FRAGILE X SYNDROME

A 3-in-1 Medical Reference

A Bibliography and Dictionary
for Physicians, Patients,
and Genome Researchers

TO INTERNET REFERENCES

ICON Group International, Inc.

Fragile X Syndrome

A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers

James N. Parker, M.D.
and Philip M. Parker, Ph.D., Editors

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About the Editors

James N. Parker, M.D.

Dr. James N. Parker received his Bachelor of Science degree in Psychobiology from the University of California, Riverside and his M.D. from the University of California, San Diego. In addition to authoring numerous research publications, he has lectured at various academic institutions. Dr. Parker is the medical editor for health books by ICON Health Publications.

Philip M. Parker, Ph.D.

Philip M. Parker is the Chaired Professor of Management Science at INSEAD (Fontainebleau, France and Singapore). Dr. Parker has also been Professor at the University of California, San Diego and has taught courses at Harvard University, the Hong Kong University of Science and Technology, the Massachusetts Institute of Technology, Stanford University, and UCLA. Dr. Parker is the associate editor for ICON Health Publications.

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with fragile X syndrome is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about fragile X syndrome, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to fragile X syndrome, from the essentials to the most advanced areas of research. Special attention has been paid to present the genetic basis and pattern of inheritance of fragile X syndrome. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on fragile X syndrome. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to fragile X syndrome, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. We hope these resources will prove useful to the widest possible audience seeking information on fragile X syndrome.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/**.

CHAPTER 1. STUDIES ON FRAGILE X SYNDROME

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on fragile X syndrome. For those interested in basic information about fragile X syndrome, we begin with a condition summary published by the National Library of Medicine.

Genetics Home Reference

Genetics Home Reference (GHR) is the National Library of Medicine's Web site for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions. Here you can find a condition summary on fragile X syndrome that describes the major features of the condition, provides information about the condition's genetic basis, and explains its pattern of inheritance. In addition, a summary of the gene or chromosome related to fragile X syndrome is provided.[2]

The Genetics Home Reference has recently published the following summary for fragile X syndrome:

What Is Fragile X Syndrome?[3]

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and mental retardation. Usually males are more severely affected by this disorder than females. In addition to learning difficulties, affected males tend to be restless, fidgety, and inattentive. About one-third of males with fragile X also have autism, a developmental disorder that affects communication and social interaction.

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[2] This section has been adapted from the National Library of Medicine: **http://ghr.nlm.nih.gov/**.

[3] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/condition=fragilexsyndrome**.

Most males with fragile X have characteristic physical features that become more apparent with age. These features include a long and narrow face, large ears, prominent jaw and forehead, unusually flexible fingers, and enlarged testicles (macroorchidism) after puberty.

How Common Is Fragile X Syndrome?

Fragile X syndrome occurs in approximately 1 in 4,000 males and 1 in 8,000 females.

What Genes Are Related to Fragile X Syndrome?

Mutations in the **FMR1** (**http://ghr.nlm.nih.gov/gene=fmr1**) gene cause fragile X syndrome.

Nearly all cases of fragile X syndrome are caused by a mutation in which a DNA segment, known as the CGG triplet repeat, is expanded within the FMR1 gene. Normally, this DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormally expanded CGG segment inactivates (silences) the FMR1 gene, which prevents the gene from producing a protein called fragile X mental retardation protein. Loss or a shortage (deficiency) of this protein leads to the signs and symptoms of fragile X syndrome.

Men and women with 55 to 200 repeats of the CGG segment are said to have an FMR1 premutation. Most people with a premutation are intellectually normal. In some cases, however, individuals with a premutation have lower than normal amounts of the fragile X mental retardation protein and features of fragile X syndrome.

In women, the premutation can expand to more than 200 repeats in cells that develop into eggs. This means that women with the FMR1 premutation have an increased risk of having a child with fragile X syndrome. By contrast, the premutation CGG repeat in men remains a premutation as it is passed to the next generation.

In a small percentage of cases, other types of mutations cause fragile X syndrome. These mutations delete part or all of the FMR1 gene or change one of the building blocks (amino acids) used to make the fragile X mental retardation protein. As a result, no protein is produced, or the protein is disabled because its size or shape is altered.

How Do People Inherit Fragile X Syndrome?

This condition is inherited in an X-linked dominant pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. In most cases, males experience more severe symptoms of the disorder than females. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Where Can I Find Additional Information about Fragile X Syndrome?

You may find the following resources about fragile X syndrome helpful. These materials are written for the general public.

NIH Publications - National Institutes of Health

- National Center for Biotechnology Information: Genes and Disease:
  http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.ShowSection&rid=gnd.section.172
- National Institute of Child Health and Human Development:
  http://www.nichd.nih.gov/health/topics/fragile_x_syndrome.cfm

MedlinePlus - Health Information

- Encyclopedia: Fragile X syndrome:
  http://www.nlm.nih.gov/medlineplus/ency/article/001668.htm
- Health Topic: Fragile X Syndrome:
  http://www.nlm.nih.gov/medlineplus/fragilexsyndrome.html

Educational Resources - Information Pages

- American College of Medical Genetics Practice Guideline:
  http://www.acmg.net/resources/policies/FragileX_GIM_2005.pdf
- California Department of Developmental Services: fragile X syndrome:
  http://www.ddhealthinfo.org/ggrc/doc2.asp?ParentID=3169
- CDC fact sheet: FMR1 Gene and Fragile X Syndrome:
  http://www.cdc.gov/genomics/hugenet/factsheets/FS_FragileX.htm
- CDC HuGE Review: FMR1 and Fragile X Syndrome:
  http://www.cdc.gov/genomics/hugenet/reviews/FragileX.htm
- Centre for Genetics Education (Australia):
  http://www.genetics.com.au/factsheet/32.htm
- Emory University School of Medicine:
  http://www.genetics.emory.edu/docs/Fragile+X.pdf
- Fragile X Information Center, University of North Carolina at Chapel Hill:
  http://www.fpg.unc.edu/~fxic/
- Kennedy Krieger Institute:
  http://www.kennedykrieger.org/kki_diag.jsp?pid=1086
- Madisons Foundation:
  http://www.madisonsfoundation.org/content/3/1/display.asp?did=77
- NOAH: New York Online Access to Health:
  http://www.noah-health.org/en/genetic/conditions/fragilex/index.html
- Orphanet:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=908

- Public Health Genetics Unit (UK):
  http://www.phgu.org.uk/pages/info/diseases/fragilex.htm
- Stanford University:
  http://spnl.stanford.edu/disorders/fragilex.htm
- The Wellcome Trust:
  http://genome.wellcome.ac.uk/doc_WTD022302.html
- University of Michigan Health System:
  http://www.med.umich.edu/1libr/yourchild/fragilex.htm

Patient Support - for Patients and Families

- Carolina Fragile X Project:
  http://www.fpg.unc.edu/~fx/
- Conquer Fragile X Foundation:
  http://www.conquerfragilex.org/about.php
- FRAXA Research Foundation:
  http://www.fraxa.org
- March of Dimes:
  http://www.marchofdimes.com/pnhec/4439_9266.asp
- National Fragile X Foundation:
  http://www.fragilex.org/html/home.shtml
- National Organization for Rare Disorders (NORD):
  http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Fragile+X+Syndrome

Professional Resources

You may also be interested in these resources, which are designed for healthcare professionals and researchers.

- Gene Reviews - Clinical summary:
  http://www.genetests.org/query?dz=fragilex
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://ghr.nlm.nih.gov/condition=fragilexsyndrome/show/Gene+Tests;jsessionid=252503BA524741F34F577D9D0C09B8EF
- Genetic Tools - Teaching cases:
  http://www.genetests.org/servlet/access?fcn=y&filename=/tools/cases/fragilex-16/
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22fragile+x+syndrome%22?recruiting=fals
- **PubMed - Recent literature:**
  http://ghr.nlm.nih.gov/condition=fragilexsyndrome/show/PubMed;jsessionid=252503BA524741F34F577D9D0C09B8EFe
- OMIM - Genetic disorder catalog:
  http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=309550

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These sources were used to develop the Genetics Home Reference condition summary on fragile X syndrome.

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- Willemsen R, Oostra BA, Bassell GJ, Dictenberg J. The fragile X syndrome: from molecular genetics to neurobiology. Ment Retard Dev Disabil Res Rev. 2004;10(1):60-7. Review. PubMed citation

A summary of the gene related to fragile X syndrome is provided below:

What Is the Official Name of the FMR1 Gene?[4]

The official name of this gene is "fragile X mental retardation 1."

FMR1 is the gene's official symbol. The FMR1 gene is also known by other names, listed below.

[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=fmr1;jsessionid=252503BA524741F34F577D9D0C09B8EF**.

What Is the Normal Function of the FMR1 Gene?

The FMR1 gene provides instructions for making a protein called fragile X mental retardation 1, or FMRP. This protein is present in many tissues, especially in the brain and testes. In the brain, it may play a role in the development of connections (synapses) between nerve cells, where cell-to-cell communication occurs. The connections between nerve cells can change and adapt over time in response to experience (a characteristic called synaptic plasticity). FMRP may help regulate synaptic plasticity, which is important for learning and memory.

Researchers believe that FMRP acts as a shuttle within cells by transporting molecules called messenger RNA (mRNA), which contain information for making proteins. FMRP likely carries mRNA molecules from the nucleus to areas of the cell where proteins are assembled. Some of these mRNA molecules may be important for the function of nerve cells.

One region of the FMR1 gene contains a particular DNA segment known as a CGG trinucleotide repeat, so called because this segment of three DNA building blocks (bases) is repeated multiple times within the gene. In most people, the number of CGG repeats ranges from fewer than 10 to about 40.

What Conditions Are Related to the FMR1 Gene?

Fragile X Syndrome - Caused by Mutations in the FMR1 Gene

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the FMR1 gene. In these cases, CGG is abnormally repeated from 200 to more than 1,000 times, which makes this region of the gene unstable. As a result, the FMR1 gene is turned off (silenced) and does not make any protein. Without adequate FMRP, severe learning problems, mental retardation, and the other features of fragile X syndrome can develop.

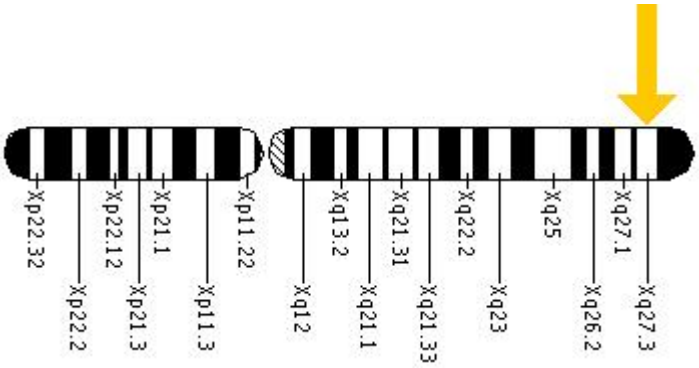
Other Disorders - Increased Risk from Variations of the FMR1 Gene

Almost all cases of fragile X syndrome are caused by an expansion of the CGG trinucleotide repeat in the FMR1 gene. In these cases, CGG is abnormally repeated from 200 to more than 1,000 times, which makes this region of the gene unstable. As a result, the FMR1 gene is turned off (silenced) and does not make any protein. Without adequate FMRP, severe learning problems, mental retardation, and the other features of fragile X syndrome can develop.

Where Is the FMR1 Gene Located?

Cytogenetic Location: Xq27.3

Molecular Location on the X chromosome: base pairs 146,801,200 to 146,840,302



The FMR1 gene is located on the long (q) arm of the X chromosome at position 27.3.

More precisely, the FMR1 gene is located from base pair 146,801,200 to base pair 146,840,302 on the X chromosome.

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These sources were used to develop the Genetics Home Reference gene summary on the FMR1 gene.

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Federally Funded Research on Fragile X Syndrome

The U.S. Government supports a variety of research studies relating to fragile X syndrome. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[5]

CRISP (Computerized Retrieval of Information on Scientific Projects)

CRISP is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions. Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to fragile X syndrome.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore fragile X syndrome. The following is typical of the type of information found when searching the CRISP database for fragile X syndrome:

- **Project Title: 10TH INTERNATIONAL FRAGILE X CONFERENCE**

  Principal Investigator & Institution: Miller, Robert Michael.; National Fragile X Foundation 1615 Bonanza St., Ste 320 Walnut Creek, Ca 94596

  Timing: Fiscal Year 2006; Project Start 14-JUN-2006; Project End 13-DEC-2006

  Summary: (Provided by the Applicant): 10th International Fragile X Conference: The National Fragile X Foundation's 10th International Fragile X Conference in Atlanta, Georgia, at the OMNI Hotel - CNN Center, July 19-23, 2006, will bring together the world's leading researchers in molecular biology and genetics as well as leading clinicians and treatment specialists, selected by its Scientific and Clinical Advisory Committee, with hundreds of parents, extended family members and students engaged in research training. Both scientific and family-friendly sessions covering the three

[5] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

conditions resulting from the fragile X gene mutation will be addressed: **fragile X syndrome;** fragile X associated tremor ataxia syndrome; fragile X related premature ovarian failure. Keynote presentations, breakout session lectures, research abstract sessions, panels and posters will present the latest knowledge regarding the underlying mechanisms for the fragile X related conditions, plus evidence-based medical, therapeutic and educational interventions. The conference will benefit multiple disciplines including those engaged in clinical practice, epidemiology and delivery system organization. The National Fragile X Foundation will publish and disseminate the results in conference proceedings as well as other formats and utilize the recommendations as the basis for advancing the research and treatment fields.

- **Project Title: 16TH BIENNIAL MEETING OF THE INTERNATIONAL SOCIETY FOR DEVELOPMENTAL NEUROBIOLOGY**

  Principal Investigator & Institution: Levitt, Pat R.; Director; Pharmacology; Vanderbilt University Medical Center Nashville, Tn 372036869

  Timing: Fiscal Year 2006; Project Start 01-JUL-2006; Project End 30-JUN-2007

  Summary: (provided by applicant): The 2006 International Society for Developmental Neuroscience (ISDN) meeting will take place in Banff, Canada in August, 2006, and represents the biannual meeting of the ISDN, an international organization based in the United States. This meeting is a premier developmental neuroscience meeting open to all, which usually attracts 400-500 international participants. The meeting itself has three primary goals. First, to disseminate information and unpublished data in both the development and neurological/psychiatric disease fields, and to promote enhanced links between these different communities. Second, to foster interactions and collaborations amongst scientists worldwide. Third, to provide a forum for interactions between students and postdoctoral fellows and more established senior scientists. In this regard, the meeting is very cost-attractive for trainees, and as a consequence, this group usually comprises approximately half of the attendees. The program for ISDN 2006 has been established, and is comprised of 55 scientists who are both well known and at more junior stages of their careers (see attached program; all of the speakers are confirmed). Five of six plenary speakers (including Nobel prize winner Linda Buck) and 30 of the symposium chairs/speakers are based in the USA, and 10 of the speakers are women. The program spans many areas of developmental neuroscience, as well as psychiatric and nervous system conditions and diseases that include autism, **Fragile X Syndrome,** perinatal stroke, and brain tumors. The meeting runs from the evening of Aug. 24th to the afternoon of Aug. 28th, and is comprised of (a) two hour-long plenary lectures per day, (b) two sets of two concurrent symposia, which include both invited speakers and short oral presentations chosen from the abstracts, and (c) poster sessions. Project Narrative (Relevance): Mental health and neurological disabilities currently represent major unmet medical needs in our society. Many mental health disorders, including autism and schizophrenia, and many neurological disorders, such as mental retardation and cerebral palsy, arise developmentally. In this meeting, we hope to make a major contribution to resolving these medical problems by bringing together scientists interested in development of the nervous system with those interested in these major public health problems. Such interactions are essential if we are to attack these problems in a cohesive, rational fashion.