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Fragile X syndrome: the FMR1 CGG repeat distribution among world populations

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SUMMARY

Fragile X Syndrome (FXS) is characterized by moderate to severe intellectual disability which is accompanied by macroorchidism and distinct facial morphology. FXS is caused by the expansion of the CGG trinucleotide repeat in the 5′ untranslated region of the Fragile X mental retardation 1 (*FMR1*) gene. The syndrome has been studied in ethnically diverse populations around the world and has been extensively characterized in several populations. Similar to other trinucleotide expansion disorders, the gene specific instability of *FMR1* is not accompanied by genomic instability. Currently we do not have a comprehensive understanding of the molecular underpinnings of gene specific instability associated with tandem repeats. Molecular evidence from *in vitro* experiments and animal models supports several pathways for gene specific trinucleotide repeat expansion. However, whether the mechanisms reported from other systems contribute to trinucleotide repeat expansion in humans is not clear. To understand how repeat instability in humans could occur, the CGG repeat expansion is explored through molecular analysis and population studies which characterized CGG repeat alleles of *FMR1*. Finally, the review discusses the relevance of these studies in understanding the mechanism of trinucleotide repeat expansion in FXS.

Keywords

FMR1 gene; fragile x mutation; prevalence

INTRODUCTION

Fragile-X syndrome (FXS) (OMIM 300624) is caused by the expansion of the CGG repeat in the 5′ untranslated region (UTR) of fragile X mental retardation 1 (*FMR1*) gene (OMIM 309550) located on the X chromosome (Fu et al., 1991, Verkerk et al., 1991). The prevalence of FXS is estimated at ~1/4000 males and ~1/8000 females which have been substantiated by other reports (Crawford et al., 2001, Coffee et al., 2009, Garber et al., 2006, Turner et al., 1996, Murray et al., 1996,). In over 98% of the patients, FXS is caused by expansion of the triplet repeats in addition, others have reported rare single point mutations and genetic variants also cause FXS without expansion of the CGG repeat (Collins et al., 2010, De Boulle et al., 1993, Tarleton et al., 2002,). Non-CGG genetic variants account for about ~1% (Collins et al., 2010) with length of the CGG being the most important genetic variant which causes FXS and determines the carrier status of individuals. For example, individuals with 5–45 copies of the CGG repeats are unaffected, 45–54 CGG repeats are called intermediates or “gray zone”, 55–199 CGG repeats being classified as premutations

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and > 200 CGG repeats as having a full mutations with associated intellectual and developmental disability (Kronquist et al., 2008). The CGG repeat is unstable over a specific threshold, for example premutation carriers can expand to full mutation upon transmission from female to offspring (Fu et al., 1991). Repeat expansions in the intermediate or "gray zone" have variable expansion characteristics which is attributed to familial factors that influence the stability of the repeat upon transmission to offspring (Nolin et al., 1996). Examination of gametes from fetuses that harbor the FXS mutation show the *FMR1* mutation exist in maternal oocytes in the unmethylated state (Malter et al., 1997). Individuals with FXS receive the full mutation allele from their mothers, because sperm from full mutation males carry only premutation alleles; however, some reports demonstrate asymptomatic males can transmit the full mutation to offspring (Zeesman et al., 2004).

The lengthening of the CGG repeat, the cause of FXS is hypothesized to occur with the addition of length specific interruptions (e.g. AGG, CGA or CGGG) at the distal end of the CGG array with incremental additions of smaller CGG arrays (Eichler et al., 1995a). The molecular basis of CGG repeat lengthening is suggested to arose from independent mutational events with rapid proliferation of interspersion events (Eichler et al., 1995a). Homogeneity of the interspersions are incompatible with known rates of mutation and random mutation theory suggesting a short evolutionary period for CGG repeat polarized lengthening (Eichler et al., 1995b, Miyamoto et al., 1987). This polarized lengthening mechanism could have occurred via recombination (i.e. unequal chromatid exchange), gene conservation or replication slippage suggesting a complex mutational history in primates (Eichler et al., 1995b).

Genetic basis

FMR1 and its protein product, fragile X mental retardation protein (FMRP) are highly conserved proteins found in primates species and other mammals (Eichler et al., 1995b). FMRP is an mRNA binding protein expressed in various tissues and is essential for neuronal and intellectual development (Bassell and Warren, 2008). FMRP inhibits translation of numerous genes involved in synaptic plasticity by altering the expression of these genes via mRNA sequestration (Bassell and Warren, 2008). The localization of FMRP with polyribosomes of dendritic spines suggest that FMRP can regulate local protein synthesis important for spine development and synaptic plasticity which are essential for learning and intellectual development (Antar and Bassell, 2003, Antar et al., 2005). In the absence of FMRP, dysregulation of local translation of mRNA occurs leading to imbalance in the spatial and temporal control of protein levels at synaptoneurosomes (Muddashetty et al., 2007). Individuals with FXS display long, thin and immature dendritic spines, which are similar to the dendritic spine morphology of *Fmr1* knockout (*KO*) mice (Baker et al., 2010, Comery et al., 1997, Grossman et al., 2006, Mineur et al., 2006). In addition, *Fmr1 KO* mice also display the learning behaviors which are also associated with FXS (Baker et al., 2010, Grossman et al., 2006, Mineur et al., 2006).

The CGG repeat in *FMR1* is transcribed into mRNA, but the translation initiation site is downstream of the CGG repeat thus the repeat is not translated (Tassone et al., 2011). The length of the CGG is shown to be inversely associated with translational efficiency as shorter CGG repeats allow for efficient translation (Ludwig et al., 2011, Tassone et al., 2011). Beyond a certain threshold, the length of CGG repeats decrease translational efficiency resulting in both increased *FMR1* expression but decreased FMRP production (Tassone et al., 2007, Peprah et al., 2010a). When the *FMR1* CGG repeat expands to the full mutation, methylation of the CGG repeats occurs. The expanded CGG track is recognized as a CpG island which significantly decrease transcription of *FMR1* resulting in significant ablation of FMRP expression (Godler et al., 2010).

Clinical manifestations

Premutations carriers have increased *FMR1* transcript levels with decreased FMRP levels (Tassone et al., 2007). FXS adult males tend to be tall, have macroorchidism, a prominent forehead, and a long narrow face with highly arched palate, prominent mandible and large ears which become more pronounced with age (Terracciano et al., 2005). Females with FXS have the typical long face and mandibular prognathism phenotype seen in affected males, and large averted ears (Terracciano et al., 2005). Affected individuals of both sexes also have delayed speech and intellectual disability with an IQ range between 20–70 (Terracciano et al., 2005). Mosaicism of FXS has been observed; these individuals have IQ which varies from high functioning to moderate or low functioning (Fengler et al., 2002, Han et al., 2006). Psychiatric and mood disorders have been examined in permutation carriers. Several reports indicate a significant association of psychiatric and mood disorders in both male and female premutation carriers (reviewed by (Bourgeois et al., 2009). Further work is needed to delineate between disorders not associated with premutation carrier status (i.e. environment cause and/or life circumstances) from psychiatric disorders attributed to the FMR1 premutation allele (Bourgeois et al., 2009).

1) Female premutation carriers—Traditionally, it was believed that carriers of the *FMR1* premutations were clinically normal; however, recent data has indicated that these individuals have problems associated with their carrier status. Recently, increased psychological symptoms in premutation carriers have been reported (Hessl et al., 2005). In females, one third of individuals with the full mutation have mild intellectual impairment with associated behaviors including shyness, poor eye contact and learning disabilities (Terracciano et al., 2005).

The length of the CGG repeat contributes to the variation in age at menopause. The *FMR1* repeat sizes in the intermediate or gray zone is associated with an increased risk of Fragile X associated Premature Ovarian Insufficiency (FXPOI) (Bretherick et al., 2005, Bodega et al., 2006). FXPOI is defined as menopause before the age of 40 associated with *FMR1* premutation carrier status (Bodega et al., 2006, De Caro et al., 2008, Kenneson and Warren, 2001,).When the *FMR1* repeat size exceeds 79 CGG repeats the risk for ovarian dysfunction is clinically significant, however this risk appears to plateau or decrease among women with very high CGG repeats (Sullivan et al., 2005, Ennis et al., 2005).

Several groups have demonstrated female premutation carriers have a higher incidence of FXPOI when compared to women in the general population (Bodega et al., 2006, De Caro et al., 2008, Kenneson and Warren, 2001). It is estimated that approximately 20–28% of female premutation carriers manifest FXPOI (Oostra and Willemsen, 2003, Welt et al., 2004). The hormonal changes exhibited by these women are consistent with early ovarian aging attributed to decreased follicle number and function (Welt et al., 2004).

Clinical effects of FXPOI are loss of fertility and hypoestrogenism (Woad et al., 2006, De Caro et al., 2008). Due to the serious consequences of FXPOI, women that experience ovarian dysfunction atypical for their age without another medical explanation are being tested in increasing numbers for the *FMR1* premutation (Pastore et al., 2006). However, pregnancy has occurred in 5–10% of women whose diminished ovarian function lead to a diagnosis of FXPOI (Woad et al., 2006, Kalantaridou et al., 1998).

2) Male premutation carriers—Male carriers of premutation alleles exhibit mechanistically distinct problems from female carriers (Terracciano et al., 2005). Evidence suggests that premutation males have a reduced ability to recruit the left hippocampus during recall (Koldewyn et al., 2008). Premutation males preformed significantly worse on immediate recall tasks compared to age matched controls (Koldewyn et al., 2008).

Examination via functional magnetic resonance imaging in premutation males indicate a reduced amygdale volume, with reduced FMRP expression being one of the primary factors for alteration of brain function and behavior (Hessl et al., 2010).

Fragile X associated Tremor/Ataxia Syndrome (FXTAS) is estimated to occur in 30% of male premutation carriers (Hagerman et al., 2001, Hagerman et al., 2008). FXTAS is a significant cerebral and cerebellar white matter disease, and in males exhibit signs of onset of tremor in their 50s with gradual progression of symptoms to incorporate ataxia (Greco et al., 2006, Hagerman et al., 2001, Hessl et al., 2005). The neuropathological characteristics of FXTAS have been extensively characterized (Greco et al., 2006, Hagerman et al., 2001, Hessl et al., 2005). Neurohistological studies of the brains of symptomatic elderly premutation carriers have demonstrated that neuronal degeneration occurs with the presence of eosinophilic intranuclear inclusions in both neurons and astroglia (Oostra and Willemsen, 2003, Iwahashi et al., 2006, Greco et al., 2006). Iwahashi and colleagues (2006) examined the inclusions in the brains of premutation elderly males and found several inclusion-associated proteins. Surprisingly, there were no dominant protein species in the inclusions and ubiquitinated proteins represented a minor component (Greco et al., 2006, Hagerman et al., 2001, Iwahashi et al., 2006). In FXTAS, inclusion formation is not due to a lack of proteasomal degradation of nuclear proteins but is due to a gain of function by the *FMR1* transcript (Handa et al., 2005, Garber et al., 2006). Female carriers also develop FXTAS, but the symptoms are less severe compared to male premutation carriers (Hagerman et al., 2004).

Genetic studies of the *FMR1* CGG repeat in diverse populations

FXS has been studied extensively in several western European populations. In most studies analysis of the CGG repeat number has occurred due to its ability to expand to the full mutation and its corresponding associated diseases for premutation carriers (Willemsen et al., 2011). In addition, various methods have been used to produce CGG repeats sizes for different reports making it difficult for cross population comparisons; however several reports used protocols by Fu and colleagues (1991) making cross population comparisons at the CGG repeat possible. In *FMR1*, 30 and 29 copies of CGG repeats are the most common repeats found in western European ancestry populations (Oudet et al., 1993a, Oudet et al., 1993b, Buyle et al., 1993, Malmgren et al., 1994, Tranebjaerg et al., 1994, Matilainen et al., 1995, Syrrou et al., 1996, Arrieta et al., 1999) (Table 1). There is substantial evidence of a strong founder effect in western European populations (Buyle et al., 1993, Chakravarti, 1992, Chiurazzi et al., 1996b, Malmgren et al., 1994, Oudet et al., 1993b, Richards et al., 1992). However the founder effect is not present in eastern European populations of Slavic origin (Đokić et al., 2008). Within western European populations, significant differences in allelic and haplotypic distributions exist between normal chromosomes found in the general population and chromosomes that harbor the full mutation which causes FXS (Rousseau et al., 1995, Crawford et al., 2001). This particular distribution of normal and fragile X chromosomes is hypothesized to occur because a limited number of primary events may have been at the origin of most present-day chromosomes that harbor the full mutation in founder western European populations (Chakravarti, 1992, Morton and Macpherson, 1992). Such founder chromosomes may have carried a number of CGG repeats in an upper-normal range or “gray zone”, from which recurrent multistep expansion mutations could have arisen (Oudet et al., 1993a, Oudet et al., 1993b, Buyle et al., 1993, Malmgren et al., 1994).

Faradz and colleagues (2000) conducted an extensive survey of male samples in 12 sub-populations in Indonesia. In the population 32 different CGG repeat alleles were present (Faradz et al., 2000). 29 and 30 CGG repeats accounted for 72% of the alleles present in the population. 29 repeats was the most frequent which was similar to Chinese ancestry populations (Faradz et al., 2000, Zhou et al., 2006). The Indonesian population showed a

much lower frequency of CGG repeat alleles with fewer than 29 repeats and a higher frequency of alleles greater than or equal to 36 repeats when compared to western European ancestry populations (Faradz et al., 2000). The data was similar to other Asian populations in which the 29 is present at a higher frequency than the 30 allele (Faradz et al., 2000, Zhou et al., 2006, Chiu et al., 2008) (Table 1). FXS is present in 2.8–8.6% of the intellectually disabled institutionalized males from the Japanese and Chinese populations respectively (Arinami et al., 1986, Zhong et al., 1995). In the Chinese populations the most common CGG repeat alleles are 29 followed by 30 (Zhong et al., 1995, Tzeng et al., 1999, Zhong et al., 1994).

In Mexican populations the trinucleotide repeat number varied from 16–40 (Rosales-Reynoso et al., 2005). The modal repeat number of 32, second peak at 30, and minor peak at 34 was detected within this population (Rosales-Reynoso et al., 2005). The 32 repeat is the most frequent allele for Mestizos and Tarahumaras in the Mexican population (Barros-Nunez et al., 2008). Huichols display the 30 and 29 profile found in other populations (Barros-Nunez et al., 2008). 10.5% of the Mexican population had larger repeats (i.e. 34+ repeats) which is similar to patterns observed in Indonesian and Chinese ancestry populations (Rosales-Reynoso et al., 2005). Rosales-Reynoso et al (2005) concluded that the Mexican population with a significant number of large alleles (34–40) would be at a higher risk for allelic expansion. However, cytogenetic expression of the Xq27.3 fragile site showed no statistical differences when compared with those from other populations (Diaz-Gallardo et al., 1995, Gonsalez-del Angel et al., 2000)

Data collected in Brazil among different ethnic groups found that samples from quilombos, Amerindians, and the ethnically mixed, but mainly European-derived population of Sao Paulo revealed that the 30 CGG repeat allele of *FMR1* was the most frequent in all groups. A second peak at 20 repeats was present in the population of Sao Paulo only, confirming the population as a western European peculiarity (Mingroni-Netto et al., 2002, Mingroni-Netto et al., 1999, Angeli and Capelli, 2005). Similar to the Brazilian study, studies conducted in the Chilean population showed most common CGG repeat allele was 30, with 29 being second most common (Aspillaga et al., 1998, Arrieta et al., 1999, Jara et al., 1998).

Molecular screening of institutionalized populations in India revealed that the prevalence of FXS was 7–8% (Sharma et al., 2001). In the population, 26 distinct alleles were present ranging from 19–50 repeats (Sharma et al., 2001). The most frequent allele size in the population was 29 repeats, 28 repeats, and minor peaks at 30 and 31 repeats (Sharma et al., 2001, Zhou et al., 2006). The frequency of FXS was fourfold higher in males than observed in females, however due to the stringent criteria employed in the Indian study comparison cannot be made with studies conducted in Western countries of institutionalized populations which include all unexplained intellectual disability case while the Indian study only included mild to moderate intellectually disabled with or without family history and a Fragile X clinical phenotype (Sharma et al., 2001).

Studies conducted on African ancestry populations for the frequency of the fragile X allele are small in number (Chiurazzi et al., 1996a, Eichler and Nelson, 1996, Kunst et al., 1996, Peprah et al., 2010b) however African Americans *FMR1* alleles have been well characterized (Crawford et al., 1999, Crawford et al., 2002, Crawford et al., 2000a, Crawford et al., 2000c). In African Americans (AA), 37 distinct repeat sizes are present (Crawford et al., 2002). The prominent peak was a CGG repeat of 30, followed by 29 and 31 repeats (Crawford et al., 2002). 20 different CGG repeats size alleles and 55 different CGG structures were identified in AA which showed a greater heterozygosity than other populations (Crawford et al., 2000c). The African study by Chiurazzi et al (1996) demonstrated that the predominant repeat size was 29 and 30 repeats with 31 and 32 repeats

also high in frequency. In Ghanaians, the distribution of CGG repeat is similar to AA with 30 and 29 CGG repeat being the most frequent alleles (Peprah et al., 2010b). This Ghanaian population has provided significant insight to the frequency of CGG repeats in this African population. Characterization of the *FMR1* CGG repeat in diverse populations is starting to occur. Substantial ascertainment of diverse populations is needed before a thorough understanding of the CGG repeat instability can occur in world populations.

Prevalence of the *FMR1* mutation in diverse populations

Several studies have elucidated the haplotypic background of the *FMR1* instability in unaffected and affected populations. In many cases the data could not be compared between studies containing different populations because of diverse methods used for genotyping. These include different haplotype reconstruction schemes, differences in publication nomenclature used for flanking markers, and utilization of different number of short tandem repeats (STRs) (e.g. two flanking markers instead of the commonly used three STRs). Many studies consisted of screenings of institutionalized individuals with intellectual disabilities only without further analysis being conducted that would allow prevalence estimates to be calculated. These investigations yielded cursory confirmation of FXS but could not be extrapolated to general population. Reports that address most of these issues and produced prevalence estimates abound but one limitation are that these reports utilized populations of primarily European ancestry, with few exceptions (Hill et al., 2010). With these issues, we attempted to summarize the current literature on FXS prevalence rates worldwide (Table 2). Table 2 indicates that the majority of the studies being conducted in non-European populations are currently in their infancy.

Several different populations have been surveyed for the *FMR1* premutation which include extensive research on intellectually disabled individuals in diverse populations (Jacobs et al., 1986, Arinami et al., 1986, Zhong et al., 1995, Elbaz et al., 1998, Crawford et al., 1999). Children with learning disabilities have also been tested for the *FMR1* full mutation (Crawford et al., 1999, Webb et al., 1986, Slaney et al., 1995). Screening for the *FMR1* mutation is occurring beyond institutionalized individuals with intellectual disability to encompass women of reproductive age (Hill et al., 2010).

General population surveys have occurred in western European ancestry populations and have contributed to accurate calculations of prevalence estimates. The lowest prevalence estimates for FXS has been reported in Canada, Estonia, Japan, and Taiwan (Table 2). The prevalence estimates for these countries were significantly lower when compared to the other western countries which have carried out fragile X testing (Crawford et al., 2001). Since 2008, other reports from countries including Egypt and Iran characterizing the *FMR1* mutation in special needs populations have been published (Table 2). This suggests that (i) diagnostics for FXS is becoming widely accepted, (ii) characterization of the *FMR1* CGG repeat is recognized as a method to determine the etiology of intellectual disability in diverse populations (iii) the method is cost effective and accurate. These are a few of the parameters that must be met by the various screening methodology for the protocols bto be adopted and used in population screening of *FMR1* mutation (Pembrey et al., 2001). As more reports on the distribution of CGG repeats from normal, premutations and fully mutations in diverse populations are produced, these data can be compared to well-characterized (e.g. western European) populations, a better understanding of the frequency of CGG repeat expansion variants of the *FMR1* loci in diverse populations will occur. This information will be important in; 1) understanding genetic instability at the loci, 2) *cis* elements which are associated with genetic instability, 3) and finally understanding CGG expansion risk which could be of interest for genetic counselors and also FXS families and premutation carriers who would eventually want to have children.

Factors associated with repeat instability

Several different populations have been surveyed to determine the role in which *cis*-elements contribute to the expansion of CGG repeats utilizing population based or targeted studies which include intellectually disabled individuals with and without full mutations (Jacobs et al., 1986, Arinami et al., 1986, Elbaz et al., 1998, Crawford et al., 1999). At present, the evidence supports both a *cis* model (chromosomal structure and genetic elements listed in Table 3) and a *trans* model (DNA replication and repair enzymes listed in Table 4) in expansion disorders. Due to the enigmatic nature of FXS and other trinucleotide repeat disorders, a "unified" model is needed to describe the instability encompassing both *cis* elements and *trans* factors.

Current data suggests three mutational pathways that could explain the stepwise progression to the full mutation allele (Crawford et al., 2000c, Eichler et al., 1996). These mutation pathways were identified via haplotype associations based on the three flanking STRs of *FMR1* CGG repeat. These three STRs include DXS548, FRAXAC1, and another dinucleotide microsatellite and FRAXAC2 (description of each STR can be found in (Peprah et al., 2010b)). The mutation pathways for each haplotype rely mainly on the multiallelic model of CGG repeat expansion through the loss of AGG interruption and addition of CGG repeats, eventually resulting in the full mutation (Eichler et al., 1996, Morton and Macpherson, 1992). The pathway represented by the 2-1-3 haplotype was associated highly interrupted CGG repeats which contained several AGG interspersions; proposed to retain the AGG interruptions while slowly expanding into the intermediate CGG repeat alleles through additions of CGGs at the polar end (i.e. 3′ end of the repeat track) (Eichler and Nelson, 1996). The second pathway, the 6-4-5 haplotype, was associated with "asymmetrical" CGG repeat patterns and was hypothesized to progress rapidly toward CGG expansion due to the loss of the AGG interruption within the CGG repeat allowing the alleles on this haplotype to bypass intermediate CGG repeats (Eichler et al., 1996). The third pathway, the 4-4-5 haplotype, suggested that the absence AGG interruption in the CGG array (i.e. AGG interruption at 5′ of CGG repeat) increased instability of the repeat (Crawford et al., 2000c). Each expansion mechanism was hypothesized to result from different mutational processes. The mutational process could include several mechanism which mediate the mutation (Gunter et al., 1998, Zhong et al., 1995, Eichler et al., 1994, Eichler et al., 1996, Crawford et al., 2000c, Kunst and Warren, 1994, Snow et al., 1993, Crawford et al., 2000b). If one mechanism was the initial predisposing factor, it might not be the primary mechanism in which the CGG repeat would reach the premutation threshold. The exact expansion mechanism(s) still remains to be elucidated.

Haploinsufficiency in DNA repair/replication proteins

FXS similar to other trinucleotide repeat expansion disorders are loci specific, suggesting the mechanism of repeat expansions might not be caused by mutations in the *trans*-acting factors (Mirkin, 2006) due to the lack of genome wide instability observed in some cancers (Foulkes, 2008). Locus specific expansions infer participation of DNA repair/replication proteins in expansion disorders (reviewed by (McMurray, 2010)). Many enzymes in the DNA repair/repair replication include resolving stalled replication forks and also important in replication repair which include ATR, ATM, MSH2 and MSH3 (Entezam and Usdin, 2008, Pearson et al., 1997, Spiro et al., 1999) (Table 4). ATR is known to play a role in the resolution of stalled replication forks and removal of DNA lesions. ATR haploinsufficiency is reported to increased intergenerational expansion of CGG repeats with a maternal bias (Entezam and Usdin, 2008). In contrast, ATM haploinsufficiency is associated with repeat expansion with significant paternal bias (Entezam and Usdin, 2009). The ATR-sensitive mechanism is hypothesized to occur on maternal transmission and an ATM-sensitive mechanism shows a male expansion bias (Entezam and Usdin, 2009). The role of MSH2 and

MSH3 other proteins in trinucleotide repeat instability have been extensively reviewed by others (McMurray, 2010, Brouwer et al., 2009). The model of trinucleotide expansion via haploinsufficiency of DNA repair/replication proteins has been primarily explored in mouse models. These and other proteins including MSH6, FEN1 and OGG1 may have roles as potential indicators of repeat expansions in FXS.

Recently, expression analysis of transcripts has occurred in human FX patients (Rosales-Reynoso et al., 2010, Bittel et al., 2007). The expression data indicated significant down regulation of Rad9A, a DNA repair and cell cycle check point protein within the response to DNA damage via the ATR/ATM pathway (Rosales-Reynoso et al., 2010). Rad9A, expression decreased in fragile X patients compared to controls supporting the hypothesis that reduced expression of at least Rad9A could lead to loci specific expansion in humans. However, because transcript expression data is not easily correlated to protein expression *in vitro* follow-up will be needed to determine if Rad9A haploinsufficiency also leads to *FMR1* CGG repeat expansion.

CONCLUSION AND PROSPECTIVE

CGG expansion in *FMR1* is associated with FXTAS and FXPOI for premutation carriers of the expanded repeats and FXS for individuals with the full mutation. This group of disorders caused by the *FMR1* mutation impact families making screening of the CGG repeat critical to understanding expansion risk in families and populations (Crawford et al., 2001). The *FMR1* full mutation offers simple detection by identification via molecular means and phenotypic features has allowed successful screening and diagnosis of affected individuals and carriers of the premutation.

A number of studies focused on newborn screening or general population surveys have occurred (Coffee et al., 2009, Tzeng et al., 2005). FXS screening have used robust methods which has substantiated the prevalence estimates of FXS in the general Caucasian population (Coffee et al., 2009). However, the prevalence rate of FXS in the Taiwanese population is suggested to be lower compared to European ancestry populations (Tzeng et al., 2005). Other studies have found that non-expansion variants in or around *FMR1* marginally contribute to the prevalence of FXS (Collins et al., 2010). The use of these screening methodologies with previously undiagnosed conditions of intellectual disability will be beneficial in finding the cause of these conditions.

Due to the current enigmatic nature of trinucleotide expansion disorders a “unified” model is needed to describe the instability of repeat disorders encompassing both *cis* elements and *trans* factors. Simply stated, if haploinsufficiency of repair replication proteins are present in FX families with the DNA structures associated with expansions, this will be a significant contribution to understanding trinucleotide repeat expansion disorders (Crawford et al., 2000c, Eichler et al., 1994, Eichler and Nelson, 1996, Morton and Macpherson, 1992). The current understanding of trinucleotide expansion disorders suggests that many of these expansions arose from several different mechanisms. DNA elements (e.g. expanded repeats), must be present in addition to the decrease in expression of *trans* factors creating a mutable background predisposing individuals or families to locus specific expansions. In most animal models, expansions are observed in large premutation repeat backgrounds which suggest that one mechanism could be the initial predisposing factor, but would not be the primary mechanism in which the repeat would reach the pathogenic threshold. Understanding the mechanism of trinucleotide repeat expansion in FXS would be beneficial to other trinucleotide repeat expansion disorders (i.e. myotonic dystrophy (DM) and Huntington Disease). Finally, the evolutionary significance of loci specific repeat expansion

disorders cannot be understated which will also engender greater understanding of the evolution of the human genome and how genome fidelity is maintained.

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Table 1

Distributions of CGG repeat alleles in among world populations Adapted from (Sharma et al., 2000)

Country (Population)	Sample Size	# of CGG Repeat Variants (Range)	Common Repeat(s)	Reference
Brazil (African Brazilians)	255	26(15–43)	30,29	Mingroni-Netto et al., 2002
Brazil (Ameridians)	46	26(15–43)	30, 29	Mingroni-Netto et al., 2002
Brazil (EuropeanBrazilians)	64	26(15–43)	30, 20	Mingroni-Netto et al., 2002
Cameroon (Bamileke, Bororo, Sanga)	47	22(22–41)	29,30	Chiurazzi et al., 1996a
Chile (European and Asian ancestry)	NR(192 X chrs screened)	19(19–44)	30,29	Jara et al., 1998
China (Chinese ancestry)	177	16(19–40)	29, 30	Zhou et al., 2006
Croatia (European ancestry)	74	26(20–45)	30, 31	Dokic et al., 2008
Ghana (multi-ethnic)	350	23(18–54)	30,29	Peprah et al., 2010
India (multi-ethnic)	265	26 (19–50)	29, 28	Sharma et al 2001
India (multi-ethnic)	99	15(19–40)	30, 29	Zhou et al., 2006
Indonesia (multi-ethnic)	1069	32(NR)	29,30	Fradaz et al., 2000
Indonesia (Malay)	178	18 (19–40)	29,30	Zhou et al., 2006
Japan(Japanese ancestry)	946	24 (6–54)	27, 26	Otsuka et al., 2010
Mexico (Mestizos)	207	23(15–87)	32,30	Barros-Nunez et al., 2008
Mexico (Tarahumaras)	140	13(15–87)	32,30	Barros-Nunez et al., 2008
Mexico (Huichols)	138	14 (19–87)	30, 29	Barros-Nunez et al., 2008
Mexico (Western Region)	129	23(16–76)	32,30	Rosales-Reynoso et al., 2005
United Kingdom (multi-ethnic)	254	30(13–49)	30, 29	Jacobs et al., 1993
United States (African American)	213	32(14–55)	30, 29	Crawford et al., 2000
United States (European Ancestry)	200	39(11–56)	30, 29	Crawford et al., 2000

Table 2

Reported prevalence estimate of the fragile X syndrome among world populations Adapted from (Crawford et al., 2001)

			Estimated Prevalence		
Country	**Population**	**No.Positive/No. Tested**	**General Pop**	**Targeted Pop (%)**	**Reference**
Australia[a]	SN	10/472	1/4,350	2.1	(Turner et al., 1986, Turner et al., 1996)
Brazil	SN	0/83	–	–	(Mulatinho et al., 2000)
Brazil	SN	5/256		2.0	(Haddad et al., 1999)
Canada	GP	1/24,446	1/24,446	–	(Rousseau et al., 2007)
Chile	SN	4/214	–	1.9	(Aspillaga et al., 1998)
Croatia	SN	4/114	–	0.9–2.6	(Hecimovic et al., 2002)
Croatia	SN	14/81	–	17.3	(Hecimovic et al., 2000)
Estonia	GP, SN	14/516	1/27,115	2.7	(Puusepp et al., 2008)
Egypt	SN	34/200	–	5.9	(Behery, 2008)
France	SN	10/403	–	2.5	(Gerard et al., 1997)
Greece & Cyprus	CR	8/611	1/4,246	1.3	(Patsalis et al., 1999)
Guadeloupe, FWI	IR	11/163	1/2,359	6.7	(Elbaz et al., 1998)
India	SN	3/146	–	2.5	(Pandey et al., 2002)
India	CR	19/360	–	5.3	(Jain et al., 1998)
Israel[C]	GP	3/14,334	–	1.5	(Tolendano-Alhadef et al., 2001)
Iran	GP, SN, CR	32/508	–	3.4–15.3	(Pouya et al., 2009)
India	SN	9/93	–	9.7	(Sharma et al., 2001)
Japan	GP	0/946	1/10,000	–	(Otsuka et al., 2009)
Japan	SN	2/256	–	0.8	(Nanba et al., 1995)
Korea	SN	4/65	–	6.15	(Yim et al., 2008)
Kuwait	SN	11/182	–		(Bastaki et al., 2004)
Mexico	GP, SN	0/129	–	–	(Rosales-Reynoso et al., 2005)
Mexico	CR	2/53	–	3.8	(Gonzalez-del Angel et al., 2000)
Netherlands	CR	10/197	–	5.1	(van den Ouweland et al., 1994)
Netherlands	SN	9/866	1/6,045	2.0–2.4	(de Vries et al., 1997)
Poland	GS, SN	6/201	–	3.0	(Mazurczak et al., 1996)
Saudi Arabia	SN	12/94	–	6.4	(Al Husain et al., 2000)

			Estimated Prevalence		
Country	**Population**	**No.Positive/No. Tested**	**General Pop**	**Targeted Pop (%)**	**Reference**
Spain	SN	8/92	–	8.7	(Arrieta et al., 1999)
Spain	GP	2/5,000	1/2,466	–	(Rife et al., 2003)
Spain	SN	11/182	–	6.0	(Mila et al., 1997)
Spain[b]	GS, SN, CR	5/180	1/6,200–1/8,200	2.7	(Millan et al., 1999)
South Africa	SN	9/148	–	6.1	(Goldman et al., 1997, Goldman et al., 1998)
Tasmania	GP, SN	0/1253	–	–	(Mitchell et al., 2004)
Taiwan	GP	1/10,046	1/10,000	–	(Tzeng et al., 2005)
Taiwan	SN	4/206	–	1.9	(Tzeng et al., 2000)
Thailand	SN	5/94	–	5.3	(Ruangdaraganon et al., 2000)
Turkey	CR	5/166	–	3.0	(Tuncbileck et al., 1999)
Turkey	SN	14/120	–	11.7	(Demirhan et al., 2003)
Yugoslavia[d]	SN	2/97	–	2.06	(Major et al., 2003)
United Kingdom[a]	GS	4/180	1/8,918	2.2	(Jacobs et al., 1993)
United Kingdom	SN	1/138	–	0.7	(O'Dwyer et al., 1997)
United Kingdom	SN	4/103	1/4,130	3.9	(Slaney et al., 1995)
United Kingdom	SN	20/3,738	1/5,530	0.5	(Youings et al., 2000, Murray et al., 1996)
USA	GS	7/2,324	1/2,545–1/3,717	0.3–0.4	(Crawford et al., 2002)
USA	GP	7/36,124	1/5,161	–	(Coffee et al., 2009)
USA	GP,GS,CR	1,226/119,232	–	0.61–1.4	(Strom et al., 2007)
USA	CR	10/188	3.7	–	(Kaplan et al., 1994)

General Population (GP), General Special needs population (GS),Special Needs population with intellectual disability (SN), Clinical Referral for individuals with Intellectual disability of unknown etiology (CR)

C calculated based on premutation carriers (n=207),

d calculated based on available data

a Only point estimated provided

b Provided a range not a point estimate, in which Millian et al(Millan et al., 1999)acknowledge that person with mild intellectual disability could have been missed

Table 3

Chromosomal elements that affect FXS repeat instability

Factors	Effect on repeat expansion (somatic)	Reference
Length repeat	increase or decrease expansion	(Eichler et al., 1994)
Number of interruptions within the repeat	increase repeat stability	(Eichler et al., 1996)
CGG repeatpurity of the repeat at the 3′ end	decrease stability	(Crawford et al., 2000)
5′ position of the first AGG interruption	increase stability	(Eichler et al., 1995)
Haplotype background of the mutation	increase of decrease stability	(Kunst and Warren, 1994)
SNP associated with expansion (ss71651738)	increase repeat instability	(Ennis et al., 2007)

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Table 4

Gene associated with Trinucleotide repeat instability Adapted from (Kovtun and McMurray, 2008)

Gene	Effect on repeat expansion	System	Reference
ATR (Mec1)	increase in repeat expansions*	FXS mouse	(Entezam and Usdin, 2009)
ATM	increase in repeat expansions	FXS mouse	(Entezam and Usdin, 2009)
FEN1 (Rad27)	increase in repeat expansions*	Yeast/HD mouse	(Spiro et al., 1999)
MSH2	decrease in repeat expansions*	DM/HD mouse	(Savouret et al., 2003, Pearson et al., 1997, Tome et al., 2009)
MSH3	decrease in repeat expansions*	DM/HD mouse	(Manley et al., 1999, Foiry et al., 2006, Owen et al., 2009)
MSH6	decrease in repeat expansions	DM/HD mouse	(Savouret et al., 2003)
OGG1	decrease in repeat expansions	HD mouse	(Kovtun et al., 2007)
Pms2	decrease in repeat expansions	DM mouse	(Gomes-Pereira et al., 2004)

ATR (Ataxia telangiectasia and Rad3 related Kinase); Fen-1 (Flap Endonuclease); Msh2, Msh3 and Msh6 (MutS homologue 2; MutS homologue 3; MutS homologue 6; OGG1, (7,8-dihydro-8-oxo-guanine-DNA glycosylase); Pms2, (*) absence of gene has been shown to effect intergenerational expansions