

Marfan and Loeys-Dietz Syndromes

Molecular Genetic Testing



What is Marfan Syndrome?

Marfan syndrome (MS) affects about one to two people in 10,000 and can affect people of all ages, races and ethnic backgrounds.¹⁻⁴

MS is a systemic disorder of connective tissue with a high degree of clinical variability. Cardinal manifestations involve the cardiovascular, musculoskeletal, ocular, and central nervous systems. Of particular concern is the risk for the development of a life threatening, aortic aneurysm or dissection.

The most serious problem associated with MS is weakness of the aorta, the body's largest artery. A weakened aorta is at increased risk of a complete tear or rupture, causing sudden death.

What is Loeys-Dietz Syndrome?

Loeys-Dietz Syndrome (LDS) a new aortic aneurysm syndrome characterized by hypertelorism, bifid uvula/cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection.



What causes MS and LDS Syndromes?

MS is an inherited connective tissue disorder caused by mutations in the fibrillin (FBN1) and transforming growth factor, beta 2 (TGFB2) genes. Mutations in the FBN1 gene are detected in approximately 80 percent of patients that meet Ghent diagnostic criteria for MS, and 40 percent who do not.

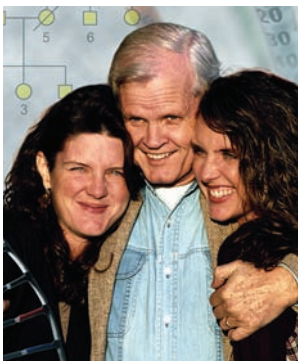
LDS has recently been associated with mutations in TGFB1 and TGFB2 genes.⁵⁻⁶

While there are some overlapping features between MS and LDS, ectopia lentis seems to be a very rare finding in individuals with

TGFB mutations, and LDS patients often have craniofacial abnormalities such as hypertelorism, and bifid uvula.

For patients presented with a diagnosis of LDS, the detection rates range from 100 percent to 30 percent for Type I and II, respectively.⁶

The purpose of connective tissue is to hold the body together and provide a framework for growth and development. A mutated FBN1 or TGFB1/2 gene results in abnormal connective tissues and weakened heart, blood vessels, lungs, eyes, bones, ligaments and nervous system.



Usually, the defective gene is inherited from a parent who has the disorder. In about 25 percent of fibrillin cases, a new mutation occurs during the formation of sperm or egg cells. In these cases the defective gene is not inherited from a parent.

Can MS and LDS Syndromes be cured?

At present, there are no cures for MS and LDS syndromes: however, early diagnosis may help prevent serious complications.

How are MS and LDS Syndromes treated?

Most of the problems associated with MS and LDS syndromes can be managed if diagnosed early.

Drugs such as beta blockers have been used to control some of the cardiovascular symptoms of MS; however, these drugs are not effective against skeletal and ocular problems.

Advances in treatment have greatly increased the life span of patients with MS. Presently, the life expectancy of individuals with MS who receive proper treatment is about 70 years.

Who should be tested for mutation in FBN1 and/or TGFBR1/2?

- Individuals with a Marfan-like features, or LDS
- Individuals with a Marfan-like presentation, or major features of MS
- Individuals who are related to someone with MS
- Certain individuals with a dilated aorta

We strongly recommend obtaining professional genetic counseling prior to having any genetic test performed.

Who does the testing for mutations in the FBN1 and TGFBR1/2 genes?

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

Test Procedures

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 will be surveyed for genetic mutations in FBN1 and TGFBR1/2.

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

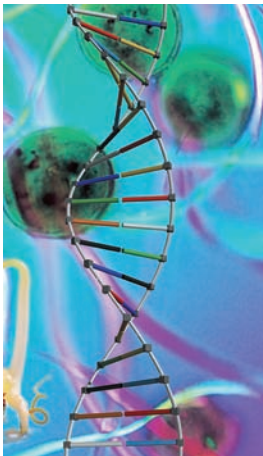
The National Marfan Foundation

Phone: 1-800-8-MARFAN

Web: www.marfan.org

References

1. 1996. American Academy of Pediatrics Committee on Genetics. Health supervision for children with Marfan syndrome. *Pediatrics* 98: 978-982.
2. Gott, V.L., et al. 1999. Replacement of the aortic root in patients with Marfan's syndrome. *New England Journal of Medicine* 340: 1307-1313.
3. De Paepe, A., et al. 1996. Revised diagnostic criteria for the Marfan syndrome. *American Journal of Medical Genetics* 62: 417-426.
5. Loeys et al. (2005) *Nat. Genet.* 37: 275-281
6. Loeys et al., *NEJM*, 355:788-798, 2006



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

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