VHL FAMILY FORUM

Family, Friends, Physicians, & Researchers dedicated to improving diagnosis, treatment, and quality of life for people affected by von Hippel-Lindau.

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The VHL gene, genetics, and mutations

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The VHL gene is a Tumor Suppressor, a class of genes that encode proteins that work to limit cell proliferation. Inactivating mutations in Tumor Suppressors result in an increased likelihood to develop tumors. However, it is important to keep in mind that tumor suppressor gene mutations, such as those seen in the VHL gene in people with von Hippel-Lindau disease, do not cause tumors directly. Rather, multiple genetic mutations must occur in a single cell in order for a tumor to develop.

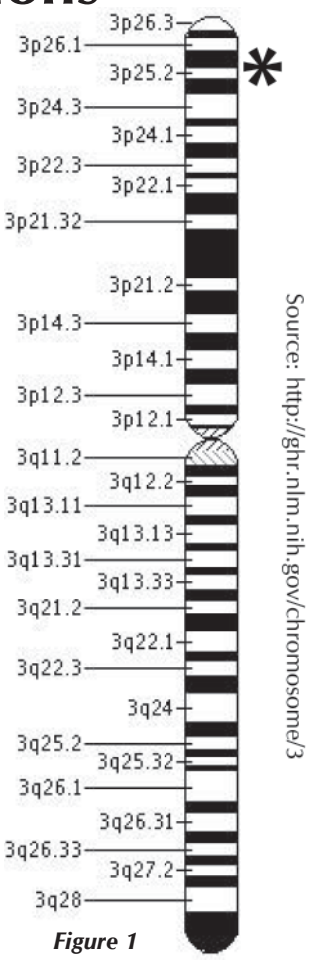
In genetic terms, people with VHL gene mutations have an increased predisposition to develop tumors in certain organs. However, we cannot predict when or where tumors will develop simply based on the knowledge that a VHL gene mutation exists. We can to some extent predict the spectrum of tumors that may arise based on the type of VHL gene mutation that a person carries. These so-called Type 1, 2a, 2b, and 2c mutations and their associated risks are shown in Table 1. (on page 2) Consultation with genetic counsellors and physicians who have a strong understanding of VHL disease is necessary to determine whether a mutation falls within a certain VHL subtype.

The VHL gene is located near the end of the "short arm" of Chromosome 3, which is indicated by the "*" in Figure 1. Most genes are interrupted by stretches of DNA, called introns, that do not contain instructions for making a protein. The parts of genes that do contain protein-making instructions are called exons. The VHL gene has 3 exons and 2 introns (see Figure 2 for an example).

When genes such as VHL are expressed, the information from the DNA is translated into a protein through a messenger RNA intermediate. The messenger RNA is made from the DNA, the introns are removed and the exons are joined together through a process called RNA splicing (Figure 2). It is important that the process of exon joining occur correctly, or the messenger RNA will have mistakes, resulting in an improper protein being made. In the end it is the protein that is made up of a string of amino acids that typically does the work in a cell.

The basic building blocks of genes are DNA nucleotides, or "bases," that contain adenine, thymine, cytosine, or guanine (A, T, C, or G). The sequence of the nucleotides in a gene will determine the sequence of the protein that is made from that gene. While the DNA nucleotide sequence of a gene is composed simply of A's, T's, C's, and G's, the specific order of these nucleotides is interpreted in the cell just as we are able to interpret the order of words that make up a sentence. Mutations are mistakes (or misspellings) in the gene sequence that

continued page 2



Source: http://ghr.nlm.nih.gov/chromosome/3

Figure 1

> ***"VHL does not cause tumors directly... multiple genetic mutations must occur in a single cell for a tumor to develop."***

Inside this issue!

Table 1: VHL disease subtypes

VHL Subtype	Representative VHL Mutation	Hemangio-blastoma	RCC	Pheochromo-cytoma
1	Deletion Nonsense Missense	High risk	High risk	Low risk
2A	Missense	High risk	Low risk	High risk
2B	Missense	High risk	High risk	High risk
2C	Missense	Low risk	Low risk	High risk

result in a misspelled protein. The misspelling of a protein frequently affects how that protein works in a cell. Some mutations may be quite severe, such as insertions, where DNA may be added into a gene, or deletions, where a portion of the gene might be lost. In addition, some mutations affect the splicing of the messenger RNA, such that the exons are not joined correctly, which results in mistakes in the spelling of the messenger RNA.

Other mutations may have less severe effects, such as a missense mutation, where a single amino acid in a protein may be different. Take for example a famous quote from Yogi Berra, "It ain't the heat, it's the humility." A single letter change in a commonly-understood sentence results in some level of puzzlement. (Try that sentence again using "humidity".) In the case of a protein, a missense mutation may completely garble the meaning of the protein or it may cause subtle confusion in the cell.

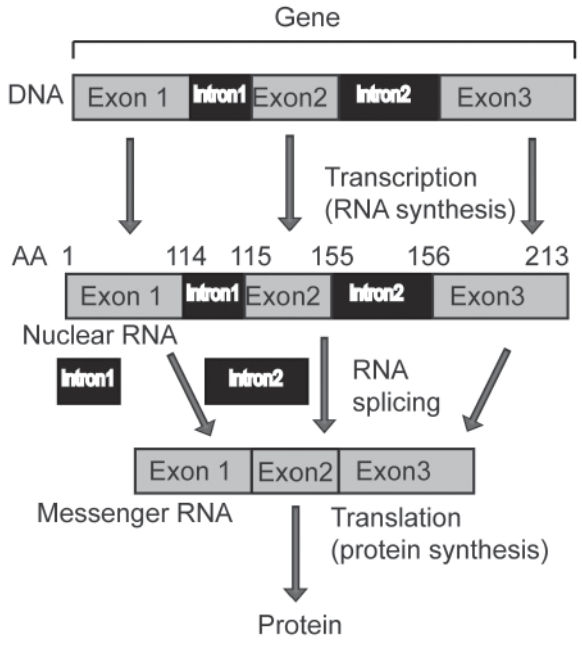


Figure 2: *Diagram of the VHL gene with three exons and 2 introns, dropping the introns and splicing the exons to create the RNA template for synthesizing the VHL protein. A gene is a recipe for a protein.*

The VHL gene is approximately 20,000 nucleotides long, and the VHL messenger RNA is approximately 5,000 nucleotides long after it is spliced. Of these 5,000 nucleotides only 639 nucleotides of the messenger RNA actually contain the information to spell out the sequence of the VHL protein. Mutations may occur at any point within these 639 nucleotides, although most are found between nucleotides 100 and 639, as is shown in Figure 3, which is borrowed from Dr Christophe Béroud and the VHLFA web site.

When mutations are reported to patients, the numbering system is based on the VHL protein sequence. The absolute amino acid position that is changed, as well as the VHL exon that is affected, is given. As is shown in Figures 2 and 3, amino acids 1-114 are found in VHL exon 1, amino acids 115-155 are in VHL exon 2, and amino acids 156-213 are in VHL exon 3.

Some patients may have received reports of mutations that used an older numbering system that was based roughly on the beginning of the gene rather than the beginning of the protein. The difference between these two numbering systems is 213 nucleotides. For example common mutations identified at nucleotide 505 in the old numbering system are now referred to as nucleotide 292 (i.e., 505 – 213 = 292), or the previous nucleotide 712 mutations are now referred to as nucleotide 499 (712 – 213 = 499).

Since three nucleotides encode a single amino acid, one divides the nucleotide position of a mutation by 3 to get the amino acid position. For example a mutation at nucleotide 450 corresponds to amino acid 150 (450 / 3 = 150), also known as codon 150. However, we cannot have fractions of amino acids. Therefore, mutations at nucleotides 499, 500, and 501 all correspond to amino acid 167 (499 / 3 = 166.33; 500 / 3 = 166.67; 501 / 3 = 167), or codon 167. Similarly, mutations at nucleotide 292 correspond to amino acid 98 (292 / 3 = 97.33). The only mutations that are not identified based on amino acid position

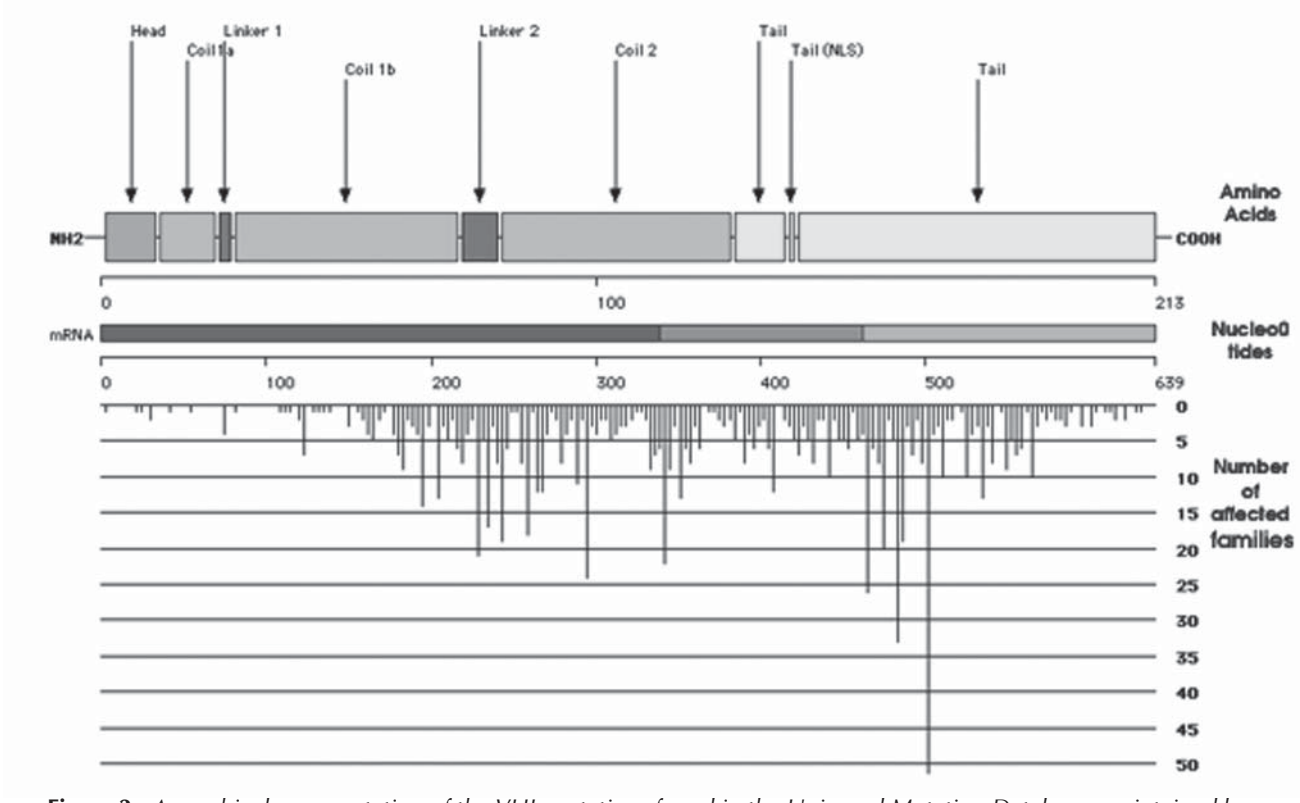


Figure 3. *A graphical representation of the VHL mutations found in the Universal Mutation Database, maintained by Dr. Christophe Béroud and his team at the Arnaud de Villenueve Hospital in Montpellier, France. See http://vhl.org/research/beroud.php*

are mutations that are found in the two introns in the VHL gene. As described earlier these mutations affect the proper splicing of the VHL messenger RNA resulting in proteins with the wrong sequence. These mutations are identified by their nucleotide position relative to the boundary between the VHL intron and the nearest exon.

While the nucleotide sequence of the VHL gene and the amino acid sequence of its protein have been known since its identification in 1993, there is still much research to be done in order to learn how particular mutations affect the activity of the protein and how this impaired activity results in VHL disease.

Additional internet resources:

The VHLFA website (www.vhl.org) provides excellent patient-oriented information that is specific for von Hippel-Lindau disease.

Genetics Home Reference is another excellent site that is written in plain language and helps to explain complicated genetic conditions:

http://ghr.nlm.nih.gov/condition/von-hippel-lindau-syndrome

Gene Reviews is a genetics information resource for health care providers and researchers. Certainly suggest this site as a starting point for any health care provider who may need a refresher on VHL disease. If the language is too technical, there are additional links for consumer resources: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=vhl

Gene Tests provides an up to date list of genetic testing sites: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2171?db=genetests&report=Full

Quiz:

1. How many nucleotides are in the VHL gene?

2. How many amino acids are in the VHL gene?

3. Your DNA test results say"heterozygous for a C to T mutation at nucleotide 694 of the VHL gene that changes a codon for arginine CGA to a stop codon TGA at amino acid position 161 of the protein." What exon is the mutation in? This is important for calculating the risk of pancreatic tumors.

Answers: 1. 639; 2. 639 divided by 3 is 213; 3. 694 - 213 = 481 divided by 3 is 160.3 which is in codon, which is at moderate risk of metastasis in pancreatic tumors.

Difficulty Sleeping?

from Dr. Nan Fuchs, Women's Health Letter

Aromatherapy, especially using the scent of jasmine has been shown to be an effective tranquilizer. A group of German scientists tested hundreds of frangrances on the GABA receptors in both people and mice. They discovered that Vertacetal-coeur, the fragrance in jasmine, has the same molecular action and strength as barbiturates or propofol. In fact, when the researchers exposed mice to this fragrance, they stopped running around and quietly laid down.

GABA (gamma-aminobutyric acid) is your brain's master neurotransmitter. It's essential for your brain and central nervous system to function. It also helps produce "feel good" endorphins. When you have enough GABA, your brain — and you — can relax and rest.

These scientists found that jasmine fragrance works by enhancing the activity of GABA. None of the other fragrances they tested worked as well as jasmine. It increased GABA as much as pharmaceuticals. It looks like jasmine could be a drug-free replacement for some benzodiazepines, barbiturates, and even anesthetics like propofol.

But before you throw away your tranquilizers you should know that this study was a laboratory study, not one conducted on people. We don't know that it will work the same way in humans. That said, it can't hurt to try it. You might want to try sniffing Jasmine essential oil before going to bed at night to see what effect it has on you.

If smelling this essential oil doesn't work, you can take a GABA supplement, available in health food stores and on the Internet. Begin with 100 mg taken half an hour before going to bed. If that's not enough, try 200 mg.

Getting enough sleep is essential to your ability to get and stay healthy. But that doesn't mean you need drugs to get your zzz's. Jasmine could be all you need.

Note: Sergeeva, O.A., O. Kletke, A. Kragler, A. Poppek, W. Fleischer, S.R. Schubring, B. Goerg, H.L. Haas, X.R. Zhu, H. Luebbert, G. Gisselmann, and H. Hatt. "Fragrant dioxane derivatives identify 1 subunit-containing GABA receptors." Journal of Biological Chemistry, 2010; DOI: 10.1074/jbc.M110.103309.

Jody and Frank

Love in Time of Sickness

By Jody D., Canada

In February 2008, my husband and I sat in an exam room at our doctor's office and got the news we were hoping we wouldn't get. MRIs and CT scans revealed several small tumours in my hubby's cerebellum and a considerably larger one on his right adrenal gland.

While we were aware that he likely had inherited a rare genetic disease, we had no idea that we were dealing with something of this magnitude. What was even more frightening was knowing that if I hadn't taken the initiative myself to research this disease, its symptoms, routine screening protocol, and treatment, Frank's condition could have become much worse and potentially life threatening.

Within a matter of a couple weeks, we no longer had just a family doctor. Our team had expanded to include: an endocrinologist, a neurologist, and a urologist. Add to that multiple visits for consults, more MRIs and CT scans, blood, urine...it seemed overwhelming. Oh, and I was pregnant too. LOL!

Here are a few things that I learned along the way:

Trust your gut instinct

I knew Frank was sick. I just knew. So, I headed straight for Google. I made myself an expert. I read. I printed. I highlighted. I even put it all into a well organized binder that became Frank's book. I felt

slightly neurotic, but in the end the book proved to be invaluable. Hence...

Make a book

Frank's book is a binder filled with plastic page protectors. It resembles a scrapbook of the un-fun kind. I have kept everything; my research, appointment cards, notes from every visit with every doctor, notes of Frank's symptoms and most importantly, test results. Those records are yours, and having your own copy is very important. Our book was imperative because more than once we would have a visit with a doctor and they couldn't find the results they called us in to talk about. Sad, I know, but true. Just do it. Time is way too valuable.

It's also good because sometimes the visits would get very stressful, and when that happened, my brain would just go to mush and I would forget everything I had to say and the questions we wanted to ask. With the book I could just review the questions and notes I had written out. I think it helped us feel like we were more active in the process too.

Be prepared to be an advocate

Serious health issues are scary and everyone deals with that fear differently. Some people just shut right down. Dealing with feeling like crap everyday is enough as it is. Frank and I always talked about how he wanted everything to be handled, and it was my job to enforce it. When you are sick you still know what you want, you just don't have the energy to make it happen.

Network

I looked for anyone else with this same disease and condition. Reading about how other people made it through, gave me lots of material for encouraging Frank. I also researched all of his doctors and talked to as many people as possible so that I could help Frank have faith in his team.

Suck it up

I was plenty scared and had lots of hard days, but I absolutely couldn't let it show. The best way you can help to preserve and improve the patient's condition is to remain positive and optimistic. Stress, negativity, and the patient's concern for your well-being can wear them out even more. (I let the flood gates open right after Frank's surgery, while he was in recovery. His surgeon came out to talk to us, and to tell us how everything went. Poor Dr. Pautler! I was a big pregnant mess for a good 10 minutes. Then, relief that we had made it past this obstacle took over. LOL!)

Supporting a loved one through a health crisis is definitely hard work, but it is also a great outlet for all of your anxieties. It also helps you feel like you are doing your part, and are not just a helpless bystander.

Jody and Frank with daughter Neve

I always teased Frank that I would make sure he would be presented with an opportunity to make it all up to me. And he sure did get it ... 20 hours of helping me when I was in labour! I made him work!

Originally appeared in Jody's blog in http://yummymummyclub.ca

Notes: LOL is internet shorthand for Laughing Out Loud

Jody is a regular contributor to the VHL Awareness Group on Facebook, http://www.facebook.com/vhlfa

Jody with Neve

My Story

by Christy T., North Carolina

Christopher, Sarah, and me

In 1989 I was fifteen and just starting my freshman year of high school when I went to my regular local eye doctor to see about getting contact lenses. I had no problems of any kind with my vision.

During the eye exam the doctor noticed a spot "on the optic nerve of my left eye." He recommended that my parents take me to see a retinal specialist before he gave me the contact lenses, to make sure this wasn't something that might be made worse by the contact lenses.

I asked members of my local church to pray for me, and I began praying myself. I had always been taught "give it to God, for him to handle for me." I went to go see the specialist for more tests, with and without dilation. He said he thought it was a small tumor on the optic nerve. He thought it was okay to get contacts, and that he should look at it again in a year. Neither one of my doctors seemed too worried or concerned about it at this time.

After getting the contact lenses everything was fine until around about 1991, I started having migraine headaches really bad and would pass out if I got too hot during running. I began praying and wondering, "OK, God, What is it now? What is going on now with my body?" One night in the winter of 1991 I didn't feel well. My father took me to the emergency room. They did an MRI and CT scan of my body. They recommended I see a neurologist, Dr. Thaddeus Coin, who next sent me to Dr. Allan Friedman, a Duke University neurosurgeon. He told me that it looked to him like I might have a tumor condition called "VHL." He explained that this is a disease that affects different areas of your body, such as your brain, spinal cord, kidney, pancreas, adrenal glands, eyes, ears, and reproductive system. The brain tumor was only 3mm, which was really small. He suggested that we should wait six months to a year and then scan again before we talk about removing it. If any more problems came up between now and then, we might need to remove the tumor before that time. From 1991 to 1993 we did regular scans, and thankfully the tumor did not change very much. I felt truly blessed to have gotten so far without the surgery.

In 1993 they noticed the tumor was starting to change just a little, and they wanted to see me back in six months. That would put us into 1994. I had been doing fine. This was my senior year of high school. All of a sudden I started having migraine headaches, getting sick to my stomach, and was unable to keep down certain foods. Even certain smells would upset my stomach. I told my parents, "We need to call and go see Dr. Friedman at Duke!" I would cry because of the headache pain and I was scared knowing there was a tumor inside of me that could cause all kinds of problems. Clearly it was growing!

I went to see Dr. Friedman. He ordered another MRI. The brain tumor had grown from 3 mm in 1991 to 24 mm now, and needed to be removed as soon as possible. I had only about three weeks of school left before my spring break. I asked Dr. Friedman if I could wait until then. He held out his appointment book for the coming week and pointed with his pen. "You may have any day of this week that you want for your surgery, but we can't wait for your spring break in three weeks. I'm sorry!" So, with no more to say, I looked at the dates and picked the 23rd of February of 1994 to have my first brain surgery. I couldn't believe this was happening to me! Of all times, why now? This was senior year of high school! My mid-term exam was going to be due, my graduation, etc., and what was I going to do now? I continued praying.

My surgery and the time in the recovery room took a total of 16 ½ hours. There were six feeder vessels to the tumor in my cerebellum. Even though the surgery had taken longer than expected, Dr. Friedman was sure he had gotten the entire tumor. My face was swollen after the surgery, but when I woke up my dad said that all I wanted was to get up! I had things I had to do and time was running out! Everyone told me to rest. The very next day after major brain surgery, I was sitting up in my bed, with the laptop working on my mid-term paper for school! The doctor was amazed with my progress. My prayers had been answered.

In June I graduated with my class. What a blessing it was to find I had the strength to heal from the surgery and complete all the work for graduation in spite of what I had just gone through. I didn't give up. I didn't let that brain tumor stop me from doing what the Good Lord had in store for me to accomplish.

From 1994 until 1996, I just did regular follow-up MRI and CT scans to watch for any new tumors of

any kind. Well in 1996, I was hit with another brain tumor in the same area and had to have it removed, also with Dr. Friedman at Duke.

I was blessed with three beautiful children in the next few years. In July of 1997, I became pregnant with my first child. I carried him fine up until the last few months, when I got Gestational Diabetes. I had scheduled a C-Section due to the risk factors and all went well. I named my first son Christopher Alan, to have "Christ" in his name. My second pregnancy went well until at 32 weeks or so, when I was placed on full bed rest until time for the scheduled C-Section to be done at 38 weeks. My daughter was born in May of 2002. As I went through my third pregnancy I found out that I needed to check on my sugar levels. They would drop low one minute and then would run high during parts of the day. I was on bed rest as well, as my body began to go into labor early again. But we managed to get to the scheduled C-section at 38 weeks. Samuel, my second son, was born in March 2003.

I was losing weight during this last pregnancy, was often tired and had no energy at all. My endocrinologist thought we should do a CT scan of the abdomen. The CT Scan results showed that my left adrenal gland had a tumor on it, called a pheochromocytoma, that was causing all of the current problems and that tumor would need to come out soon! My doctor told me there was a place in Bethesda, Maryland, called the NIH Clinical center, where they had a large study of people with VHL. He contacted them.

Well in July of 2003, I went for my first time to NIH. While at NIH, I was able to finally find out that it was definitely true, I was a carrier for the VHL gene. I was told at NIH after years of watching for any new tumors or cysts, that I had a tumor on my left adrenal gland that was rather big and that needed to be removed. In October of 2003, just a little over 4 months after the birth of my third and final child, NIH removed the tumor on my left adrenal gland as well as the whole adrenal gland. Everything went fine. I thanked and praised God and I flew back home until the next visit.

In July of 2007 I underwent my third brain surgery. The surgery went well, leaving me with a little paralysis in my left hand. It's hard to have only one hand that works when you need two! But this is the time when you see how much we just take things for granted in our life and we don't realize just what we do have when things here could be so much worse for us!

Another hard thing for me to go through was DNA testing for my children. In December 2007 I took all three of my kids to Chapel Hill, NC, to the Children's Hospital, to have a DNA test done, to check them for the VHL Mutation in them! When I received the test results, I just wanted to hold them

Tiny Miss Sarah and Wee Master Samuel, winners in the 2010 pageant

and cry!! The results showed that my oldest son, Christopher, is a carrier of the VHL mutation and so is my daughter, Sarah! My youngest one, Samuel, does not have the VHL mutation. Other than losing my Dad back in July of 2001, these two things have been the worse things I've had to happen to me!! I still cry at times thinking about my Christopher and Sarah, but I know that if they will only look toward the Lord for help they will receive it. I have shared the VHL Handbook with their doctor and they are being screened to keep them healthy.

As of today, July 9th 2010, I have been free of tumors for two solid years. Sarah and Samuel decided this year to compete in a pageant in our home town, Whiteville, NC, called the Columbus County Relay For Life, to help with finding a cure for cancer. Sarah won the title of Tiny Miss and Samuel won Wee Master. They both dedicated their efforts to the memory of their grandfather and in honor of me, their mother, and some friends who have died of cancer.

Sarah saved the tabs from aluminum drink cans to send in to the Ronald MacDonald House as her way of helping to find a cure. (See note below) Sarah had people calling me left and right, to tell her they had drink tabs for her. Sarah's dad and I helped her box them for mailing – altogether two large priority mailing boxes!

I would like to thank My Heavenly Father and Lord and Savior Jesus Christ, my wonderful, loving husband, my children, Dr. Allan Friedman and all the wonderful nurses at Duke University Medical, and Dr Russell Lonser and all my nurses at NIH in Bethesda, Maryland!

That's it for now, but it's not the end of my life story – the adventure continues!

Note: The only charity currently collecting pull-tabs are some of the Ronald McDonald houses.

http://www.rmhccanisters.com/c-4-national-pop-tab-collection-program.aspx

London Marathon, 2011

by Chloe D., London, UK

In 2011 my big sister Jo will turn 40. To mark this occasion most people throw a party, put pictures around of when they were oh so much younger, but not my sister; she is going to attempt to run but definitely complete the 2011 Virgin London Marathon. Why? Because we are a family who know the effects of VHL and through the Silver Bond scheme (see Note 1) she can enter this event and raise money directly for VHL.

- UK donations are best through this site
  http://www.justgiving.com/Chloe-Doherty
- US donors please donate through
  http://www.firstgiving.com/jorunning

Our family's story isn't so different from others. If you'd like to know a bit of background, read on.

My father's mother died of a brain tumour in the days before MRI. He was 5 years old. The autopsy found Pheos too.

Back then in the 1950's this didn't mean much to the hospital that did the autopsy. Nobody knew that Dad had the gene, and at the age of 9 he had exploratory surgery to find out why he kept collapsing. They found a pheo the size of a grapefruit. They just opened him up and took it out -- no beta blockers or anything -- and believe it or not he was fine.**

As a young and now married man with three children, he experienced some very nasty headaches and had the scan that wasn't available to his mother. It revealed a brain tumour in the cerebellum. It was after this surgery that someone thought, "Hang on, this is all adding up to VHL." So as a child we grew up with eye tests and in the 1990's we had genetic tests called "linkage analysis" to determine whether we were at high risk or low risk for VHL. This was an early predictive test, not as accurate as today's DNA tests.

My brother Conrad and I were high risk and Con had his first and only operation to remove a pheo when he was 22. Something went wrong, no one knows quite what, but a day after his operation his brain began to swell and it crushed inside his skull, his heart decided to end it but the doctors started it again, twice, leaving him physically alive but, as we were told 2 days later, brain dead. We switched off the machines, my mother held his hand till his strong (and much wiser than the doctors) heart stopped.

A year later following my annual ultra sound we found out I also had my first Pheo. I was very frightened and so was everyone else, including the medical team who made it clear that they couldn't be sure the same thing that happened to my brother would happen to me. It didn't, so here I am now.

Sisters Jo and Chloe

Over the years my father and I have had several procedures and operations, including most recently the gamma knife. No one has been able to count the number of small lesions and tumours Dad has in his brain but he has become very disabled over the past 3 years. I can count mine: 2 spinal tumours, one on the optic nerve and a hole in the macula as a result, and something -- not quite a tumour yet -- in my kidney. My big sister has been there every step, always ready at the end of the hospital bed or the end of the phone with whatever I've needed, and now she's running for me too. For all of us.

Please support my sister's efforts and help to find a cure for VHL!

Editor's note: Today drugs are given for several days or a week prior to the surgery to block the effects of the pheo. It is important to follow the instructions of your physician and take these drugs to prevent a possibly life-threatening situation during or following this surgery.

Note 1: As a fundraising event, there is no race in the world that comes close to the London Marathon. More than three quarters of competitors now run for a good cause and a third of all entry places are offered by charitable organisations. Charities with "gold bonds" are guaranteed five running places each year. "Silver bond" charities are guaranteed one slot every five years.

Create Your Own Fundraising Page!

18 people are currently raising money for VHLFA with personal online pages. Others are hosting events. Please help raise awareness and money: http://www.firstgiving.com/vhl

Shawn and Kim

Rock 'n'Roll, Peachtree 10K, to help all with VHL

by Shawn M., Philadelphia

My training buddies and I are running to raise awareness and money for the VHL Alliance-Cancer Research Fund. Doug and I have signed up for the Rock'n'Roll 1/2 marathon in Philadelphia, Pennsylvania, and Gary is running the Peachtree 10K in Atlanta, Georgia. Together, we hope that we can help others with VHL.

I am running in memory of my Dad who passed away from VHL in 1980 and in honor of my brother, Brian, who also has VHL and all those who are affected by VHL. Brian has had over 30 brain surgeries and has been on a vent for the last 5 1/2 years. I also have had several other relatives pass away from VHL. For everyone with VHL, we need to find a cure!

I realize that these are tough economic times but every little bit adds up. Donating through the Firstgiving site is simple, fast and totally secure. It is also the most efficient way to make a contribution to our fundraising efforts.

If you would rather donate by check that is okay too. Simply make your check payable to the VHL Alliance-Cancer Research Fund and mail it to 2001 Beacon Street, Suite 208, Boston, MA 02135. Be sure to say it is in honor of Shawn's run.

Either way your tax deductible donation goes directly to the VHL Alliance-Cancer Research Fund which is dedicated to improving diagnosis, treatment, and quality of life for individuals and families affected with VHL.

Many thanks for your support! You can also find me on Facebook if you want to cheer me on! Together, we will make a difference.

Shawn, Doug and Gary

http://www.firstgiving.com/shawn_rat_mastrantonio

Gamers take on Protein Challenges

Computer scientists and biochemists at the University of Washington launched a project in 2008 that taps into the brainpower of computer gamers to fold proteins. Almost 60,000 people around the world have taken on the challenge.

In the process, Foldit players have been able to do better than computers on problems that require radical moves, risks, and long-term vision.

There are more than 100,000 different kinds of proteins in the human body.

While scientists already know the genetic sequences of many, they're still working to understand how they fold up into complex shapes that play vital biological roles.

It turns out that in Foldit, which is free, people tend to outperform computers when a problem requires intuitive leaps or strategy shifts.

Foldit has been compared to Tetris, but instead of stacking blocks, players fold a protein. Players are awarded points based on the internal energy of the 3D protein structure, and every puzzle has a high score that players can try to best.

Although the players have yet to design proteins that can, say, disable viruses or generate energy, the team at UW is confident that with so much brain and computing power involved, it is only a matter of time before medical issues are tackled. They even included in their author list an acknowledgement of more than 57,000 Foldit players.

Why is shape important? This structure specifies the function of the protein. For example, a protein that breaks down glucose so the cell can use the energy stored in the sugar will have a shape that recognizes the glucose and binds to it (like a lock and key) and chemically reactive amino acids that will react with the glucose and break it down to release the energy.

Shape is important in VHL too. In some cases, the VHL gene might be correctly spelled, but for some reason fails to fold correctly, so it does not join with other proteins as it should.

"The integration of human visual problem-solving and strategy development capabilities with traditional computational algorithms through interactive multiplayer games is a powerful new approach to solving computationally-limited scientific problems."

http://fold.it/portal/info/science

Seth Cooper, et al., "Predicting protein structures with a multiplayer online game" Nature 466, 756-760 (5 August 2010).http://www.nature.com/nature/journal/v466/n7307/full/nature09304.html

VHL in Brazil

By Jamile Mansour, President
Aliança Brasileira de von Hippel-Lindau (ABVHL)

It was well known in my family that many members had numerous tumors in various parts of the body. When My cousin Viviane went for an abdominal ultrasound, they found several cysts in the pancreas. At the time the doctor simply said "it is nothing." But Viviane was not content with this answer. Her mother had already had several operations to remove tumors. She decided to investigate herself and see if she could find an explanation.

She went to several doctors, explaining her own case and her mother's, until one day she met a doctor who said she probably had von Hippel-Lindau syndrome. At this point she sought the help of the department of Genetics and Oncology at the Hospital in Camargo, under the supervision of Dr. José Claudio Casali da Rocha.

Dr. Casali da Rocha drew up a genetic pedigree, mapping the people in her family in order to identify others who might be carriers of the disease.

When the news broke, I had already been identified as a possible carrier, since my mother too had gone through several surgeries and had died when I was 11 years old.

I went immediately to be checked with abdominal ultrasound and examination of the retinas. The ultrasound found numerous cysts in both kidneys. I told the doctor about the syndrome affecting my family, and that cysts in the kidneys were a sign of VHL.

My doctor, who was not familiar with VHL, explained to me that cysts are nothing more than an accumulation of urine and then you release them. He chided me for making this into a disease! Clearly I was not talking with the right doctor.

I went to an ophthalmologist who was a specialist in myopia (near-sightedness) and had already performed two surgeries to correct myopia as early as 1995. He checked my retinas and found a hemangioblastoma on the retina. This confirmed the diagnosis of VHL.

At this point, I and my cousin Viviane went to the genetics service and requested MRI's of various parts of the body. They found numerous hemangioblastomas, cysts, and tumors in the organs normally affected by VHL – kidney, pancreas, retina, cervical spine, thoracic spine, lumbar spine, and cerebellum.

Since that time Dr. Casali da Rocha has worked to identify other people with VHL throughout Brazil. He has appeared on television and radio, explaining the kinds of symptoms and issues that people with VHL might get. At this time he has identified more than 85 people in 25 families in Brazil with VHL, and has done some important genetic studies which had been published in important journals.

I have continued to go regularly for eye exams every three months, and a whole body check-up every six months. I had a partial nephrectomy in 2008 and have had many ophthalmic procedures (photocoagulation, Avastin, and cryosurgery). I am still working hard with my doctors to keep my eye well.

For the past several years it has been my pleasure to work with Dr. Casali da Rocha to build a patient support organization in Brazil. There have already been two national meetings. We are looking forward to the third National Meeting of the Brazilian patient support organization, which will take place on Sunday following the International Medical Symposium.

Dr. Casali da Rocha has organized translation support so that we can work together with representatives from the Spanish-speaking countries of Latin America, and with our many international participants in the Congress in English. We are very excited to be hosting the Symposium, and are looking forward to learning from the many world experts in VHL who will attend and make presentations.

Won't you please join us in Rio in October? We look forward to meeting you and sharing ideas for how we can improve care and finally find a cure for VHL.

PRELIMINARY PROGRAM – Condensed

For the full program, see vhl.org/conf2010

22nd October - Friday

Basic and Molecular Biology of VHL

Chair: James Gnarra

Co-chair: Jose Claudio Casali da Rocha

Presentations by James Gnarra, USA; Eric Jonasch, USA; Stephen Lee, Canada; Rachel Giles, The Netherlands; Arnim Pause, Canada; Michael Ohh, Canada; Maria F. Czyzyk-Krzeska, USA; Andrew Roberts, Canada; Ester de Andrade Barreto, Brazil; Hiroshi Kanno, Japan

Non-VHL Inherited RCC Syndromes: Exploring the Links between Metabolomics and Inherited RCC Syndromes

(includes BHD, HLRCC, HPRCC)

Chair: Laura Schmidt

Co-Chair: Sunil Sudarshan

Presentations by: Federico Monzon, USA; Jorge Toro, USA; Laura Schmidt, USA; Maria F. Czyzyk-Krzeska, USA; Sunil Sudarshan, USA; Patrick J Pollard, UK; Chris Ricketts, UK

Clinical Aspects of VHL - Part I

Presentations by: Joyce Wilcox Graff, USA; Douglas Guedes, Brazil; Jose M de Campos, Spain; Maria Elena Kusak, Spain; Hiroshi Kanno, Japan; Douglas Guedes de Castro, Brazil

23rd October – Saturday

New Drugs, New Targets & Clinical Trials

Chair: Eric Jonasch

Presentations by: Ruhee Dere, USA; Eijiro Nakamura, USA; Eric Jonasch, USA; Jochen Decker, Germany; João Paulo Vidal, Brazil; Ana Carolina Laus, Brazil

Genetic Aspects of VHL

Chair: Jose Claudio Casali da Rocha

Presentations by: Jose Claudio Casali da Rocha, Brazil; Jeffrey Weitzel, USA; Mercedes Robledo, Spain; Ana Carolina Laus , Brazil; Ester de Andrade Barreto, Brazil; Israel Gomy, Brazil; Mette Bertelsen , Denmark

Clinical Aspects of VHL - Part II

Chair: Marie Luise Bisgaard

Presentations by: Marie Luise Bisgaard, Denmark; Karel Pacak USA; Surena Matin, USA; Ian McCutcheon, USA; Monica Gadelha, Brazil; Jose M de Campos, Spain; Sven Gläsker, Germany; Marie Louise Mølgaard Poulsen, Denmark; Caroline Abadie, France; Valérie Krivosic, France

24th October - Sunday

3rd VHL Family meeting

A day designed for families, focusing on managing one's health

What is VHL?

Neurological Manifestations

Gastrointestinal Manifestations

Urological Manifestations

Ophthalmic manifestations

New treatments

Prevention, medication and surgery

Bioethics, tumor bank

Patients' Rights

VHL Brazilian Association - VHL Familly Alliance

Case reports, exchange of experiences

José Cláudio Casali da Rocha, MD, PhD, Director of the Brazilian National Tissue Bank and Chairman of the Symposium

Please Join us in Rio de Janeiro!

We have a rich program of exciting advances in VHL research and clinical care waiting for you in Rio. We will also be announcing an exciting new initiative among the Latin American countries. All talks will be available in English, Spanish, and Portuguese.

Please join us! See vhl.org/conf2010 for details.

The meeting will be held in the Pestana Rio Atlantic Hotel on Copacabana Beach in Rio de Janeiro. Prices are quoted in R$, Brazilian Reales. Divide by 2 to get approximate price in US$

We look forward to welcoming you to one of the most beautiful cities in the world!

I See Courage

By Sally Swift

Editor's Note: *It is with great sadness that we say farewell to Karen Anderson, one of our hardworking volunteers from New Jersey. Karen and her son Alex were the instigators of a number of fund-raising initiatives for VHLFA, including selling BookSox, recycling inkjet cartridges and cell phones, Alex's Alex's Lemonade Stand, Alex Jay VHL Day, and the global VHL Day in May to raise the visibility of VHL. Through their efforts, the Alex's Lemonade Stand Foundation provided partial funding for our research database for two years. The recycling program and Global VHL Day continue.*

Alex is so far the only person in his family to have VHL. Now 14, Alex was diagnosed with VHL at age 4 when a large endolymphatic sac tumor was removed from his brain and right ear. Karen worked hard to help find the best treatments for him, and to raise money to strive for a cure.

Meanwhile, Karen herself was stricken with Uveal Melanoma in 2007, which caused her to lose her right eye two years ago, ironically under the care of the same doctors who continue to treat Alex for the retinal angiomas of VHL. Unfortunately Karen's melanoma metastasized and despite a valiant battle, she passed away on August 27, 2010 at age 48. We will all miss her very much. Her Aunt Sally, who writes frequently about Alex's VHL and Karen's melanoma in her online blog, wrote the following at the time of Karen's enucleation (eye removal) surgery.

10 July 2008

I want to howl to the heavens: HOW MUCH PAIN MUST ONE FAMILY TAKE?

I know the answer. As much as they're given.

Okay. So the goal is quality of life.

Long term prognosis? Not on Karen's radar, thank you. We'll know when we know. Right now, things look good. Even through only one eye. She's driving again. Bike riding. Cooking. Computing.

Except. Karen too will need MRI's, liver scans, chest X-rays and biopsies every 6 months for as long as she lives. Which we hope and pray will be a very long time.

And she shares something else special with Alex -- they both have the same eye surgeon, they've both had eye tumors removed.

But again, she jokes about it. "Most people plan family vacations," she says. "In our family we plan trips to the hospital."

Karen and Alex. Mother and son. Different cancers, similar losses, totally the right attitude. We all work hard to assure Alex he won't lose an eye too, though he knows his sight is still in danger. Never mind. That's in the future.

For now, fight back. Mobilize. Energize. Laugh. Love. Live. Learn all you can. Gather your physical and emotional resources. Seek and accept support and counsel and advice. Lean on your loved ones and stand on your own two feet.

According to Karen's example, that's what you do to survive. More, that's how you live life to the fullest.

Karen is a survivor of the highest order. An inspiration to cancer victims, mothers of cancer victims, other survivors and those who are trying to be. An object lesson to those of us who waste time moaning about petty problems.

Karen is such a warm, courageous, loving person. She virtually glows with goodness and light. Which she can only see from one side now.

I can tell her what I see when I look at her -- I see unbelievable courage.

Quoted from Sally Swift's blog http://open.salon.com/blog/sally_swift/2008/07/10/i_see_courage

Painless Donations!

-What if every gift you bought this season resulting in a donation to VHLFA?

--What if every search you did on the internet resulted in a donation to VHLFA?

VHLFA has affiliations with TWO online shopping services that collect coupons, alert you to bargains, and give a small commission to VHLFA -- and those donations add up!

Please consider iGive.com or goodsearch.com or any of the other interesting ways to support VHLFA in its quest for a cure. For more information, see http://vhl.org/help

New NIH Study of Pheochromocytomas

The research group under Dr. Karel Pacak at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the U.S. National Institutes of Health (NIH) has opened a new protocol, or research study, on all kinds of pheochromocytomas. The goal of this study is to find better ways to screen for pheochromocytoma in the general population.

Some of you who are old enough to remember President Dwight Eisenhower will remember that he had heart problems. In March 2008 the results of his autopsy were released: he had a pheochromocytoma that was causing his heart disease, which was not identified until the autopsy – a little late to be of help to him. Unfortunately this is not at all unusual. But it is useful to note here because here was a man who was getting the best available health care at the time, and they still missed diagnosing the pheo.

Pheochromocytoma is a neuroendocrine tumor of the adrenal gland, meaning that it produces hormones. Neuroendocrine describes certain cells that release hormones (neurohormones) into the blood in response to stimulation of the nervous system. These hormones interact with the nervous system, As one example, the neurohormone adrenaline gives you extra strength and speed in an emergency. In the case of pheochromocytoma, the hormones produced by the tumor cause the heart and blood vessels to run faster, work harder, even when there is no reason to do so.

Pheos can occur in VHL. When they do, 80% of them occur in or near the adrenal glands, which sit on top of the kidneys. 20%, however, can occur in other parts of the body. These "extra-adrenal" (outside the adrenal) pheos are called paragangliomas. When they occur in the neck, near the mass of nerves near the carotid artery, they are sometimes called carotid body tumors. All of these neuroendocrine tumors are in a family that we call pheochromocytomas.

Under Dr. Pacak's earlier study, there were very high requirements for being accepted into the study. For the current protocol, however, people with any pheochromocytoma can apply in order to obtain a diagnosis. The study does not pay for transportation and housing, and the tests and treatment are free.

There are five genetic flaws that can increase a person's risk of having a pheochromocytoma. If you know you have VHL, then you know you are at risk and can watch for signs. But in most cases, people may not know there is a genetic predisposition in their family that might lead to a pheo. And even when the symptoms are very clear, doctors are frequently slow to make a diagnosis of pheochromocytoma, wrongly feeling that "they are so rare, I would never do the test." Clearly we need better tests, easier to administer, that will tell the doctor clearly that they are dealing with a pheo.

If you know you have a pheo but your doctor can't find it, or if you feel you may have a pheo, and your local doctors are reluctant to call it a pheo, feel free to call and apply to be part of the protocol. As a participant in this protocol you will be asked to undergo a series of tests to determine whether it's a pheo, where the pheo is, and potentially receive a recommendation for treatment. You would then have the option of accepting treatment at the NIH or taking these results back to your local doctors.

The protocol is "Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma and Paraganglioma", Principal Investigator is Dr. Karel Pacak. Karen Adams is the clinical research nurse on his team. You can reach Karen to discuss your own situation at adamskt@mail.nih.gov or (301) 402-7785. The complete protocol can be found at http://clinicaltrials.gov/ct2/show/NCT00004847

Join us at a local meeting! See list of upcoming events on page 16 or on the web at http://vhl.org/meetings

Warning: Deceptive Gene Tests

An undercover investigation of some firms that sell genetic test kits to consumers found misleading test results and "egregious examples of deceptive marketing."

It is important to obtain tests for the VHL gene only through legitimate sources, and through a genetics professional (geneticist or genetic counselor) so that you will get the counseling and good explanations that you will need to understand the results.

See http://vhl.org/dna for a list of the best sources of DNA testing to which your genetic counselor can send your samples for reliable results.

See the full story http://prescriptions.blogs.nytimes.com/2010/07/22/federal-sting-slams-gene-tests/

Our Thanks for donations from:

The thank-you list appears only in the print edition

In Memory Of, cont'd from page 14

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Please join us at one or more of the following events coming up! see also vhl.org/meetings

California Chapter
Pancake Breakfast
September 25, 8-11 am
Woodland Hills Church,
23363 Burbank Blvd.
Woodland Hills, CA
For more info, contact Michelle at (818) 402-4577 or treasurer@vhl.org

Netherlands Regional Meeting
Saturday 9 October 2010
Van der Valk Hotel, Leusden-Amersfoort
info@vonhippellindau.nl

Benefit Bluegrass Concert for VHL at the Mac Gray Auditorium in Statesville, NC
featuring: Lou Reid & Carolina
October 10, 6PM
click here for details
for more information call April at (704) 876-3390 or email carter@vhl.org

Virginia Chapter meeting
Saturday, October 16, 2010, 1-5 pm
Northern Virginia
for details, call 800-767-4845, ext 4
International Medical Symposium

Rio de Janeiro, Brazil
October 22-24, 2010
see pages 10-11 for details and vhl.org/conf2010

German National Meeting
22-24 October, Cologne, Germany
http://www.hippel-lindau.de/

Watch next newsletter for meetings in
Ohio
Texas

Want something closer to you? Call the office and help us plan it!

Please check http://vhl.org/meetings for updates and directions or call the office, 800-767-4845, ext 4