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# Is Fragile X Syndrome Protective For Subsequent Cancers? A review of literature

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## Abstract

Fragile X Syndrome (FXS) is a key inherited basis of intellectual disability (ID) . It initiated by an expansion of over 200 CGG (cytosine-guanine-guanine) repeats in the 5 untranslated region (UTR) of the fragile X mental retardation 1 (FMR1) gene and consequently, the lack of fragile X mental retardation protein (FMRP) in the neurons causes developmental abnormalities in the brain.

Although one of the largest studies on cancer risk in patient with ID demonstrated increased risk of leukemia and gastrointestinal cancers, few existing articles in FXS tell us about decrease of cancer in these patients.

everyday many mechanism are described involving in FMR1 mRNA and FMRP interaction with other genes, and new information about cancer oncogenesis of FXS. This review summarizes the available articles and provides an overview of some databases contain data pertinent to cancer in this field.

**Keywords:** Fragile X syndrome • Cancer

## Introduction

Fragile X syndrome is an X-linked cause of intellectual disability characterized by unstable CGG trinucleotide repeat expansions. Herbert Lubs first described the disorder in 1969, when he noted the correlation between retardation and a “marker X”in affected family members. The Fragile X Mental Retardation 1 (FMR1, NM_002024.4) gene was cloned and sequenced in 1991. It is expressed during early embryonic development. Fragile X Mental Retardation Protein (FMRP) is a RNA-binding protein with broad range of functions, associated in regulating transport, stability and translation of its mRNA ligands. As the name implies fragile sites are specific chromosomal loci that are susceptible to gaps, constrictions, breaks and eventually cancer. During the last 50 years, there have been significant improvements in life expectancy among people with intellectual disability (ID), and subsequently their incidence of age-associated diseases, such as cancer, is rising [1]. In different studies, the prevalence of cancers in FXS patients has been considered both with the ID approach and the trinucleotide repeat. The results are very heterogenous. This review summarizes the available articles and provides an overview of some databases contain data pertinent to cancer in this field [2].

## Methods

FMR1gene (NG_007529.2) on chromosome Xq27 is the only gene so far characterized in this region is responsible for fragile-X syndrome. Over half of cancer-specific translocations containing breakpoints within fragile sites. Depending on their frequency, there are two types of fragile sites, common and rare. Common fragile sites, as part of normal chromosome structure, occur in nearly all individuals. They are sensitive to replication stress, and have been a major focus of cancer research. Rare fragile sites are often composed of nucleotide repeats and are inherited. Unlike common form, they are mostly susceptible to spontaneous breakage during replication and found in less 5% of the human population. Clinically, one of the most important rare fragile site is folate sensitive tandem CGG microsatellite repeats, which are associated with the fragile X syndrome. Increased instability in human cells at fragile sites are often associated with other chromosomal abnormality such as deletions, translocations or rearrangements, and these pose a hypothetical risk of tumorigenesis [3,4]. This implicates that FXS could be associated with an increase in cancer susceptibility, as in the cases of fanconi anemia with heritable fragility. The number of CGG repeats located in the 5(UTR) untranslated region of the FMR1

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is associated with a constellation of disorders that can affect patients both young and old. Individuals with full mutations (>200 CGG repeats) often present classic FXS, Permutation carriers (55-200 or 59-200 CGG) are known to be at risk for fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X associated tremor and ataxia syndrome (FXTAS) (10).It has been highly expressed in brain, testis, placenta, lung and kidney tissue while low expression has been found in liver, skeletal muscle and pancreatic tissue.Cancer, autism, parkinson's disease, immune disease, schizophrenia, bipolar disorder, major depressive disorder are associate with FMR1 gen in addition to fragile X syndrome. Macroorchidism is a hallmark of fragile X syndrome, Adult male patients carrying the full fragile X repeat expansion produce sperm that carry a contracted premutation but never the full expansion implying that sperms carrying a full mutation are selected against at a premeiotic stage, allowing only those with a contracted FMR1 repeat to reach maturity [5]. It is now recognized that FMR1 premutation carriers are at risk to develop a range of neurological, psychiatric, and immune-mediated disorders during adulthood. The ability of the CGG repeat, to form both quadruplex and hairpin secondary structures in fragile sites presents a significant block to replication both in vitro and in vivo and increase chromosomal instability.

The role of repeat expansion size as a key determinant of cancer risk is not fully clear. Nucleotide repeat expansions are longer in myotonic muscular dystrophy (MMD) patients compared with huntington disease or fragile X patients. investigation on 104 patients with MMD from the Swedish and Danish patient registries revealed they were at increased risk of cancer both overall and for selected anatomic sites. In contrast, study on 372 consecutive patients with Huntington disease (HD) and spinocerebellar ataxia (SCA) in France demonstrated a decreased cancer rate in PolyQ diseases despite high incidence of risk factors. Intriguingly, skin cancer incidence was higher, suggesting a crosstalk between neurodegeneration and skin tumorigenesis. study on 147 Italian women, free of cancer or affected by breast and/or ovarian cancer, suggested that FMR1 CGG repeat test is not a candidate prescreening tool for identifying women with a high probability of being carriers of BRCA mutations [6]. Obviously these figures will be affected by the overall age range in the study cohort and cancer types, and it is probably not possible to make a firm comment on either until a suitably stratified and diagnosed population is subject to study. A comprehensive review of FMR1gene and cancer type is not as yet available.

## Literature review

**FMRP and cancer:** FMRP, as multipotential factor, is a component of messenger ribonucleoproteins (mRNPs). These proteins contain two types of RNA- binding motif: two ribonucleoprotein K homology domains (KH domains) and a cluster of arginine and glycine residues (the RGG box) RGG sequences are substrate recognition sites for protein arginine methyltransferases (PRMTs). These motifs and the proteins that harbor them have been linked to several human diseases, such as cancer and neurological disorders. Ewing sarcoma, leukemia, Amyotrophic lateral sclerosis, autism, spinal muscular atrophy also has this property.FMRP is widely expressed in all fetal and adult tissues, suggest that, in addition to its effects in brain and testis , it may have important roles in other organs.Although FMRP is predominantly localized in the cytoplasm , a very small portion ( 4%) of FMRP is reported to be present in the nucleus, where its function has remained largely unknown.Full mutations of FMR1 gene, result a hypermethylated state of the FMR1 promoter, with consequent inhibition of FMR1 transcription and loss or heavy reduction of the FMRP product . Therefore, the FXS phenotype is a direct consequence of the absence of FMRP. Very recently FMRP was also identified as a chromatin-binding protein that functions in the DNA damage response, suggesting that nuclear FMRP could regulate genomic stability at the chromatin interface. In the absence of FMRP, the accumulation of DNA insults is associated with multiple diseases, from neurodegenerative disorders to cancers. Hundreds of FMRP putative target mRNAs (>1,000 in brain and>6,000 in nonneuronal cells) were identified. Some are tumor suppressor or proto-oncogen . FMRP can regulate mRNAs half-life, either by favoring or preventing mRNA decay Inaccurate mRNA processing of some genes in individuals with FXS may result in clinical manifestations of disease or affect regulatory proteins within biochemical networks affecting the genome-wide transcription. Furthermore, evidence that FMRP exhibits an inhibitory activity within the translation complex has been highlighted. FMRP appears to be also linked to micro-RNAs, as a class of short (∼22 nucleotide), single-stranded non-coding RNAs, adding more complexity to the role that it plays in regulating the RNA transport and translation. The regions encoding some miRNAs have been found to be located in cancer-associated genomic regions or at fragile genomic sites. Human study of Alvarez-Mora demonstrated down regulation of miR-574-3p in fragile X-associated tremor/ataxia syndrome, with significant deregulation in both deep sequencing- based technologies and microarray technology and it was confirmed by RT-qPCR demonstrated the aberrant expression of miR-574-3p in gastric cancer. Functional study revealed that cell proliferation, migration and invasion were significantly inhibited in miR-574-3p-transfected gastric cancer SGC7901 cells.

There are several studies on human cancer, murine cell line and drosophila to describe mechanism involving in FMR1 mRNA and FMRP interacrion with other genes. Drosophila has proved to be an excellent model for the dissection of FMRP-regulated biological pathways. Some tumors in the testes, brain, lungs, kidneys or hematolymphoid system in persons with FXS have been reported in case studies, where FMRP is expressed in normal people. It could suggest that FMRP might have tumor suppressing properties. Also, the occurrence of some other rare tumors in persons with FXS have been suspected to be more than coincidental. study showed that, the tendency for decreased cancer risk may be related to a below-normal level of mRNA in methylated full mutation FXS carriers, if there is a direct relationship between mRNA levels and cyclic adenosine monophosphate (cAMP) response-element binding protein CREB expression. CREB, which seems to have an important role in oncogenesis, is known to be actively involved in FMR1 transcriptional activity. This also indicates that there could be an increased cancer risk among the premutation carriers, because the mRNA levels are highest among them. experience on 10 males revealed that decreased expression of WNT7A gene as a ligand of the b-catenin pathway, as well as c-Myc, c-Jun, cyclin-D and PPARd genes as target of the b-catenin pathway in FXS patients. Results suggest that this diminished expression of the WNT7A gene may be related to a supposed protection of FXS patients to develop cancer. found that FMRP and FMR1 mRNA levels correlate with prognostic indicators of aggressive breast cancer, lung metastases probability and triple

negative breast cancer (TNBC). They establish that FMRP overexpression in murine breast primary tumors enhances lung metastasis while its reduction has the opposite effect regulating cell spreading and invasion. FMRP binds mRNAs involved in epithelial mesenchymal transition (EMT) and invasion including E-cadherin and Vimentin mRNAs, hallmarks of EMT and cancer progression. Upregulation of Ras proto-oncogen signaling is a common cause of cancer. Surprisingly, work on cultured slices and intact brains of wild-type and FMR1 knock-out mice suggest aberrant Ras signaling as a novel mechanism for fragile X syndrome and indicate manipulating Ras-PI3K- PKB signaling to be a potentially effective approach for treating patients with fragile X syndrome. It was also observed that individuals with fragile X syndrome may be at increased risk of developing cancers, especially the unusual types such as Ewing's sarcoma, seminoma, sperm granuloma, malignant ganglioma. Consequently, FMRP, is overexpressed in hepatocellular carcinoma cells. Next studies by demonstrated that chromosomal translocations in Ewing's sarcoma often lead to the deletion of the three EWS C-terminal RGG/RG motifs and, as a result, the absence of RGG motifs up regulates its oncogenic potential Destouches found that in hepatocarcinoma cell surface nucleolin expression has been found to be elevated. The cell surface nucleolin, via its RGG/ RG motif, acts as an attachment factor for various growth factors.

It would be expected that the emergence of the functional and biochemical properties of the RGG/RG motif will contribute to its role in infrequent cancer states in FXS. There are evidences both in favor of and in contrast to the association of FMRP expression level with cancer. It seems that epidemiological studies are parallel with increased cancers incidence and molecular studies are in favor of low expression of oncogenes and high expression of tumor suppressor regulated by FMRP.

## Fragile X syndrome and cancers

In the general population, age has been described as the most important descriptive determinant of cancer. The age-standardised incidence of all cancers in people with ID was not significantly different from the general population. Information on 9409 individuals registered with the Disability Services Commission of Western Australia by Sullivan was demonstrated that, males with ID were observed to have a significantly increased risk of leukemia, brain and stomach cancers, and a reduced risk of prostate cancer, while leukemia, corpus uteri and colorectal cancers were significantly higher in females (5).In general population, for the year 2012, the World Health Organization (WHO) estimated that there were about 14.1 million new cancer cases worldwide, leading to 8.2 million deaths (approximately 22,500 deaths per day). Moreover, due to increasing population size, by the year 2035 the WHO projects that the numbers of cancer cases and deaths worldwide will increase to 24 million and 14.6 million, respectively (based on current mortality rates). Prostate, lung, colorectal, cancer are the most common types of cancer in men, while breast, lung, colorectal cancer are the most common among women. Major cancer risk factors obtained by epidemiologic studies categorized into two groups: environmental conditions that are potentially preventable and genetic conditions. In addition to chemical carcinogens (tobacco, alcohol, toxins), Radiation carcinogenesis (UV rays of sunlight, radiographs, nuclear fission, radionuclides) and viral and microbial oncogenesis (HTLV1,HPV,EBV, Helicobacter pylori) cited a number of studies where findings specific to this client group identify an increased cancer incidence amongst a range of genetic conditions. These include Down syndrome, Cowden syndrome, Fragile X ,Prader-Willi and Angelman syndromes. However, in the people with ID, the incidence of cancer is poorly documented and thus reports vary broadly from between 5% and 18%. Fragile X patients have been reported by Schultz-Pedersen et al to display a lower incidence of cancer (28%) studied on mortality of 781 affected or carriers for the fragile X syndrome. The most common causes of death were cardiovascular, cerebrovascular and malignant disease similar to those in the general population. The behavioral factors leading to limited exposure to carcinogens may have a major role in decreased cancer risk, but possible genetic mechanisms that protect against malignant transformation cannot be ruled out There is a complex links between genetic disease and cancer. Review of the literature from population based studies and case reports have suggested that FXS patients could be at decreased risk of cancers. However, the difference was not statistically significant. The most comprehensive cumulative report of tumors in FXS obtained From 1988 to 2013 they collected all case reports and case series of tumor associated to FXS publidhed in valid journals.The frequency of reported gastrointestinal tract (from lip to rectum) were 11/44 (25%), genitourinary tumors 9/44 (22%) and nervous system 8/44 (18%) in these patients is high, far exceeding that seen in the general population. However, the rate of the most common malignancy in men, prostate, lung and colorectal were 3/44 (6.8%) and 2/44 (4.5%) and 1/44 (2.3%) respectively (50). That is significantly less than expected estimated cancer incidence by site in normal population (21%.14% and 8%) respectively. The male to female ratio was 27/17(1.58 to 1) and female incidence of the three most common cancer breast, lung, colorectal were 3/44(6.8%),2/44 (4.5%), 1/44 (2.3%) respectively in comparison with normal population (29%.13% and 8%). Age rang in male and female was (1.5 to 81 year) and (neonate to 73 year) respectively.

We continued their way in data gathering on related articles from 2010 to the end of July 2020 with five cases summaries in below table.

| Case | Researcher(s) | age | Sex | Diagnosis | Year | Ref. Number |
|---|---|---|---|---|---|---|
| 1 | Agustini Utari | ≥ 40 years | Male | Adenocarcinoma of the testicle | 2010 | 51 |
| 2 | Agustini Utari | ≥ 40 years | Male | Malignant liver cancer (did not have a pathological diagnosis) | 2010 | 51 |
| 3 | C. A. Hoeffer | 64 | Male | Liver neoplasm (metastasis to brain) | 2012 | 52 |
| 4 | D. T. Collins | 31 | Male | Acute lympho | 2015 | 53 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | blastic leukemia | | |
| 5 | Lesage, Candice | 32 | Male | Melanoma | 2017 | 54 |

Higher prevalence of disease and subsequent cancer in men is due to X-dependent nature of disease, the fewer cases of women carrying or suffering from syndrome may not be significantly different from normal population. In recent decade, Noncoding RNSs opened new window for us in the era of cancer occurrence mechanisms.

Murmann worked on HeyA8 (ovarian) and A549 (lung) cancer cells in friedreich's ataxia, fragile X tremor ataxia syndrome and fragile X mental retardation in addition to huntington's disease to test whether trinucleotide repeat (TNR) disease-derived sequences were toxic to cancer cells when introduced as small interfering RNA (siRNAs) or not. Among the four tested TNR siRNA duplexes two were super toxic to both cell lines, and two showed no toxicity. CAG/CUG family of related TNRs are the most toxic to both human and mouse cancer cells. And siCAG/CUG TNR-based siRNAs induce cell death in vitro in all tested cancer cell lines. Interestingly siCGA/UCG the same base composition as the super toxic siCAG/CUG was among the nontoxic repeats. siCGG/CCG had the similar effect.

siRNAs based on trinucleotide repeats in huntington's disease show specific toxicity against cancer cells, explaining the low cancer incidence in triple repeat diseases. However, it seems that the nontoxic repeats of siCGG/CCG in FXS had no or less than 50% loss in viability of cancer cells. It would be more appropriate to take into consideration the other aspects of gene regulation such as long noncoding RNA(LNCR) and epigenetic modifications.

Also, concern on the individual characteristics of each type of cancer, instead of regarding cancer as a single phenomenon would be important.

## FMR1 and FMRP in cancer data bases

The download size of database had grown from mega bite to giga bite using in publications and consortia. P38. There is an exponential growth of cancer-associated data from diverse resources, such as scientific publications, genome-wide association studies, gene expression experiments, gene-gene or protein-protein interaction data, enzymatic assays, epigenomics, immunomics and cytogenetics, stored in relevant repositories. Data are complex and heterogeneous, ranging from unprocessed, unstructured data in the form of raw sequences and polymorphisms to well-annotated, structured data. The purpose of the database is to allow cancer researchers to quickly determine whether or not a gene, or list of genes, has been identified as a potential cancer driver in a forward genetic screen. Among several innovative and comprehensive databases, we employed specifically the Catalogue Of Somatic Mutations In Cancer, COSMIC, The Cancer Genome Atlas, TCGA, (cancergenome.nih.gov), The human protein atlas (proteinatlas.org ) cBioPortal, and intogen (intogen.org) for exploring role of FMR1gene and FMRP and its target in the molecular basis of variable cancers.Very interesting results that did not match together were found. Pasciuto listed a precise and valuable summary of forty from hundreds FMRP targets or FMRP / mRNA functional interaction And FMR1 (figure 1,2) and MAP1B were two of the most common genes shown in the table1 below.

| Gene name | Databases | | | | |
|---|---|---|---|---|---|
| | The human protein atlas (Gene level) | The human protein atlas (Protein level) | Intogen | COSMIC (Gene expression level) | Cbioportal (that use TCGA) |
| MAP1B | Glioma | Glioma (with two different IHC staining antibodies) (HPA022275 and CAB009792) | MAP1B has not been detected as a mutational cancer driver | Adrenal cortical carcinoma | Glioma (in TCGA provisional studies)<br>GBM (in all studies) |
| FMR1 | Thyroid Carcinoma | Thyroid cancer (HPA050118 and CAB012444)<br>Glioma(HPA056048) | Lung Squamous Cell Carcinoma | Adrenal cortical carcinoma | Chromophobe RCC (in TCGA provisional studies)<br>GBM (in all studies) |

HPA: Human Protein Atlas

MAP1B: Microtubule-associated protein 1B

**Table 1.** Cancers linked to different level of target genes are different in incidence with respect to gene level, expression level and protein level and they are not necessarily the same.

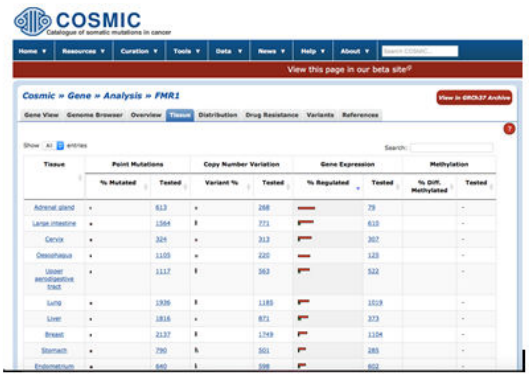


**Figure 1.** Tissue oriented tumors are sorted by FMR1gene expression data for both over(Red ) and under( Green ) in COSMIC respectively .As it appears , from 29380 Samples tested on tumor cells and culture cells, FMR1 gene overexpression is the most common finding in adrenal gland carcinoma , large intestine and cervix carcinoma respectively. While in-vivo cancer studies are most in favour of brain and testicular cancer in FXS.

**Figure 2**.Two-dimensional TCGA scatter plots depicting correlations between demonstrated higher levels of FMR1 expression are strongly correlated with in GBM (arrow) and in turn the lower levels of FMR1 in stomach carcinoma.

While databases are made easily navigable with graphical presentations, they cannot provide easy methods to ask any in-vivo clinical question. The remarkable difference between cancer types and FMRP targeted genes verify it. Maybe the lack of access to all published article for researcher is the reason for this discrepancy.

## Conclusion

A relatively low reported rate of cancer, in some studies may reflect decreased detection and under-reporting as a result of inadequate screening, as well as impaired ability among people with intellectual disabilities to communicate symptoms of disease.

Canadian consensus guidelines on primary care of adults with developmental disabilities

focused on cancer screening as an essential aspect of preventive care. Adults with DD are less likely than those in the general population to be included in preventive screening programs such as colon cancer, cervical screening, breast examination, mammography, and digital rectal examination for prostate cancer. They are also less likely to do self-examination or to report abnormalities.

In the recent decade, with progress in method and instruments, several diverse molecular and epidemiological studies in cancer linked to FXS have been acknowledged, nevertheless none of them and the present review can confirm the exact difference between cancer rate in patient with FXS and normal population. Indeed, regarding numerous unknown and known functions of FMRP, we are in the beginning-of-the-road of identifying facts and details of this entity.In conclusion, regardless of higher or lower incidence of cancer in FXS and other ID, the most essential point is prevention. Health worker contributions and patient education could improve insight to have a healthy lifestyle and decrease cancer mortality and morbidity.

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