Letter to the editor

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Congenital hyperinsulinism due to *NEUROD1* gene mutation

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To the editor,

Congenital hyperinsulinism (CHI) is a rare disease, but the most frequent cause of persistent hypoglycemia in infants and children. CHI is caused by an unregulated insulin secretion by the pancreatic β cells. In these patients, recurrent episodes of hyperinsulinemic hypoglycemia lead to significant risk of permanent brain damage [1]. Usually, CHI is clinically diagnosed when plasma insulin levels exceeded 2 μU/mL, despite a blood glucose concentration of <50 mg/dL, free fatty acids (FFA) <1.7 mmol/L, β-hydroxybutyrate <1.8 mmol/L, and a glycemic response to glucagon >30 mg/dL [2]. Transient hyperinsulinemic hypoglycemia usually resolves on its own within a few days or months [3,4]. A prompt diagnosis of CHI and immediate management of glucose levels is critical to prevent complications such as epilepsy, cerebral palsy and neurodevelopmental deficits [1,3,4]. Disease-causing variants in 16 different genes have been reported to cause isolated CHI. Recently, advances in genetic analysis technology have made improved accessibility to genetic diagnosis, as a result, more new genes causing CHI are continuously being identified. According to recent studies, *FOXA2*, *CACNA1D* and *EIF2S3* gene mutations have been considered as a cause of CHI [4]. These can be classified into defects in genes encoding the pancreatic ATP sensitive potassium channels (*ABCC8* and *KCNJ11*) and other channels/transporter proteins (*KCNQ1*, *CACNA1D* and *SLC16A1*), enzymatic gene defects (*GLUD1*, *GCK*, *HADH*, *UCP2*, *HK1*, *PMM2* and *PGM1*) and defects in genes encoding the transcription factors (*HNF1A*, *HNF4A*, *FOXA2* and *EIF2S3*) [4].

Herein, we report a case of CHI with a novel heterozygous variant in *NEUROD1* detected by next-generation sequencing (NGS) panels associated with CHI.

A 3-day-old girl presented with hypoglycemia for 4 days. She was delivered via cesarean section at a gestational age of 39^{+2} weeks and had a birth weight of 3.0 kg (30.2 percentile). Her mother had no gestational diabetes. She was diagnosed with transient tachypnea of the newborn immediately after birth and received high-flow nasal cannula therapy. On the third day post-birth, hypoglycemia developed, and intravenous fluids were administered with a glucose infusion rate of 13.3 mg/kg/min. Laboratory findings during the hypoglycemic episode (44 mg/dL) revealed plasma insulin of 3.5 μU/mL, FFA levels of 0.198 mmol/L, and negative ketones, fulfilling the diagnostic criteria for CHI. Diazoxide therapy was initiated at a dose of 10 mg/kg/day for 2 days, followed by a reduction to 6.75 mg/kg/day, which resulted in effective blood glucose control. The medication was discontinued after 70 days without any side effects except for mild hirsutism, with sustained euglycemia observed postdiscontinuation. NGS panel test was conducted in the patient at the diagnosis of CHI, resulting in the NEUROD1 gene variant,c.79C>T, p.Leu27Phe (NM_002500.4). This variant was initially classified into variant of uncertain significance. Minor allele frequency of the variant is estimated to be 0.0008% (gnomAD). In silico analysis predicted the p.Leu27Phe is disease-causing variant

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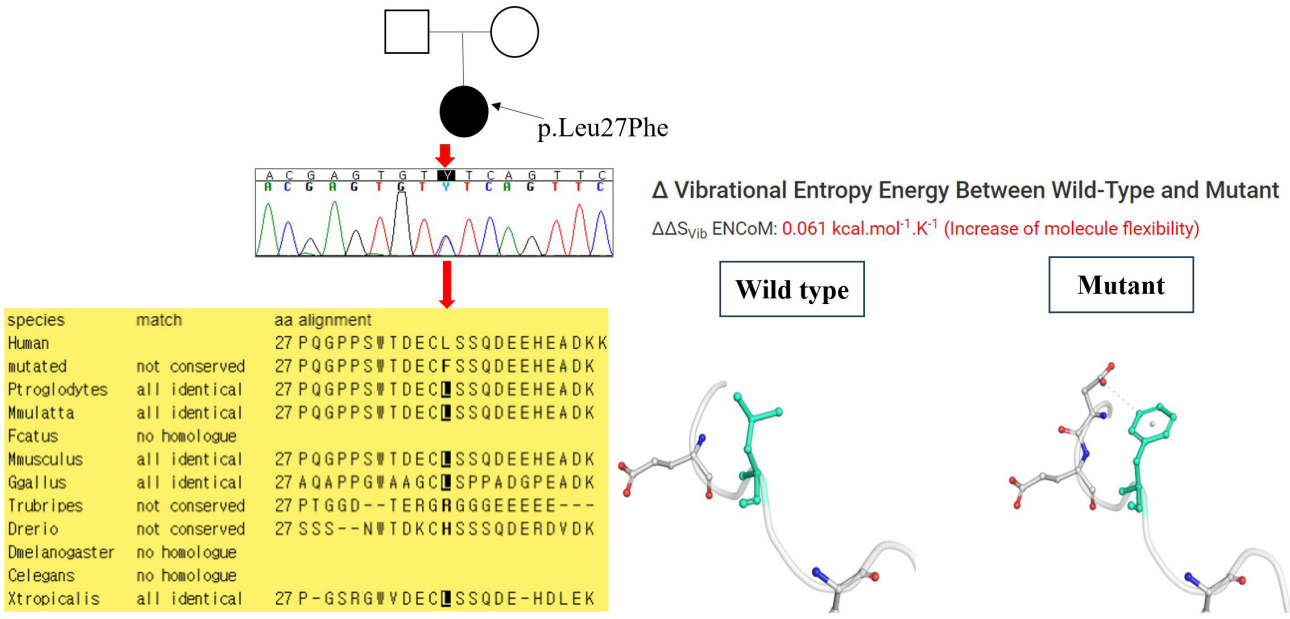

Fig. 1. Sanger sequencing confirmed a de novo variant, c.79C>T (p.Leu27Phe) in NEUROD1 from the patient, shown by the red arrow. L27 residue is partially conserved among species, shown in the dark square box. Sequence was aligned using blast (https://blast.ncbi.nlm.nih.gov/); wild-type and mutant residue (p.L27F) in the Neurof1 protein is shown in light-green and are also represented as sticks alongside the surrounding residue, indicating any type of interaction. The crystal structure of the domain from wild-type Neurod1 was generated by SWISS-MODEL (https://swissmodel.expasy.org/) and depicted as a cartoon representation. All structural images were generated using PyMOL (https://pymol.org/).

(score 0.98 in Mutation Taster, score 0.70 PolyPhen-2). The variant was partially conserved across the multiple species (Fig. 1). The vibrational entropy change ($\Delta\Delta S_{Vib}$ ENCoM) provides information on the configurational entropy of the proteins with single minima of the energy landscape. The $\Delta\Delta S_{Vib}$ ENCoM was calculated for the mutant and wild-type protein to calculate the vibrational entropy energy change between wild-type and mutant. The $\Delta\Delta S_{Vib}$ ENCoM calculated for the mutant revealed a positive value (0.061 kcal.mol^{-1}.K^{-1}) signifying the flexibility of protein structure upon mutation in p.Leu27Phe which suggests destabilizing mutant protein. In addition, segregation analysis revealed a *de novo* variant, resulting in a likely pathogenic variant (PS2+PP1+PP3). Basically, *NEUROD1* gene is known to be causal gene of maturity-onset diabetes of the young (MODY) 6. Similarly, transient hyperinsulinemia is also reported in newborns with MODY1 and MODY3 related genes (*HNF4A* and *HNF1A*) [5]. Approximately 6% of patients with diazoxide-responsive hyperinsulinemia had HNF4A and HNF1A variants. The clinical features also were extremely variable. At the time of analysis, diazoxide was discontinued in individuals within months or years. Therefore, if there is a family history suggestive of MODY, genetic testing for *HNF4A* and *HNF1A* should be considered because these conditions can cause transient hyperinsulinism in the newborn period [6].

NEUROD1 protein is a transcription factor necessary for insulin synthesis and secretion and also plays an important role in the function of the brain [7]. This transcription factor is active in the pituitary gland and progenitor cells of the endocrine pancreas during development and adulthood. Beyond supporting α and β cell development, this plays roles in differentiating pancreatic polypeptide and δ cells, activating glucagon, and inhibiting somatostatin expression [8]. In addition, it was reported that the NEUROD1 deletion altered the properties of α and β endocrine cells, resulting in severe neonatal diabetes [9]. Recently, Bohuslavova et al. [10] suggest that NEUROD1 reprograms the transcription factor and epigenetic landscapes, favoring the differentiation of endocrine cells and facilitating the generation of funcztional insulin-producing β cells. In a recent study using NEUROD1 knockout mouse embryos, it has been reported that the stability of the NEUROD1 protein is controlled by extracellular signal-regulated kinase (ERK)-dependent phosphorylation, resulting in neuronal cell activation [11]. The reliability experiment of NEUROD1 protein by ERK-dependent phosphorylation using pancreatic cells has never been conducted. Still, considering

this mechanism in neuronal cells, it is estimated that misfolding of p.Leu27Phe mutant protein interferes with ERK-dependent phosphorylation, which affects the activation of pancreatic cell function.

With increasing reports regarding the association between *NEUROD1* and glycemic control mechanisms, further functional studies will be needed in the future regarding the association between the *NEUROD1* gene and the occurrence of CHI and the association between the *NEUROD1* mutant type and the permanent or transient CHI type in terms of treatment and prognosis of the patients. Furthermore, performing whole exome sequencing, including next generation sequencing panels, for genetically locus heterogeneous conditions such as CHI, will also be an important factor in clinical practice in order to discover additional susceptibility or more candidate genes for CHI.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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