

# Nonsyndromic X-linked Mental Retardation

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Molecular Genetic Testing



## What is nonsyndromic XLMR?

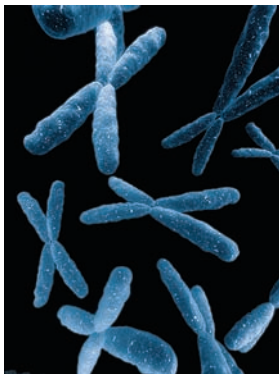
X-linked mental retardation (XLMR) refers to a spectrum of inherited conditions characterized by limitations in cognitive skills and development. Specific facial and body features generally distinguish affected individuals, including in some cases poor muscle tone, enlarged ears or vision deficiencies. The prevalence of XLMR in the general population is roughly 3 per 1,000, and accounts for more than 10 percent of all mental retardation.<sup>1</sup> “Nonsyndromic” X-linked mental retardation is inherited mental retardation without characteristics consistent with a known syndrome.

## X-linked or sex-linked inheritance.

Humans have a total of 46 chromosomes; they inherit half from the mother and half from the father.

Females have two copies of the “X” chromosome (XX), whereas males have one copy of the “X” and one copy of the “Y” chromosome (XY). The X and Y chromosomes do not necessarily carry genes for the same traits.

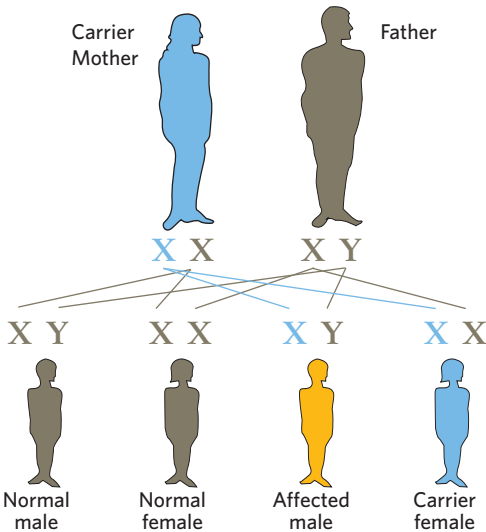
Disorders associated with an X-chromosome (called X-linked or sex-linked disorders) affect males more often than females, because males don't have the extra X that females do to act as a back-up (i.e., when there is an alteration in a gene on one X chromosome, females have another copy of that gene to compensate; males do not).



X-linked disorders are transmitted to male offspring by carrier mothers, who usually have mild or no symptoms. A carrier has an altered (mutated) gene on one of her X chromosomes and an unaltered (working) gene on the other.

Overall, there is a one in four chance for a female carrier to have a male child with symptoms (see illustration). The risk remains constant with each pregnancy. Sometimes it is only after giving birth to an affected son that a mother learns that she carries an X-linked condition.

## X-Linked Inheritance



In the above chart, the mother carries an X chromosome with the condition (**X**), but because she also has a healthy copy (**X**), she displays mild or no symptoms. There is a 50:50 chance that her offspring will inherit the affected chromosome (**X**). Daughters that inherit it will also be carriers (**XX**). Sons that inherit it will have the condition (**XY**).

## Testing for X-linked Disorders

Until recently, very few genetic diseases could be detected and treated early enough to prevent them; however, research on identifying X-linked disorders is progressing. Genes related to syndromic X-linked mental retardation have been identified, and currently are available to detect mutations in those genes.

On the other hand, genes related to nonsyndromic X-linked mental retardation have only been identified recently.<sup>2-12</sup> Multiple genes have been shown to be associated with nonsyndromic XLMR.<sup>2-12</sup> Those genes are: *ARX*, *DLG3*, *FACL4*, *FTSJ1*, *JARID1C*, *PBQP1*, *TM4SF2*, and *ZNF41*. Mutation will be found in an estimated 20 to 25 percent of patients with nonsyndromic XLMR. **CMDL has developed tests for detecting mutations related to nonsyndromic XLMR in these 8 genes.**

## Who should be tested for Nonsyndromic XLMR?

- Individuals with a diagnosis of nonsyndromic mental retardation, especially for those in whom fragile X disease and abnormal chromosomes have been ruled out
- Members of a family where a mutation in an affected male has been identified
- Expectant women identified as carriers of the mutation when the mutation has already been identified

*Genetic counseling is recommended prior to genetic testing.*

## Who does the testing for Nonsyndromic XLMR?

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

## How is the test performed?

A blood sample will be drawn from the individual to be tested. The samples sent to CMDL will be surveyed for genetic mutations in eight genes on the X chromosome. If prenatal testing is desired and a mutation has been identified in the family, amniocentesis or CVS samples are taken by your physician and sent in along with a blood sample from the mother.

## 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 Arc of the United States**

1010 Wayne Avenue, Suite 650

Silver Spring, MD 20910

**Phone:** 301-565-3842

**E-mail:** [Info@thearc.org](mailto:Info@thearc.org)

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

[www.TheArcPub.com](http://www.TheArcPub.com) (Publications)

### **American Association on Mental Retardation (AAMR)**

444 North Capitol Street NW, Suite #846

Washington DC 20001

**Phone:** 800-424-3688;

202-387-1968

**Fax:** 202-387-2193

**E-mail:** [aamr@access.digex.net](mailto:aamr@access.digex.net)

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

### **Mental Retardation Association of America, Inc (MRAA)**

211 East 300 South, Suite 212

Salt Lake City, Utah 84111

**Phone:** 801-328-1574

### **NICHCY**

P.O. Box 1492

Washington, DC 20013

**Phone:** 800-695-0285

**Fax:** 202-884-8441

**E-mail:** [nichcy@aed.org](mailto:nichcy@aed.org)

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

## References

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## 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 physician 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)  
1500 East Duarte Road  
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>