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LETTER TO THE EDITOR
Novel Mutations in the Von Hippel–Lindau Gene Associated with Congenital Polycythemia

To the editor: Polycythemia is a rare disorder in children and the vast majority of cases are secondary to causes such as cyanotic congenital heart disease, congenital lung diseases, liver and kidney disease, and masses producing erythropoietin. Mutations in exon 3 of the *VHL* gene are the most common cause of congenital erythrocytosis [1–3]. Several reports have shown evidence of heterozygous and homozygous mutations in exon 2 of the *VHL* gene as a cause of congenital polycythemia [4–6].

We report on a 9-month-old female who was referred to the hematology clinic for evaluation by her pediatrician with plethora and erythrocytosis (RBC count 7.67 million/mm^3, hemoglobin 21.5 g/dL, hematocrit 66.2%, MCV 86.3 fL). The erythropoietin level was 48 IU/L (normal 4–27), in the face of marked erythrocytosis. The patient was started on phlebotomy treatments of 5 ml/kg of blood which has progressed to 10 ml/kg of blood with normal saline replacement every 4 weeks with good results. She was

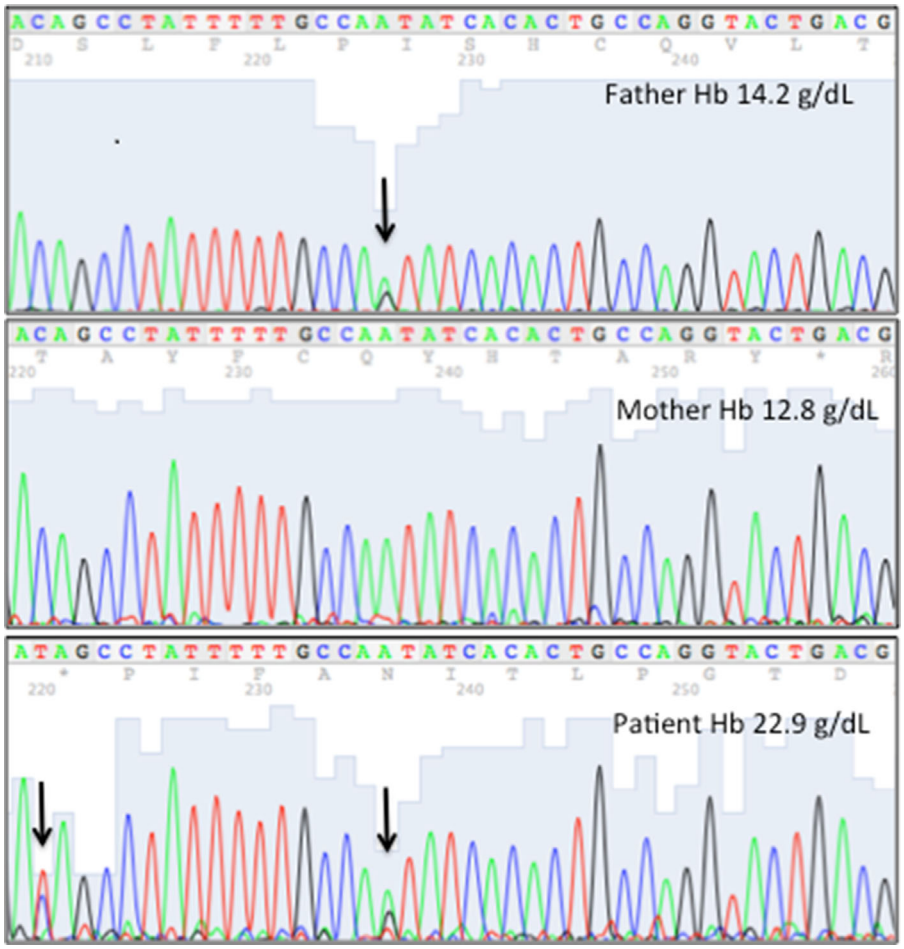

Fig. 1. Parental sequence analysis of exon 2 of the *VHL* gene showed that the patient carries a paternally inherited c.662A>G (p.Asn150Ser) and a de novo c.646C>T (p.Gln145X) mutation (arrows). The hemoglobin levels are denoted in the sequence reads.

Conflict of interest: Nothing to declare.

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started on ferrous sulfate supplementation which continues till date for iron deficiency secondary to phlebotomy.

After a thorough evaluation for secondary causes of polycythemia ruled out cyanotic congenital heart disease, congenital lung diseases, liver or kidney disease, and masses producing erythropoietin, von Hippel–Lindau (*VHL*) gene sequencing analysis was performed. Our patient carries a paternally inherited [c.662A>G (p.Asn150Ser)] and a denovo (c.646C>T [p.Gln145X]) mutation, previously reported in VHL patients [7] (Fig. 1). In silico analysis using the NCBI HomoloGene tool for orthologous sequences for the *VHL* gene shows the two residues to be conserved amongst species. The de novo mutation leads to a premature stop codon and is predicted to result in a non-functional protein. We believe the paternally inherited mutation (c.662A>G [p.Asn150Ser]) alters interaction of the VHL protein with HIF-2 alpha (Hypoxia-Inducible Factor) leading to clinical manifestations seen in the proband. The details of the interaction are outside the scope of the present report. VHL syndrome is a highly penetrant autosomal dominant disorder associated with tumors such as pheochromocytoma and hemangioblastomas of the retina, liver and cerebellum. To date, at age 9, our patient does not exhibit any of these manifestations. Patients with Chuvash polycythemia have frequent thrombotic events which have not been reported in either the proband or her father [6]. Previous reports have demonstrated mutations in exon 3 of the *VHL* gene, including Chuvash polycythemia [8]. Few reports have shown both heterozygous and homozygous mutations in exon 2 of the *VHL* gene leading to congenital polycythemia [4–6]. Our case adds to the present literature of growing evidence of exon 2 mutations, validating the importance of *VHL* mutational analysis in children as part of workup for congenital polycythemia. Based on our patient and previous reports, these exon 2 mutations do not seem to predispose either the proband or their carrier parents to an increased risk for VHL-related tumors. Additional studies will be required to elucidate the molecular basis and genotype–phenotype correlation of these mutations that has a potential to greatly impact the surveillance guidelines for VHL-associated tumors.

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