

genes that cause asthma in Hutterites may or may not be relevant to other groups with asthma. Thus the scientist must weigh the advantages of performing genetic studies in small, historically isolated populations with the potential disadvantage of being unable to eventually generalize the studies' results. SEE ALSO GENETIC DRIFT; HARDY-WEINBERG EQUILIBRIUM; INBREEDING; LINKAGE AND RECOMBINATION; MAPPING; POPULATION BOTTLENECK; POPULATION GENETICS; TAY-SACHS DISEASE.

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## Fragile X Syndrome

Fragile X syndrome is one of the most common causes of inherited mental retardation. Individuals with fragile X syndrome can exhibit moderate to severe mental retardation. Additional characteristics may include autistic-like behavior, hyperactivity, mitral valve prolapse (a heart valve defect), a large head circumference, a long face with a prominent forehead and jaw, protruding ears, flat feet, hyper-extensive joints ("double-jointedness"), and, in males, enlarged testicles. Fragile X syndrome is not restricted to any ethnic group. It was the first of the so-called triplet repeat diseases to be discovered, and study of it has led to a growing understanding of DNA instability and its role in disease.

### Discovery of the Syndrome

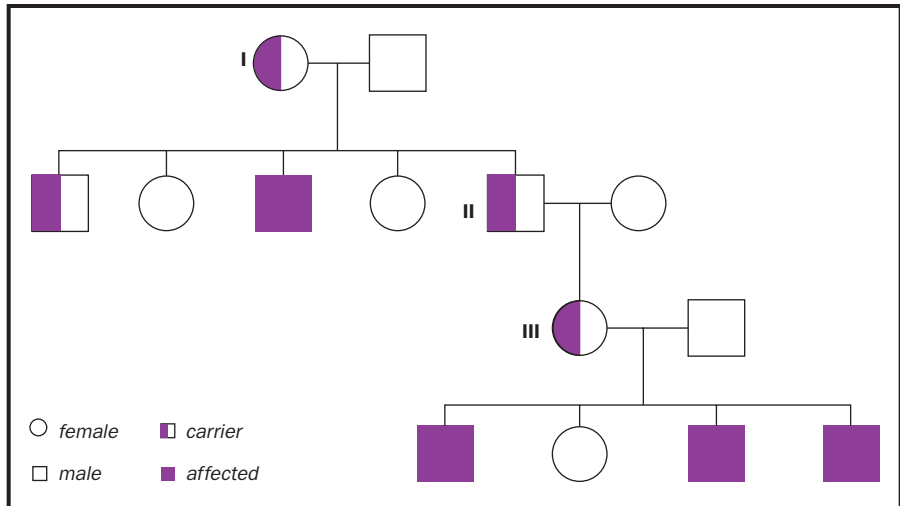
The first family with fragile X syndrome was described by J. Purdon Martin and Julia Bell in 1943. This family had eleven severely retarded males, and the inheritance pattern of the mental retardation appeared to be X-linked. X-linked traits are inherited on the X chromosome and are more common in males, who have only one X chromosome, than in females, who have two.

In 1969, in a different family, Herbert Lubs observed a constriction near the end of the long, or q, arm of the X chromosome in four mentally retarded males and two of their mentally normal female relatives. This constriction made the X chromosome appear to be broken. Hence the name "fragile X."

For years, little attention was paid to Lubs's finding. Renewed interest in the observation emerged in the late 1970s, when additional families were identified with mental retardation and the same chromosome abnormality, or fragile site. Moreover, in 1977 Grant Sutherland discovered that the ability to detect this fragile site was dependent on the chemicals used to study patients' chromosomes. Sutherland's crucial observation helped develop the



The Sherman Paradox. The daughter (III) of an unaffected male carrier (II) is more likely to have affected offspring than the mother (I) of the male carrier is.



first diagnostic test for fragile X syndrome. Using this knowledge, investigators reexamined chromosomes from the original fragile X family described in 1943 and demonstrated that, indeed, affected individuals in this family carried the characteristic fragile site.

### Puzzling Inheritance Pattern

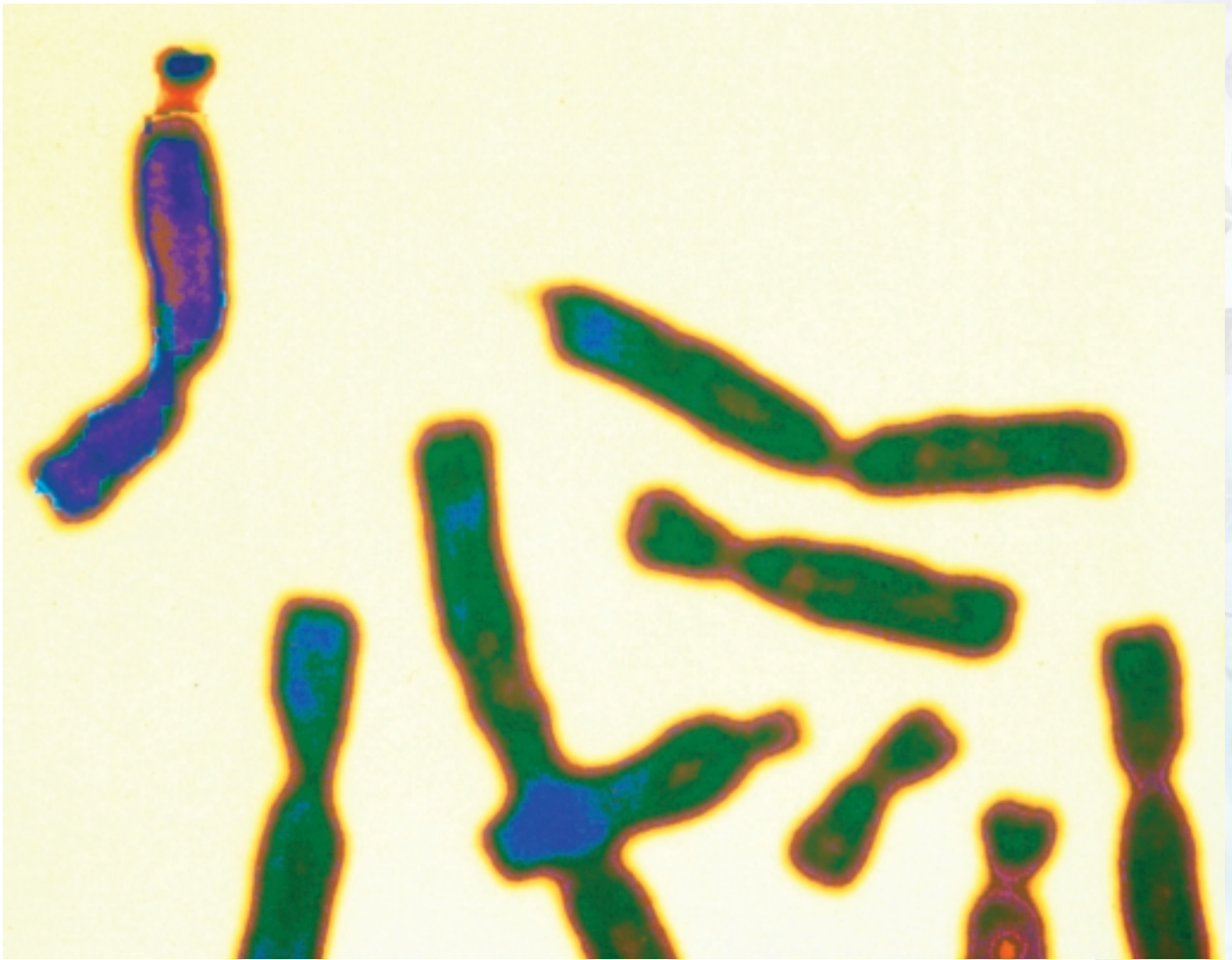
While the location of this fragile site established that fragile X syndrome was indeed X-linked, inheritance of this disorder was clearly not typical of other X-linked disorders. At first, it was believed that fragile X syndrome was an X-linked recessive genetic disorder. However, there were many observations inconsistent with this inheritance pattern.

If the disorder was truly inherited in an X-linked recessive manner, **heterozygote** carrier women would not display any characteristics of the syndrome, and all carrier males would. But there were reports of affected females, and of males who carried the fragile site but were unaffected. It was particularly difficult to reconcile that some male carriers could be so severely affected while others were completely unaffected.

Because of these puzzling observations, in 1985 Stephanie Sherman and her colleagues studied the inheritance pattern of fragile X syndrome more closely. They demonstrated that the risk of expressing mental retardation was dependent on the individual's position in the pedigree, with risk increasing in later generations. The daughter of an unaffected male carrier was more likely to have affected offspring than the mother of the unaffected male carrier was: something had changed on the X chromosome over the two generations. This observation became known as the "Sherman paradox" and was crucial to understanding the genetic mutation that causes fragile X syndrome.

To explain the unusual inheritance pattern, Sherman, her colleagues, and several other scientists hypothesized that the alleged gene for fragile X syndrome was mutated in a two-step process. They proposed that the first mutation caused a "premutation" state that produced no clinical symptoms, and that a second mutation was required to convert the premutation to a "full mutation" form that was associated with the characteristic symptoms

**heterozygote** an individual whose genetic information contains two different forms (alleles) of a particular gene



of fragile X syndrome. Moreover, conversion from a premutation to a full mutation was proposed to occur only when the premutation was transmitted from a carrier female.

### An Expanding Gene

In 1991 an international team of scientists identified the gene and mutation that causes fragile X syndrome. They found that in families with fragile X syndrome, there is a piece of the *FMRI* gene, called a CGG repeat, which is abnormally expanded.

In the general population, the repeat length can range from about six to fifty-four copies of the CGG, and the repeat is stable, or is passed from parent to child without change. In fragile X families, the premutation form of the repeat contains between fifty and two hundred copies of the CGG repeat, and the repeat is unstable.

Premutation alleles can expand to full mutation **alleles** (with more than two hundred copies of the CGG repeat) by transmission of the premutation from a mother to her child. A woman's risk of having a child with the

The fragile X chromosome is stained with purple dye. The affected chromosome is described as "fragile" because of the extra constriction near the end of the long arm of the X chromosome. Mental disability presents in 80 percent of carrier males, and 50 percent of carrier females.

**alleles** particular forms of genes

full mutation correlates to her own repeat size. The larger her premutation, the more she risks having a child who carries the full mutation.

The CGG repeat is usually interrupted by a single AGG trinucleotide every ten CGG repeats, but this can vary from individual to individual. Because premutation alleles have fewer AGG interruptions compared with normal-size *FMR1* alleles, it is believed that the AGG interruptions are important for stability of the CGG repeat.

Individuals with a premutation do not express the clinical symptoms associated with fragile X syndrome, although it has been reported that premutation carrier females can experience premature ovarian failure. Individuals who carry the full mutation can express symptoms of fragile X syndrome because they are missing the protein produced by the *FMR1* gene. Males with a full mutation always exhibit some symptoms of the disorder. Due to X inactivation, females with a full mutation may or may not express symptoms.

Although there is currently no cure for fragile X syndrome, scientists are making great progress in understanding the biology of the disorder. In the mid- to late 1990s, Stephen Warren and colleagues determined that the *FMR1* gene product, named FMRP, is an RNA-binding protein that shuttles in and out of the nucleus and is involved in binding various messenger RNAs. Moreover, scientists successfully developed mice that lack the *FMR1* gene, which will greatly aid research. Symptoms of fragile X mice include learning disabilities, hyperactivity, and, in males, enlarged testicles. Prevailing hypotheses about FMRP suggest that this protein is involved in forming neural connections in the developing brain.

The identification of *FMR1* and the expanded CGG repeats was a landmark discovery in human genetics because it established a novel class of human genetic mutations, trinucleotide (or triplet) repeat expansions. Since the discovery of *FMR1* and the expanding CGG repeats, scientists have identified more than ten other human genetic disorders that are caused by expansions of trinucleotide repeats, including disorders such as Huntington's disease and myotonic muscular dystrophy. SEE ALSO INHERITANCE PATTERNS; INTELLIGENCE; MOSAICISM; TRIPLET REPEAT DISEASE; X CHROMOSOME.

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#### Internet Resource

*Online Mendelian Inheritance in Man: Fragile Site Mental Retardation 1; FMR1*. Johns Hopkins University and National Center for Biotechnology Information. <<http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?309550>>.

## Fruit Fly: *Drosophila*

*Drosophila melanogaster*, a common fruit fly, was one of the first model organisms used in genetic research, and continues to be one of the most important. Thomas Hunt Morgan (1866–1945) developed *Drosophila* as a model system in 1909. Morgan, along with his students, Calvin Bridges, Alfred