# FEMALES WITH FRAGILE X SYNDROME: AN OVERVIEW

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Many articles have been written on females with Fragile X syndrome. The purpose of this article is to summarize some of what we know about females who carry the fragile X gene (or the FMR-1 gene).

Early articles on fragile X syndrome reported that up to 30% of mothers of children with fragile X syndrome were mentally retarded. In those days there were no DNA studies, and chromosome studies were not accurate enough to detect all females with fragile X syndrome so the information was limited. The fact that so many mothers of children with fragile X syndrome were mentally retarded may not be surprising to lay people but it was to scientists because females with fragile X syndrome have two X chromosomes and only one of the chromosomes usually have an abnormal gene. Many scientists expected that the chromosome that did not carry the fragile X gene would have offered more protection to these women. This happens to be true for other genetic disorders that are associated with abnormalities of the X chromosome, like hemophilia. For some of us in medicine who have worked with other organ systems besides the brain, this information was very surprising, too -- after all if you lose a kidney you still function well because you have another kidney. If you lose a lobe of a lung, there are others. Clearly the systems in the brain that are affected by fragile X are not as expendable and a high percentage of women with fragile X syndrome have cognitive problems because they do not have two normal FMR1 genes. Why some women who had children with fragile X syndrome seemed perfectly fine while others were mentally retarded was impossible to comprehend back in the early 1980s.

In the mid-eighties many articles were published on the emotional problems of women with fragile X syndrome. In some ways this information was similar to the information that was being reported on males with the fragile X syndrome except that the emotional problems described in females were not quite as severe. For example, many articles describe young boys as making poor eye contact. While we still do not know if this is because they are shy or anxious or because they have a hard time looking at complex human faces, we do know that their eye contact can be very poor. Articles on females with fragile X often describe them as being shy which may be a less severe version of the same problem as in the male. Other emotional problems described in females are fairly serious and some females are prone to depression, anxiety, and Attention Deficit Hyperactivity Disorder. Occasionally a female with fragile X syndrome may have autism. This information is important for many reasons. Emotional problems in individuals with fragile X syndrome may be just as important as developmental delays and just as debilitating. Some of these problems may be helped with the assistance of medication or therapy and females with fragile X syndrome should know to get help when they need it. Finally, since the same gene is involved in the female with fragile X syndrome as the male, we may learn more about the spectrum of the behaviors associated with fragile X syndrome. For example, is shyness and anxiety in a girl with fragile X syndrome in the same spectrum of behavior as the autism that we often see in males with fragile X syndrome? I don't know the answer to that question, but issues like this will surely be addressed by researchers of the future.

Other articles in the mid 1980s that were written on females with fragile X syndrome helped us understand more about the problems of females who were not mentally retarded. One of the prominent findings was that they tended to have much more difficulty with learning mathematics than with learning to read and write. Some adult women with fragile X syndrome describe extreme difficulty managing a checkbook but they may be avid readers. Many girls with fragile X syndrome may not be mentally retarded or learning disabled, but they may have difficulty with many areas of learning. These females would probably be described by the school systems as slow learners but they might not qualify for any special education services. Our experience has

been that once the diagnosis of fragile X syndrome is made, it is possible to obtain special education services for these girls because they have a neurological reason for their learning problems. The strange sounding label that we often use in North Carolina to obtain services is a label called "Other Health Impaired."

Other research studies have been sophisticated and describe difficulties that some women have with tasks that involve using the frontal lobes of the brain. Problems with repetitive thinking or difficulty with abstract concept formation may exist (Mazzocco et al. 1992). In these studies, women with fragile X syndrome were found to have real strengths, as well as weaknesses, and these strengths included enhanced verbal short term and long term memory.

In the early 1990s, the gene that causes fragile X syndrome was found and DNA studies became available. The genetic abnormality that causes fragile X had never been described before. Since 1991, this type of genetic abnormality has been described as a cause for several other medical conditions as well. What happens is that part of the gene that causes fragile X syndrome expands as the gene is passed down through many generations. This gene causes little or no problems until it reaches a certain size and becomes methylated. At that stage the gene loses function. This genetic defect partially explains the variability in females with fragile X syndrome. Females with small expansions and no methylation of the gene are unlikely to show any or many problems. Serious problems occur among the females who have a large expansion and methylation of the gene.

During the past couple of years, researchers also began to study the protein produced by the fragile X gene. It is often referred to as FMRP. Information is still very limited about this protein. We do know, however, that each brain cell only utilizes one X chromosome while the other one is more or less dormant. If the X chromosome that is active in the brain cell is the X chromosome that carries the abnormal fragile X gene, that brain cell will not produce the protein that it is supposed to make. While the neighboring cells may be producing FMRP well, this protein is unable to travel to cells that are unable to produce protein (nondiffusable protein). Therefore, some brain cells will produce normal protein and other cells will make no protein. Since the brain consists of nerve cells that interconnect with one another, the brain cells that produce protein are both limited in number and must interact with brain cells that produce no protein. We know this failure to produce adequate FMRP within cells results in developmental disabilities, but we still do not know what is happening within each cell.

There are still many concerns and questions about females with fragile X syndrome. While females with an incomplete mutation of the fragile X gene seem to have good ability to function, there is considerable variability among females with the full mutation. For example, at the recent international meeting in Albuquerque, New Mexico, Dr. Michelle Mazzocco described identical twins with the full mutation. One twin had an average IQ but she had a few subtle difficulties on cognitive testing that were consistent with the fragile X syndrome. Her identical twin sister was mentally retarded. While it is possible that unrelated problems caused these differences in IQ, it is more likely that this variability will be seen in identical twins. As a clinician, I look forward to reading about studies that will provide us with insight into why this variability occurs.

Hopefully we will all learn much more about fragile X syndrome in the next few years, many questions about fragile X syndrome will be answered, and treatments for specific problems will be initiated.

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