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EDITORIAL

FMR1 Premutation: Basic Mechanisms and Clinical Involvement

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Abstract The wide spectrum of clinical phenotypes associated with the *FMR1* premutation affect more than two million people worldwide. The clinical implications have only been recognized recently despite this disorder constitutes a relevant health problem. The present issue of *The Cerebellum* is focused on the "2nd International Conference on the *FMR1* Premutation: Basic Mechanisms and Clinical Involvement" held in Sitges, Barcelona (Spain), from September 30th to October 2nd, 2015. The conference was attended by professionals from different countries in Europe, the USA, Chile, Israel, Australia, and Indonesia and covered the latest clinical and molecular findings resulting from *FMR1* premutation studies. Although the pathologies associated with the *FMR1* premutation are considered as rare diseases, seventy abstracts were presented. This reflects the relevance of this topic in the medical community and the growing interest among professionals from other disciplines. The major topics discussed included why and how the mRNA toxicity due to a gain of function and non-canonical RAN are responsible for disorders associated with the premutation. Several presentations addressed the impact of these mechanisms in FXTAS and FXPOI, two clinical presentations caused by the *FMR1* premutation. Interestingly, a deterioration of the DNA repair machinery was first proposed as the pathogenicity cause of premutation alleles. Communications related to FXTAS and FXPOI animal models were also presented. These models facilitate studies aimed to understand disease progression and early treatment interventions. Finally, there were presentations related to psychiatric, psychological, neurological, and radiological aspects. Interesting discussion on intermediate alleles and their involvement in clinical and reproductive aspects was generated. In this regards, genetic counselling is improved by taking into account the AGG interruptions and including information about the *FMR1* premutation associated pathologies although there are still some uncertainties linked to the spectrum of these pathologies. Overall, the meeting covered all aspects of the different pathologies associated with the premutation of the *FMR1* gene.

FMR1 Premutation: Basic Mechanisms and Clinical Involvement

The clinical implications for men and women carrying the *FMR1* premutation, estimated in more than two million people in the world, have been known for only a relatively short time, but currently constitute a relevant health problem that should be noted. The *FMR1* premutation causes fragile X-associated primary ovarian insufficiency (FXPOI) as well as fragile X-associated tremor/ataxia syndrome (FXTAS). Additional clinical phenotypes include fibromyalgia, hypothyroidism, migraine headaches, sleep apnea and other related disturbances, restless legs syndrome, central pain syndrome, neuropathy, and several neuropsychiatric alterations. Several lines of evidence suggest that carriers of the *FMR1* premutation allele present with a higher risk of medical, psychiatric, and cognitive features than the general population.

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During the last 2 years, more than 150 manuscripts have been published on different aspects of the *FMR1* premutation thereby reflecting its importance in the medical community. This growing interest among researchers and medical professionals from many health science fields point to the increasing awareness of these conditions, and have resulted in two recently held scientific conferences devoted entirely to the study of *FMR1* premutation carriers. This issue of *The Cerebellum* is dedicated to the "2nd International Conference on the *FMR1* Premutation: Basic Mechanisms and Clinical Involvement", which was held in Sitges, Barcelona (Spain), from September 30th to October 2nd, 2015. The conference was attended by 83 professionals from different countries in Europe, the USA, Chile, Israel, Australia, and Indonesia. Among the different aspects covered during the conference several papers summarized and reported the latest clinical and molecular findings resulting from *FMR1* premutation studies. Herein, a summary of the meeting is highlighted.

Fragile X-associated Primary Ovarian Insufficiency (FXPOI) and Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

In the last years, we have obtained more in depth knowledge on FXPOI and FXTAS, especially in understanding its molecular basis: from the toxic gain-of-function of the expanded CGG-repeat mRNA model proposed for the pathogenesis of FXPOI and FXTAS to a protein-mediated toxic mechanism. In the latter scenario, translation would be initiated in the CGG repeat in an AUG independent manner (RAN translation), leading to the production of toxic peptides (i.e., poly-glycine, FMRpolyG). Accordingly, accumulation of inclusion bodies containing the FMRployG protein has been demonstrated in granulose cells as well as brain cells from *FMR1* premutation carriers. Apart from these two models based on the involvement of the *FMR1* mRNA at the post-transcriptional level, newer evidence suggests that, at least in FXTAS, the RNA may act co-transcriptionally by increasing the propensity for DNA damage, in part through the formation of transcriptional R-loops [1].

Regarding FXTAS more topics were discussed, including phenotype-genotype relationships, neurobehavioral function as well as updates on clinical and genetic aspects. In addition, this special issue includes a review examining the current use of mouse models to study the *FMR1* premutation and FXTAS. The use of animal models has shed light on the underlying neurobiology of the altered pathways involved in FXTAS encouraging the development of potential treatments.

All the advances achieved to date support ongoing efforts to develop new targeted treatments for premutation disorders [2]. In this regard, two promising studies were presented at the meeting: one on allopregnanolone infusion for the treatment of memory and neurological impairment in FXTAS and another using the N-methyl D-aspartate (NMDA) receptor antagonist memantine for improving attention and working memory.

Clinical Involvement in *FMR1* Premutation Carriers

It is worthy to note that many clinical studies have also been published on psychiatric, psychological, neurological, and radiological aspects associated with the *FMR1* premutation allele. In this issue, several papers address these relevant aspects. However, despite the great effort made in describing and characterizing the broad clinical involvement affecting *FMR1* premutation carriers, most of these studies point to the relatively small sample size [3]. In order to overcome this limitation, the development of an International Registry to collect samples along with genetic and clinical information of *FMR1* premutation carriers was suggested during the conference. The information gathered in this registry would not only move forward research efforts, but would also allow the identification of patients suitable for clinical trials.

Due to incomplete penetrance across the phenotypic spectrum, it is difficult to predict which carriers will develop any of the possible clinical phenotypes associated with the *FMR1* premutation. This is likely related to a combination of genetic and environmental factors, which may confer specific vulnerability to present any of the associated pathologies. Genetic factors that may contribute to premutation-associated disorders include CGG repeat length, expression levels of the expanded *FMR1* mRNA, chromosome X inactivation in women, aberrant translation of the repeat sequence as well as genomic changes in other regions of the genome. Moreover, it has recently been suggested that carriers of *FMR1* premutation alleles presenting with intellectual disability, seizures or autism spectrum disorder are likely to have a second hit in the genome, since *FMR1* premutation carriers show a significant enrichment of copy number variants (CNVs) compared to controls [4]. Regarding environmental factors, it has been suggested that smoking, prolonged surgery with anaesthesia, drug and alcohol abuse or having a child with fragile X syndrome may act as additional determinants influencing the phenotypic variability among *FMR1* premutation individuals. Finally, further longitudinal studies are required to determine the context in which any of the premutation associated phenotypes are developed and what protective factors might reduce the risks of more negative outcomes.

FRM1 Gray Zone Alleles

Another important area discussed during the conference was related to individuals carrying a "gray zone" (45-54 CGG repeats) allele. Several studies have reported phenotypes similar to those observed in premutation carriers, including neurological, molecular, and cognitive signs [5]. Some carriers of

gray zone alleles presenting Parkinsonism display its associated typical features, including bradykinesia, rigidity and a positive response to dopaminergic medication. These patients have a higher prevalence of peripheral neuropathy and psychiatric complaints than the general population. In relation to this observation, an important issue raised at the meeting was whether these alleles should be better characterized in terms of clinical involvement and thus, if the diagnostic criteria for FXTAS need to be revised. Furthermore, this observation underscores the need to carefully revaluate if it is advisable to accept these alleles in gamete donation.

The exact mechanism responsible for the repeat expansion still remains unknown 25 years after the discovery of the *FMR1* gene [6–8]. Moreover, neither has the cause of different *FMR1* premutation-associated pathologies been determined. However, we have moved forward in our knowledge of the wide spectrum of *FMR1* actions. This special issue reflects some of the key aspects presented and discussed during the 2nd International Conference on the *FMR1* premutation. It is important to highlight that due to its high prevalence, 1 in 130 to 250 females and 1 in 250 to 810 males, it is critical for the medical community to be aware of the comorbidities associated with the premutation of the *FMR1* gene.

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