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Original Article

Investigation of an inherited PCGF2: p.Pro65Leu mutation causing Turnpenny-Fry syndrome

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Abstract: Background: Turnpenny-Fry syndrome (TPFS) has recently been defined as an uncommon monogenic disease and is characterized by global developmental delay (GDD), intellectualdisability (ID), facial dysmorphology, and skeletal abnormality. *PCGF2* is the only known causative gene for TPFS, which is a component of polycomb repressive complex 1 (PRC1). PRC1 is a multi-protein complex controlling the knockdown of gene expression. Methods: The present study included the clinical evaluation of a 2.5-year-old boy with GDD and ID using cerebral MRI and the genetic testing with whole-exome sequencing. Additionally, the *in silico* molecular dynamic (MD) simulation was carried out on the identified variant. Results: A recurrent missense variant, namely *PCGF2*: c.194C > T (p.Pro65Leu), was identified and suggested to be inherited from a mosaic father based on Sanger sequencing validation. MD results suggested a deleterious effect on the intramolecular structural flexibility and stability of PCGF2 protein by this variant. Conclusion: Our results indicated that PCGF2: p.Pro65Leu might be a hotspot for GDD and highlighted the effect of this variant on protein function.

Keywords: Turnpenny-Fry syndrome, *PCGF2* gene, whole-exome sequencing, molecular dynamic simulation

Introduction

Undiagnosed global developmental delay (GDD) in pediatrics has been a major challenge for individualized management since most of these cases are likely to be linked to genetic causes [1, 2]. With the advancement of molecular genetic technologies, the disease detection rate markedly increases, and new pathogenic genes for GDD have been continuously identified [3]. Turnpenny-Fry syndrome (TPFS, MIM No. #618371) has recently been defined as an extremely rare monogenic developmental disorder [4]. To our knowledge, only 15 cases with this condition have been reported, which greatly hinders the elucidation of its pathogenesis [4-7].

PCGF2 (Polycomb Group Ring Finger Protein 2, MIM No. *600346, also known as Zinc Finger Protein 144, ZFP 144, or Mel18) gene, located at chromosome 17q12 and spanning a 15.9 kb genomic region, is the only known gene responsible for TPFS (https://www.omim.org) [4]. The implication of *PCGF2* in etiology for GDD was initially revealed in a large collaborative research project named Deciphering Developmental Disorders Study. The study revealed the identical *de novo* PCGF2: Pro65Leu mutations in two kids who shared the high similarities in facial appearance and GDD manifestations representing a distinctive dysmorphic disorder [4]. Subsequently, the study detected missense mutations in the *PCGF2* gene in a GDD cohort of 13 patients. Coincidentally, 11 unrelated individuals in this cohort carried an identical mutation, c.194C > T (p.Pro65Leu), while a pair of twin sisters showed the distinct mutation of an identical residue, c.193C > T (p.Pro65Ser) [5]. Based on the clinical and genetic findings, the group defined this GDD subtype as the Turnpenny-Fry syndrome. In a Saudi Arabian cohort, Monies *et al.* reported a patient displaying motor and speech delay, intellectual disability, and carrying a heterozygous *PCGF2*: c.1026delC (p.Leu343*) mutation [6]. Recently,

another new case in Turkey reported a child carrying the Pro65Leu mutation, which suggested its role as a potential hotspot for GDD diagnosis [7].

In the present study, a 2.5-years old boy exhibiting GDD symptoms was enrolled and subjected to a comprehensive genetic detection with whole-exome sequencing (WES) and chromosome microarray analysis (CMA). The same Pro65Leu mutation was detected in him, but peculiarly, it was inherited from his mosaic father. Molecular dynamic (MD) simulations were also performed to predict its intramolecular influence.

Materials and methods

Subjects

The present study was prospectively reviewed and approved by the Ethics Committee of the Chinese PLA General Hospital (Aprroval No. S2016-057-02). Informed consent wassigned by the patient's guardian. Each human procedure was carried out following the Declaration of Helsinki 1964, together with corresponding subsequent amendments and relevant ethical criteria.

A 2.5-year-old boy with typical GDD was referred to our Outpatient unit. We performed a comprehensive clinical evaluation on him, including an electroencephalogram (EEG), encephalofluctuogram (EFG), and magnetic resonance imaging (MRI). The EDTA anticoagulated peripheral blood was sampled from the boy and his parents for further study.

Genetic detection

This study used the QIAamp DNA Blood Mini kit (Qiagen, Germany) to isolate genomic DNA (gDNA) in peripheral blood. To detect copy number variations (CNVs), CMA in the proband was carried out by adopting CytoScan 750 k platform (Affymetrix, USA), and the data was analyzed using ChAS Analysis Suite (Affymetrix, USA).

Besides, we performed WES for identifying sequence variants in proband-derived samples according to the published method [8]. Briefly, Agilent Sure Select Human Exon Sequence-Capture Kit (Agilent, USA) was employed to enrich target-region sequences. qRT-PCR was conducted to determine the expression of DNA libraries, whereas Agilent Bioanalyzer 2100 (Agilent, USA) was employed to determine their size, content, and distribution. In addition, the NovaSeq6000 platform (Illumina, Inc.) was utilized according to the NovaSeq Reagent kit for sequencing DNA (~300 pM/sample) based on paired-end reads of ~150 bp. Furthermore, the Burrows-Wheeler Aligner approach was used to align raw reads (Q30% > 90% quality level) to the human reference genome (accession no. hg19/GRCh37), and Picardv1.57 was used for removing PCR duplicates. Genome Analysis Tool Kit (https://software.broadinstitute.org/gatk/) together with Verita Trekker® Variants Detection system (v2.0; Berry Genomics, China) was employed for variant calling. Then, variant annotation and interpretation were conducted using Enliven® Variants Annotation Interpretation systems (Berry Genomics) and ANNOVAR (v2.0) [9], following the American College of Medical Genetics and Genomics (ACMG) guidelines [10]. For pathogenicity interpretation, HGMD pro v2019 (Human Gene Mutation Database) together with three frequently used databases (1000G_2015aug_eas, https://www.internationalgenome.org; gnomAD_exome_EAS, http://gnomad.broadinstitute.org; ExAC_EAS, http://exac.broadinstitute.org) were utilized. Moreover, Revel score (an integrative approach to predict pathogenicity) [11] and pLI score (indicating truncating variant tolerance) were used.

This work included Sanger sequencing by adopting 3500DX Genetic Analyzer (Applied Biosystems, USA) for validation. Variant frequency was checked from 3 databases, including 1000 g2015aug_eas (https://www.internationalgenome.org/), gnomAD_exome_EAS (http://gnomad.broadinstitute.org/), and ExAC_EAS (http://exac.broadinstitute.org). The pathogenicity of the missense variant was analyzed using SIFT (http://sift.jcvi.org/) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) web-based tools. MEGA7 (http://www.megasoftware.net/previousVersions.php) was used to analyze the evolutionary conservatism of amino acid (AA) residues affected by identified missense variance using default parameters.

Molecular dynamic analysis

The SWISS-MODEL program was utilized to model the PCGF2 (Residue 3-102) segment

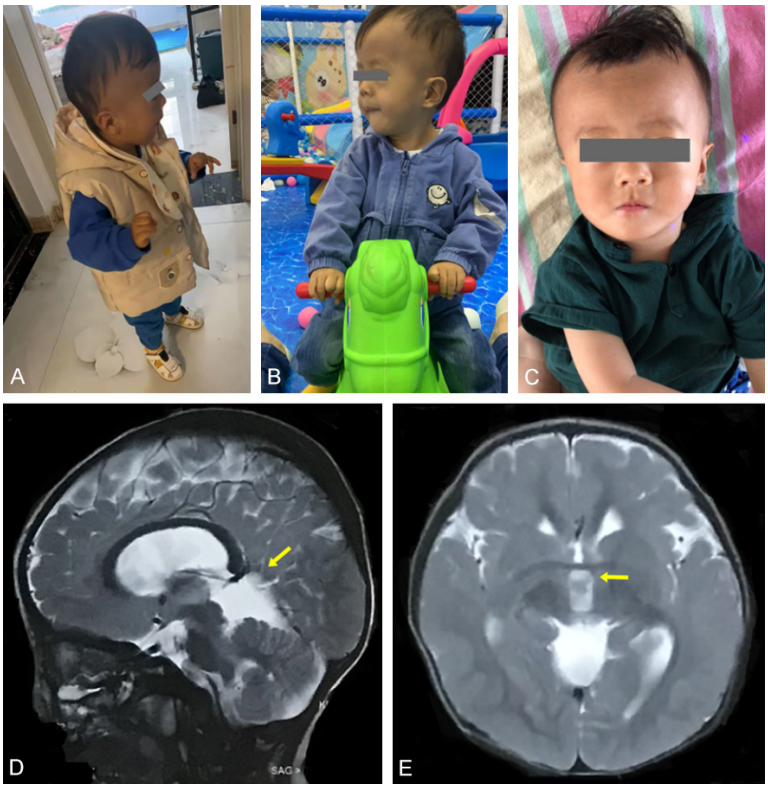

Figure 1. The case clinical presentation. (A-C) The appearance showed a predominant forehead, periorbital fullness, declivitouslateral canthus, low-set special ears, and malar hypoplasia. (D, E) MRI images indicated widened bilateral ventricles and the third ventricle, slightly enlarged superior cerebellar cistern and greater occipital cistern, and slightly deepened regional sulci.

containing mutation site (P65L) using a1.7 Å X-ray crystal structure as a template [12].

The MD simulation was carried out using GROMACS (version 2020.6) [13], and the calculations were performed on wild-type (WT) PCGF2 and P65L-PCGF2 models. In addition, the CHARMM^{3}6 force field was used for patching N-/C-terminal with hydrogen atoms into the models [14]. Subsequently, we immersed the MUT or WT protein structure in a cubic box of water molecules and placed it ≥ 1.0 nm away from the box edge. Cl^- and Na^+ ions were utilized to neutralize the pH. The MD simulations were carried out for 60 ns at 300K after energy minimization and equilibration. MD trajectories were analyzed using the following GROMACS distribution programs: gmxrmsf, gmxrms, gmxhbond, gmxsasa, and gmx gyrate. MD trajectory analysis produced the graph of root-mean-square fluctuation (RMSF), root-mean-square deviation (RMSD), solvent accessible surface area (SASA), radius of gyration (Rg), and h-bond.

Results

Clinical presentation

This boy was born at term and showed normal neonatal presentations but low birth weight (2600 g, < 10th percentile). He took 5 months to roll over with difficulty, 8 months to sit, 18 months to stand only for a few seconds, and 23 months to hardly walk with support. By 2 years old, he could not perform general hand movements, could not imitate speech sounds, and occasionally made an involuntary "Ma" sound. His dysmorphic appearance was not distinct, but the predominant forehead, periorbital fullness, declivitouslateral canthus, low-set special ears, and malar hypoplasia were recognizable (**Figure 1A-C**). By 27 months, his height reached 91 cm (< 10th percentile), and his weight was 12.5 kg (< 15th percentile).

The EEG result was abnormal but with an absence of epileptiform discharges. EFG results indicated cerebral dysfunction especially enhanced 5-hydroxytryptamine levels and reduced γ-aminobutyric acid, glutamic acid, acetylcholine, excitatory transmitter 3/6, and dopamine levels. MRI result indicated that his bilateral ventricles and the third ventricle were widened, the superior cerebellar cistern and greater occipital cistern were slightly enlarged, and the regional sulci was slightly deepened (**Figure 1D**, **1E**).

Genetic findings

The family pedigree diagram was drawn and presented in **Figure 2A**. The CMA result of the proband was normal. WES identified a heterozygous pathogenic variant, *PCGF2*: NM_007144.3: c.194C > T (p.P65L) in this proband (**Figure 2B**). Sanger sequencing-based family verification confirmed the inheritance of this variant from his mosaic father, with a mosaicism ratio of around 10% (**Figure 2B**). The affected AA residue of this variant, P65 in PCGF2 protein, showed a high evolutionary

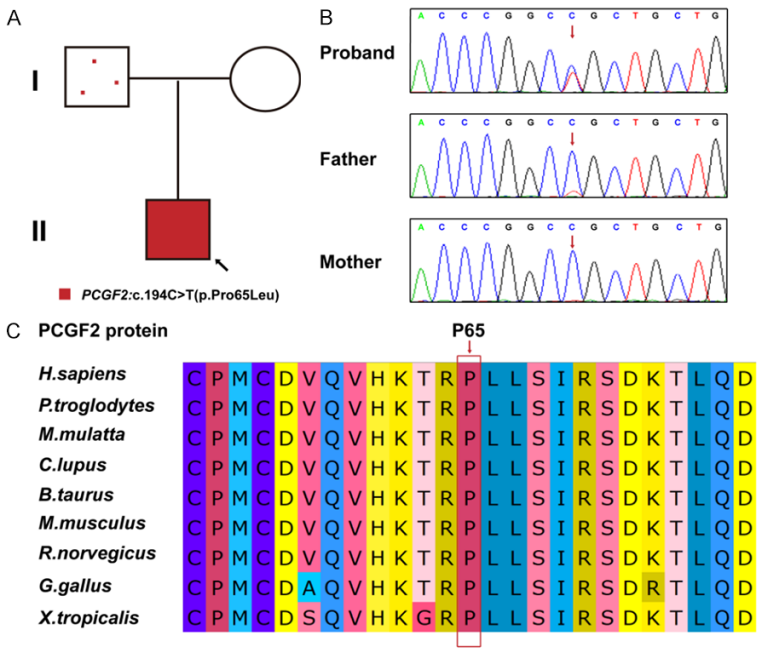

Figure 2. The genetic finding in the affected family. (A) The pedigree diagram. The scarlet block represents the c.194C > T variant (The scattered dots in the father's icon indicate that he hasmosaicism). (B) Sanger sequencing peaks of the family members for c.194C > T variant. (C) The conservatism of PCGF2: P65 amino acid residue among multiple species.

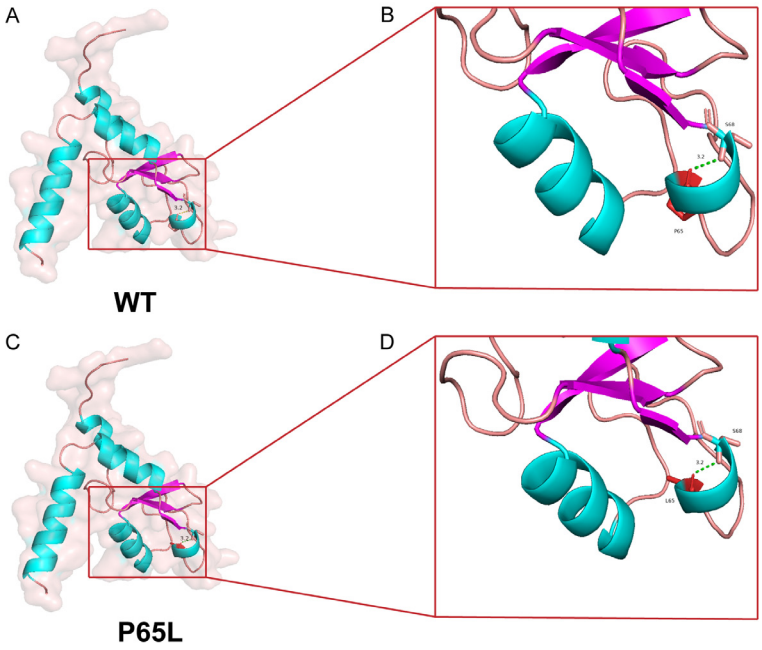

Figure 3. The structural models of PCGF2 protein segments containing the wild-type or P65L mutant. (A, B) The wild-type segment and the magnified view. (C, D) The P65L mutant segment and the magnified view.

conservation degree across species (**Figure 2C**).

Intramolecular impact of the PCGF2: Pro65Leu variant

Figure 3 (A and B for wild-type, WT; C and D for P65L) presents the converged and eventual models based on structural estimation. The MD simulation results a represented in **Figure 4**. Although PCGF2^{P65L} slightly affected thetotal flexibility (**Figure 4A**), the flexibility in the 65th residue was affected profoundly (**Figure 4B**). P65L mutant inducted numerous hydrogen bonds in the overall protein segment compared to the wild-type (**Figure 4C**). P65 residue in wild-type generated fewer hydrogen bonds with additional residues compared with variant residue P65L (**Figure 4D**). Additionally, the P65L mutant decreased the compactness of the protein segment (**Figure 4E**) and slightly increased the exposed surface in protein structure (**Figure 4F**).

Discussion

GDD, along with autism spectrum disorder (ASD), communication disorders, and intellectual disability (ID), constitute chronic neurodevelopmental disorders with the highest prevalence observed in pediatric primary care [15]. Dozens of genetic disorders involving GDD and copy number variations (CNVs) have been identified due to advanced molecular techniques developed in recent decades [16]. However, there is no clear genetic diagnosis for half of the GDD cases. It creates a barrier for caregivers to understand the potential prognosis and provide corresponding assistance and for physicians to develop targeted medication [17, 18].

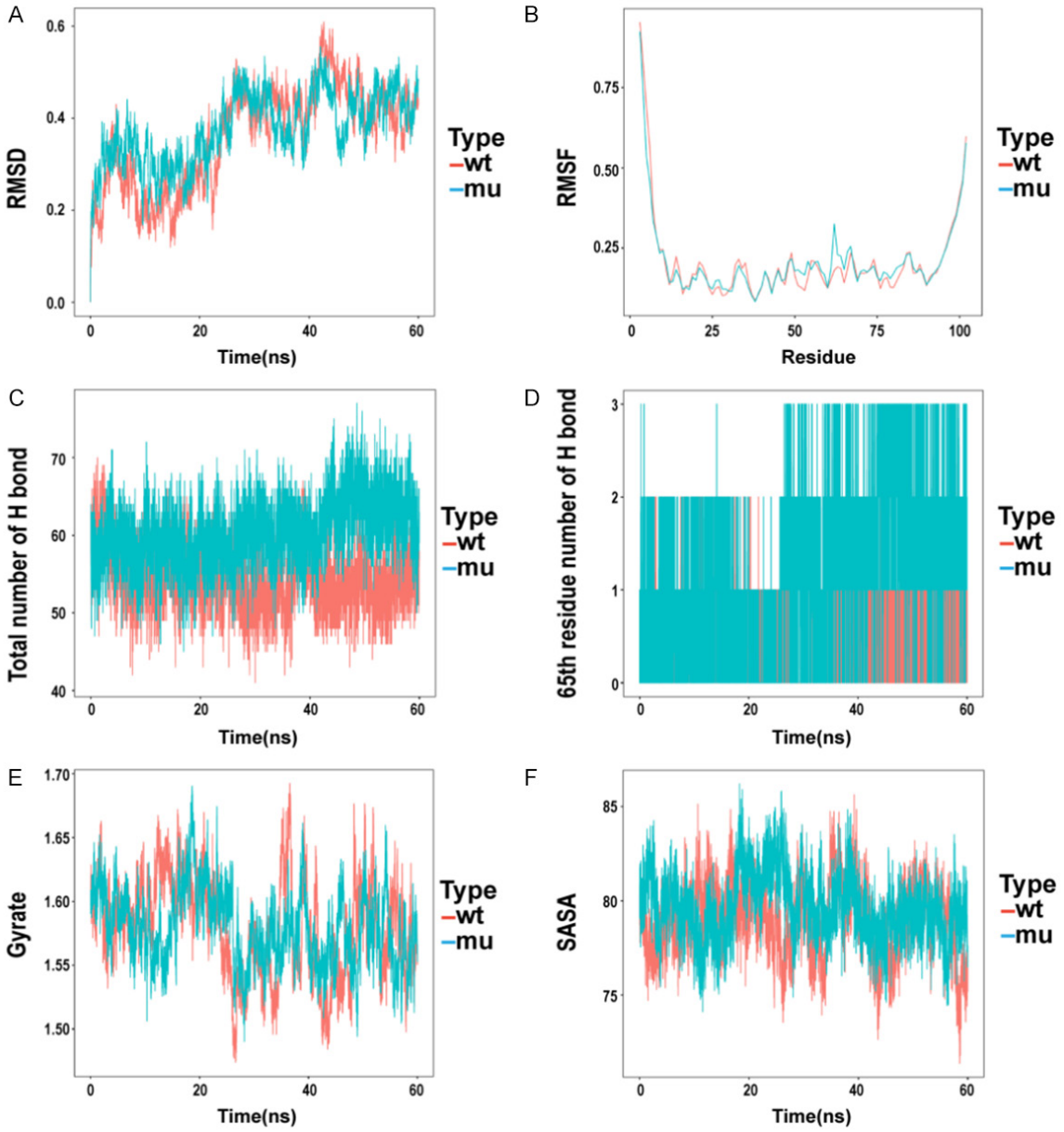

Figure 4. The results of molecular dynamic simulations of the PCGF2: P65L mutant. (A) RMSD (Ca) trajectory of two proteins, in which all structures were compared withinitial/reference frame (0 ns) through RMSD. (B) RMSF for both proteins was determined based on every simulation, which determined RMSF for atomic positions within this trajectory after being fitted to the initial/reference frame (0 ns). (C) Hydrogen bond quantity generated for MUT or WT protein. (D) Hydrogen bond quantity generated for residue P65 or P65L as well as additional residues for all structures within this trajectory. (E) Gyrate: Rg analyses on WT PCGF2 together with the corresponding variants. Rg represents the measure of protein atomic structural displacement from the corresponding common mass center during simulationsand providesintegrative data regarding protein compactness with time. (F) SASA analyses on WT PCGF2 as well asP65L variants. SASA determines the exposed protein structuresurface accessible to the solvent molecules and corresponding data for its exposure to the solvent environment with time.

Since 2015, when Turnpenny *et al.* defined this GDD condition, only 3 *PCGF2* mutations from four studies have been identified, including c.194C > T (p.P65L), c.193C > T (p.P65S), and c.1026delC (p.L343*) [4-7]. Among these mutations, the Pro65Leu mutation was repeatedly detected in 12 patients of different ethnic groups, indicating its potential as a hotspot mutation for TPFS or ID. The majority of these cases carried *de novo* variants, excluding one

that came from a mosaic mother [5]. Similarly, the variant in our study was inherited from a mosaic father, which required us to provide genetic counseling and fertility guidance carefully to the affected family. Specifically, necessary measurements like preimplantation and prenatal diagnosis are recommended. All cases diagnosed with TPFS have similar developmental delay, facial abnormalities, and radiographic indications. But a fine genotype-phenotype association of this condition needs to be established as more cases and variants are being discovered.

The PCGF2 protein was initially isolated by Tagawa *et al.* from various tumor cells [19]. It shows specific binding to the 5'-GACTNGACT-3' DNA sequence and acts as a transcriptional repressor and the linker of certain PRC1-like complex to histone H2A lysine 119 for programmed ubiquitination [20-22]. However, its specific function in the development of the central nervous system (CNS) needs to be further explored [23-25]. The P65 residue in PCGF2 is evolutionarily conserved, and the P65L mutation has been predicted to be deleterious at the structural level [5]. In our study, we performed MD simulations to investigate its intramolecular impact. Our results indicated that the P65L variant could primarily impact the local flexibility of the 65th residue and alter the protein stability by changing the number of hydrogen bonds. This evidence pointed toward a possible dominant-negative effect of the P65L variant.

In summary, this study, for the first time in the Chinese population, identified the recurrent P65L mutation in *PCGF2* causing Turnpenny-Fry syndrome. *In silico* analysis strongly supported the pathogenesis of this mutation. Our findings further highlighted the potential of the PCGF2: p.P65L variant as a mutation hotspot for the diagnosis of GDD and emphasized its risk of autosomal dominant inheritance from a mosaic parent.

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Disclosure of conflict of interest

None.

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