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Rett Syndrome in India: demographics, clinical features, and genetic profile of 6 Rett Syndrome cases as part of "Genetics in Autism" research study

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Abstract:

Rett syndrome is a complex neurodevelopmental disorder, caused by mutations in MECP2 gene. At present, around 900 different variations, both benign and pathogenic of the gene are known. Different mutations can lead to variable levels of severity, different clinical features and may be associated with variable demographic profile. We present here a case study of 6 Rett Syndrome cases, a part of "Genetics in Autism" research study and their genotype-phenotype profile. The study includes two novel variants, c.23_27del in exon1 and c.538C>T variant (male mosaic) known in females but not in males. Although it is a small sample size, the study highlights the importance of genetic tests and counselling in children with features of autism spectrum disorder.

Key words:

Rett syndrome, genetics, demographics, clinical features

Introduction:

Rett syndrome (OMIM#312750) and susceptibility to X-linked autism-3 (OMIM#300496) are caused by mutations in the MECP2 gene (OMIM*300005). It is a genetic neurodevelopmental disorder and is seen predominantly in females. The MECP2 gene is a protein coding gene and via the protein MeCP2, modifies chromatin and helps regulate expression of gene activity. Disorders associated with MECP2 gene are Rett syndrome and Intellectual developmental disorder, X-linked syndromic intellectual developmental disorder-13. Most of the cases of Rett syndrome are due to sporadic, de-novo mutation in the sperm [1,2,3]. As the inheritance pattern is usually de novo, recurrence risk in subsequent pregnancy is approximately 2%. Genetic counselling is advised for interpretation of the consequences of the variant(s).

Clinically, Rett syndrome is characterized by developmental regression between 6-18 months of age with loss of acquired skills, speech, stereotypical hand movements, microcephaly, seizures and intellectual disability [4]. Many of the children also present with symptoms of autism spectrum disorder (ASD) or it is diagnosed

as ASD. We present a case study of 6 children diagnosed as Rett Syndrome as part of "Genetics in Autism" research study.

Design:

106 children with features of ASD on DSM-V [5] criteria (social-communication: level-2/3, sensory /repetitive: level-2/3) were enrolled in the study between the period of April 2020 - April 2021. Detailed demographics, clinical features, investigations data was collected. Karyotype, fragile X (for male children) and Whole Exome Sequencing (WES) was done for each child. Validation of the variants and parental segregation analysis was done by Sanger Sequencing.

Results:

Genetic profile: Table-1

Out of 106 children enrolled in the study, 6 had MECP2 mutation on WES (5.66% of study population). It was the most common recurring gene with an X-linked inheritance as well as the most common recurring gene in the entire cohort. 5 were female children with X linked de-novo mutation (heterozygous), 1 was male child with X linked post-zygotic de-novo mutation (somatic variant). The variations seen in exon 3 were: c.842dupC, c.491C>G, c.433C>T, c.538C>T, c.952C>T. The variation seen in exon 1 was c.23_27del.

There were 2 novel variants [6] in the study, c.23_27del in exon1 (figure-1) and c.538C>T variant (male mosaic) known in females but not in males (figure-2).

Table-1: Rett syndrome- genetic profile

No	kar	gene	variant	Zygosity	(omim)	inheritance	F	M
1	XX	MECP2	c.842dupC (p.R282Pfs*61) in exon 3	hetero	Rett	x-linked de novo	N/A	N/A
2	xx	MECP2	c.23_27del (p.A82Efs*32) in exon-1	hetero	Rett	X linked de novo	N/A	N/A
3	xx	MECP2	c.491C>G (p.P164R) in exon 3	hetero	Rett	X linked de novo	N/A	N/A
4	xx	MECP2	c.433C>T (p.R145C) in exon 3	hetero	Rett	X linked de novo	N/A	N/A
5	xy	MECP2	c.538C>T (p.R180*) in exon 3	Somatic variant	Rett	x-linked, post zygotic, de-novo	N/A	N/A
6	xx	MECP2	c.952C>T (p.R318C) in exon 3	hetero	Rett	x- linked de novo	N/A	N/A

Kar-Karyotype, Hetero-heterozygous F-father, M-mother

Figure-1: c.23_27del variant in exon1

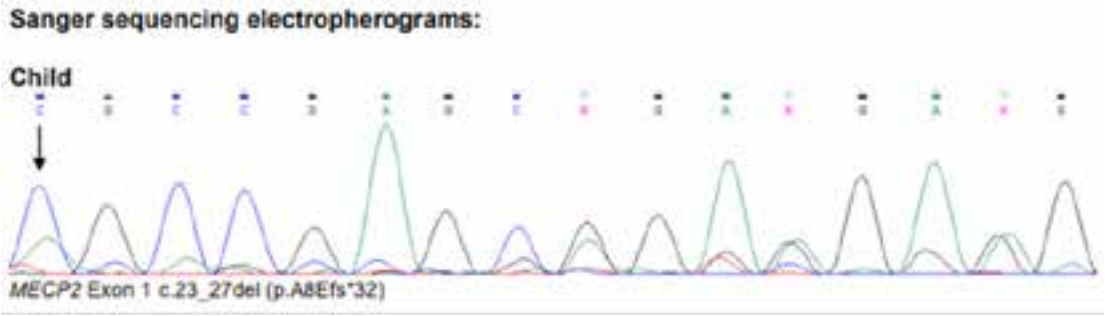
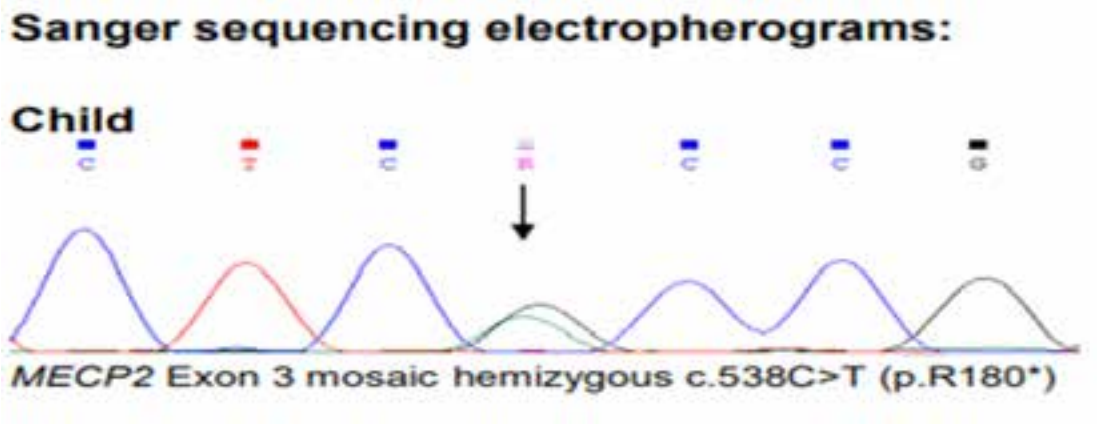


Figure-2: c.538C>T variant (male mosaic)



Demographics & clinical features: Table-2

The female children in the study were between 2-12 years of age, all were full- term born with no maternal or perinatal complications. One parent had 3rd degree consanguineous marriage and one had twin pregnancy with miscarriage of one foetus at 4 months of gestation. The mean birth weight was 2.3 kg. MRI scan (done in 5/5), BERA (4/5), eye exam (2/5) was normal. EEG was abnormal in 2/5 kids with one on antiepileptics. Microcephaly was noticed in 3/5 kids and 2/5 children had bruxism. 4/5 girl's had siblings who were normal.

Male child (2.7 years- born at 32 weeks of gestation), had normal MRI/eye/ear exam/head circumference, abnormal EEG (one episode of convulsions) and right thumb polydactyly [7].

Table-2: Rett syndrome- demographics and clinical features

no	Age (years)	sex	term	BW (kg)	seizure	MRI	EEG	BERA/ Eye	Head size	Sib (year)
1	12	F	FT	2.2	none	N	N	N/N	<3rd centile	Bro-7
2	3.1	F	FT	2.5	none	N			<3rd centile	Sis- 5
3	2	F	FT	1.58	1 episode	N	AB	N	<3rd centile	Sis- 6
4	6.4	F	FT	3	ongoing	N	AB	N	In range	Sis-9, bro-7
5	2.7	M	32week	2.1	1 episode	N	AB	N/N	In range	none
6	3	F	FT	2.2	none	N	N	N/N	In range	none

F-female, M-male, FT-full term, BW-birth weight, N-normal, AB-abnormal, Sib-sibling, Bro-brother, S-sister

Conclusion:

Rett syndrome is a complex neurodevelopmental disorder which can present with variable clinical findings and demographic [8] profile. As different mutations may lead to variable clinical presentations and severity, it is imperative to study genotype-phenotype association to help in management and to provide counselling support to the parents.

Also, with increase in prevalence of ASD many of the Rett syndrome cases are diagnosed and treated as ASD especially in developing country like India. It is important to provide access to genetic tests and counselling to parents for long term management and understanding of the prognosis.

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References:

1. U.S. Department of Health and Human Services. (n.d.). *What causes Rett Syndrome?* Eunice Kennedy Shriver National Institute of Child Health and Human Development. Retrieved November 29, 2021, from https://www.nichd.nih.gov/health/topics/rett/conditioninfo/causes.
2. Townend, Gillian S et al. "MECP2 variation in Rett syndrome-An overview of current coverage of genetic and phenotype data within existing databases." *Human mutation* vol. 39,7 (2018): 914-924. doi:10.1002/humu.23542
3. Kyle, Stephanie M et al. "Rett syndrome: a neurological disorder with metabolic components." *Open biology* vol. 8,2 (2018): 170216. doi:10.1098/rsob.170216
4. "Rett Syndrome." *Mayo Clinic*, Mayo Foundation for Medical Education and Research, 11 Oct. 2018, https://www.mayoclinic.org/diseases-conditions/rett-syndrome/symptoms-causes/syc-20377227.
5. "Rett Syndrome and the DSM V." *Rett Syndrome News*, Rett Syndrome Research Trust, 18 Dec. 2020, https://rettnews.org/articles/rett-syndrome-dsm-v/.
6. Das, Dhanjit Kumar et al. "Spectrum of MECP2 gene mutations in a cohort of Indian patients with Rett syndrome: report of two novel mutations." *Gene* vol. 515,1 (2013): 78-83. doi:10.1016/j.gene.2012.11.024
7. *Boys with Rett*. International Rett Syndrome Foundation. (2021, May 13). Retrieved November 10, 2021, from https://www.rettsyndrome.org/about-rett-syndrome/boys-with-rett
8. Geetha, Bharathi et al. "Autism in India: a case-control study to understand the association between socio-economic and environmental risk factors." *Acta neurologica Belgica* vol. 119,3 (2019): 393-401. doi:10.1007/s13760-018-01057-4