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LETTER TO THE EDITOR

Discrepancy in the degree of polycythemia in a family with a novel nonsense *EPOR* mutation

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Dear Editors,

We read with interest a case report of primary familial congenital polycythemia (PFCP) by Toriumi et al. [1]. The report described a 10-year-old female patient with PFCP associated with a novel *EPOR* mutation who presented with polycythemia requiring venesection to keep Hct level below 50%. The polycythemia was alleviated after the patient reached menarche. The same finding was observed in her mother who also had PCFP with the same *EPOR* mutation of c.1220C>A, p.Ser407X. It was concluded that in female patients with the type of *EPOR* mutation, remission of polycythemia may occur after the start of menstruation.

Herein, we describe a similar finding of a discrepancy in the degree of polycythemia in a family with a novel nonsense *EPOR* mutation. An 11-year-old male patient was incidentally detected to have high Hb level. Both parents and his elder brother were healthy. Physical examination showed only plethoric appearance without cyanosis.

The hematologic parameters from the family members were as shown in Table 1. The patient had isolated erythrocytosis, while both parents and the elder brother had normal cell counts. Further investigations in the patient to look for the cause of polycythemia revealed normal findings from echocardiography and abdominal ultrasonography, normal Hb analysis pattern (Hb AA_2, Hb A_2 2.7%), normal transferrin saturation, absence of *JAK2*V617F mutation and low serum erythropoietin level < 1.00 mIU/mL (3.7–29.5 mIU/mL). The whole-exome sequencing (WES) analysis was performed which demonstrated a heterozygous mutation in *EPOR* (c.1218C>A, p.Cys406Ter) in the patient and his mother, but not the father and brother as summarized in the Table 1.

PFCP or Familial erythrocytosis type 1 (ECYT1, OMIM#133100) is a primary congenital erythrocytosis with an autosomal dominant inheritance pattern [2]. The condition is caused by mutations in the erythropoietin receptor gene (*EPOR*) resulting in loss of negative regulatory domain of the receptor, leading to hyperresponsiveness to EPO.

EPOR encodes an erythropoietin receptor precursor which consists of 508 amino acids. The mature erythropoietin receptor consists of 484 amino acids which contain an extracellular, a transmembrane and a cytoplasmic region. The C-terminal of the erythropoietin receptor contains binding sites for SHP-1 and SOCS-3 which results in a negative regulation of signal transmission [2]. *EPOR* p.Cys406Ter mutation identified in our patient and his mother results in a premature stop codon and a truncated erythropoietin receptor by 103 amino acids, lacking the negative regulatory region.

The father and elder brother who did not harbor the *EPOR* mutation had normal Hb levels. However, the mother who also had the *EPOR* mutation had only borderline-high Hb level. Possible coinherited genetic and acquired causes of the discrepancy in the degree of polycythemia were searched for. Re-examining of the WES results did not show any genetic variants that may have lowered the Hb level.

Similar to the findings from the report by Toriumi et al., blood loss with menstruation was likely the explanation in our case that the mother had only borderline-high Hb level;

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Table 1 Hematologic parameters and whole-exome sequencing analysis results of the patient and his family

	Patient (11 years)	Brother (14 years)	Father (42 years)	Mother (35 years)
Hb (g/L)	198	152	163	149
Hct (%)	58.3	44.8	45.5	44.2
WBC ($\times 10^9$/L)	8.39	5.55	6.23	6.55
Neutrophil (%)	45	53	69	66
Lymphocyte (%)	46	38	24	26
Monocyte (%)	2	5	3	4
Eosinophil (%)	6	3	2	3
Basophil (%)	1	1	2	1
Platelets Count ($\times 10^9$/L)	240	216	190	252
RBC ($\times 10^{12}$/L)	7.75	5.74	5.44	5.04
MCV (fL)	75.2	78	83.6	87.7
MCH (pg)	25.5	26.5	30	29.6
MCHC (g%)	34.0	33.9	35.8	33.7
RDW (%)	18.4	13.5	13	13.8
Mutations identified by WES analysis	*EPOR* c.1218C>A, p.Cys406Ter; HET	–	–	*EPOR* c.1218C>A, p.Cys406Ter; HET

HET heterozygous, *WES* whole exome sequencing

while, the patient had typical presentation of polycythemia [1]. The mother could not recall whether she had polycythemia when she was young, so this was difficult to prove. A similar case of absence of polycythemia in a 6-year-old girl with a p.Tyr426Ter while other three male adults in the family had polycythemia was reported. An in vitro study demonstrated that the erythroid progenitors from the patient and her father with the *EPOR* mutation had hypersensitivity to EPO. The absence of polycythemia in the patient was thought to be due to other unidentified environmental or genetic factors [3].

The novel *EPOR* mutation identified in our patient and family adds to the molecular characterization of PFCP and confirms the significance of the negative regulatory region in the C-terminal of erythropoietin receptor. Follow-up of the mother after post-menopausal period is necessary to identify if polycythemia may ensue to provide appropriate management. As clinical presentations vary, molecular analysis is suggested in family investigation of PFCP to ensure a correct diagnosis and genetic counseling.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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