

## MECP2 Mutations Associated with Rett Syndrome - Molecular Approaches

V Ramakrishnan\*

Genetics Lab, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Kelambakkam, Chennai, India

\*Corresponding author: V Ramakrishnan, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Chettinad Health City, Kelambakkam, Tamil Nadu, India, Tel: +9840636315; E-mail: [rkgenes@gmail.com](mailto:rkgenes@gmail.com)

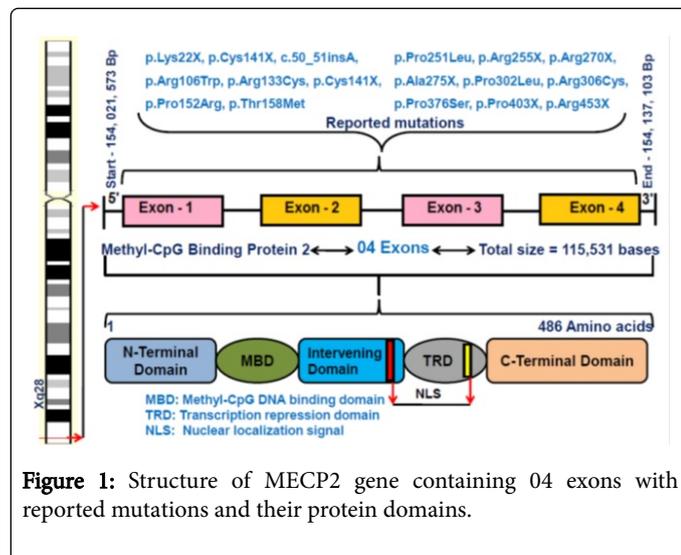
Received date: October 18, 2016; Accepted date: October 31, 2016; Published date: November 04, 2016

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### Short Communication

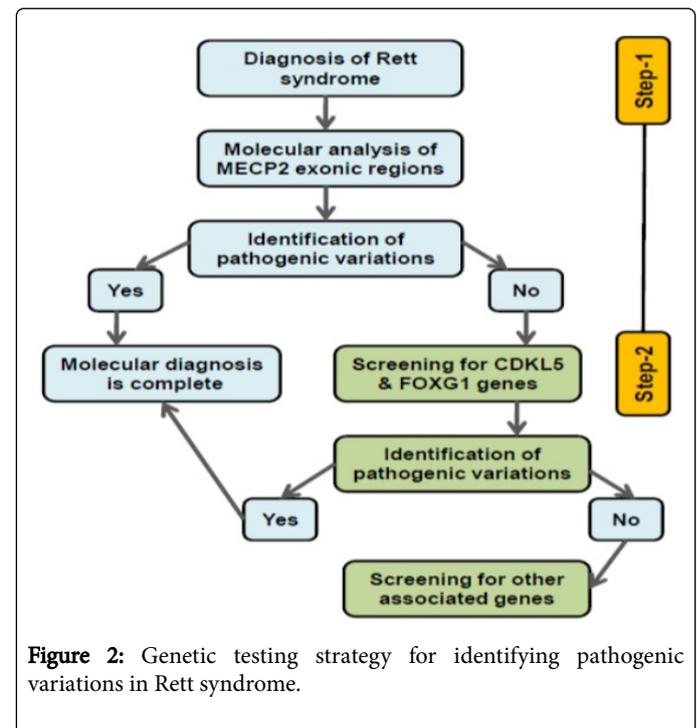
Rett syndrome (RTT) is defined as a monogenic, X-linked neurological disorder leading to delayed neurodevelopment in females and characterized by scoliosis, seizures, microcephaly, intellectual disability, repetitive hand movement, impaired sleep, excessive saliva, autonomic symptoms, typically little or no verbal skills. Worldwide RTT has been estimated to affect 1 in every 10-15,000 live female births in all ethnic groups [1]. Methyl-CpG binding protein 2 (MECP2) located at chromosomal position q28, containing 4 exons with five protein domains, was identified as the gene responsible for RTT in the year 1999 [2]. This gene was identified by the binding of methyl-CpG binding domain (MBD) to nucleic acid sequences that are being methylated at cytosine. Subsequently, the functional domains such as the nuclear localization signal (NLS) and transcriptional repression domain (TRD) were also identified [3]. MECP2 protein involve in various functions such as chromatin architecture, heterochromatin rearrangement, nuclear organization, regulates splicing and DNA methylation [4].

Rett syndrome is caused by point, sporadic mutations, polymorphisms, intronic variations in the MECP2 gene and greater than 1000 distinct MECP2 mutations have been documented in various ethnic populations, resulting in 738 distinct amino acid changes observed in these 3 functional domains [5]. Figure 1 explains the structure of MECP2 gene containing exons with pathogenic mutations and their protein domains. The mutational hotspots occur in the two domains such as, methyl-CpG binding and transcriptional repression domains affecting both the isoforms of MECP2 [6].



The Rett syndrome is clinically classified into the typical and atypical forms. In the atypical forms, some specific variants have been described such as the “Hanefeld variant” showing the pathognomonic early onset of seizures, the “Congenital variant” onset of the symptoms from birth and “Zappella variant” characterized by mild abnormalities, late speech [7].

The Hanefeld variant (early-onset seizure) is clinically characterized by seizures with the subsequent development of rett syndrome features. A translocation involving in the chromosome 1p13.2-p13.1 has been reported in a patient with atypical RTT [8]. There are four stages in this disorder; Stage-1 is early onset, starts from 6-16 months of age, Stage-2 the rapid destructive stage begins in 18 months, Stage-3 the pseudo-stationary plateau stage starts from age 3-10 years, Stage-4 late motor deterioration stage lasting for years [9]. A functional consequence of mutation (c.48C>T) in the exon-1 of MECP2 with typical form of Rett syndrome, C/T transition leads to change in the codon, which is coding for the same amino acid (Glycine to Glycine) and at transcriptional level (silent change) this mutation affects the gene expression leading to removal of 16 nucleotides of the coding sequence from the transcripts of MECP2 [10].



Researchers have documented mutations in Forkhead box G1 (FOXG-1) and Cyclin dependent kinase like-5 (CDKL-5) genes in individuals who have atypical/congenital RTT, not all the carriers of

MECP2 mutation show clinical symptoms of this disease, but still the pathogenesis of rett syndrome remains inconclusive [11]. A study published in the year 2014 from India with 34 RTT patients screened for variations in genes like MECP2 and FOXP1 which identified novel mutation (frameshift) p. D263V fsX190 in RTT. This mutation was observed at forkhead binding domain, resulting in the disruption of secondary structure making it non-functional protein. These probands did not harbor any mutations in the MECP2 and CDKL5 genes. This FOXP1 transcription factor acts as transcriptional repressor through DNA binding in the embryonic telencephalon and also in other neurodevelopmental processes [12]. Similarly, a study from Italy documented the mutations in CDKL5 gene in two patients with the clinical symptoms of RTT. Both the patients had frameshift deletions in CDKL5 gene; first patient with 9 years of age had mutation in 5th exon (c.163\_166delGAAA), this deletion interrupts the catalytic domain which in turn lead to non-functional CDKL5 and the second patient with 8 years of age harboured variation in 18th exon (c. 2635\_2636delCT), this change eliminates the putative signal peptidase-I serine in the active sites [13].

Multiplex ligation-dependent probe amplification, Bi-directional DNA Sequencing Array-based comparative genomic hybridization and Quantitative fluorescence are the methods available for detecting variations in the genes. Figure 2 illustrates the genetic testing strategy for identifying pathogenic variations in Rett syndrome. We are in the post genomic era where the knowledge of genomics is getting broader, it is clearly documented that MECP2 gene mutations contribute to the major pathogenesis of the disease, with the help of next-generation sequencing technologies, a mutation panel can be designed comprising all the mutations observed in the genes associated with this syndrome and use them for genetic diagnosis.

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