lower-rate policy. Remember rates don't change on a given policy, but you could be offered a new policy.

Warburg and Glycolysis

As always I much enjoyed the VHL Family Forum. I was delighted by the box on HIF-1; a small point of fact is that Otto Warburg actually got his Nobel Prize in 1931 for his work on glycolysis -- showing that cellular respiration was enzymatic in nature. Later he worked on respiration by tumour slices, and found that they showed a higher rate of glycolysis than normal tissues. He thought that this might be the cause of malignant behaviour; subsequently it became clear that this wasn't the case. However, his classical observations that glycolysis is enhanced in tumours have stood the test of time, and may be explained (at least in part) by the fact that HIF is commonly activated in cancer. While in VHL associated tumors this is probably due to HIF stabilisation, in many other tumours it is probably due to hypoxia acting through HIF.

-- Patrick Maxwell, M.D., FRCP, Ph.D., University Lecturer & Consultant Physician, Wellcome Trust centre for Human Genetics, Oxford, England.

Smoking and Depression

by Marilyn Elias, USA Today, October 3, 2000

Smoking doesn't just endanger teens' physical health; it promotes major depression, possibly through the impact of nicotine on youthful brains, suggests a study published October 2.

In 1999, 35% of U.S. high school boys and an equal percentage of girls smoked, up from 27% of girls and 28% of boys in 1991.

An estimated 15% to 20% suffer major depression at some time during adolescence.

A well-known link between smoking and teen depression exists because depressed teens start smoking to cope, scientists have assumed.

But for many, the reverse may be true. Among mentally healthy teens, smokers are nearly four times as likely as non-smokers to develop depression within a year's time, the study shows.

Parents should realize that "smoking in kids is never something to just shrug off," says study leader Elizabeth Goodman of Children's Hospital Medical Center in Cincinnati.

Her report, in the journal *Pediatrics*, followed 9,205 U.S. teens for one year.

When she accounted for other factors that can affect smoking rates, kids depressed at the start were no more likely than the non-depressed to smoke at least a pack a week after a year.

The new findings "are important because they show you can't take a one-size-fits-all approach. . . . Smoking could be causing depression through effects on the brain we don't understand yet, and other kids may use cigarettes to help them with depression," says Linda Pederson, an expert on teen smoking at the federal Office on Smoking and Health.

Recent evidence that antidepressants help adults quit smoking raises the possibility that "there's a common pathway" in the nervous system causing both nicotine addiction and depression, Goodman says.

More research is needed to clarify the tie between cigarettes and depression, Pederson says.

This is just a brief message to thank you for the most complete and effective website I've visited. As a Clinical Geneticist, I'm constantly searching for clear, concise information for my patients and for my own use. You certainly exceeded my expectations. *-- Patricia Gordon, M.D., St. Jude's Children's Cancer Research Center, Memphis, Tennessee*

We've Come a Long Way!

by Susan McGuire, North Carolina

She was told in 1964, she was one of a handful of people ever diagnosed with the rare disease von Hippel-Lindau. Celebrating with family and friends, in July, her 70th birthday, Neatha D., has beaten the odds and lived twice the expected age, predicted in the 1960's, for persons with this hereditary cancer.

In 1964, Neatha was determined to have VHL when a tumor was discovered in her left eye on the optic nerve. She had gone to an optometrist who sent her to an ophthalmologist believing she had Histoplastamosos. The ophthalmologist made the diagnosis of VHL. Neatha underwent laser surgery to restore her sight. She was a "guinea pig" for the ophthalmology students at Indiana University. Neatha confesses each visit to the Medical Center was longer than usual because several students needed to do examinations and learn about the eye manifestations of this little known disease.

Neatha feels very fortunate to have had an early diagnosis and excellent medical care which has improved her quality and length of life. She had surgery in 1975 to remove a hemangioblastoma that had caused severe headaches and loss of balance. She says, "that first brain surgery was extensive, involving a large incision from the back of her right ear to the midline of the back of the skull down to the middle of the back of the neck." She spent several days in recovery and it was months before the incision had healed.

Since 1975, Neatha has had two more brain surgeries, the last one in 1992. Annual MRI's have helped to diagnose and quickly treat the brain tumors. The last surgery was less invasive and Neatha healed within a few weeks. She says, "Medical technology and treatment has "come a long way, baby" since her diagnosis 36 years ago.

Neatha believes her father may have been the carrier of the mutated gene for VHL. She has no brothers or sisters and no genetic testing has been done. Her father had died, in his thirties, from a growth in his abdomen, but no autopsy was ever performed. Neatha has two adopted children and she has been widowed for 24 years. She retired in 1992 at the age of 62, and she continues to do volunteer work. She enjoys living independently and her favorite hobby is bridge. Neatha says, "I do the crossword puzzle everyday to keep my mind active."

Neatha is one of two unrelated persons in her church congregation with VHL. She is pleased to have found in the VHL Family Alliance a global community of people with VHL.

Neatha is a wonderful example of the results of early diagnosis, testing and treatment. She continues to live a full life enjoying her two children, four grandchildren and one great grandchild. Neatha is a testimony to all those who once believed that the diagnosis of VHL was a prognosis for a short life. And she is not alone. We have many members in their 60's and 70's, and half a dozen in their 80's. With careful monitoring, early diagnosis and appropriate treatment, people with VHL are living longer, healthier lives than ever before.

Neatha D., Indiana, at her 70th surprise Birthday party, July 2000. Grandson Aaron, Jamie and my great-granddaughter Taylor Kathleen behind me.

Pheo Test Confirmed

by Graeme Eisenhofer, Ph.D., U.S. National Institutes of Health

A paper has just come out in the *Archives of Internal Medicine* (160:19, 2957-2963) replicating our plasma free metanephrine studies in pheochromocytoma (and a bit more) from a group in Austria.

This group is one of the first to reproduce our plasma free metanephrine assay and their findings provide important independent confirmatory proof of the diagnostic superiority of plasma free metanephrines over other tests.

The title of the article is "Diagnostic Efficacy of Unconjugated Plasma Metanephrines for the Detection of Pheochromocytoma". The paper can be found on the internet at http://archinte.ama-assn.org/issues/v160n19/fig_tab/ioi00068_ft.html

For a complete discussion of this test, please see "Finding Elusive Pheochromocytomas," *VHLFF*, December 1999.

Predisposed -- Not Inevitable

a conversation from egroups

Tara: One could argue that VHL is genetic and therefore regardless what you eat you will get tumors because you're predispositioned for them.

Joyce: The good news is that the "predisposition" just means the odds are higher in your case -- it does NOT mean they are inevitable. Yes, if you take steps not to provoke tumors, most people can slow the progress of VHL.

- Smoking accelerates the number and size of tumors

- All that "nutrition for cancer prevention" does seem to help slow them

- Bolstering the immune system also seems to help (conversely, if you're run down and your reserves are depleted, you may be more vulnerable)

There's no magic formula that we can rely on 100%, but there are strong indications that genistein, an element in soy, is particularly helpful. There was a study done in Heidelberg that showed that genistein inhibited vascular tumors of the retina.

Has anyone else found something to be helpful? Or have you tried any of the family recommendations on the website and had any success?

Tara: Your comments reminded me of a question my husband and I have been asking but getting no answers to, and that is the "second hit" idea. That being predispositioned with the VHL gene is hit one and there is another "hit" that initiates tumor growth. Do you know what the second hit may be? I read somewhere that tumors develop following some trauma to the body 20% of the time. I tore my ACL in late November 1999, but I had headaches prior to that so I'm sure I've had the brain and spinal tumor long before then.

My husband and I hope that if we can figure out what the second hit is for me we can do what we can to avoid that. I don't doubt nutrition plays some kind of role in that. Any ideas? -- *Tara E., Colorado*

Joyce: Here's the notion behind the "two-hit theory" which is now an accepted principle in cancer.

Everybody on the planet has two copies of the VHL gene. In people who have the condition called VHL, they are born with a tiny flaw in one copy of that gene. Just a tiny little misspelling is all it takes -- two letters swapped, or one letter wrong, or a few letters added or deleted -- with the result that that copy of the VHL gene doesn't know how to make the correct VHL protein. It makes some other (wrong) protein instead. It's like making pudding without sugar. The consistency is right, but it doesn't work as dessert.

ACTGACTGACTGATCG...oops...ACTG...

BUT that second copy of the VHL gene does make VHL protein, and works just fine.

Every day, every person on the planet sustains some kind of "event" that causes genes to change. Radiation (from sunlight and other sources), gases in the air, various pollutants, and random chance in the copying of genes as the body makes normal repairs -- any of these can cause genetic changes in any of our genes. When I was learning this for the first time from Dr. Maher in England I commented to him wryly that we needed a spelling-checker for our genes. He said that in fact we have a spelling checker! In the cell there are cells whose job it is to check the code, make sure it's right, and if a cell has been copied wrong (if it finds a spelling error) it directs the cell to self-destruct. You'll hear about these in the press. They are called "T-cells" or "killer cells". Those "oops" cells are normally deleted before they cause trouble. That's a normal part of the body's defense system, its immune system response to infection or damage.

In order for a VHL tumor to form, both copies of the VHL gene have to be inactive, and the body's spell-checker has to fail to find it and delete the faulty cell before it goes on to become a tumor. You can see that in the general population, if you have to have random occurrences hitting two copies of the same gene in one specific cell, you can see that it takes years of cumulative uncorrected damage for that to happen by chance. That's why there is more of the random cancer in older people. But in people with a "predisposition" to some kinds of tumors, one copy is already unactivated -- in other words, you have a head start in the process, and it only takes one other uncontrolled hit for a tumor to get launched.

Notice that there are "checks and balances" in your body to try to prevent it. If your spell-checker is thorough and catches the problem early, it never gets beyond one or two cells. No problem! All the sun-tanning that might have led to skin cancer gets repaired at very early stages, and most of those cells with double-hits to the VHL gene are getting deleted before they become a problem.

But if your immune system is not working at full power, then you can see that the chance that some damaged cell slips through the cracks and goes on to form a tumor are greater.

We don't know all the kinds of things that can cause that second hit, so we don't know what all to avoid. As with sunshine, the list is probably so long that it is impossible to avoid them all. So what we understand so far is that whatever we can do to keep our body's natural defenses strong, and whatever we can do to implement the suggestions from the cancer experts, all that is helpful even if it is not the only answer.

- stop smoking

- reduce exposure to second-hand smoke

- follow suggestions for nutrition for cancer prevention

- eat those fruits and veggies, *washed* with soap to remove pesticides

- add some soy products to your diet for the genistein

- watch out for exposure to harsh chemicals (there are strong suspicions about tri-chlorethylene). Use industrial rubber gloves, be sure to have adequate ventilation.

- learn to manage stress in healthy ways (you can't avoid it altogether)

Sharing your stresses in a group like VHLFA is a healthy way of managing stress. Meditation, exercise, music, whatever works for you. And if you do get a tumor, it is not a failure on your part, so don't add the stress of feeling guilty. One of those random misspellings slipped past your spell-checker. There are no guarantees in nature.

The researchers are on the trail of "modifier genes" that make a person's trip with VHL easier or more difficult -- other genes in our bodies that if they are also damaged make a combination with VHL that accelerates or decelerates the process of tumor formation and growth.

If we understood some of these factors, we might be able to turn them into therapies -- maybe add some of that protector ingredient into our bodies. Over the next few years we will see many different angles on the problem. It's an exciting time!

What to do with Tofu?

from Nakao K., Japan

I understand that VHLFA members are looking for recipes for tofu. May I suggest the following website for some Japanese recipes: http://www.asahi.co.jp/cooking/cookingE.html

Please click "Tofu / Bean Products / Beans'', and you will see the menu.

Click a menu, and the recipe will appear on screen with a picture.

Instructions for Life

Take time to light some great smelling candles.
Look back and reflect on all you have overcome.
Swing in the park.
Treat yourself to a massage.
Call someone just to tell them you care.
Forgive someone and move on.
Give thanks for the good in your life.
Praise those around you for their accomplishments.
Sing along to your favorite song.
Visit with someone wise so you can learn from them.
Focus on positive thoughts;
Let anxieties float away like feathers on the wind.

Ask the Experts

Question: I had a cerebellar lesion which was removed. I can't change direction quickly without losing my balance. I can walk very quickly if it's in a straight line, but if I need to zig, zag, I lose my balance and can easily fall.

Anybody know of good exercises that don't cause loss of balance or dizziness? -- *R., California*

Answer: I've got a good exercise for balance that I do with someone else.

Take two poles, broom handles or the like, about five to six feet long. Face each other and each hold a pole in each hand. First at waist level, the "normal" person uses gentle changes in force to try and throw the VHL-er off balance, who then tries to maintain balance. Not twisting and pulling really hard, but back and forth, changing the forces at play, alternating pulls and pushes between the two.

A more difficult exercise advanced from the above is to hold the poles at shoulder level.

Another thing I have found helpful is Tai Chi, which emphasizes balance and shifting weight from one foot/leg to the other.

Once I was able to walk/run fairly easily, I have found running slowly while pushing a soccer ball to be great practice.

What was explained to me is that the cerebellum is the most simple part of the brain, and that it retrains itself. The key to getting your balance back after a deficit is to practice. Balance and motion are learned responses, not reflexes. It is possible to gain back much of what is lost.

Hope this was some help. Again, I'm not a doctor or a physical therapist, these are just my own experiences. -- *Brian D., Kentucky*

Note from Physical Therapist:

Brian, the exercises that you recommended for balance are great. I actually do the broomstick one with patients that have low back pain so that they can learn to control their trunk motion and strengthen their abdominal muscles. I have had patients stand on an uneven surface, i.e. foam or a balance board, and then toss a ball to me. Just standing at the kitchen sink on one foot, holding on with as few fingers as possible works too.

I would recommend that someone with severe balance problems get professional assistance in the beginning or work with someone who can spot you, work with you, in case you fall. -- *Deb Hogan, P.T., Massachusetts*

Meet us in Palo Alto!

see page 13

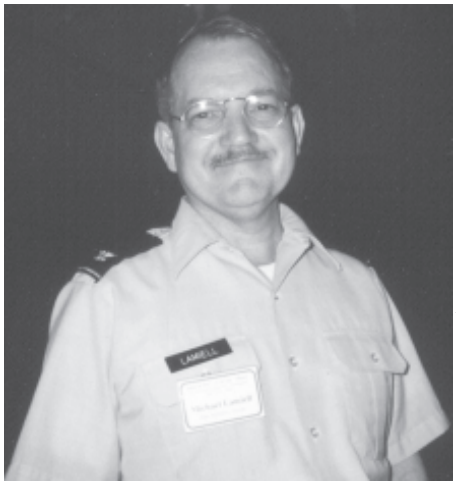
Juliet Yuen Hsia 1936-2000

by James M. Lamiell, MD, San Antonio, TX

I last talked to Juliet Hsia (pronounced "Shah") at her Waikiki apartment in mid-May 2000. She had just begun her courageous five-month battle with pancreatic cancer. She was as vivacious, warm, and outgoing as ever when we spoke that day. As usual, it was wonderful to talk to her. However I was filled with grief and apprehension knowing her advanced cancer diagnosis. Juliet died peacefully at home in the evening on 16 September 2000, surrounded by her loving family and friends. Her death ended our friendship of almost 23 years, but her inspiration, influence, and memory will be with me for the rest of my days.

I first met Juliet and Ted Hsia in January 1978. I was working at the Army hospital in Honolulu, Hawaii and had recently encountered my first von Hippel-Lindau (VHL) patients. I wanted to continue to see these VHL patients, but it could only be done at an Army hospital in the context of research since many in the extended Hawaiian VHL family were not eligible for military health care. As an internal medicine resident, I knew very little about genetics and VHL. Therefore my supervisor referred me to Dr. Ted Hsia, who was a University of Hawaii professor of genetics, to investigate the possibility of a collaborative VHL research study. Ted ran the clinical genetic service at Kapiolani Medical Center in Honolulu with his wife Juliet, who was a genetic counselor.

I instantly liked Juliet and Ted, and I have rarely experienced such immediate and profound friendship. They listened intently as I described my VHL encounters. Ted was exceptionally knowledgeable, and he had a seemingly endless supply of VHL research ideas. Juliet was warm, receptive, and intense. It was obvious that Juliet was primarily concerned with the people who might be VHL research subjects. At times, she was outspoken in her patient advocacy. Juliet did everything she could to support Ted, in their marriage as well as their professional lives. Juliet and Ted made a perfect team. They quickly and willingly became my mentors, and I am profoundly grateful for their guidance. Meeting them certainly changed my life, and it is fair to say, also changed the lives of many affected by VHL.



James M. Lamiell, M.D., Honolulu 1996

For more than two years, I met frequently with Juliet and Ted at Kapiolani Medical Center to discuss the Hawaiian VHL family members I had seen, which totaled about 200 by the time the study was finished. I always looked forward to seeing Juliet and Ted. Juliet and Ted began to see VHL family members as well, and we had several meetings with as many family members as possible. Juliet always provided what Ted has called "the human touch" to our technical clinical endeavors, and she constructed the large pedigree chart for this family. She was an essential and valuable team member.

Ms. Yuen, a genetic counselor, was a member of one of the first concentrated efforts to study large families with VHL and find the VHL gene. From those beginnings in 1978, the VHL gene was first mapped in 1993, and the gene for the Hawaii family was identified in 1996.

I left Hawaii in July 1980 and did not see Juliet until 1996. We did talk frequently since our VHL research continued, and Ted and I took some time to write a paper about the clinical features of VHL that was not published until 1989. Juliet fully supported Ted's early involvement with the VHL Family Alliance, created in 1992 by Joyce Graff, Peggy Graham, and Susan Warnick. Juliet and Ted attended the VHL Meeting organized by Dr. Hartmut Neumann in Freiberg, Germany in 1994. Juliet and Ted were primarily responsible for the 1996 Honolulu VHL Meeting.

The Hawaiian VHL family was the largest ever reported. The full support and participation of this family led to the first linkage study, which was unsuccessful, because of the technology limitations in 1980.

After Dr. James Gusella at Harvard University located the Huntington disease gene on chromosome 4 in 1984, Ted enticed him to look for the gene change causing VHL, which we felt was a single gene based on our studies. Dr. Gusella gave the project to his post-doctoral fellow, Dr. Bernt Seizinger, who worked indefatigably on this project. Dr. Seizinger, worked closely with Juliet, Ted, and me, accepting blood from the Hawaiian VHL family and convincing many scientists to collaborate by donating samples from several other families, especially the large one in Newfoundland.

Ted and Juliet Hsia in Indonesia.

After four years, the VHL gene was located on the short arm of chromosome 3. Perhaps the reports on the Hawaiian family spurred the work by the NIH, the Cambridge group in England under Dr. Maher, and many others, to race to identify the VHL gene and study its properties, as well as the many other studies and advances that were reported in the late 1980's and 1990's. None of this may have happened without the full cooperation of the Hawaiian VHL family, due in no small part to the psychosocial rapport Juliet established with this family.

Juliet Yuen was born and raised in Kuala Lumpur, Malaysia. Ted Hsia, who was born in Shanghai, attended medical school at Oxford University, England, followed by resident training in London, and post-doctoral training in genetics at Yale University. Juliet and Ted met in London, and they married in 1956.

Ted, who was a medical geneticist at the Yale University School of Medicine in Connecticut, moved to Hawaii with Juliet and their children in 1977. Juliet stepped into a void to become Ted's office administrator and genetic counselor, ably based on her past expertise and on-the-job-training. She worked with genetic counselors nationally and internationally, to assist people with birth defects, genetic disorders, or who have high risk of inherited conditions like VHL. Genetic counselors explain, in simple terms, the complicated diagnoses made by medical geneticists, as well as treatment options.

Juliet Hsia, known professionally by her maiden name Yuen, played a major role in establishing genetic counseling in Hawaii after 1977. She worked closely with Ted at Kapiolani Medical Center and the University of Hawaii until her retirement in 1996. For many years, Juliet was the only genetic counselor in the state of Hawaii. Juliet was instrumental in helping to provide testing for inherited anemias common in Hawaii's Chinese, Filipino and Laotian populations. She was heavily involved with counseling members of the extended Hawaiian VHL family. Juliet was a past officer of the National Society of Genetic Counselors, she published papers in national and international journals (some cited below), and she lectured in several countries. Juliet was well known for her strong patient advocacy. Juliet was an excellent teacher. One of her former University of Hawaii students, Janet Brumblay, noted that, "She was one of the best teachers I ever had. She could take something very scientific and make it easy for anyone to understand. She also just had a way of making everyone part of her own family."

Juliet had a deep Christian faith. She was active at Calvary-by-the-Sea Lutheran Church in Hawaii, serving as a past president of the Council of Deacons. She championed the role of women and minorities as a national and international delegate to the Evangelical Lutheran Church of America.

Juliet and Ted raised five sons: Martin, Calvin, Franklin, Duncan, and Gordon; and there are seven grandchildren.

The Juliet and Ted Hsia Foundation was recently formed with the intent of supporting many worthy causes for generations to come, just as Juliet and Ted did during their many years together. Those interested can log into the website at http://www.hsiafoundation.org, make email contact at Info@HsiaFoundation.org, or call (808) 943-1058 for more information. The Website contains many pictures of Juliet, her family, and friends.

Juliet was an inspiration for all that knew her. We will miss her.

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My Daughter Saved My Life

by Tim Nielsen, California

We've all heard the stories about children who heroically save a parent's life. The three-year-old dialing 911 in the nick of time for Mom; the teen who saves his father from drowning in a boating accident; and the list goes on. My child saved my life as well. And, although the method may not be as newsworthy or heroic in scope, I can't thank her enough—or be any prouder of her.

In the fall of 1997 the joy of my life, my perfectly healthy 22-year-old daughter, went in for a routine eye exam. That simple test raised red flags that led her to ophthalmologists, specialists and ultimately to the Mayo Clinic for more in-depth testing. She was found to have retinal cysts and tumors on both of her eyes that needed to be removed. After days of poking and prodding, it was determined that the root of her problem was a rare disease known as "von Hippel-Lindau" or VHL.

My daughter underwent surgery on one of her affected eyes, which resulted in her losing most of her vision in it. It was decided the other eye would remain untreated in the hope that the cysts would stay dormant. After the operation, she showed an amazingly positive attitude and inner strength that were contagious. Despite a total lifestyle alteration, wearing a patch for months to avoid sunlight, and other major discomforts, she made everyone around her feel sure that everything would be alright.

My daughter and her team of specialists urged me to be tested for VHL as well. At first I resisted because I'd never felt better in my life. But she was relentless, and so I agreed to take the next step. Because of my age, I was told to get an ordinary ultrasound on my kidneys. When the test results arrived, my doctor was so shaken that he couldn't discuss them. He couldn't even make eye contact with me. Rather, he simply read the report aloud. I remember it now as being somewhat surreal; nothing he was saying could possibly be about me…both kidneys were covered with tumors and cysts—some nearly as large as the kidneys themselves…without immediate surgery to remove my kidneys, the tumors would surely metastasize…I'd need to go on dialysis…maybe I was a good candidate for a transplant. So it was that, mere weeks after my daughter's eye operation, I was preparing to undergo radical surgery myself.

With my daughter's Mayo Clinic team helping by telephone, my surgeon removed one kidney, but was able to save roughly a third of the other during my nine-hour procedure. Luckily, there was no evidence of cancer in my lymph nodes and no other visible VHL lesions. The best guess was that I'd be tumor-free (and able to keep my kidney-ette) for two years on the

Tim and Jill Nielsen

outside, at which point the fistula I'd been prepped with would come into play for dialysis.

And, by family standards, I was extremely lucky—I had been given warning.

Cancer, it seemed, had been my family tree's Dutch Elm disease for generations. My father had died at 43 from cancer of an unknown origin that had suddenly spread throughout his body; and his father from a brain tumor at age 55. So after receiving a clean bill of health at 40 years old, I was sure I'd beaten the hereditary hex. Then came my daughter's eye exam. It was explained to us in painstaking detail that VHL is basically a disease that alters the tumor-suppressor gene. In effect, for people with VHL, their bodies think it's normal to produce tumors—not stop them. Without any telling symptoms whatsoever, it causes cysts and tumors on the retinas, brain, spine, kidneys, adrenal glands and pancreas, but affects everyone differently. Undetected, it is potentially quite lethal. And, in keeping with family tradition, it's genetic.

With the assistance of my very helpful geneticist, DNA testing was arranged, and we've learned that our particular version of VHL had never been detected before. We've also found out more about the nature of the disease. We were told that, with no other treatment available, patients frequently have several procedures to remove numerous tumors. Multiple surgeries are not only possible, but also probable for VHL patients.

Armed with my DNA results, other members of my family were urged to undergo testing as well. Most were anxious to get screened in the hopes that they could confirm whether or not they and their children had the VHL gene. By contrast, others in the family tried to convince themselves that something like VHL simply couldn't happen to them—so why bother with blood tests? Luckily, all of my father's siblings eventually tested negative for VHL, effectively removing the cloud of doubt for them and their families. Remarkably, my brother still refuses to undergo full DNA testing, although he has had some standard kidney and pancreatic screenings.

For the past two-and-a-half years, both my daughter and I have been on three-month schedules of ultrasounds, MRIs and other screening procedures, with annual "full-body" testing. While cysts began appearing on my kidney remnant almost immediately, they had posed no immediate danger until recently. Certain of the half-dozen cysts are starting to show potential for becoming cancerous, so we're formulating a plan as to when it will be necessary to remove what's left of my kidney. And, my life-saving daughter may need surgery on her other eye as the cysts we hoped would remain dormant are showing signs of growth. What may be a VHL-related spot has also recently been detected on her spine.

Learning you're genetically responsible for your child having an affliction of this nature is devastating, and one of the most helpless feelings I've ever experienced. Having your child save your life from the disease you've passed on to her is even more numbing.

On the positive side, my daughter's career and personal life have flourished despite the ongoing distractions VHL patients must endure. Best of all, we've grown closer than ever before. We've become kind of a built-in, 24-hour-a-day internal support group—with a deeper understanding of what lies ahead and a much stronger appreciation for each other and life itself.

As rare as this disease is, knowing we have each other is a huge comfort indeed.

Tim Nielsen is the Creative Director of a Los Angeles-based advertising agency. Nielsen relocated to Los Angeles from Nebraska, where his daughter Jill still resides.

Meet us in Palo Alto!

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This issue is dedicated in honor of Dr. Neumann's father, Joachim Neumann, who passed away in October. "He was not only my father but also the best friend. He followed all my projects with so much interest and understood so well what it means to have VHL and to run an VHL project." – *Hartmut Neumann, M.D.*

Thank you for contributions..

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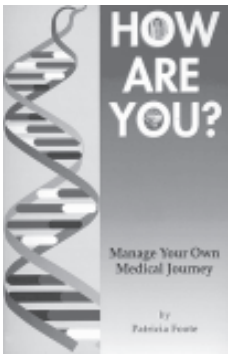

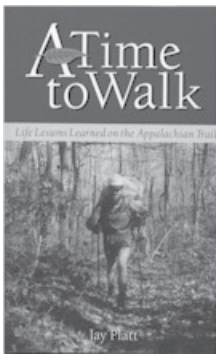

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Canadians, please send donations to Canadian VHL Family Alliance,
709 River Road, P.O. Box 68, Braeside, Ontario, K0A 1G0 Canada

Progress in Spain...

Dr. Karina Villar, a young doctor in Spain who has relatives with VHL, is heading up an effort to develop a VHLFA affiliate in Spain. Karina moderates the online discussion group in Spanish, and has prepared an overview of VHL for physicians in Spanish which was recently published in a medical magazine sponsored by the Official College of Physicians of Toledo (Spain). She has teamed up with Dr. Mercedes Robledo (a more established research clinician) to develop a Spanish VHL Family Association. They are in touch with about 25 VHL families in Spain. Along with Karina, Dr. Robledo has put together a committee of clinicians that is working to prepare a set of guidelines for VHL management nationwide. It adopts guidelines established by the VHLFA, but takes into consideration specific aspects of the Spanish culture and health care system.

Dr. Robledo is working at the recently inaugurated Spanish National Cancer Center and has started to create a VHL database. They are gathering several types of information from individuals with VHL: 1) DNA, 2) an extensive survey of lifestyle, habits, etc, and 3) (whenever possible) tissue samples. They are not only seeking to match specific VHL mutations with particular phenotypes, but they are also investigating the influence of other genes and environmental factors on the development of VHL -- age of onset, severity of disease, number and location of tumors, etc.

Such a complex study can only be carried out successfully if the number of subjects is large enough. Therefore, they are networking with other physicians who treat persons with VHL to create a large repository of DNA samples and patient information. They hope to get in touch with many doctors that treat people with VHL all over the world. Physicians and patients willing to participate in their efforts should contact Kareen@jazzcyber.com

...and South America

The Chilean Medical Association just approved a booklet in Spanish about VHL, to be distributed to 40,000 South American doctors. This booklet was prepared by member Pierre Jacomet, based on the *VHL Handbook* but modified to align with the South American health care system and culture. The booklet was reviewed by Dr. Myriam Gorospe, Research Chairman of the VHL Family Alliance, and funded by Recalcine Pharmaceuticals. Special thanks to Alejandro Weinstein, Sr., CEO, and Dr. Pablo Rodriguez, Medical Director, of Recalcine, and the Colegio Médico de Chile.

Dr. José Claudio Rocha from Saõ Paulo, Brazil, reported to the VHL Symposium in Minnesota that in the three years since the beginning of his study on VHL, he has identified 16 distinct families with VHL in Brazil, and is projecting a very similar penetration of VHL in the population there (approximately one in 34,000). Dr. Rocha, who is also doing DNA testing for VHL in Brazil, has a website in Portuguese and Spanish at http://www.hcanc.org.br/diagmol.html

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