Non Coding CGG Repeat Expansion Diseases: An Update

Dr Rajib Dutta¹*, Swatilekha Roy Sarkar²

¹MD Neurology, India
²MDS, Consultant Orthodontist, India

*Corresponding Author: Dr Rajib Dutta, MD, Neurology, India, Email: rajibdutta163@gmail.com

Abstract: In recent years neurological disorders specifically neurodegenerative diseases have been recognised worldwide and has been diagnosed more and more by clinicians with the ever improving genetic techniques and is currently considered a leading cause of disability and death right from young to elderly age and might surpass the diagnosis of cancer in future as predicted by World Health Organization (WHO). This type of disorders are common in both high- and low-income countries and it is only predicted to increase as time goes by. Expanded trinucleotide repeats are GGGGGC, CAG, CGG, CCG, CTG, CUG, GAA, and GCN etc in the genome are considered to cause major neurodegenerative diseases in general population. Pathogenesis is different for different repeats however time of onset of the disease and severity will depend on trinucleotide repeat number. So, these type of disease comes under category of Trinucleotide repeat expansion disorders (TREDs). Here in this article we further update about the disease spectrum caused by CGG repeat expansion. Founder haplotypes and haploinsufficiency have been identified recently and its analysis in families may reveal a shared haplotype. Attention should be paid not only to familial cases but also to sporadic cases presenting with similar clinical features otherwise the diagnosis can be missed in early stages.

Keywords: CGG, neurodegeneration, CGG trinucleotide expansion.

1. INTRODUCTION

Unstable tandem repeat expansions are involved in a wide variety of neurological diseases which may or may not share similar clinical features. Non coding repeat expansions are known to cause amyotrophic lateral sclerosis (ALS), Fronto temporal dementia (FTD), spinocerebellar ataxias (SCA 1,2,3,6,7,17), Huntington's disease (HD). Dentatorubro pallidoluysian atrophy (DRPLA), benign adult familial myoclonic epilepsies (BAFME), myotonic dystrophies (DM1). Spino bulbar muscular atrophy (SBMA), Friedreich ataxia (FRDA), Oculopharyngeal muscle dystrophy (OPMD), Jacobsen syndrome, Fragile XE syndrome (FRAXE) to name a few. Gene expansion repeat diseases can arise from 5'UTR, coding exons, introns or even 3'UTR region.

Proposed mechanism can be loss of function, gain of function (polyglutamine/alanine expansion, RNA toxicity and RAN translation). CGG expansion causes disease initiation as well as progression either by sequestration of crucial proteins or by repeat-associated non-ATG translation (RANT) [1]. In this article the focus will be on non coding CGG repeat expansion and diseases associated with it.

Previous literature on CGG repeat expansion disorders mainly focused on Fragile X syndrome (FRAXA/FXS), Fragile X associated tremor/ataxia syndrome (FXTAS), Fragile X associate primary ovarian insufficiency (FXPOI) [1], but recently, neuronal intranuclear inclusion disease (NIID), oculopharyngeal myopathy with leukoencephalopathy (OPML) and oculopharyngodistal myopathy (OPDM) has been added to the list [4]. These abovementioned diseases can arise from either 5'UTR or intron region. Loss and gain of function in terms of RNA toxicity and RAN translation are thought to be the primary mechanism involved [5].

2. DISEASES CAUSED BY CGG REPEAT EXPANSION

2.1. Fragile X Syndrome (FRAXA/FXS)

FXS first came into light when an affected person presented with intellectual disability, macroorchidism and dysmorphic features [6]. It is best known as fragile X syndrome a term coined by Mr Lubs [7]. The prevalence of FXS is roughly 1 in 7000 females and 1 in 4000
It depends on the age of the person such as 1 in 813 males [11]. Hagerman et al. have reported guidelines and criteria to reduce errors and misdiagnosis [20]. Recently Shoji Tsuji and colleagues have also reported the clinical spectrum of the condition which includes peripheral neuropathy, cognitive decline, ataxia, tremor and brain MRI findings including middle cerebellar peduncles (MCP) sign, white matter involvement cerebellum > cerebrum and high DWI signal intensity [4]. Hoem et al. recently reported about the expression of the FMRpolyG, in the absence of any CGG mRNA, is sufficient to cause reduced cell viability, lamin ring disruption and aggregate formation. Furthermore, it was found that FMR poly G to be a long-lived protein degraded primarily by the ubiquitin-proteasome-system. Together this data indicate that accumulation of FMRpolyG protein per se may play a major role in the development of FXTAS [49].

Recently Ma et al. used FACS (fluorescence-activated cell sorting) and liquid chromatography tandem mass spectrometry (LC-MS/MS) based proteomics for isolating FXTAS inclusions and found highly enriched levels of conjugated small ubiquitin-related modifier 2 (SUMO2) proteins and p62/sequestosome-1 (p62/SQSTM1) protein within the inclusions. Current analysis has also allowed the first direct detection, through peptide sequencing, of endogenous FMRpolyG peptide, the product of repeat-associated non-ATG (RAN) translation of the FMR1 mRNA. The abundance of the inclusion-associated ubiquitin- and SUMO-based modifiers supports a model for inclusion formation as the result of increased protein loads and elevated oxidative stress leading to maladaptive autophagy [46].

2.2. Fragile X Tremor Ataxia Syndrome (FXTAS)

FXTAS is hereditary neurodegenerative diseases which primarily affects males [11] and have a diverse clinical presentation which can cause diagnostic uncertainty among clinicians.

The root cause and pathomechanism of the disease is still not understood clearly. It is relatively a newly reported disease and more and more case are surfacing with time, however clinicians are not familiar with the variable symptomatic presentation of the disorder which may lead to incorrect diagnosis and management. FXTAS is caused due to the premutation range of expanded CGG repeats in 5′ UTR of the FMR1 gene. In FXTAS, fragile X mental retardation protein (FMRP) is produced in normal range but the mRNA level is increased significantly in the brain cells and leukocytes [12, 13] which causes more cellular injury, leading to increase morbidity and ataxia in aging males [14, 15]. In FXTAS, ubiquitinylated inclusions have been shown in brains and non-neuronal tissues [21]. RAN proteins have been revealed to be a component of the ubiquitinylated inclusions in FXTAS [22]. The premutation of carriers of FXTAS are 1 in 260 females [16] and 1 in 813 males [17]. The penetrance of FXTAS depends on the age of the person such as 40% of males over 50 years of age [18] while 8% of female carriers are over 40 years of age [19]. There should be high risk of suspicion of the risk of disease development in the patient’s family [11].

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Polymerase chain reaction based advanced molecular techniques has helped us to identify DNA methylation pattern that provide more sensitivity and specificity in diagnosing the disease rather than karyotyping under microscope which has minimal sensitivity and specificity [10]. Randi Hagerman et al reported autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) in boys with the Fragile X premutation carriers, and even those who do not present clinically, may be at increased risk for an ASD and/or symptoms of ADHD.

If the premutation is identified through cascade testing, then further assessment should be carried out for symptoms of ADHD, social deficits, or learning disabilities [52]. Ursula Froster et al. reported female carriers of the fra-X premutation have a broad variety of psychopathological symptoms and relatives of fra-X carriers should be assessed regarding genotype phenotype interaction [54].

2.3. Fragile X with Primary Ovarian Insufficiency (FXPOI)

FXPOI is caused by expanded CGG repeats in 5′UTR of FMR1 gene. Most females carrying CGG repeats in the range of 55–200 have a probability of developing hypergonadotropic hypogonadism resulting in early menopause effectively before the age of 40 years.

It is considered as a premature ovarian failure (POF) with a frequency of 1 in 350 in the general population. Primary ovarian insufficiency leads to positive feedback in hypothalamic gonad axis resulting in elevated level of follicle-stimulating hormone (FSH). Decreased level of anti-
Mullerian hormone has also been found in this disorder. The reduced level of estrogen due to ovarian failure in FXPOI leads to endothelial dysfunction [23], bone fracture [24], and early onset of coronary heart diseases [25] and significant perimenopausal symptoms. In addition to all the above women with early menopause also have psychosomatic and mood disorders symptoms in form of anxiety, depression, somatization disorders, and various other psychological problems [26].

Huang et al recently concluded close association between premutation of the FMR1 gene and increased susceptibility to idiopathic POI (POI and diminished ovarian reserve) of each stage and no correlation between intermediate repeat length or allele of the FMR1 gene and the severity of idiopathic POI [45].

2.4. Fragile Xe Syndrome with Intellectual Disability (FRAXE ID)

David R. FitzPatrick & R. Frank Kooy et al [2] described molecular characterization of an autosomal FSFS (Folate sensitive fragile sites) called FRA2A on chromosome 2. An expansion of a CGG repeat within the 5′ UTR or promoter region of the respective gene subsequently resulted in silencing of the neighboring gene AFF3. Expansion of the AFF2 CGG repeat causes FRAXE ID.

2.5. Autistic Spectrum Disorder (ASD)

R. Frank Kooy & David R. FitzPatrick et al [3] also reported de novo occurrence of the 7p11.2 folate-sensitive fragile site FRA7A in a male with an autistic spectrum disorder (ASD) due to a CGG-repeat expansion mutation (450 repeats) in a 5′ intron of ZNF713. Mariel Ormazábal et al reported autistic spectrum disorders in one third of the patients, and affects males with higher prevalence [50].

2.6. Neuronal Intranuclear Inclusion Disease (NIID)

NIID is a neurodegenerative disease characterized clinically by various combinations of cognitive decline, parkinsonism, cerebellar ataxia and peripheral neuropathy, and neuropathologically by eosinophilic hyaline intranuclear inclusions in the central and peripheral nervous systems as well as in other tissues including cardiovascular, digestive and urogenital organs [29,30,31,32] and age of onset usually ranges from infancy to late adulthood. An autosomal dominant mode of inheritance has been thought [33, 34, 35] of previously but about two thirds of cases have been reported to be sporadic in nature [31].

Recent advances include characteristic magnetic resonance imaging (MRI) findings, including high-intensity signals in diffusion-weighted imaging (DWI) in the corticomedullary junction and eosinophilic intranuclear inclusions in skin biopsy, has been described as useful diagnostic hallmarks for NIID[36,37]. Recently lot of late adult onset NIID cases has been reported from Japan and China which gives us more insight about repeat expansion spectrum [4, 31, 35, 38, 39].

Similarity has been found in the MRI findings between NIID and FXTAS and the presence of eosinophilic intranuclear inclusions[21,31,35]. It is found that NIID shares a common molecular basis with FXTAS—a disease caused by mildly expanded CGG repeats (premutation) in the 5′ untranslated region (UTR) of FMR1, with 55–200 repeat units.[11] By TRhist technique [40] recently few researchers found accumulation of short reads filled with CGG repeats in the 5′ UTR of NBPF19 (NOTCH2NLC) in NIID.

Fiddes et al. [41] reported that NBPF19/NOTCH2NLC (NOTCH2NLC-like paratype) had variable copy numbers with the frequencies of zero, one and two copies being 0.4, 6 and 92%, respective, indicating that haploinsufficiency of NBPF19 is unlikely to cause NIID.

2.7. Oculo Pharyngeal Myopathy with Leukoencephalopathy (OPML)

Noncoding CGG repeat expansions has been found in oculopharyngeal myopathy with leukoencephalopathy in LOC642361 locus with mild ataxia, tremor, oculopharyngeal myopathy, white matter involvement (cerebrum>cerebellum) with high DWI signal intensity [4]

2.8. Oculo Pharyngoe Distal Myopathy (OPDM)

It is considered as an autosomal dominant disease and its non coding CGG repeat expansion in LRP12 locus in 5′UTR presents with characteristic distributions of muscle involvement, including ptosis, external ophthalmoplegia and dysphagia because of the weakness of the masseter, facial, pharyngeal and distal limb muscles [27, 28, 42] with no specific brain MRI findings and pathologically characterized by tubulo filamentous inclusions [4, 42, 43].

Till date cause of OPDM is not well understood, however biopsied muscle specimens of 17
families and 17 sporadic patients with OPDM confirmed the presence of myopathic changes with rimmed vacuoles (which is consistent with the diagnosis of OPDM) [44].

3. DISCUSSION

These trinucleotides CGG repeat expansion disorders (TREDs) which we have discussed primarily affects the nervous system and commonly lead to neurodegeneration through toxic protein gain or loss of function, and toxic RNA gain-of-function mechanisms. However, recent advancement in genetics which discovered unconventional Repeat Associated Non-AUG (RAN) translation from putatively non-coding regions of the genome has made things more difficult and complicated for clinicians and researchers to predict the genotype and phenotype of this type of diseases. Mechanism of RAN translation and how nucleotide repeats such as RNA and translated proteins influence liquid-liquid phase separation, membrane less organelle dynamics, and nucleocytoplasmic transport need more understanding [5].

Alexander E Linsalata et al recently reported multiple modifiers of toxicity and RAN translation from an expanded CGG repeat in the context of the FMR1 5’UTR. These include the DEAD-box RNA helicase belle/DDX3X, the helicase accessory factors EIF4B/4H, and the start codon selectivity factors EIF1 and EIF5. Disrupting belle/DDX3X selectively inhibited FMR1 RAN translation in Drosophila in vivo and cultured human cells, and mitigated repeat-induced toxicity in Drosophila and primary rodent neurons. These findings implicate RNA secondary structure and start codon fidelity as critical elements mediating FMR1 RAN translation and identify potential targets for treating repeat-associated neuro degeneration in future [47]. Ma et al reported screening for CGG repeat expansion mutation in FMR1 gene as a recommended investigation in women with the history of spontaneous abortion or induced abortion due to delayed growth of the embryos [48]. Thomas L. Wise reported FXS patients also frequently have autistic-like symptoms, suggesting that the signaling pathways affected in FXS may overlap with those affected in autism. He also suggested that the pathways altered by the loss of the FMR1-encoded protein (FMRP) may overlap with the pathways affected by changes in Igf signaling or that one or more of the proteins that play a role in Igf signaling could interact with FMRP. IGF2 may play a more important role in altering the AGS phenotype (and possibly autism) than IGF1 [51]. H Zhang et al reported previously about reelin gene alleles and susceptibility to autism spectrum disorders in polymorphic trinucleotide repeat (CGG/GCC) diseases [53].

4. CONCLUSION

Hereby, we further expand the disease spectrum caused by mutation of CGG repeat motif. With further development of genetic techniques, more diseases related to this trinucleotide repeat expansion is expected to be reported in near future. More studies are required at molecular level to understand the real mechanism about the unstability of short microsatellite sequences, RAN translation, organelle dynamics and nucleocytoplasmic transport.

ACKNOWLEDGMENT

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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