Research Square

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A maternal GOT1 novel mutation associated with early-onset severe preeclampsia identified by whole-exome sequencing

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Abstract

Purpose: This study wants to know the genetic cause of preeclampsia (PE) which is a leading cause of maternal and perinatal death, but the underlying molecular mechanisms that cause PE remain poorly understood. Many single nucleotide polymorphisms have been identified by genome-wide association studies and were found to be associated with PE; however, few studies have used whole-exome sequencing (WES) to identify PE mutations.

Methods: Five patients with severe early-onset preeclampsia (EOPE) were recruited, and WES was performed on each patient. Sanger sequencing was used to confirm the potential causative genetic mutation.

Results: After a stringent bioinformatics analysis, a rare mutation in the *GOT1* gene, c.44C>G:p.P15R, was found in one patient. Bioinformatics analysis showed that the mutation site is highly conserved across several species and was predicted to be a pathogenic mutation according to several online mutational function prediction software packages. Further structural biology homology modeling suggested that P15R would change the electric environment of enzymatic center, and might affect the binding affinity of substrate or product.

Conclusion: We demonstrated for the first time that the mutation in *GOT1* may be associated with EOPE, the results of this study provide researchers and clinicians with a better understanding of the molecular mechanisms that underlie maternal severe EOPE.

Introduction

Preeclampsia (PE) is a pregnancy-specific multi-systemic syndrome that affects several organs, including the kidneys, liver, and brain, and is a leading cause of maternal and perinatal morbidity and mortality. PE affects approximately 5% of pregnancies and is characterized by new-onset hypertension and proteinuria at ≥ 20 weeks of gestation [1]. The main manifestation of preeclampsia is proteinuria, as well as thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances. The placenta plays a key role in the development of this disorder. The pathogenic mechanism of PE includes defective deep placentation, oxidative and endoplasmic reticulum stress, autoantibodies to type–1 angiotensin II receptor, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction, presence of an antiangiogenic state, and maternal angiogenic imbalances caused by placental antiangiogenic factors [2–8].

Genetic alteration is one of the main causes of PE [9–11], but the exact underlying molecular mechanism remains unclear. Maternal or fetal sequence variants located in or near some genes, such as *FLT1* [12, 13], *PLEKHG1* [14], *APOL1* [15], *ERAP2* [16, 17], *WNK1,* and *AKR1C3* [18], *CYP2D6* and *CYP2C9* [19], were shown to be associated with PE. Genome-wide association studies and Sanger sequencing are frequently used in the genetic analysis of PE, while high-throughput sequencing technology such as whole-exome sequencing (WES) is rarely used to find the genetic cause of PE.

Here, we recruited 5 unrelated patients with severe EOPE and performed WES for each patient. Sequence variants were filtered according to standard procedures. A novel mutation in *GOT1* was identified in one patient (P1), and is considered to be a potentially pathogenic mutation associated with PE, according to *in silico* analysis and structural biology predictions.

Materials And Methods

Subjects

PE can be characterized into 2 different disease entities: early-onset PE (EOPE, corresponding to preeclampsia registered at < 34 weeks) and late-onset PE (LOPE corresponding to preeclampsia registered at > 34 weeks). They are associated with different fetal and maternal effects, heritability, biochemical markers, and clinical symptoms [20]. We chose patients diagnosed with EOPE at the Beijing Obstetrics and Gynecology Hospital between January 2018 and June 2018. The diagnostic criteria of severe PE include: blood pressure of 160/110 mmHg or higher; thrombocytopenia (platelet count below 100,000/μL); impaired liver function as indicated by abnormally elevated blood concentration of liver enzymes; severe persistent right upper abdominal pain; progressive renal insufficiency (serum creatinine concentration above 1.1 mg/dL or doubling of serum creatinine concentration); pulmonary edema; and cerebral or visual disturbances. Women with high risk factors [21] for PE, such as those with chronic hypertension, pre-gestational diabetes, maternal body mass index (BMI) >30 kg/m^2, antiphospholipid syndrome/SLE, or who had received assisted reproduction, were excluded from our study. However, we did not rule out women with a prior history of pre-eclampsia. Using the above criteria, we identified 5 patients with severe EOPE (Table 1).

All procedures involving human participants were performed in accordance with the ethical standards of the Ethics Committee of Beijing Obstetrics and Gynecology Hospital and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from each patient.

Whole-exome sequencing analysis

Genomic DNA was extracted from peripheral blood using a DNeasy Blood and Tissue Kit (Qiagen, Valencia, CA, USA). Whole-exome sequencing (WES) was performed by Annoroad Gene Technology Co., Ltd, Beijing. Briefly, exomes were captured using a SureSelect Human All Exon V6 Kit (Agilent Technologies), and were sequenced using a HiSeq X10 Sequencer (Illumina). Raw Reads were mapped against the human reference genome hg19 using Burrows-Wheeler Aligner (BWA). Single nucleotide variants (SNV) were identified by SAMTools and Genome Analysis Toolkit (GATK) software, and ANNOVAR was used for SNV functional annotation and filtering. Variants fulfilling the following criteria were retained: (i) missense, nonsense, frame-shift, or splice site variants; (ii) absent from the Exome Aggregation Consortium database (ExAC, http://exac.broadinstitute.org/), Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/), 1000 Genomes (http://browser.1000genomes.org/index.html), ESP6500 (http://evs.gs.washington.edu/EVS/), and our inhouse database.

Sanger sequencing validation

The whole-exome sequencing results were validated using Sanger sequencing. For the *GOT1 (*c.44C>G:p.P15R) variant, forward (5'-ATTGGTTAATCGCGTTGCCAA–3') and reverse (5'-CCACACCTGCATCTGTAAAATGG–3') primers were used for PCR amplification and Sanger sequencing. DNA products were electrophoresed on an ABI 3730 XL DNA sequencer (Applied Biosystems, Bedford, MA).

Results

WES analysis of the five patients

Five patients with severe EOPE were recruited in this study; their clinical information and data are shown in Table 1. The incidence of EOPE was about 0.5–0.8%, so the incidence of severe EOPE is much lower than EOPE. We speculated that genetic factors may play an important role in patients with severe EOPE; therefore, WES was performed for each patient. The quality of sequencing met the requirements of the bioinformatics analysis, as shown in the WES report (Supplementary Table 1).

Next, we performed a filtering process on the WES data (Supplementary Table 2). First, we retained missense, nonsense, frameshift, and splice site mutations, then filtered out the variants with allele frequencies above 1% in the 1000G, ESP6500, ExAC, and gnomAD databases. We then used our inhouse database to further filter out duplicate mutations, and thus obtained variants for each patient. For example, we identified 419 single nucleotide variants and 36 insertion-deletion mutations in Patient No. 1 (P1, Supplementary Table 2). All variants were further filtered according to the list of 40 selected candidate genes that are known to be associated with severe preeclampsia [9]. In this way, we were able to narrow down the scope of the target. We identified a rare variant of the *GOT1* gene c.44C>G:p.P15R in P1; the mutation was confirmed by Sanger sequencing (Figure 1A).

In silico analysis of the *GOT1* variant

The Pro15 site is highly conserved across species from human to zebrafish (Figure 1B), suggesting that Pro15 plays an important role in the function of the GOT1 protein. After searching exome and genome sequencing databases, we found that the allele frequency of c.44C>G was 0 in all databases (Table 2), indicating that the mutation is extremely rare. Furthermore, several online mutational prediction tools predicted P15R to be a pathogenic mutation (Table 2). As the variant is heterozygous, we wanted to know whether the heterozygous variant influences disease tolerance. Constraint Metrics Z score for missense variation analysis [22] found that *GOT1* was predicted to be intolerant to variation (z = 2.17, http://exac.broadinstitute.org/gene/ENSG00000120053). Thus, the above bioinformatics analysis suggests that the rare variant c.44C>G:p.P15R of the *GOT1* gene may be associated with severe EOPE.

Molecular modeling of the mutated protein

Fortunately, we found that the structure of GOT1 protein had been resolved (PDB 3ii0, Figure 2A). By structure analysis, we found that there was an ‘open pocket’ at the surface of GOT1 protein, which was positive charged (Figure 2C). The 15th residue proline was located at the edge of this pocket (Figure 2C). In our study, this residue mutated to arginine (Figure 2B). Arginine is a basic amino acid with a big side

chain (Figure 2D). We proposed that this point mutation would change the electric environment of enzymatic center, meanwhile, affect the binding affinity of substrate or product even more the whole process of enzyme-catalyzed reactions. Computer modeling had confirmed our proposal that P15R mutation changed the electricity and enhanced the positive charge of this area (Figure 2D).

Detailed clinical information for P1

Patient No. 1 (P1) is a 35-year-old woman, body weight 62.5 kg, with a BMI of 22.9 kg/m^2 prior to pregnancy. Six years ago, she delivered a baby girl by cesarean section because the umbilical cord was wrapped around the fetus's neck. During the same period, she was diagnosed with severe PE (gestational age of onset is unknown), and her blood pressure returned to normal postpartum. She refused to provide a personal medical history or a family history. The patient's blood pressure rose to 140/90 mmHg at 25 weeks of gestation, and an ultrasound examination showed that the fetus was small. She began to experience limb edema at 26 weeks of gestation but was not treated at this time. At 28 weeks of gestation, her blood pressure rose to 197/114 mmHg and urinary protein appeared as 3+, but she made no complaints. When the patient visited our hospital at that time, her body weight was 80 kg, and an ultrasound test showed that umbilical cord blood flow was S/D 4.8 and fetal growth was restricted. Her urinary protein went up to 4+, and 24 h urine protein was 7431.2 mg. The highest level of serum creatine was 85.6 μmol/L, blood urea nitrogen was 10.56 mmol/L, uric acid was 472.9 mmol/L, with no detected anemia or thrombocytopenia. The lowest level of albumin was 22.6 g/L. As for liver damage, the highest level of alanine aminotransferase was 52.5 U/L, aspartate aminotransferase was 41.6 U/L, and lactate dehydrogenase was 332 U/L. The highest level of d-dimer was 10.87 mg/L. Echocardiography showed no abnormalities. Both antinuclear antibodies, antibody spectrum, and cardiolipin antibody were all negative. After administering drugs and inducing labor, P1 gave birth to a stillborn child. She recovered well and was released from the hospital 10 days later.

Discussion

In this study, whole-exome sequencing was performed in 5 patients with severe EOPE. A rare mutation in the *GOT1* gene, c.44C>G:p.P15R was found in one patient (P1). Bioinformatics analysis showed that the mutation was highly conserved across different species and was predicted to be a pathogenic mutation according to several online mutational function prediction software packages. Further structural biology homology modeling suggested that P15R may change the electricity and enhance the positive charge of this area.

The *GOT1* gene—full name glutamate oxaloacetate transaminase—is also known as aspartate aminotransferase. GOT1 can catalyze L-cysteine or L-aspartate substrates. L-cysteine can be converted into 3-mercaptopyruvate by GOT1, and then H_2S can be obtained by 3-mercaptopyruvate sulphurtransferase. L-aspartate can be catalyzed into L-glutamate by GOT1, which is a pyridoxal phosphate dependent enzyme found in the cytoplasm.

Previous studies suggest that maternal aspartate metabolic or catalytic processes are associated with severe preeclampsia [9]. A study using high-resolution magic angle spinning nuclear magnetic resonance spectroscopy (HR-MAS MRS) found that aspartate levels are higher in the placenta of patients with preeclampsia, while glutamate levels are lower [23]. Another study using ultra performance liquid chromatography-mass spectrometry (UPLC-MS) found that glutamate levels were low in explanted placental villous fragment cultures of preeclampsia patients [24]. The P15R mutation identified in the present study is located near the GOT1 enzyme activity center. Arginine is an alkaline amino acid, while both the substrate (L-aspartate) and product (L-glutamate) involved in GOT1 reaction are acidic. The mutated protein thus, may enhance alkalinity near the active center of the enzyme, which may increase the binding ability of the substrate or the product, and in turn affect the release of the product. Thus, the decrease in L-glutamate release due to the P15R mutation in the *GOT1* gene could be related to the occurrence of preeclampsia in this patient.

A previous study found that hydrogen sulfide (H_2S) is essential for a healthy placental vasculature, and that a decrease in H_2S activity is related to the onset of preeclampsia [25]. H_2S can cause contraction and relaxation of human umbilical vein endothelial cells [26]. The formation of hydrogen sulfide is catalyzed by GOT1, which is expressed by human umbilical artery endothelial and smooth muscle cells [26]. Thus, the P15R mutation may reduce the release of 3-mercaptopyruvate, thereby affecting the production of hydrogen sulfide, which could then induce preeclampsia owing to an abnormal placental vasculature.

In summary, the P15G mutation in the *GOT1* gene identified in the present study may lead to preeclampsia by causing abnormal synthesis of glutamate or hydrogen sulfide. Furthermore, the findings suggest that abnormal aspartate metabolic or catalytic processes, together with placental vasculature contraction or relaxation abnormalities, may be associated with preeclampsia. This study provides a genetic basis for the etiology and molecular mechanisms that underlie preeclampsia.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital and was in accordance with the 1964 Helsinki Declaration and its later amendments. Each participant in this study signed an informed consent form to participate in this study.

Consent to publish

Each participant in this study signed an informed consent form for publication of all of the participants' clinical details.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare no conflict of interest.

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Authors' Contributions

L. Z. carried out the majority of the experiment; L. L. performed WES data analysis and *in silico* analysis; F. F. performed the molecular modeling analysis; samples from the patient were collected by L. Z., Z. C., and Y.-N. X.; L. L., and H. G. designed the experiments and wrote the manuscript.

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Tables

Table 1. Clinical features of the patients with early-onset severe preeclampsia

Variables	P1	P2	P3	P4	P5
Age (years)	35	27	29	31	31
Pro-gestational BMI (kg/m^2)	22.9	22.1	20	26.8	22
Prior pre-eclampsia	+			+	
Registered gestational age (weeks)	28	27	27	26	31
First birth		+	+	+	+
Anemia					
Thrombocytopenia			+	+	
Impaired liver function			+	+	+
Progressive renal insufficiency	+	+	+	+	
Serous membrane fluid		+			+
Pulmonary edema			+		+
Hypoproteinemia	+		+		-
HELLP syndrome			+	+	+
Intrahepatic cholestasis of pregnancy					+
Placental abruption					
Late abortion		+	+	+	
Premature birth					+
Cesarean delivery		+	+		+
Fetal growth restriction	+				
Stillbirth	+			+	
Low birth weight infant		+	+		+

Table 2. ***In silico*** **analysis of** ***GOT1*** **mutation**

Variants	Amino acid change	Polyphen-2[a]	SIFT[b]	PROVEAN[c]	Mutation Taster[d]	SNPs&GO[e]	FATHMM-MKL[f]	gnomAD[g]	ExAC[h]	1000 Genomes[i]	ESP6500[j]
c.44C>G	p. P15R	Possibly damaging (0.924)	Damaging (0.015)	Deleterious (-7.30)	Disease causing (0.9999)	Disease (0.918)	Damaging (0.918)	0	0	0	0

[a]Polyphen-2. Prediction Scores range from 0 to 1 with high scores indicating probably or possibly damaging.

[b]SIFT, i.e., Sorting Intolerant From Tolerant. Scores vary between 0 and 1. Variants with scores close or equal to 0 are predicted to be damaging.

[c]PROVEAN. Variants with scores lower than -2.5 (cutoff) are predicted to be deleterious.

[d]Mutation Taster. The probability value is the probability of the prediction, i.e., a value close to 1 indicates a high 'security' of the prediction.

[e]SNPs&GO. Probability: Disease probability (if >0.5 mutation is predicted Disease).

[f]FATHMM-MKL. Values above 0.5 are predicted to be deleterious, while those below 0.5 are predicted to be neutral or benign.

[g]Frequency of variation in total of gnomAD database.

[h]Frequency of variation in total of ExAC database.

[i]Frequency of variation in 1000 Genomes database.

[j]Frequency of variation in ESP6500 database.

Figures

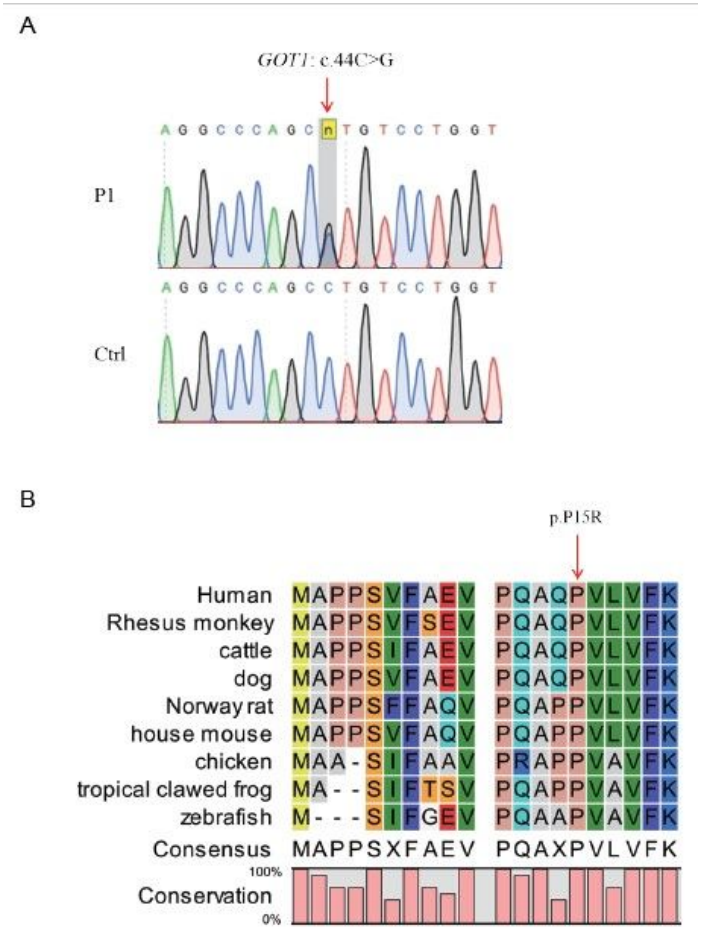

Figure 1

Analysis of the GOT1 variant. (A) Sanger sequencing validated the heterozygous c.44C>G variant in the GOT1 gene. Red arrow indicates mutation site. (B) Amino acid sequence alignment of GOT1 in different species. Red arrow indicates mutated amino acid. Proline at position 15 is 100% conserved in all species.

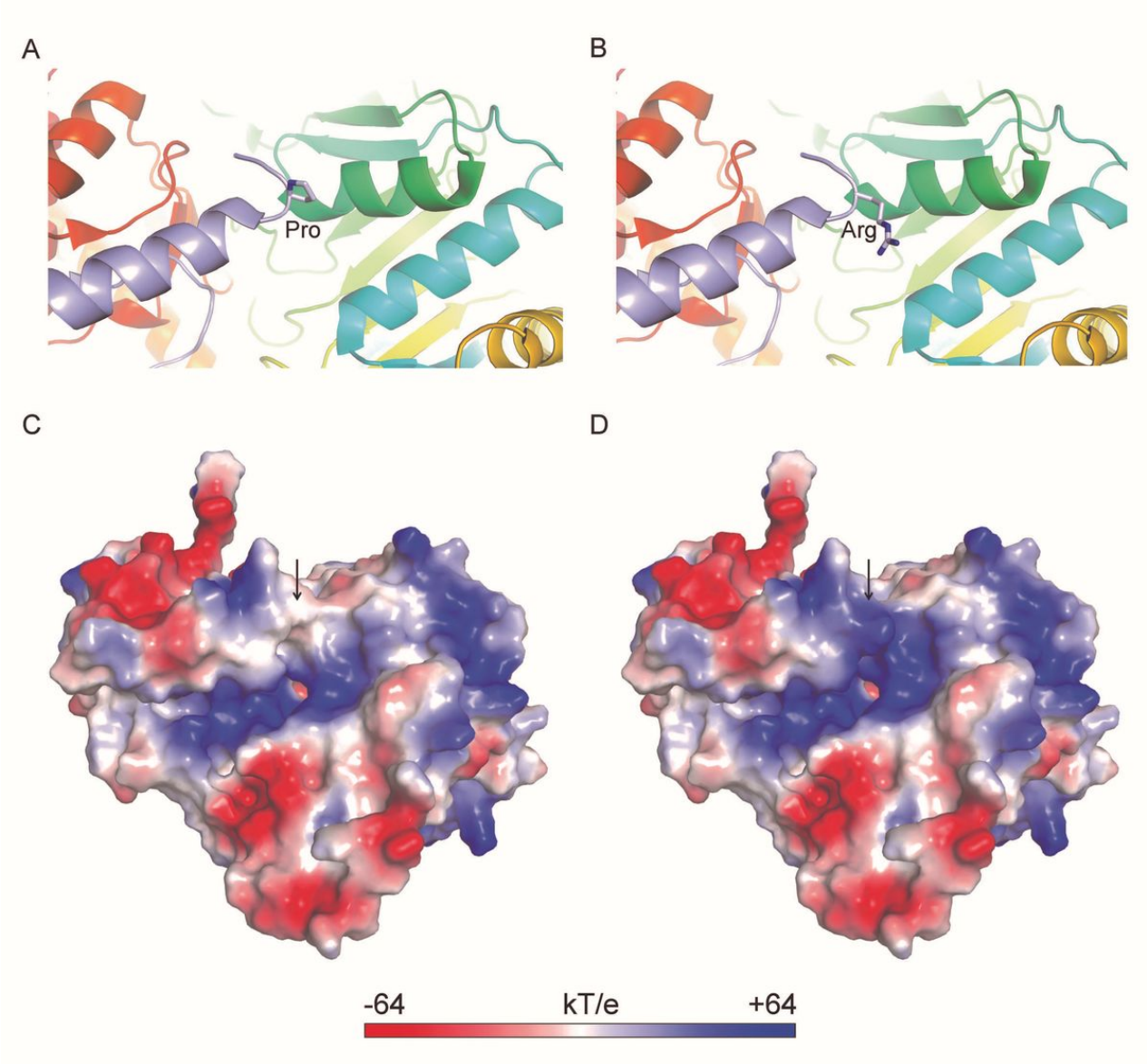

Figure 2

The molecular model of GOT1 protein. (A) Close view of wild type GOT1 protein structure (PDB ID: 3II0, Ugochukwu, E., Pilka, E., Cooper, C., Bray, J.E., Yue, W.W., Muniz, J., Chaikuad, A., von Delft, F., Bountra, C., Arrowsmith, C.H., Weigelt, J., Edwards, A., Kavanagh, K.L., Oppermann, U., Structural Genomics Consortium (SGC). Crystal structure of human Glutamate oxaloacetate transaminase 1 (GOT1)). The whole protein is shown as cartoon in rainbow and 15th proline side chain is shown as sticks. (B) Close view of P15R mutant type GOT1 protein structure. The whole protein is shown as cartoon in rainbow and 15th arginine side chain is shown as sticks. (C) Electrostatic surface view of the wild type GOT1 protein. Electrostatic potential is expressed as a spectrum ranging from -64 kT/e (red) to +64 kT/e (blue). Black arrow indicates the 15th residue proline. (D) Electrostatic surface view of the P15R mutation GOT1 protein. Electrostatic potential is expressed as a spectrum ranging from -64 kT/e (red) to +64 kT/e (blue). Black arrow indicates the 15th residue arginine.

Supplementary Files

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