MECP2 Gene-Related Disorders

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Abstract

Classic Rett syndrome is a neurodevelopmental disease in females caused by mutations in the *MECP2* gene. With recent advancements in molecular techniques, point mutations and small and large deletions/duplications have been identified in the *MECP2* gene associated with varying disease phenotypes in both males and females. This review on *MECP2* gene-related disorders discusses the various disease phenotypes associated with *MECP2* gene mutations.

MECP2 gene (OMIM No. 300005) is located on chromosome X (Xq28) and has been known since long to be the causative gene for Rett syndrome in females. But with the advent of new advanced molecular techniques, new point mutations and copy number changes are being increasingly recognized as the cause of different intellectual disability phenotypes of varying severity in both males and females. Due to the phenomenon of X inactivation in females, *MECP2*-related genetic diseases have a phenotypic spectrum varying from being clinically silent to severe neurodevelopmental syndromes. Earlier it was thought that *MECP2* disorders are lethal in males but now it is being increasingly recognised that *MECP2* accounts for a clinically significant proportion of intellectual disability phenotypes in males.

The *MECP2*-gene related disorders include:

1. Rett syndrome – classical and atypical
2. Severe neonatal onset encephalopathy with microcephaly in males
3. *MECP2* duplication syndrome
4. Intellectual disability associated with manic depressive psychosis, pyramidal signs, parkinsonian features, and macro-orchidism (PPM-X syndrome)

1. Rett syndrome (OMIM # 312750) – Classic

Classical Rett syndrome is an X-linked neurodevelopment disorder with a prevalence of 1 per 10,000 girls. The most important feature to diagnose Rett syndrome is regression after a period of normal development and postnatal microcephaly (Neul et al., 2010).

The revised diagnostic criteria given in 2010 are as listed in Table 1 (Neul et al., 2008).

Table 1 Diagnostic criteria for Rett syndrome.

Inclusion criteria	Exclusion criteria
1. Secondary / postnatal microcephaly	1. Brain injury secondary to trauma, asphyxia and infections
2. A period of regression followed by recovery or stabilization	2. Grossly abnormal psychomotor development in the first six months of life.
3. Partial or complete loss of acquired purposeful hand skills and stereotypic hand movements (Figure 1).	
4. Partial or complete loss of acquired spoken language	
5. Gait abnormality	

In a patient with Rett-like features but no regression, the patient should be followed up till the age of 5 years, and in case there is no evidence of regression by 5 years, the diagnosis of Rett syndrome should be questioned. The other important features include- seizures, failure to thrive, scoliosis and osteopenia. Autistic features, apnea and bruxism are also observed but are more indicative of atypical Rett syndrome. Differential diagnoses

include atypical Rett syndrome and other *MECP2* related disorders, Angelman syndrome, cerebral palsy and autism.

Figure 1 A girl with Rett syndrome showing the typical hand movement.

Patients suspected to have Rett syndrome following detailed clinical evaluation need to be confirmed by molecular testing. The first step is sequencing of the *MECP2* gene (exons 1 to 4), which identifies pathogenic mutations in more than 80% of classical Rett syndrome patients (Bienvenu et al., 2000). In the remaining patients, deletion and duplication analysis identifies partial and whole *MECP2* gene deletions in around 8-10% patients with classical Rett syndrome (Hardwick et al., 2007). Treatment is symptomatic and multidisciplinary. Surveillance for development of scoliosis and ECG finding of prolonged QTc is required.

- Genetic counseling and prenatal diagnosis: More than 99 percent of cases of classical Rett syndrome cases are simplex cases, resulting from a *de novo* pathogenic variant and in these cases the risk of recurrence in the next pregnancy is negligible. However, germline mosaicism has been reported. In very rare cases the mother can be a carrier of the *MECP2* gene mutation but might not have any clinical features due to an extremely favourable X chromosome inactivation. In such very rare cases, the risk of recurrence is 50%. Hence, though chances of recurrence in the next pregnancy are rare, prenatal testing can be provided in the next pregnancy considering the possibilities of germline mosaicism and carrier mother with skewed X inactivation.

- Rett syndrome variants / Atypical Rett syndrome: Atypical Rett syndrome/ variants include Rett syndrome patients with neuroregression and postnatal microcephaly which do not fulfil all the criteria given above for the diagnosis of classical Rett syndrome and have more atypical features. Presence of congenital microcephaly, severe progression, preservation of speech, milder presentation and late onset are some of the variations which differentiate these cases from classic Rett syndrome. Genetically also, only around 40-50% have *MECP2* gene mutation and other important genes include *CDKL5* and *FOXG1*. Revised diagnostic criteria for atypical Rett syndrome are given below in Table 2 (Neul et al., 2010).

There are three main atypical Rett syndrome variants:

1. Preserved speech- Zapella variant- As the name suggests, this is a milder form of Rett syndrome with onset of regression at 1-3 years and simple speech recovers by five years of age. Other features include- better retention of hand function, milder intellectual disability and autistic features. The important features of classic Rett syndrome like seizures, failure to thrive, scoliosis and microcephaly are less frequently observed. Gene involved is *MECP2* in majority of cases (30-50%) (Bienvenu et al., 2000)

2. Early seizure variant- Hanefeld Variant- The main diagnostic features of this variant are early onset of seizures, at less than five months, and before neuroregression. The important features of classic Rett syndrome are also less frequently observed in this variant. Mutations are mainly found in the *CDKL5* gene and very rarely in the *MECP2* gene.

3. Congenital variant-Rolando Variant- There is severe psychomotor developmental delay, seizures, regression and severe postnatal microcephaly as early as four months. Typical features found are the autonomic system abnormalities, stereotypical tongue movements and jerky limb movements. Mutations are mainly found in the *FOXG1* gene and very rarely in the *MECP2* gene.

An approach to the genetic testing of classic Rett and atypical Rett syndrome is shown in Figure 2.

Table 2 Diagnostic criteria for atypical Rett syndrome.

Essential Criteria for diagnosis	Any two out of following four main criteria	Any five out of eleven supportive criteria		
Secondary/ Postnatal microcephaly	Partial or complete loss of acquired purposeful hand skills	Breathing disturbances when awake	Bruxism when awake	Impaired sleep pattern
A period of regression followed by recovery or stabilization	Stereotypic hand movements	Abnormal muscle tone	Peripheral vasomotor disturbances	Scoliosis/Kypho-sis
	Partial or complete loss of acquired spoken language	Growth retardation	Small cold hands and feet	Intense eye contact
	Gait abnormality	Inappropriate laughing/ screaming spells	Diminished response to pain	

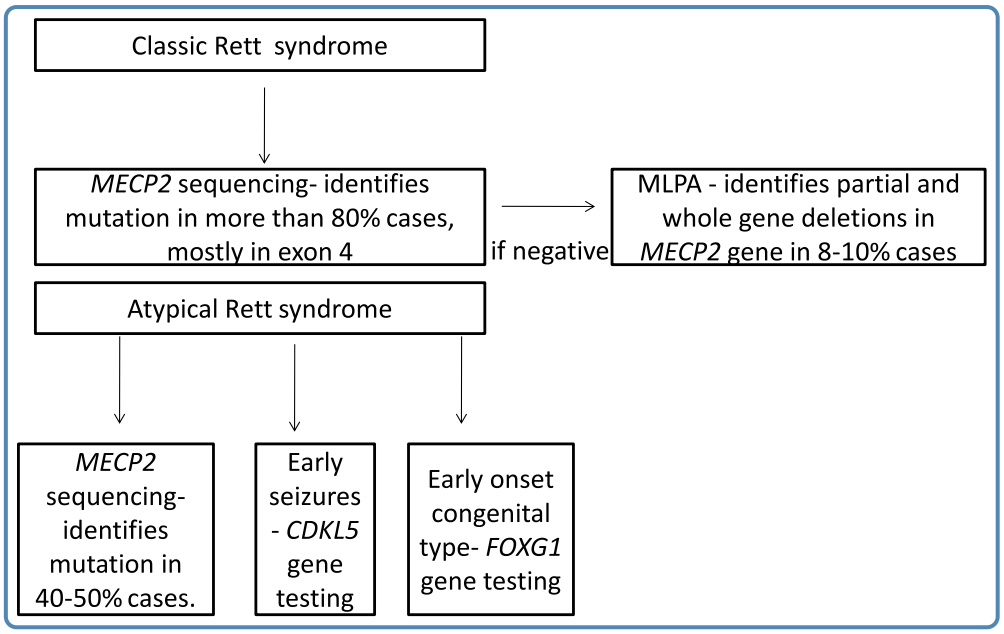

Figure 2 Investigative approach to a case with possible *MECP2*-related phenotype.

2. Severe neonatal onset encephalopathy with microcephaly (OMIM # 300673)

Rett syndrome occurs due to heterozygosity for pathogenic *MECP2* variants in females. As males are hemizygous for *MECP2* mutations (single X chromosome, no *MECP2* produced), it is usually lethal in males. In the rare surviving males, the most common clinical presentation is the so-called severe neonatal-onset encephalopathy with microcephaly, abnormal tone, involuntary movements, severe seizures, breathing abnormalities and death before two years of age. (Kankirawatana et al., 2006)

3. *MECP2* duplication syndrome (OMIM # 300260)

MECP2 microduplication syndrome is a severe neurodevelopmental syndrome seen exclusively in males. The females are asymptomatic carriers. Infantile hypotonia is a predominant feature, which is usually the first presenting sign as severe feeding abnormalities within few weeks of birth. Gradually hypotonia fades way to spasticity especially of lower limbs. There is delay in motor and language milestones. Around 70% males have no speech, and one third never learn to walk. Mild facial dysmorphism like brachycephaly, mid face retrusion, large ears, and depressed nasal bridge is observed. There is an increased predisposition to infections, commonest being recurrent respiratory tract infections. Refractory seizures develop in 50% of affected males. Other features include gastrointestinal dysfunctions, developmental regression and autistic features. Management remains symptomatic and most affected males die by the age of 25 years.

In *MECP2* microduplication syndrome there is duplication of the region encompassing the *MECP2* gene usually 0.3 to 4Mb in size and it can be identified easily with Multiplex Ligation Probe Amplification (MLPA) and cytogenetic microarray. Larger duplications of more than 8 Mb, found in five percent cases, can be identified by karyotype. MRI and EEG show nonspecific changes. It shows complete penetrance in males. Females are always asymptomatic carriers unless there is X- autosome translocation. Many a times, the female carriers might develop psychiatric illnesses.

- Genetic counseling: Mothers of all affected males are always carriers of *MECP2* microduplication, though very rare *de novo* cases have been reported. All carrier females are unaffected due to extremely skewed X inactivation. All mothers being carriers, there is 50% risk of males being affected and 50% risk of the female offspring being asymptomatic carriers in each pregnancy.

One other disorder that needs to be mentioned here, mainly because of close proximity of the region to *MECP2* on X chromosome, **is the Xq28 duplication syndrome (OMIM # 300055)**. It involves a 0.5 Mb region containing 11 genes but not *MECP2*. This is a recently recognised X-linked intellectual disability syndrome characterised by developmental delay and intellectual disability, behavioural defects, obesity, subtle dysmorphism (tall forehead, puffy eyelids, wide nasal bridge, thick vermillion). It may rarely have associated eye and limb abnormalities. Males are all affected and females are either mildly affected (learning disability and dysmorphism) or unaffected (El-Hattab et al., 2015). There is 0.5Mb duplication on the Xq28 region, from intron 22 homologous region 1 to intron 22 homologous region 2 (due to inversion and non-allelic recombination between low copy repeats in this region). The phenotypic effects are due to increased dosage effects of the *CLIC2* and *RAB39* genes in the 0.5Mb duplicated segment. Testing involves identification of the duplicated region by MLPA, interphase FISH or cytogenetic microarray.

- Genetic counseling: Till date all affected cases have been inherited from carrier mothers and *de novo* cases, though theoretically possible, have not been described. So, if the mother is a carrier of the 0.5Mb Xq28 duplication (mild affected or unaffected), 50% of the sons and 50% of the daughters will inherit the same, and such males will be affected and females might be mildly affected or unaffected. In females, the X chromosome harbouring the 0.5Mb Xq28 duplication is not preferentially inactivated, as there is random skewing of X chromosomes.

The other important differential diagnosis is alpha Thalassemia X linked intellectual disability syndrome, which can be diagnosed by molecular testing of the *ATRX* gene.

4. *MECP2*–associated intellectual disability, autism and parkinsonian features, and macroorchidism (OMIM # 300055 / PPM–X syndrome)

Recently, many case reports and studies have shown that *MECP2* mutations, especially missense mutations, are associated with non-lethal intellectual disability, autistic features, psychiatric manifestations, pyramidal signs, parkinsonism like features etc. in males. The phenotype can be modified by karyotypic abnormalities like 47,XXY and somatic mosaicism. *MECP2* gene might be an important cause of intellectual disability in males after fragile X syndrome (2.8% vs 1.3%) (Gomot et al., 2003). Also, milder intellectual disability, autistic features etc., without any Rett-like features might manifest with *MECP2* mutations in females, probably due to skewed X inactivation. So, in

all males and females with intellectual disability, the importance of *MECP2* gene testing is being increasingly recognized (Villard, 2007).

Conclusion

MECP2 gene-related disorders vary in clinical phenotype from classic Rett syndrome and atypical Rett syndrome to non-syndromic intellectual disability. *MECP2* gene should be tested for point mutations and deletion/duplications in Rett phenotypes, males with neonatal onset encephalopathy, and males and females with intellectual disability or autism.

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