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MeCP2 Protein in RETT Syndrome and Autism.

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ABSTRACT

The RETT(RTT) syndrome is a x-linked dominant disorder in the development of nervous system. It has been found out that mutation in the MeCP2 gene considered as a transcription suppressor is responsible for the occurance of 90% of RETT syndrome. Autism is a common brain developmental irregularity that shows complicated genetic mechanisms on analysis. However, it is not very well known if the mutation in the MeCP2 gene may lead to autism. This review explains both the disorders and describes the role of MeCP2 in the functioning of the disease. The review also summarizes the experiment performed on 69 autistic females to observe the MeCP2 gene mutation in them.

Keywords: RETT syndrome (RTT), autism, MeCP2 gene

INTRODUCTION

The RETT syndrome is a x-linked dominant disorder in the development of nervous system. Normal development of the brain and the nervous system occurs till six to eighteen months of age in female children after which the symptoms start showing.[1] It is usually found in females since it is usually fatal in males (due to presence of just one X chromosome). However, studies have found a small number of males to also develop the disease. The common symptoms include seizures, irregular sleeping patterns, a C-shaped spine. During the first six to eighteen months of age in females with this disease normal mental development occurs after which there is a developmental pause followed by reverse mental development. [2] Other symptoms include repeated typical hand movements, bouts of screaming and crying, hyperventilation and social communication problems. Most of these symptoms are also observed in autism. [3]

Autism is a common brain developmental irregularity that shows complicated genetic mechanisms on analysis. The step-wise development of these genetic disorders involve both environmental as well as genetic factors. Two such development steps are prenatal imprinting and X-chromosome inactivation that are involved in various autism associated disorders such as 15q duplication, RETT and Fragile-X syndrome. The brain analysis of the people with RETT syndrome show that they have similar cerebral and pathological abnormality at its primary level [4]. Firstly, the cell size and the branching in dendrites becomes smaller both in the case of neurons in RETT patients as well as autistic brains [4][5]. The spines in the neurons also do not undergo full maturation in case of both RTT and autism brain [6].

DNA methylation is the process by which methyl groups are added to the DNA and it is done to repress transcription. MeCP2 gene codes for the MeCP2 protein which is responsible for the proper functioning and maturation of nerve cells. The MeCP2 gene acts as a repressor switch to “turn off” various genes so that they do not make the proteins when they are not needed by the body. MeCP2 binds to the methylated cytosine sites of the CpG regions of DNA. They then block the transcription factors that ultimately leads to the suppression of transcription. [7]. Mutation in the MeCP2 gene is the main cause of the RETT syndrome. Mutations in the MeCP2 gene can also cause other neural development diseases like X-linked mental retardation (XLMR), Angelman’s syndrome, autism [8]. However, the exact involvement of the RETT gene mutation in the development of each of these genes individually is not constant. More than ninety five percent of RETT syndrome is caused due to the mutation of this gene but the mutation is not responsible for all types of autism.

Clinical Features of RTT and How to Identify It

The identification and diagnosis of the disease is based on a series of clinical features recognized and acknowledged by experts [9]. It is defined by normal physical and mental development followed by a stagnation after which a regression in the development occurs. Social interaction, proper eye contact, proper speech ability becomes impaired during the regression period. Proper walking ability also becomes impaired. The symptoms stabilize after the regression period which is also a distinguishing feature of this disease.

The phases of RTT syndrome

The development of the disease can be categorized into 3 different levels or phases The child born after a normal

and uncomplicated pregnancy has a normal physiological and menta development till six months of age till it reaches the phase1 [10] During this phase development slowing occurs and the child fail to do all the activities that the other children of the same age are able to do. Then the child reaches phase 2 [10] which is a stage of regression at one to four years of age though the age is variable. Repeated typical hand movements occur in this stage, the child starts showing social anxiety, lack of communication, disinterest to the surroundings and starts showing behaviors that can be confused with autism. After the regression period the child reaches phase 3 [10] where little improvement may be observed, however repeated typical hand movements, difficulty in walking and posture becomes more prominent in this phase. This phase continues till late teens and twenties. The phase [10] is the final phase of the disease some patients shift directly from phase 2 to phase 4 if they are not able to walk at all, others remain in phase 3 and may never enter phase 4. In this phase the patient loses their ability to walk completely and may lead to complete rigidness. The patient may also show some symptoms of Parkinson's disease.

Additional symptoms of RETT syndrome

In addition to repeated typical hand movements other abnormal muscle twitching and spasms are also observed. The child initially born with low amount of muscle tone can develop to abnormal amount of muscle tone especially in the lower body regions leading to jerking movements, spasms and tremors. Teeth grinding and chattering are also observed. Normal growth of physical characters is not observed in RETT syndrome. There is an absence of proper development and growth of the head and body [11]. During the birth of the child all the physiological parameters are normal however, the fail to develop and can be observed when the child is two months old. Patients also suffer from digestive and other abdominal problems. Since this disease causes problems in muscle movement and balance even in the abdominal tract it also causes problem in food ingestion, digestion as well as expulsion of waste from the body thus leading to various abdominal problems [12]. People suffering from RETT suffer from muscle spasms throughout their body [13]. They are given medications to control these spasms. A lot of people suffering from RETT syndrome suffer from breathing problems and can even lead to occasional stopping of breathing for short periods of time leading to loss of consciousness [14]. The breathing problems can increase during periods of stress and wakefulness however does not completely disappear during sleep. This ultimately leads to coronary problems and may even lead to unexpected death [15]. The patients of RETT syndrome show a lot of autism like features [16] such as reduced ability of social interaction, communication, unwillingness to look at others, increased apprehension and nervousness in especially new and unexpected situations and surroundings [17]. Some patients with RTT syndrome have the tendency to harm themselves they also have difficulty in sleeping [18].

Not all people suffering from RETT syndrome show all the above-mentioned symptoms therefore there are other non-classic forms of the disease. In the "preserved speech variant" form of RTT syndrome the patients regain their ability to talk partially or even completely after phase 2, they even regain their ability to walk, repeatitive hand movements lessen [19]. Almost all the people suffering from this particular form of RETT syndrome show mutations in MeCP2 gene. "early seizure" form of RTT involves seizures and spasms in the initial years of life which distinguish them from the common forms of RETT syndrome [20]. The people suffering from this form of RTT show symptoms to autism including reluctance in social conversations and eluding direct eye-contact with others. However instead of mutations in MeCP2 gene mutations in Cyclin dependent kinase like 5 (CDKL-5) are more commonly found [21]. In "Congenital variant" form of RETT syndrome there is absence of proper brain development from birth. Since from the beginning there is an absence of proper brain development determination of a proper regression period becomes difficult. Along with mutations in MeCP2 gene mutations in the FOXG1 gene are also found to be responsible for this form of RTT syndrome [22].

Role of MeCP2 gene in RETT syndrome

In 1999 [23] it was discovered that the mutation in the MeCP2 gene was involved in the onset of RETT syndrome. Since then the study about its gene and its role in the onset of the disease has become more predominant. MeCP2 gene was thought to be a universal suppressor of transcription [24] but it was found out that it is most required during the period after childbirth when the expression is very high. The maintenance of the functioning of MeCP2 gene is complicated and not only involves the rise of transcription but also includes splicing and polyadenylation one after the other. Earlier it was assumed that MeCP2 links with transcription suppressor sin3A and histone deacetylase (HDAC) and thus implements a procedure for the suppression of the transcription in the CpG regions of DNA [25]. It has been found out that MeCP2 suppresses transcription of the methyl carrying promoters in-vitro and the promoters carrying SV40/GAL4 and this suppression can be altered to some extent using a HDAC suppressor. However, the above-mentioned role has been disregarded for the suppression of transcription in brain cells which is where it has been found out that MeCP2 does not form a stable linkage with either sin3A or HDAC [26]. Even though MeCP2 was considered to be a global suppressor of transcription methylated and imprinted genes continue to be non-functional in cells with the absence of MeCP2 or with a mutation in MeCP2 [27]. It has been observed with the help of chromatin immunoprecipitation assay that MeCP2 can form linkage with a number of promoters that have been methylated like the H19, Bdnf, Sgk and Fkbp5, Dlx5 and Dlx6, Id1-3, Crh, Fxyd1, and Gtl2 which exhibits a superior rate of transcription in cells that show mutation in the MeCP2 gene. Moreover, it has been observed that

the inhibition of MeCP2 gene does not suppress the function of H19 and SNRPN/snrpn . This shows that the function of MeCP2 gene in transcription suppression is not uncomplicated. MeCP2 incubated with DNA from a compact elliptical structure with strong bonds formed within the molecules in DNA strands. This shoes that MeCP2 was capable of making strong bonds. However, this strong bond formation does not depend on the methylation activity this implies that the regions containing the methyl group in the CpG islands denote the locations of nucleus addition of nearby chromatin for the condensing of chromatin. This is the constructional form of MeCP2 functioning in our body. The third type of MeCP2 functioning is the "chromatin looping" which gives proof of the functioning of MeCP2 in the formation of chromatin loop according to the observations of the chromatin immunoprecipitation assay that also shows that the suppression or silencing or absence of MeCP2 increases the function of Dlx5 and Dlx6 regions showed that 59% of the MeCP2 was outside the boundaries of the gene 5.9% was in the CpG region [28]. Of all the promoters attached to MeCP2 sixty percent of them are functionally active and six percent of them are bound to methyl group. JUNB, an intermediate recent gene responsible for the occurrence of RTT is one of the genes who functioning is dependent on the binding of MeCP2 to the promoter attached to the methyl group. Chahrour et al. examined the hypothalamus of mouse where there was both an absence of MeCP2 and multiple copies of MeCP2 and these examinations provided evidences that showed upto 85% of the genes in the hypothalamus were overexpressed and the rest were downregulated by the MeCP2 gene [29]. Six genes were selected for further examination by bisulfie study and ChIP occupancy to study the different extent of methyl addition to the promoter. It was found that MeCP2 binds to the transcriptional catalyst BRE1 at the promoter site Sst a gene whose expression is increased during MeCP2 duplication which shows that MeCP2 may show an activation mechanism. All the above results show that MeCP2 have a functionality greater than just a transcription suppressor [29].

Autism

Autism is a collection of mental growth and maturation disability where the people do not get involved with the surroundings socially, they do not like to meet the eyes of others tend to talk less or not talk at all and seem to be withdrawn from their surroundings in general. The number of people suffering from autism has increased in the last ten years and is seen mostly in males rather than females. The reason of this might be because the females suffering from this disease may not be identified from this disease or there might e certain preventive measures in females against this disease. The earliest individual who used the term "autism" in today's sense was Leo Kanner who in the year 1943 described about 8 males and 3 females who showed "an innate inability to form the usual, biologically provided affective contact with people". He established the term "infantile autism". Leo Kanner and Hans Asperger are considered the pioneers of the study of autism done today. The autism is a result of genetic and environmental elements. The genetic elements leading to autism include both genetic and chromosomal abnormalities. The people born in families with existing cases of autism show greater chances of developing autism. A single gene mutation can cause alterations in the maturation of nerve cells involve in the process of synapsis. Chromosomal abnormality can impair the proper maturation and development of nerve cells, brain, and their functioning including synapsis. Recently it was discovered that the gene ENGRAILED2, a gene responsible for the proper development of the brain was associated with the occurrence of about 40% autism. "UBR3A locus", "GABA system genes", "serotonin transporter gene" have also been found to be related to the occurrence of autism.

The environmental elements include the elements not related to genes or chromosomes that might lead to the occurrence of autism. These elements include those affecting the health of the mother before the birth of the child thus affecting the child as well as well as those affecting after the birth of the child. These include toxic substances, bacterial and viral infections, diseases, physical and mental stress. Lately researchers are suggesting that the disease is caused due to a combination of genetic and environmental elements.

Clinical Characteristics of Autism

The symptoms of autism are apparent in the first three years of age and these include reluctance of social participation, the children do no talk to others or even meet their eyes, they tend to hurt themselves show bouts of anger, screaming, mental deficiency, and are unconcerned about their surroundings. These are often accompanied by persistent body movements on repeat such as hand, head or leg movements, continuously moving back and forth, they have problems with sleeping and problems with digestion, occasional spasms and tremors and many other symptoms. They also have a problem with learning and memorizing.

All the above-mentioned symptoms are the main distinguishing symptoms of autism. However, it becomes difficult to recognize the disease when the people do not show the typical symptoms or when the patients are found outside the typical age boundary. Symptoms of non-engagement to the surroundings, showing bouts of anger rage and screaming, not sleeping properly in infants become difficult to be characterized as autism. Till one year of age children with autism cannot be distinguished from those not suffering from the disease. By the age of three the autism patients start showing distinct characters which can be easily recognized.

MeCP2 Gene in Autism

Both RETT syndrome and autism have similar phenotypic outcomes and both the disease affect a large number of people. Both the disease are affected by

genetic factors which however are not well known in the case of autism. In a very small number of autistic girls the disease was found to be due to the mutation in the MeCP2 gene [31]. Study of linkage has also shown the unequal levels of passing of MeCP2 gene variants in various autistic patients bringing forth the possibility of a relation between MeCP2 gene and autism [32]. Less functioning of the MeCP2 gene is observed in the frontal lobe of the brain of autistic patients that is related to increase in methyl group addition to the promoter of MeCP2 [33]. The unequal level of MeCP2 gene in autistic patients is due to the differences in the three regulatory components of the MeCP2 gene which is observed very frequently in autistic patients compared to normal individuals [34]. Latest study showed autism with MeCP2 duplication obtained from a mother who was a carrier and also had nervous disorder. This also showed the linkage of autism with MeCP2 protein.

MATERIALS AND METHODS

The experiment below was performed to determine if there was any mutation in the MeCP2 gene in a greater sample of patients (only girls) suffering from autism. Since it is already well known that mutation in MeCP2 gene in girls lead to RETT syndrome, this experiment was conducted to find out if there was any link between autism and MeCP2 gene mutation.

Two hundred and eighty-one autistic patients from families with no history of autism or from families with two or more earlier cases of autism were examined to recognize the genes that increase the possibility of the occurrence of autism. The patients were rejected if they had medical elements related to autism or elements if they affected the brain and nervous development in childhood that might ultimately make the examination and its analysis more complex [35]. The Vineland Adaptive Behavior Scales (VABS) [36] is a fixed quantification of normal behavior, interaction and taking ability with others and the basic ability of taking care of oneself. The process includes a half-arranged interview with a primary caretaker. VABS- defining role of less than 18 months were not included for further analysis. The recognition of autism was based on the Autism Diagnostic Interview-Revised (ADI-R) [37] the rationality of which was based on the VABS-defining role of greater than 18 months. The ADR-I recognizes autism on the basis of DSM-IV and ICD-10 recognizing method. The families and caregivers of all the 281 patients were informed about all the experimental procedures and their effects. Of the 281 patients examined the 69 females recognized with autism were further examined for mutations in MeCP2 gene. Genomic DNA from the blood samples of the patients were secured and this DNA was increased in quantity using PCR where the PCR primers were chosen on the basis of MeCP2 gene. The sorting of the patients on the basis of MeCP2 mutation was done using Denaturing High Performing Liquid Chromatography WAVE DNA Fragment Analysis System that can indicate the ideal temperature for the study. MeCP2 mutation was used as a positive control. Any divergence from control was used for sequencing. The results of PCR and sequencing were purified. The sequencing results were purified using the Edge Centriflex Gel Filtration Cartridges.

To determine the inactivation proteotype of X-chromosome Hpa-II restriction endonuclease was used to cut one microgram of genomic DNA at the sites of methyl group. The digested or undigested DNA (100 micro-gram) was magnified by PCR using a phospholabelled primer. The magnified PCR result contained the Hpa-II site and the “androgen receptor gene” occurring in recurrence in more than one form. The PCR results were segregated using gel electrophoresis (6% PAGE) and observed on a “phospher screen”. The band strength was measured by “Phosphorimager” using “ImageQuant” software. The alleles shorter in size multiplies easily so a correction factor was applied to modify the strength of the longer digested allele. Finally, the inactivation proteotype of X-chromosome was determined by dividing the band strength of the shorter allele with the sum of the intensity of the shorter and longer digested alleles.

RESULT

Of all the 69 females examined only 2 of them were identified with mutations in MeCP2 gene. However, neither of them showed all the symptoms associated with identification of RETT syndrome.

The first patient was 16 years old and had no developmental abnormality before and after birth. There was no history of RETT syndrome or autism in the family. She spoke her first word and first phrase on time but her speaking skills stopped improving at 18 months of age. The patient had no problem in breathing and no “toe-walking” that is associated with autism. She does not answer to oral stimulus but expresses her requirements with simple expressions. She did not show any other repetitive movement except occasional side to side head movement. Further analysis showed the head diameter to be one-fiftieth percentile of the original diameter and the initial head diameter was within normal boundaries. Her left hand was bent at the elbow and wrist but there was no abnormality in her walking. VABS defined the mental capacity to be equal to 60 months [36].

The examination of the MeCP2 gene showed a deletion mutation at the 41bp location nucleotides 1157-1197 which shortened the amino acids from usual 486 to 389 in length. This deletion mutation was also found earlier in two girls with RETT syndrome. The MeCP2 gene analysis for the rest of the immediate family members showed no abnormality. The father however, was not present for the examination of the gene.

The second patient was 10 years old and showed no developmental abnormality 4 and after birth. At 10 months age she showed a tendency of over activity and taking early morning walks. The patient started talking at 12 months and all her motor skills developed on time but at 30 months her motor skills and communication started to retrograde. An irregular non-specific

abnormality was observed in the electroencephalogram (EEG). Autism in the patient was identified at 42 months age. She answered to oral stimulus with one-word answers that were recognized by her caretakers but not by others. She also expressed her requirement with simple expressions. She did not show any repetitive body movement that is usually associated with autism. At present she walked with two feet spaced wide apart. Further analysis showed the head diameter to be one fortieth percentile of normal head diameter at the present. The initial head diameter at birth was not obtainable. She had cross-eye in her left eye.

The MeCP2 gene examination showed a substitution mutation in the nucleotide 880C ->T which was one of the most common mutation in RETT syndrome. The MeCP2 gene analysis done for rest of the family members showed no abnormality.

The mutations found in both the patients are usually found in people with RETT syndrome, so it was tested to determine whether it was due to asymmetrical X chromosome inactivation. The examination of blood leukocytes showed minimal asymmetrical inactivation. It showed inactivation proteotype of 31% for patient one and 29% for patient two. XCI was considered asymmetrical if it was less than or equal to 20% or greater than or equal to 80%.

DISCUSSION

Out of the 281 females tested only two females were tested positive for mutation in the MeCP2 gene. The autism in these two females were affirmed by using the ADR-I which is the ideal method for affirming all the genetic analysis involved in autistic patients. Among both the patients not one of them show all the symptoms associated with RETT syndrome that are described in the “Hagberg and Skjeldal model”. The dissimilarity in the seriousness associated with MeCP2 gene mutation is because of the differences in X chromosome inactivation (XCI). Study shows that the scope of XCI in females who show mutation in the MeCP2 gene but no autism is about 90-100% and they do not show any external symptoms. All the patients analysed in this experiment were recognized with autism which can be regarded as a subgroup of RETT syndrome, thus total inactivation of X chromosome would not be observed. The proper physical and mental development in the initial months with a sudden retrogression in development after that is found in both RTT and autism. The results observed for the experiment mentioned here showed the common clinical characters for both RETT syndrome and autism especially in the early stages of childhood. However, the genetic mechanism between both the diseases are different so there is a genetic heterogenicity between both the diseases.

So, should all autistic patients(females) be screened for MeCP2 gene mutation?

Kerr-et-al. [38] advised that patients with physical and mental disorder in late childhood should be tested for mutations in MeCP2 gene however, he did not specify the gender. Hammer-et-al. [39] advised that patients with mental retardation should also be screening for MeCP2 gene mutation since autism and mental retardation show similar characteristics. The advantages of MeCP2 gene mutation is that there can be an understanding whether the disease can occur again. Any issues with reproduction can also be identified. There is also an assessment of relatives that can help to identify the syndrome beforehand.

CONCLUSION

Autism occurs with very less frequency in girls, however the RETT syndrome occurring mostly in girls due to mutation in MeCP2 gene therefore discovering a relation between the two becomes even more fascinating. There are similarities between the symptoms of the two diseases as well a difference between the symptoms between the two diseases so there is a confusion whether both the diseases are due to mutation in the MeCP2 gene or if they are not. However even if there is no relation between MeCP2 mutation and autism, it has definitely been proved that variation in genetic factors lead to autism.

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