



August 2006

## Living with von Willebrand Disease

*Swimming, playing baseball and tag football: Erin, a pretty, slender eleven-year-old girl with blond hair and bruises on her forearms, enjoys all these activities and more. Yet she has a severe form of von Willebrand disease (type 3, see accompanying articles), so her body makes none of one of the factors needed for normal blood clotting.*

When Erin was about five months old she started bleeding from a tiny cut in the back of her mouth. Over the next 24 hours she continued to bleed, with most of the blood accumulating in her stomach, irritating her stomach and causing her to vomit up the blood, a most alarming thing to her parents. They rushed her to a local hospital where the tiny cut was stitched, but the bleeding continued and she was sent by ambulance to Children's Hospital of

Wisconsin. There one of the hematologists associated with CCBD was consulted and tests for bleeding disorders were ordered. Erin received a blood transfusion and later a diagnosis of VWD. Leslie, Erin's mom, remembers writing the long and unfamiliar name on a scrap of paper which she would consult whenever any one asked her what was wrong with her baby daughter. Leslie herself was also diagnosed at this time with a milder form of VWD (see inheritance article), and Leslie and Erin became CCBD patients.

Because Erin needed regular infusions of a factor replacement product to treat the usual scrapes and bumps of childhood, the family often spent long hours in emergency rooms waiting for treatment. Eventually, with the help of CCBD staff, Leslie was trained and certified to give Erin the infusions. Today Leslie earns her living as a phlebotomist and earns praise from Erin who says she does an "awesome" job of giving the infusions.



Erin has had two more ambulance rides since that first one, and one more blood transfusion. Eighteen days after a routine adenoidectomy she hemorrhaged and began vomiting blood. She was again rushed to the hospital by ambulance and given a blood transfusion. Since then she has had a third ambulance ride, but this was

strictly for fun: a family friend who works for an ambulance company gave her a ride. Erin knows how to have fun, despite the severity of her diagnosis. She loves hanging out with her friends, is an excellent student and a good golfer, and will attend Girl Scout camp this summer where she hopes to spend a lot of time horseback riding.

(Continued on page 3)

## What is von Willebrand Disease?

There are different subtypes of **type 2 VWD**, four of which are discussed here. They are all characterized by abnormal structure and function of VWF. **Type 2A** means that your VWF does not form together in chains (called multimers) the proper way so that it can help in the clotting process. In **type 2B VWD**, the VWF multimers are abnormal but are also overactive—they bind to platelets even when they do not need to and so both are cleared from the blood. Because the platelets are also removed, you may have increased bleeding. In **type 2M VWD**, the VWF forms normal multimers but they don't stick well to platelets. In **type 2N VWD**, VWF does not bind to factor VIII properly, so factor VIII levels are low, similar to mild hemophilia.

If you have **type 3 VWD** you have no VWF which is detectable upon testing. Factor VIII levels are also low in the range found in patients with moderately severe hemophilia.

Symptoms of VWD depend of what type of VWD you have, but can include easy bruising, frequent nosebleeds that take a long time to stop, and heavy periods in women. Frequently, a person does not know she has VWD until tooth extractions or surgery result in excessive bleeding.

*If you or someone you know has these symptoms and have not been diagnosed, call the CCBD.*

---

## Pseudohemophilia: Minot-von Willebrand-Jürgens Syndrome

In 1926, a Finnish doctor named **Erik von Willebrand** (1870-1949) published a paper detailing the bleeding disorder which would bear his name. For several years, he had studied the population on an island in the Baltic Sea, where he discovered what he recognized as a hereditary bleeding disorder. The symptoms were similar to hemophilia, but the hereditary pattern of hemophilia was not followed. Also, unlike hemophilia, joint bleeds were rare. He called the syndrome pseudohemophilia (or "false" hemophilia).

Two years later, in Boston, **Dr. George Minot** (1885–1950) described the same disorder in a paper he published in 1928. Americans would refer to it as Minot-von Willebrand syndrome in the early years. That name was still used in some academic circles through the 1960s. Minot would go on to co-win the 1934 Nobel Prize in Medicine for his work with pernicious anemia.

When von Willebrand's article was translated to German, in 1933, it caught the attention of **Dr. Rudolf Jürgens** (1898-1961). The two men collaborated, and Jürgens repeatedly returned to the original family written about by von Willebrand. Although many of Jürgens' hypotheses proved to be incorrect, the condition was also dubbed von Willebrand-Jürgens thrombopathy, especially in Germany.

After Adolf Hitler and the National Socialists had taken power in Germany, Jürgens fled the country rather than join the Nazis. He escaped to Switzerland with the help of Dr. Eduard Glanzmann (1887-1959), a Swiss pediatrician who, in 1918, had described a rare congenital platelet function disorder now known as Glanzmann thrombasthenia. Meanwhile, von Willebrand wrote to Minot, and Jürgens was soon in Boston, working at Minot's clinic.

*CCBD maintains a full library of educational materials for both children and adults regarding bleeding and clotting diagnoses, general health issues, medications, treatments and parenting information. If you would like more information, please contact one of our Clinical Services Specialists at (414) 257-2424.*

# The Inheritance of von Willebrand Disease

Most families with von Willebrand disease (VWD) know that it is a genetic condition, meaning that it can be inherited, or passed down, through a family. However, because the different types of VWD are inherited in different ways, there is often confusion about the chances that a future child or another relative in the family could have VWD. All types of VWD are caused by changes in the same pair of genes, but it is sometimes easier to think about the genetics and inheritance of VWD one type at a time.

## General information about genes and inheritance

Before trying to understand the inheritance of a specific condition, it is helpful to have a little background information on genetics and inheritance. The human body has many different physical characteristics, including some of medical significance, and these are all determined by single units of instruction, called genes. When a medical condition is described as “genetic”, it means that the condition is caused by a change in one of these genes and is present from before birth. A gene change can be passed on through a family or can occur for the first time in an individual, so “genetic” does not always mean a condition was inherited.

For some, it is easier to understand genetics if you think of a gene being like a recipe: just like a recipe has all the of instructions for making a certain type of food (the list of ingredients, the amounts and way to combine them, the cooking temperature...), a gene has all of the instructions for making a certain type of protein – in this case, the protein is von Willebrand factor (VWF). And just as there are many different ways to change a recipe so that the food turns out a little differently, there are many different changes that can occur in a gene; these different gene changes determine which type of VWD an individual has.

Genes are arranged into 46 compact structures called chromosomes, with each chromosome containing thousands of genes. The 46 chromosomes are arranged into 23 matching pairs, meaning that our genes also come in pairs. We get one

of each pair from each of our parents. The gene pair that determines whether or not someone has VWD is located on chromosome 12. When this gene has a change (also called a mutation), the person will have VWD. Both males and females have two copies of chromosome 12, and therefore two copies of the VWF gene. VWD is equally likely to occur in males and females.

When a genetic condition is present in an individual, families often look back over their family history or pregnancy history to try to find a reason why the condition occurred. It is important to remember that VWD is a genetic condition, caused by a random change of genetic material. There is nothing anyone did or could have done before or during pregnancy to cause the gene change to occur or prevent the change in the VWF gene from happening. A change in a gene is a random, chance event beyond anyone’s control, for which everyone in the general population is at the same risk.

## Inheritance of type 1 VWD

Type 1 VWD (mild VWD) is the most common type of VWD. It is estimated that perhaps as many as 1 in 100 people have type 1 VWD, although many have such mild symptoms, or even no symptoms, that they are unaware of the disease. Type 1 VWD is caused by a gene change that results in a smaller amount of VWF being produced by the body. One gene in the pair has this change; the other gene still has the regular, working instructions to make the normal amount of VWF. (This is called a quantitative change. Using the recipe analogy, the food still turns out right, but there isn’t as much as there should be.)

The inheritance of type 1 VWD occurs in a dominant manner, which means that it only takes one changed copy of a gene in a pair for a person to have the condition. As stated above, all chromosomes come in pairs; one chromosome from each pair is received from the mother, through the egg, and the other chromosome is from the father, through the sperm. Therefore, one way that a child can have type 1 VWD is by inheriting the changed gene from a parent, who has the

*Continued on page 4.*

## Living with von Willebrand Disease (continued from page 1)

Still, she does have some limitations in her activities; for example she cannot play soccer or tackle football. She finds it hard to explain her frequent bruises and she has missed out on fun activities because of bleeds.

Leslie believes that having

VWD has helped to make Erin strong. She is brave and uncomplaining about her infusions. Leslie has encouraged Erin to have as “normal” a life as possible. When asked what helped them to so successfully handle the challenge of

living with a severe bleeding disorder, Leslie said the two keys were getting as educated as possible about the disease (through CCBD), and having both of them getting very involved in the treatment. (Leslie does the infusions and Erin helps

with the preparations.) Leslie hopes that someday Erin will be able to use her experiences with VWD to help others with a bleeding disorder, perhaps as a camp counselor at one of the bleeding disorders summer camps.

(Continued from page 3)

same changed gene. A parent with type 1 VWD has a 50:50 chance to pass on to each child the chromosome 12 with the changed gene. Therefore, there is a 50% chance that any child born to a parent with type 1 VWD will also have type 1 VWD. In other families, type 1 VWD is caused by a new change, or spontaneous mutation, in the VWF gene, which has occurred in that individual for the first time in the family.

### **Inheritance of type 2 VWD**

Type 2 VWD is caused by different changes in the same gene. However, instead of causing a smaller amount of working VWF protein being produced, the gene changes in type 2 VWD cause a different, non-functional protein to be produced. (This is called a qualitative change. This is like trying to follow a recipe with a mistake in it: you still have something at the end, but it didn't turn out the way it should have, and it isn't really anything you'd be able to eat.) There are different forms of Type 2 VWD resulting from different gene changes, and these vary in severity. In Type 2 VWD, one gene in the pair has this change; the other gene still has the regular instructions to make the working VWF.

The inheritance of Type 2 VWD also occurs in a dominant manner. Therefore, someone can have Type 2 VWD because they inherited the changed gene from a parent, who has the same changed gene, or they could have a new change in the VWF gene, which has occurred them for the first time in the family. Someone with type 2 VWD has a 50:50 chance to pass on the changed gene to each child, so there is a 50% chance that any child born to a parent with type 2 VWD will also have type 2 VWD.

### **Inheritance of type 3 VWD**

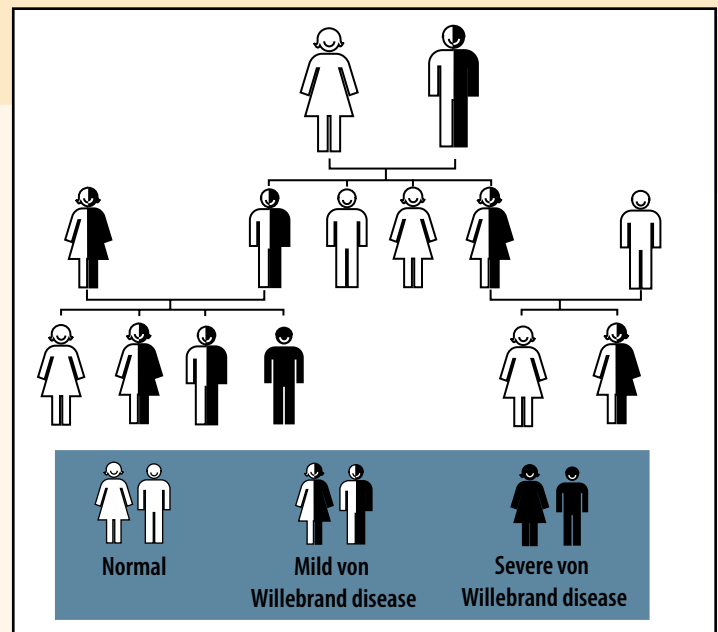
Type 3 VWD (severe VWD) is the least common type of VWD. Type 3 VWD is caused by having both changed genes in the pair, where there is no complete copy of the working instructions at all. Each change results in a smaller amount of VWF being produced, so combined, this results in very low levels of VWF in the body. (This is a quantitative change, but a more significant one than in type 1 VWD. In this case, it is like trying to follow a recipe, but it makes no food and there isn't enough to feed anyone.)

The inheritance of type 3 VWD is described as occurring in a recessive manner. Recessive means that a person must inherit two changed copies of the gene in order to have type 3 VWD. People who have one changed copy and one regular, working copy of the gene are called carriers. When a couple has a child with type 3 VWD, it is presumed that each parent carries one changed gene. Every time two carriers have a child together, there is a 25% chance that the child will inherit both changed genes, one from each parent, and have type 3 VWD.

In most genetic conditions, having one working gene is enough so that carriers do not have any symptoms. However, as described above, type 1 VWD is caused by having only one

quantitative gene change. In this way, the parents of someone with type 3 VWD often learn that as carriers, they have type 1 VWD themselves. For each pregnancy these couples have, in addition to the 25% chance of having a child with type 3 VWD, there is a 50% chance that the child will inherit one changed gene and one working gene and have type 1 VWD (and therefore be a carrier for type 3 VWD). Finally, there is a 25% chance that the child will inherit two working genes and not have any type of VWD.

This aspect of the inheritance of VWD is often the most confusing. The following diagram shows a fictional family in which both type 1 (mild) VWD and type 3 (severe) VWD are present.



With improved testing options and greater awareness of von Willebrand disease, people who might have otherwise lived with unexplained bleeding symptoms are now being diagnosed with VWD. Understanding the genetics and inheritance of VWD allows for these individuals to be more informed about their own health care, and that of their future children. And being informed is one of the best ways to be sure you are getting the medical care you need.

*Genetic counselor Stefanie Dugan, MS, CGC, is available to answer any questions you might have about the inheritance of von Willebrand disease in your family. She can be reached directly by calling her office in the Genetics Center at Children's Hospital of Wisconsin, at (414) 266-3151.*

## **Type 2M:Milwaukee-1 VWD**

What does the “M” stand for in type 2M VWD? According to Dr. Robert Montgomery, the answer to that question is mutating; which is appropriate, as the designation “type 2M” actually describes an ever growing catalog of gene mutations.

The very first specific mutation to be categorized as type 2M was type 2M:Milwaukee-1 VWD. It was identified at the Blood Research Institute of BloodCenter of Wisconsin in Dr. Montgomery’s lab. The findings were published in Blood, the Journal of The American Society of Hematology.\* Of course, this has led to the common belief that the “M” in 2M VWD stands for “Milwaukee.” According to Dr. Montgomery, it does not. Nor does it stand for “Montgomery.”

More recent sources say the “M” is for “multimer,” as type 2M VWD is characterized, in part, by normal multimers. Many articles do not offer any explanation (although most do connect type 2N with Normandy). Dr. Montgomery explains, “When we found this mutation we recognized it as type 2, but neither type 2A nor 2B. So we categorized it as type 2, miscellaneous.” What does the “M” stand for in type 2M VWD? The answer depends on whom you ask.

*For more information on the research taking place at BloodCenter of Wisconsin, including profiles of Dr. Montgomery and the other investigators, please visit [www.bcw.edu](http://www.bcw.edu), select RESEARCH, then INVESTIGATORS.*

\* Mancuso DJ, Kroner PA, Christopherson PA, Vokac EA, Gill JC, Montgomery RR: Type 2M: Milwaukee-1 von Willebrand disease: An in-frame deletion in the Cys509-Cys695 loop of the von Willebrand factor A1 domain causes deficient binding of von Willebrand factor to platelets. Blood 88:2559-2568, 1996.

## **Current Research Study Opportunities for CCBD Patients**

CCBD patients who have been diagnosed with any type of von Willebrand disease (VWD) may be able to participate in a National Institute of Health funded research study called Molecular and Clinical Biology of von Willebrand Disease. Dr. Robert Montgomery (along with Dr. Joan Gill, CCBD’s Medical Director, and Sandra Haberichter, PhD) has been awarded a five year grant to compare defects in the VWD gene and related genes and how those defects are expressed as symptoms in patients.

If you are a CCBD patient and would like to participate, please call CCBD at 414 257-2424 and ask to speak to the Clinical Research Coordinator, Megan Gavin. We will be compiling a list of people interested in participating. For this research, more than one generation of a family should participate, if possible (for example, a child diagnosed with VWD could participate along with his mother and /or father who may not have been diagnosed with VWD). If more than one generation cannot participate, in some instances siblings or other relatives could. For the study a brief bleeding history questionnaire (15-30 minutes per person) will be administered and there will be a lab draw (the cost of this is covered by the study).

Another research opportunity open to some CCBD patients is a research study entitled Prevalence of low von Willebrand factor in Women with Menorrhagia. Dr. Joan Gill, Dr. Robert Montgomery, Dr. Michael Lund and Drashti Desai, the investigators for this study, hope to identify what percentage of women with menorrhagia (long and heavy menstrual periods) will have low von Willebrand levels. If a large number of these women are found to have VWD, the investigators hope to have von Willebrand studies become a part of the regular testing that occurs for women with menorrhagia. Women eligible for this study are those with menorrhagia and who also see an obstetrician / gynecologist at Froedtert. For information about this study, please contact the CCBD Clinical Research Coordinator, Megan Gavin, at 414 257-2424.

*Although it is not affiliated with CCBD, the government web site [ClinicalTrials.gov](http://ClinicalTrials.gov) provides regularly updated information about federally and privately supported clinical research in human volunteers.*

## **SATURDAY SEMINAR – September 30, 2006**

**DISORDERS THAT CAUSE EXCESSIVE  
BLOOD CLOT FORMATION**

**(FACTOR V LEIDEN, PROTHROMBIN GENE MUTATION,  
DEFICIENCIES OF ANTITHROMBIN III, PROTEIN C,  
PROTEIN S, ANTIPHOSPHOLIPID SYNDROME)**

**Presented by Kenneth Friedman, M.D.**

**Associate Director of the Comprehensive Center for  
Bleeding Disorders – Director of the Hemostasis Laboratory,  
BloodCenter of Wisconsin**

*All seminars will be held from 9:00 - 11:30 AM in the  
Blood Research Institute Building, 8739 Watertown Plank Road,  
Milwaukee, WI*

*9:00 - 9:30 Registration & Refreshments*

*9:30 - 10:30 Presentation*

*10:30 - 11:30 Questions*

*Refreshments will be provided courtesy of  
Great Lakes Hemophilia Foundation.*

*Day care will not be provided.*

**REGISTRATION IS REQUIRED: To pre-register or to get additional  
information about the seminar, please call  
Jane Volkmann at (414) 937-6575 or toll free at (888) 312-2223.  
We look forward to seeing you there!**

## Natural Herbal Remedies and your Diagnosis

The following is a list of herbal products that we recommend be avoided by our patients who are on Coumadin (warfarin), heparin, or Lovenox and those who are being treated for a bleeding disorder. These herbal products have the ability to decrease platelet function and/or increase bleeding tendency:

Angelica	Papain from leaves and unripe fruit
Aniseed	Red Clover
Bromelain from fruit and stem	Reishi fruit bodies
Cayenne fruit	Saw Palmetto
Chamomile	Sweet clover plant
Chinese skull cap root	Sweet vernal grass leaves
Clove Oil	Sweet-scented bedstraw plant
Dan shen root	Tonka bean seeds
Fenugreek	Turmeric root
Feverfew	Vanilla leaf leaves
Ganoderma	Willow
Garlic **	Woodruff plant
Ginger **	
Ginkgo	
Guarana	
Horse chestnut bark	** Fine as minor ingredients in food preparation but supplements should be avoided.
Licorice **	
Meadowsweet	
Onion plant **	

The following is a list of plants that are high in Vitamin K. They interfere with Coumadin (warfarin). It is okay to consume foods on this list as long as your consumption is consistent day to day:

Alfalfa	Parsley leaves
Beet root and greens	Plantain leaves
Broccoli flower buds	Shepherd's Purse
Brussels sprouts bud	Smartweed plant
Cabbage leaves	Spinach leaves
Chinese cabbage leaves	Stinging nettles plant
Collard leaves	Turnip leaves
Corn silk stigmas	Watercress
Kale leaves	
Lettuce leaves	

### GLHF: Walk with the Animals...

CCBD, in cooperation with Great Lakes Hemophilia Foundation (GLHF), will hold the annual Walk with the Animals at the Milwaukee County Zoo on September 23, 2006.

Last year, close to 150 people walked through the zoo, stopping at eight tables along the route and picking up educational information on living a healthy lifestyle. Everyone then got together for a picnic lunch. Families enjoyed the exercise, educational materials and getting to meet and talk with each other.

This year, we hope to have a bigger turn-out and even more fun! You must register for this event. For more information, or to reserve your place at the zoo, please call GLHF at (414) 257-0200 or (888) 797-4543.

### CCBD Clinic Moving

The Comprehensive Center for Bleeding Disorders will continue to see patients at Children's Hospital of Wisconsin. However, effective September 15, our clinics will be held on the second floor of the hospital. If you have an appointment in either our Monday or Thursday clinics, please look for specific directions in your appointment letter. This will also affect CHW's infusion clinic.

## HAVE YOU MOVED?

Please complete the form below and return to us at the Comprehensive Center for Bleeding Disorders, PO Box 2178, Milwaukee, WI 53201-2178. It is important that we keep our mailing lists current so that you can be sure to receive current medical information along with announcements regarding our special medical programs.

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

DOB: \_\_\_\_\_

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

City, State, Zip Code: \_\_\_\_\_  
\_\_\_\_\_

New Phone Number: \_\_\_\_\_

New Dentist or Primary Doctor: \_\_\_\_\_

Office Phone Number: \_\_\_\_\_

Is this the address of patient's:

MOTHER

FATHER

BOTH

## HAVE YOU RECENTLY TURNED 18 YEARS OLD?

Check the appropriate boxes telling how we may contact you and who we may speak with regarding your medical care and return it to us at the Comprehensive Center for Bleeding Disorders, PO Box 2178, Milwaukee, WI 53201-2178. Because you are legally an adult, CCBD cannot speak to anyone but you regarding your medical care without your authorization.

I authorize CCBD staff to:

Contact me at my work phone number:

\_\_\_\_\_  
(Detailed messages will not be left)

Leave a detailed message on my home phone/voice mail:

I authorize CCBD staff to speak or leave information with person(s) in my home as follows:

\_\_\_\_\_  
Name / Relationship to patient

\_\_\_\_\_  
Name / Relationship to patient

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

DOB: \_\_\_\_\_

Patient Signature \_\_\_\_\_

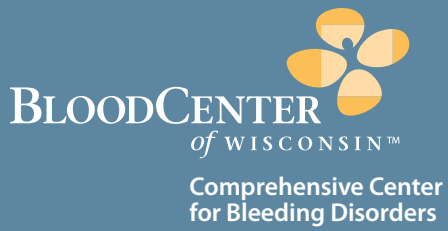
Date: \_\_\_\_\_

---

## WE WOULD LIKE YOUR INPUT

*Remember, this is your newsletter. We welcome any requests you might have for future articles. Just give us a call and let us know of your ideas or suggestions. Or, just give us a call and let us know if you feel we are providing you with an informative newsletter.*

---



Non-Profit Organization  
U.S. Postage  
PAID  
Milwaukee, WI  
Permit No. 4426

PO Box 2178  
Milwaukee, WI 53201-2178

Address Service Requested

---

***BloodCenter of Wisconsin advances patient care  
by providing life-saving solutions grounded in  
unparalleled medical and scientific expertise.***

---