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RAPID COMMUNICATION

Highlighting novel genes associated with the classical Rett syndrome patient from India

To the Editor,

Rett syndrome (RTT) is a rare X-linked brain disorder predominantly in females, caused by mutations in Methyl-CpG-Binding Protein2 (*MECP2*) gene with the characteristic features of progressive developmental delay, severe intellectual disability, microcephaly, retarded growth, loss of communication abilities, loss of purposeful hand movements, abnormal walking or gait abnormalities, repetitive hand movements, abnormal breathing, irritability and abnormal behaviours.[1] Over the last five years, more than eighty genes related to RTT were found using next generation sequencing.[2] Here we presented a comprehensive clinical report of a 38-year-old RTT woman having *de novo* heterozygous Laminin Subunit Gamma 3 gene (*LAMC3*) mutation G>A (Chr9:133944387; p.C947Y) links with RTT neurological dysfunctions, brain malformations, reduced brain volume and hypoplasia of corpus callosum. This new finding supports the possibility of targeting *LAMC3* gene for rescuing the neuropathology of RTT. Other deleterious mutations found in genes such as, *CACNA1B (rs4422842), CUBN (rs2271460), GPATCH3 (rs779537923), TUBB1 (rs463312), KCNJ5 (rs768906222), VWA5A (rs551469534), DNAAF1 (rs751148678),* and *PARP1 (rs3219145)* were unreported in RTT patients.

We observed a woman aged 38 was born at the 39th week of gestation following by a normal delivery (weight: 3.0 Kg and head circumference: 41 cm) to non-consanguineous normal parents. But she has an elder sister with severe mental retardation and encephalopathy.[3] During her childhood, she was delayed to crawl, stand, walk/run and speak. She experienced a progressive developmental delay such as reduction of head growth, loss of acquired communication and loss of motor functions. The caretakers reported that she used to sing two lines of rhymes at her childhood but now she can only speak some proto words repetitively. She used to open and close the hands repetitively (squeezing hands) without any intense. The growth deceleration with the characteristic features such as thin and short extremities with rigidity, spasticity, and apraxia. Sleeping problems at nightly basis and day time sleeping also noticed. There is no social isolation but she used to bite herself for not providing the desired food. She never experienced seizures, respiratory and vision problems. According to multi-axial International Classification of Diseases (ICD 10), the patient was diagnosed as suffering from severe mental retardation (Axis I – F 72). Her blood and urine reports were analysed and found low haemoglobin, 8.1 gm% (normal range 12–16 gm%), megaloblastic anemia (RBC - 2.8 $\times$ $10^6/\mu L$), increased mean corpuscular volume of 81.2 fL, decreased neutrophils of 0.9 $\times$ $10^3/\mu L$, decreased platelet values of 59.0 $\times$ $10^3/\mu L$, decreased creatinine, 0.44 (0.6–1.4 mg/dl), increased TSH (4.75 mIU/L) and type 2 diabetes. Her IQ, 50 (normal 70 or more) and BMI showed underweight (9.1 kg/m^2). Her electrocardiogram (ECG) revealed a normal sinus rhythm. Her endocrinological and gynecological reports are normal. The psychiatric symptomatology with factors triggering the course (relapse, exacerbation) of the psychic disturbances in RTT patients is very rare at our disposal. The first episode of psychosis was observed at the death of her beloved father. Night screaming and mood changes also reported during febrile conditions. She was having the characteristic feature of tooth decay (Gingivitis). She is reported to have repeated, unmotivated, long laughing attacks. The neuropsychiatric inventory questionnaire (NPI-Q) assessment showed the presence of agitation, delusion, anxiety and motor disturbances in this patient. The course of psychosis increased during her menstrual stress and fever conditions. She usually experiences mirror image agnosia in her day-to-day life. Handling the psychosis situations is very difficult for her 62 years aged mother. She pretends to wear napkins

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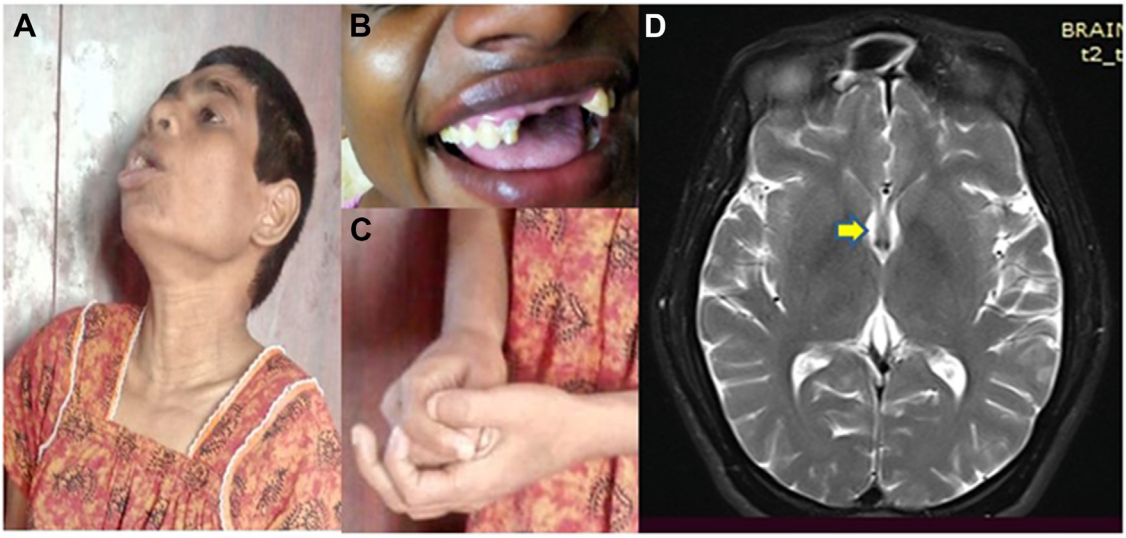

Figure 1 Clinical characteristics and neuroimaging of a 38-year-old RTT woman. **(A)** shows the characteristic features of microcephaly, short stature and dyspraxia; **(B)** shows the effect of chronic periodontitis; **(C)** shows the repetitive hand squeezing movements; **(D)** shows the moose head appearance in T2W-TSE—FS—TRA, which depicted the malformation of corpus callosum.

and inexpressive pain during menstrual period made her to irritable and threaten others. No other medications had taken other than sleeping pills during severe psychotic episodes. Based on Neul et al, 2010 RTT diagnostic criteria, she has diagnosed as classical RTT at stage III involving microcephaly, waddling gait, short stature, repetitive speech, chronic periodontitis and psychosis. The brain magnetic resonance imaging (MRI) showed reduced brain volume and hypoplasia of corpus callosum (Fig. 1).

The chromosomal analysis using GTG banding showed a normal karyotype. The whole-exome sequencing followed by sanger sequencing revealed the presence of pathogenic frameshift mutation in *MECP2* gene of c.153dup; p.Glu52fs (NM_001110792.2; nucleotide change - AAAA/AAA; protein change — E/R; variant - rs267608427). The incidence of mutation in the *MECP2* gene for classic RTT ranges between 60% and 90%. Pathogenic mutations found in exon 3, which is the mutation hot spot of *MECP2* associated with RTT phenotypic defects. Then, we found a *de novo* deleterious variant of *LAMC3* gene with G>A (Chr9:133944387) change in exon 16 at 2840 position was found in the RTT case causing protein residue change from C to Y at 947 position. Literature stated that *LAMC3* mutations associated with abnormal visual and spatial attention networks especially at the cortical and sub-cortical regions of brain.[4] Dynein Axonemal Assembly Factor 1 gene variant (*DNAAF1*: NM_178452; exon3; c.A326G; p.N109S) can be associated with severe malformation of central nervous system. Mutation in Calcium Voltage-Gated Channel Subunit Alpha1 B gene variant (*CACNA1B*; NM_000718; exon3; c.C501G; p.N167K) associated with neurodevelopmental disorder.[5] Potassium Inwardly Rectifying Channel Subfamily J Member 5 gene susceptible to psychosis (*KCNJ5*:NM_000890:exon2:c.G313A:p.G105S). Poly (ADP-Ribose) Polymerase 1 gene (*PARP1*:NM_001618; exon21; c.A2819G; p.K940R) responsible for neuroprotection against induced apoptosis. Cubilin gene variant (*CUBN*; NM_001081; exon44; c.T6788G; p.F2263C), Tubulin Beta 1 Class VI gene variant (*TUBB1*; NM_030773; exon2; c.A128C; p.Q43P), and Von Willebrand Factor A Domain Containing 5A gene variant (*VWA5A*; NM_014622; exon8; c.A974G; p.Y325C) were associated with blood related disorders. The detailed list of genetic variations and its clinical significance were reported in the supplementary file.

In this study, we reported a classical RTT patient with *de novo* mutation of *LAMC3, DNAAF1, CACNA1B, KCNJ5,* and *PARP1* were responsible for the global developmental delay, mental retardation, psychosis, mirror agnosia and neurological phenotype of reduced brain volume and corpus callosum malformation. However, the highlighted genotypic variants will provide information and make awareness to clinicians about new candidate genes responsible for RTT related symptoms that could help in the prevention of forthcoming symptoms and the discovery of therapeutic agents.

Ethical approval

Institutional ethical committee of Bharathiar University, Coimbatore, Tamil Nadu, India has approved permission to perform this study. We strictly followed Helsinki rules and ICMR guidelines while handling the human blood samples.

Informed consent

Signed informed consent obtained from the concern patient/parent for obtaining blood samples and publication of the identifying materials (photographs/videos) in the journals.

Author contributions

Gomathi Mohan - Conceptualization, Methodology, Software, Writing- Original draft preparation, Reviewing, Editing and Funding acquisition; **Ranjan Jyoti Sarma** - Data

curation, Software, Validation, Reviewing and Editing; **Mahalaxmi Iyer** - Visualization, Investigation, Reviewing and Editing; **Nachimuthu Senthil Kumar** — Investigation, Software, Validation, Reviewing and Supervision; **Balachandar Vellingiri** - Conceptualization, Methodology, Investigation, Reviewing, Supervision and Funding acquisition.

Additional contributions

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Conflict of interests

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.12.002.

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