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# Rett and Rett-like syndrome: Expanding the genetic spectrum to *KIF1A* and *GRIN1* gene

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**Abstract**

**Background:** This study aimed to investigate the new genetic etiologies of Rett syndrome (RTT) or Rett-like phenotypes.

**Methods:** Targeted next-generation sequencing (NGS) was performed on 44 Chinese patients with RTT or Rett-like phenotypes, in whom genetic analysis of *MECP2*, *CDKL5,* and *FOXG1* was negative.

**Results:** The detection rate was 31.8% (14/44). A de novo pathogenic variant (c.275_276ins AA, p. Cys92*) of *KIF1A* was identified in a girl with all core features of typical RTT. A patient with atypical RTT was detected having de novo *GRIN1* pathogenic variant (c.2337C > A, p. Val793Phe). Additionally, compound heterozygous pathogenic variants of *PPT1* gene were detected in a girl, who initially displayed typical RTT features, but progressed into neuronal ceroid lipofuscinoses (NCL) afterwards. Pathogenic variants in *KCNQ2*, *MEF2C*, *WDR45*, *TCF4*, *IQSEC2,* and *SDHA* were also found in our cohort.

**Conclusions:** It is the first time that pathogenic variants of *GRIN1* and *KIF1A* were linked to RTT and Rett-like profiles. Our findings expanded the genetic heterogeneity of Chinese RTT or Rett-like patients, and also suggest that some patients with genetic metabolic disease such as NCL, might displayed Rett features initially, and clinical follow-up is essential for the diagnosis.

KEYWORDS
*GRIN1*, *KIF1A*, Rett, Rett-like

## 1 | INTRODUCTION

Rett syndrome (RTT; OMIM 312750) is a severe neurodevelopmental disorder dominantly affecting females with an incidence of 1/10,000 female births. It was first connected with Methyl-CpG-binding protein 2 (*MECP2*) gene at 1999 by Amir, which is a crucial milestone for this disease (Amir et al., 1999). After then, 95% of patients with typical RTT and 73.2% of patients with RTT variants were found with *MECP2* pathogenic variants (Percy et al., 2007, 2010). Subsequently, *CDKL5* (cyclin-dependent kinase-like 5) and *FOXG1* (forkhead Box protein G1) were discovered as pathogenic genes of early seizure variant and congenital variant of RTT, respectively (Ariani et al., 2008; Tao et al., 2004;

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Weaving et al., 2004). According to the newly revised criteria of RTT, it is more appropriate for the early seizure variant of RTT to be classified as congenital RTT because these individuals lack the clear period of regression (Neul et al., 2010). Even so, there remains a subset of RTT or Rett-like patients without pathogenic variants in commonly known Rett genes (*MECP2*, *CDKL5*, and *FOXG1*). With the increasing use of next-generation sequencing (NGS), more and more genes related to RTT has been discovered in the last few years (Allou et al., 2017; Gold & Christodoulou, 2015; Lopes et al., 2016; Lucariello et al., 2016; Vidal et al., 2017).

In this study, targeted NGS panel consisting of 512 candidate genes was designed, and performed on 44 RTT and Rett-like patients in whom no pathogenic variants of *MECP2*, *CDKL5*, and *FOXG1* were found.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethics

This study was approved by the Medical Ethics Committee, Peking University First Hospital. Written informed consent was obtained from the parents of the patients.

### 2.2 | Patients

Patients who met the diagnostic criteria of RTT (Neul et al., 2010), or patients who did not completely fulfil the criteria, but shared some clinical features resembled RTT, including psychomotor retardation with or without regression, stereotypic hand movements, loss of hand use, and poor language, were recruited. The latter group was termed as Rett-like phenotypes. Meanwhile, genetic analysis of *MECP2*, *CDKL5*, and *FOXG1* was negative in the subjects. Finally, 44 Chinese patients including 41 females and 3 males, aged from 13 months to 12.5 years old, were enrolled into this study. This cohort consists of 21 patients with typical RTT, 19 patients with Rett-like phenotypes, and 4 patients with atypical RTT (3 patients with the congenital variant and 1 patient with the preserved speech variant).

Detailed clinical information including clinical manifestation, electroencephalogram (EEG), magnetic resonance imaging (MRI), family history, etc., was collected. Genomic DNA was extracted from peripheral leukocytes.

### 2.3 | Targeted NGS

Use "Rett syndrome," "RTT," "Rett," "RTT-like," and "Rett-like" as keywords to search the related genetic information in Online Mendelian Inheritance in Man (OMIM) and PubMed database. Finally, 46 genes were selected as candidate genes. These genes were added into commonly used genetic panel related to neurodevelopmental disorders, including epilepsy, developmental delay, and intellectual disability. Totally, 512 genes (Table S1) were contained.

Gene sequence was obtained from http://genome.ucsc.edu/, and probes were designed to capture the coding regions, including exons and exon–intron boundaries, by Roche SeqCap Target Enrichment technique. Next, NGS was performed on Ion torrent Proton high-throughput platform (Themofisher), using paired-end sequencing of 100 bp. Bioinformatic analysis included: (a) imaging analysis and base calling using Ion Torrent Suite 5.04 software; (b) aligned clean paired-end reads to the human reference genome build hg19 using Tmap software; (c) single-nucleotide polymorphisms (SNPs) and insertion–deletions (indels) identification using the Genome Analysis Tool kit (GATK); and (d) annotated rare variants using ANNOVAR (http://www.openbioinformatics.org/en/latest). Reported pathogenic variants in HGMD Professional database and Pubmed were marked, whereas the pathogenicity of other rare variants was annotated by SIFT, Polyphe-2 and Mutationtaster. PCR-Sanger sequencing was performed to confirm variations and analyze parental origin.

## 3 | RESULTS

Disease causing variants were identified in 14 patients. The hit rate was 31.8% (14/44). Aside from two *MECP2* pathogenic variants missed by previous PCR-Sanger sequencing, pathogenic variants in nine genes were identified.

Notably, a de novo *KIF1A* pathogenic variant (c.275_276insAA, p.Cys92*) was detected in patient R609, a 13 months old in vitro fertilization girl, who met the diagnostic criteria of classical RTT. Development was delayed, with raising head at 4 months, sitting alone at 7–8 months. She did not achieve independent ambulation and cannot speak any language when coming to our hospital at 13 months of age. Microcephaly was obvious with head circumference of 42 cm (13 months). Hand clapping and mouthing, loss of hand skills, grinding teeth, breathing, and sleeping disturbance appeared around 8 months of age. Brain MRI was normal.

A de novo *GRIN1* gene pathogenic variant (c.2377C > A, p. Val793Phe) was found in patient R625, a girl aged 4 years and 2 months. She developed epilepsy at 2 months of age, which was controlled by PB. Developmental milestones were prominently delayed. She could not control her head until 6 months old, and was unable to walk independently until 1.5 years old. She even could not speak any meaningful words at 4 years of age. She had some purposeful hand use before 3.5 years of age, such as pinching beans and passing things from one hand to another. Hand clapping and mouthing, as well as breathing disturbance has been noticed since 3.5 years old, and then she gradually lost the hand skills.

The pathogenic variants identified in this study and clinical information of patients were summarized in Table 1 and

**TABLE 1** Genes and mutations identified in this study

| ID | Gene | Base change | AA change | Inheritance | Heterozygous/ homozygous | N/R | SIFT | PolyPhen2 | MutationTaster | Paternal origin |
|---|---|---|---|---|---|---|---|---|---|---|
| R609 | *KIF1A* | c.275_276insAA | p. Cys92* | AD | Heterozygous | N | – | – | Disease causing | De novo |
| R415 | *KCNQ2* | c.637C > T | p. Arg213Trp | AD | Heterozygous | R | Affect protein function | Probably damaging | Disease causing | De novo |
| R625 | *GRIN1* | c.2377C > A | p. Val793Phe | AD | Heterozygous | N | Affect protein function | Probably damaging | Disease causing | De novo |
| R639 | *PPT1* | c. 163 A > T | p. Lys55* | AR | Compound heterozygous | R | – | – | Disease causing | Maternal |
|  |  | c.31_32insGG | p. Ala11Gly fs*27 |  |  | N | – | – | Disease causing | Paternal |
| R680 | *MEF2C* | c.48C > G | p. Asn16Lys | AD | Heterozygous | N | Affect protein function | Possibly damaging | Disease causing | De novo |
| R554 | *MEF2C* | c.565C > T | p. Arg189* | AD | Heterozygous | R | – | – | Disease causing | Mather was WT; father unknown |
| R746 | *MEF2C* | c.334G > T | p. Glu112* | AD | Heterozygous | N | – | – | Disease causing | Father was WT; mother unknown |
| R878 | *WDR45* | c.249G > A | p. Trp83T* | XLD | Heterozygous | N | – | – | Disease causing | De novo |
| WRY | *WDR45* | c.340_342delGAC | p. Asp114* | XLD | Heterozygous | N | – | – | Disease causing | De novo |
| R547 | *TCF4* | c.1414delG | p. Val472Phe fs*16 | AD | Heterozygous | R | – | – | Disease causing | De novo |
| R883 | *IQSEC2* | c.2776C > T | p. Arg926* | XLD | Heterozygous | N |  | – | Disease causing | De novo |
| R685 | *SDHA* | c.739A > G | p. Ile247Val | AR | Compound heterozygous | N |  |  | Disease causing | Maternal |
|  |  | c.1944_1945delTT | p. Leu649Glu fs*4 |  |  | N | – | – | Disease causing | Paternal |
| R214 | *MECP2* | c.763C > T | p. Arg255* | XLD | Heterozygous | R | – | – | Disease causing | De novo |
| R858 | *MECP2* | c.1363G > T | p. Glu455* | XLD | Heterozygous | R | – | – | Disease causing | De novo |

Abbreviations: –, truncated mutations; which were not applicable for analysis; XLD, X-linked dominant; AD, autosomal dominant; AR, autosomal recessive; WT, wild type.

Table S2, respectively. The referential transcript was listed in Table S3. Detailed clinical information was described in supplemental material 2.

## 4 | DISCUSSION

Aside from *MECP2*, nine genes were identified to be associated with RTT or Rett-like syndrome. *KIF1A* gene is located at 2q37.3, encoding kinesin family member 1A, which is involved in anterograde transport cargoes of synaptic vesicle precursors along axons. It plays a critical role in maintaining cell viability and function of neurons (Riviere et al., 2011). *KIF1A* pathogenic variants have been found in patients with variable neurological manifestations, including hereditary spastic paraplegia type 30 (OMIM 610357) and hereditary sensory and autonomic neuropathy type 2 (OMIM 614213), both inherited as autosomal recessive pattern, as well as autosomal dominant mental retardation type 9 (MRD9; OMIM 614255). Core features of MRD9 are developmental delay and intellectual disability. Additional features included progressive spasticity, optic nerve atrophy, peripheral neuropathy, progressive cerebral, and/or cerebellar atrophy. Some patients had epilepsy (Erlich et al., 2011; Esmaeeli Nieh et al., 2015; Lee et al., 2015). In this study, a truncated variant of *KIF1A* gene was discovered in a female. The patient had core features of classical RTT, including profound psychomotor retardation, lack of speech, hand stereotypies, and poor hand skills, as well as abnormal breathing patterns. Unlike previously reported patients with *KIF1A* pathogenic variants, our patient did not display any signs of brain atrophy on neuroimaging. Ophthalmologic examination was uneventful, and no seizures were reported at the last investigation (13 months old). Maybe, a long-term clinical tracking is important to evaluate the above manifestations. It can be seen that there was overlapped clinical features between *KIF1A*-related disorders and RTT, including psychomotor stagnation, stereotypic hand movements, and breathing disturbance. In addition, functional analysis revealed that vesicles containing the neurotrophin brain-derived neurotrophic factor (BDNF) might be controlled by *Kif1a* (Carabalona, Hu, & Vallee, 2016; Kondo, Takei, & Hirokawa, 2012). It is well established that *BDNF* is one of the target genes of *MECP2* (W. Li & Pozzo-Miller, 2014). Hence, it is speculated that crosstalk between *KIF1A* and *MECP2* through *BDNF,* their common target gene, may explain their overlap. To our knowledge, it is the first time that *KIF1A* was associated with RTT, which expands the phenotypic spectrum of *KIF1A*-related disorders.

*GRIN1* gene, located at 9q34.3, encoding GluN1 subunit (NR1) of N-methyl-D-aspartate receptor (NMDAR), plays a key role in the synaptic functions (Sin, Haas, Ruthazer, & Cline, 2002). Pathogenic variants of NMDAR subunits are associated with a variety of neurodevelopmental phenotypes, such as intellectual disability, epilepsy, and autism spectrum disorders (Lemke et al., 2016). The expression of NMDAR is disrupted in the brain of Mecp2-null mice, including diminish in GluN1, and increasing in GluN2A/GluN2B (Maliszewska-Cyna, Bawa, & Eubanks, 2010). NMDAR channel blocker was proved effective in ameliorating symptoms in RTT mice (Katz, Menniti, & Mather, 2016). Additionally, NR1 knockdown (KD) mice presented with erethism, repetitive behavior, impairments in memory and sociability, which is also observed in RTT mice (Milenkovic, Mielnik, & Ramsey, 2014). So far, the Rett-like phenotype as NR1 KD mice has not been described in humans yet. In our study, a de novo *GRIN1* pathogenic variant was found in a female, whose clinical features mimicked congenital variant of RTT, including early onset seizures, developmental delay, abnormal breathing pattern, no speech, stereotypical hand movements, and loss of hand use. This is the first time that *GRIN1* gene was linked to RTT, which indicated that *GRIN1* may involve in its pathogenic network, and should be referred as a candidate gene of RTT or Rett-like phenotypes.

*KCNQ2* gene, located at 20q13.13, encoding a voltage-gated potassium (Kv7.2) channel, has been associated with early onset epileptic encephalopathy type 7 (EIEE7; OMIM 613720) and benign familial neonatal seizures (OMIM 121200) (Dedek et al., 2001; Weckhuysen et al., 2012). So far, *KCNQ2* pathogenic variants have been identified in three Rett patients (Kato et al., 2015; Sajan et al., 2017). In our cohort, a de novo *KCNQ2* pathogenic variant has been discovered in a patient with congenital variant of RTT, who displayed early onset seizures, global developmental delay, lack of speech, stereotypic hand movements, abnormal breathing patterns, and scoliosis. Our study provided supporting evidence that *KCNQ2* is a candidate gene of RTT.

The *PPT1* gene is located at 1p34.2 and encodes palmitoyl-protein thioesterase (Heinonen et al., 2000). *PPT1* is a causative gene for NCL (OMIM 256730), a progressive neurodegenerative disorder, which is autosomal recessively inherited. NCL is characterized by progressive psychomotor deterioration, epilepsy, visual loss, and premature death (Mole, Williams, & Goebel, 2005). In our cohort, a girl with compound heterozygous pathogenic variants of *PPT1* presented Rett-like phenotypes at the early stage of the disease, including psychomotor regression, repetitive acts and loss of hand skills. The typical features of NCL such as refractory seizures, visual loss, and joint contractures occurred gradually after 3 years of age. Dana et al. reported a similar patient before. A girl with NCL manifested with Rett-like symptoms at onset, including psychomotor regression, microcephaly, stereotypic hand movements, and hyperventilation episodes. A full picture of NCL developed after 5 years old. The girl was detected with a compound heterozygous pathogenic variant in *MFSD8*, another gene related to NCL (Craiu et al., 2015). Dana's report and our study showed that there were clinical overlaps between RTT and the early stage of NCL. The genetic analysis of genes associated with NCL is important in Rett or Rett-like patients, for the definite diagnosis.

*MEF2C* gene, located at 5q14, encodes myocyte enhancer-binding factor 2 C, which was pivotal in myogenesis, hematopoiesis, neurogenesis, and synaptogenesis (Leifer et al., 1993). *ME*F2C (OMIM 613443) is a causative gene for neurodevelopmental disorders, which has relatively uniform clinical presentations, including severe mental retardation, delayed motor development, limited walking abilities, lack of speech, stereotypic movements, and various minor brain malformations on MRI (Vrecar et al., 2017). It is demonstrated that *MEF2C* gene can activate promoters of *MECP2* and *CDKL5*. In patient with *MEF2C* haploinsufficiency, expression of *MECP2* and *CDKL5* was diminished (Zweier et al., 2010). *Mef2c* brain null mutant mice displayed behavioral phenotypes which mimicked RTT mice model, including marked paw wringing/clasping stereotypy. Moreover, conditional knockout of *Mef2c* in mice impaired neuronal differentiation, resulting in aberrant compaction and smaller somal size, which resembled the mouse models of RTT (Li et al., 2008). This phenomenon had been concluded that Rett or Rett-like phenotypes were caused by the disruption of a common pathway involving *MECP2*, *CDKL5*, and *MEF2C*. In this study, three females were detected with *MEF2C* point pathogenic variants, of whom one displayed typical RTT and the other two presented with RTT-like features, which has been described previously in another study of us (Wang et al., 2018). The majority of *MEF2C* dysfunctions were caused by large intragenic deletions or completely deletions. Until now, only 13 point pathogenic variants of *MEF2C* were reported, including our patients, which limit the study of possible genotype-phenotype correlations (Vrecar et al., 2017). Our findings further delineated the clinical features of patients with *MEF2C* point pathogenic variants.

*WDR45* gene, located at Xp11.23, encodes a beta-propeller scaffold protein, which is involved in autophagy (Saitsu et al., 2013). *WDR45* pathogenic variants have been associated with X-linked neurodegeneration with iron accumulation-5 (NIBA5; OMIM 300894), inherited as dominant pattern. NIBA5 is featured by global developmental stagnation in childhood and a secondary neurological deterioration in early adulthood, including parkinsonism, dystonia, and dementia (Gregory, Polster, & Hayflick, 2009). MRI revealed evidence of iron deposition in the substantia nigra and globus pallidus (Kruer et al., 2012). Recent studies revealed that the phenotypic spectrum may be substantially broader. At initial stage, a subset of patients presented with some Rett features, such as normal development during infancy, followed by developmental stagnation or regression, as well as loss of acquired speech, deterioration of hand skills, and hand stereotypies (Hoffjan et al., 2016; Ohba et al., 2014). In our study, two female patients had *WDR45* pathogenic variants. They were diagnosed as typical RTT initially (3 years old), as they had a normal early developmental period, followed by developmental stagnation, repetitive hand acts and decline of hand skills. MRI (3 years old) was unremarkable for both of them. From above it can be seen that there are overlaps in clinical manifestations between NIBA5 and RTT. Typically, iron accumulation in the brain was not visible at the early stage, which makes it difficult to distinguish. In Chihiro's report, a girl displaying classical RTT had iron deposition in brain at 11 years of age, but before that several MRI (4 and 3.5 years, respectively) were normal (Ohba et al., 2014). Hence, long-term follow-up is essential.

*TCF4* gene is located at 18q21.2, encoding basic helix-loop-helix transcription factor 4, playing pivotal roles in the development of nervous system (de Pontual et al., 2009). *TCF4* pathogenic variants are associated with Pitt-Hopkins syndrome (PTHS; OMIM 610954) (Amiel et al., 2007). There is overlap between PTHS and RTT, including secondary microcephaly, stereotypic hand movements and loss of purposeful hand use, autistic behaviors, intermittent hyperventilation, and epilepsy (Marangi & Zollino, 2015). In this study, a micro-deletion of *TCF4* gene was identified in a female, who had some Rett-like features, without craniofacial anomalies. But not all PTHS patients had recognizable facial features (Marangi et al., 2011). The overlapped features bring challenges to make differential diagnosis solely based on the clinical manifestations. Hence, TCF4 genetic analysis for RTT (-like) cohort is important.

*IQSEC2* gene, encoding IQ motif and Sec 7 domain protein 2, is involved in cytoskeletal organization, dendritic spine morphology, and excitatory synaptic organization. It is located at Xp11.22, and escapes from X-chromosome inactivation (Shoubridge et al., 2010). *IQSEC2* pathogenic variants cause moderate to severe intellectual disability in males and a variable phenotype in females (Alexander-Bloch, McDougle, Ullman, & Sweetser, 2016). Most female carriers, of whom the variant was inherited from the parents, were reported unaffected. In Zerem's review, 8 of 24 female carriers had borderline intelligence and 2 had intellectual disability (Zerem et al., 2016). However, with contrary to female carriers with inherited pathogenic variants, female patients with de novo *IQSEC2* pathogenic variants usually have profound mental retardation and epilepsy (OMIM 309530). Several female patients were described with clinical symptoms similar to RTT, such as language regression, repetitive hand acts, microcephaly, and seizures (Allou et al., 2017; Olson et al., 2015). In this study, a girl was detected having a de novo *IQSEC2* pathogenic variant (c.2776C>T, p. Arg926*). She presented with mental retardation, lack of speech, hand stereotypies, poor eye-contact, and microcephaly, which resembles those of RTT. Besides, there is significant overlap between the expression profile of *Iqsec2* and *Cdkl5* in murine adult brain, suggesting a possible functional link between them (Morleo et al., 2008). These findings provided supports that *IQSEC2* is responsible for Rett or Rett-like syndrome.

*SDHA* gene, located at 5p15.33, is a causative gene of Leigh syndrome (OMIM 256000) and mitochondrial complex II deficiency (OMIM 252011) (Pagnamenta et al., 2006; Van Coster et al., 2003). Both Leigh syndrome and mitochondrial complex II deficiency were progressive neurodegenerative disorders involving multiple systems and organs. Neurological symptoms were characterized by progressive deterioration in psychomotor, hypotonia, ataxia, epilepsy, and visual loss. MRI of patients with Leigh syndrome usually showed characteristic neuropathology consisting of focal, bilateral lesions in one or more areas of the central nervous system, including the brainstem, thalamus, basal ganglia, cerebellum, and spinal cord. Prior to the discovery of *MECP2*, RTT was thought to be a mitochondrial disease (Eeg-Olofsson et al., 1990). There is clear evidence that mitochondria function was impaired in RTT, both in animal models and patients (Dotti et al., 1993). In our cohort, compound heterozygous pathogenic variant of *SDHA* gene was identified in a girl. Her clinical presentation led to the diagnosis of typical RTT, which was not completely in conformity with typical features of Leigh syndrome or mitochondrial complex II deficiency. There were no typical signs of Leigh Syndrome on the MRI (4 years old), for that reason Leigh syndrome was not highly suspected. Our findings indicate that SDHA is also a candidate gene of Rett profiles.

Through our study, pathogenic variant of *GRIN1* and *KIF1A* was firstly linked to Rett or Rett-like phenotypes. Several genes identified in this study were involved in the common pathway of *MECP2*, directly or indirectly, which might be the mechanism underlying their overlapped features of RTT. However, there is still a lot of work to do to identify the relationship between these genes. What is more, it is essential to add the new identified genes into the NGS panel of Rett or Rett-like syndrome. In summary, for Rett or Rett-like patients without common gene pathogenic variants, new causative genes should be considered. On the other hand, mosaic pathogenic variants in *MECP2* should also be taken into consideration, which has been described in another study of our group (Zhang et al., 2019).

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## CONFLICT OF INTEREST

None.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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