

# von Willebrand Disease

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Molecular Genetic Testing



## What is von Willebrand disease?

von Willebrand disease (VWD) is the most common inherited bleeding disorder affecting about 1 percent of the population.

## What causes von Willebrand disease?

VWD is a hereditary condition caused by a defect in the von Willebrand factor (VWF) gene, which is necessary for normal blood clotting.

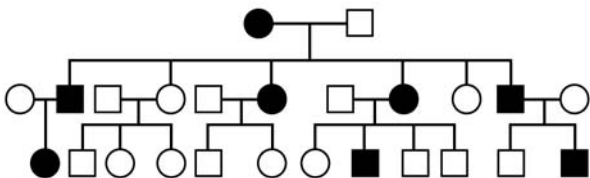
VWD symptoms can be different in every patient, even those within the same family. The symptoms can range from mild to very severe. Some common symptoms include:

- Increased or easy bruising
- Recurrent nosebleeds
- Heavy menstrual periods
- Excessive bleeding during childbirth
- Postoperative bleeding, particularly after dental extractions or tonsillectomy
- Bleeding into joints or internal organs

## What are genes?

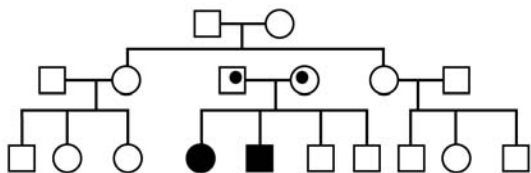
Genes are the blueprints for all of the body's traits and processes. Genes are located on our chromosomes. Every person inherits 23 chromosomes from his/her father and 23 chromosomes from his/her mother. This results in a total of 46 chromosomes — 23 matching pairs. Therefore, we have two copies of each gene.

## What is an autosomal dominant (AD) condition?



In an AD condition, only one of the two copies of a gene has an alteration that causes the condition. Most often, AD disorders are inherited from a parent who has the AD condition. When one parent is affected with the condition, there is a 50 percent chance that the parent will pass the gene to the child. (Likewise, there is a 50 percent chance that the parent will pass on the gene that is unaltered.)

## What is an autosomal recessive (AR) condition?



In an AR condition, both copies of a gene have an alteration that causes the condition. If a person possesses one altered and one unaltered gene of an autosomal recessive condition, s/he is a carrier and generally does not experience the symptoms of the condition. In most cases, when a person has an AR condition, each parent has one working gene and one affected gene. This means that both parents are carriers. However, having one functioning copy of the gene usually keeps carriers from being affected.

When both parents are found to be carriers of an AR condition, there is a 25 percent risk that their child will be affected with the condition. (If the parents are blood relatives, the risk increases). Additionally, there is a 50 percent chance that their child will also be a carrier of the condition.

If one parent is affected with an AR condition and the other is not a carrier, none of the children will be affected. In this situation, all of the children will be carriers of the AR condition.

## Inheritance of von Willebrand disease

VWF can be inherited from the mother or the father, or from both. Male and female children have an equal chance of inheriting VWD. VWD often affects several members of the same family.

Most people who have VWD are born with it and inheritance follows a pattern known as “autosomal” (see figure on previous page). This means that the disease occurs in men and women equally. However, von Willebrand disease can be passed on in either a “dominant” or a “recessive” manner.

Types 1 and 2 are usually inherited in a "dominant" pattern. If the altered gene is passed on, the child will have VWD of varying symptoms. Regardless of severity of the symptoms, the child can then pass the gene with the alteration to his or her own offspring.<sup>1</sup>

Type 3 VWD usually is inherited in a "recessive" pattern. There is a risk for Type 3 VWD when each parent has one altered VWF gene. There is a 25 percent chance that the child will inherit the altered gene from both parents. Even if both parents have mild or asymptomatic disease, their children are likely to be severely affected.<sup>1</sup>

VWD often can be traced through several generations in a family. Some have symptoms while others just carry the defective gene<sup>1</sup>.

Sometimes VWD can occur without a family history as a new mutation; however, individuals who carry this mutation, whether it is inherited or spontaneous, can pass it onto their children.

## What are the different types of VWD?

VWD is classified into three different Types (Type 1, 2, or 3) and Type 2 is further divided into four Subtypes (2A, 2B, 2M, and 2N).

VWD Type	VWF problem	Genetics	% of patients
Type 1	Decreased VWF	Autosomal dominant	75
Type 2	Qualitative defect of VWF	Autosomal dominant or recessive	20
2A	Reduced binding to platelet, absence of HMV multimers	Autosomal dominant	
2B	Increased binding to platelet, lack of large multimers	Autosomal dominant	
2M	Lack of platelet clumping with presence of multimers	Autosomal dominant	
2N	Reduced binding to FVIII, look like hemophilia A	Autosomal recessive	
Type 3	Very little or no VWF with lower FVIII levels	Autosomal recessive	5

\*HMW: High Molecular Weight

## What's the benefit of molecular diagnosis of VWD?

VWD symptoms and VWF protein levels can change over time. Therefore, results of blood tests that measure the amount of VWF protein can change over time. Levels of VWF and of FVIII are increased by environmental influences such as pregnancy, exercise, infection, severe liver disease, thyroid disease, and some medications, including oral contraceptives. Levels also are related to blood groups and race. VWF levels are lower in blood group O compared to blood groups A and B and higher in African Americans than in Caucasians; however, molecular diagnosis is definitive and is not affected by the above listed factors.

People with VWD may have mild or no symptoms at all. They live for a long time without suspecting they have the disease and may never get tested; however, it is very important to know if a person has VWD. If a person with VWD has an accident or needs surgery, he or she may bleed more than normal. People with VWD may need special medicine to control bleeding.<sup>2</sup>

## What are the indications for molecular testing?

The indications for molecular testing include:

- Individuals with a clear diagnosis of VWD
- Hemophilia patients with symptoms suggestive of VWD complicated hemophilia
- Individuals with a history of easy bruising, frequent and prolonged nosebleeds, excessive bleeding during menstruation and/or childbirth, and excessive and prolonged bleeding after injury, surgery and dental extractions
- Patients requiring determination of VWF subtype
- Individuals with a family history of bleeding or VWD, including pre-symptomatic and prenatal testing for appropriate family members
- VWD carriers with previously identified mutations who desire prenatal diagnosis

## How is the genetic test performed?

A blood test is performed on the suspected carrier or affected individual. If prenatal testing is desired and a mutation has been identified in the family, amniocentesis or CVS is performed by a physician and a sample of the fetal cells are sent along with a blood sample from the mother.

Samples sent to CMDL are surveyed for genetic mutations in the VWF gene.

## Who does the testing for VWD?

The City of Hope Molecular Diagnostic Laboratory (CMDL) performs the tests. For additional information and Test Request Forms, please visit us at <http://mdl.cityofhope.org>.



## Will medical insurance cover testing?

Testing is often covered by insurance. **Pre-verification for services must be obtained by City of Hope before testing begins.**\* Patients can always contact their insurance company beforehand to determine coverage. **Testing is held until verification is completed.**

**If a patient prefers that testing begin immediately,** the patient or institution may offer a guarantee of payment, which would be used only if insurance denies coverage for testing. Additional information regarding the insurance verification process is available at <http://mdl.cityofhope.org> or 888-826-4362, ext. 0.

\*All HMO's require the primary physician to obtain pre-authorization for the services to be rendered.

## Resources

### ZLB Behring

Phone: 610-878-4000

E-mail: [Webmaster@allaboutbleeding.com](mailto:Webmaster@allaboutbleeding.com)

[www.allaboutbleeding.com](http://www.allaboutbleeding.com)

### National Hemophilia Foundation

Phone: 800-424-2634

E-mail: [info@hemophilia.org](mailto:info@hemophilia.org)

[www.hemophilia.org](http://www.hemophilia.org)

## References

1. National Hemophilia Foundation  
[www.hemophilia.org](http://www.hemophilia.org)
2. Keeney S. 2001. *Clin. Lab. Haem.*  
23: 209-230

## About Us

The City of Hope Molecular Diagnostic Laboratory (CMDL) specializes in clinical genetic testing services for cancer, pharmacogenetics, muscular dystrophies, neuropsychiatric diseases, connective tissue disorders and coagulopathies. CMDL continues to establish new genetic tests for these diseases. For more up-to-date information about our tests, please visit our Web site at <http://mdl.cityofhope.org>.

## Contact Information for Patients

Patients should talk with their physicians about genetic testing. Genetic counseling is generally recommended when discussing the option of appropriate genetic testing, the implications of test results, residual risks and uncertainties, and reproductive or medical options. See our patient friendly Web site at <http://mdl.cityofhope.org>.

## Contact Information for Clinicians

The City of Hope Molecular Diagnostic Laboratory (MDL)  
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Northwest Building, Second Floor, Room 2236  
Duarte, CA 91010-3000  
Tel: 888-8-COH-DNA (888-826-4362)  
Fax: 626-301-8142  
E-mail: [mdl@coh.org](mailto:mdl@coh.org)  
Web site: <http://mdl.cityofhope.org>