The end of a diagnostic odyssey - a case of Chuvash polycythemia

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Introduction

We report a case of a 44-year old man in whom a first detailed haematological work-up was performed in 1978, when the diagnosis of an idiopathic congenital erythrocytosis was made.

The diagnosis was confirmed on a second haematological evaluation in 1991. At that time there was marked erythrocytosis with leucocytes and platelets within the normal range. Arterial blood gas analysis including P_{50} was normal with no evidence of hypoxia nor of a left shift of the oxygen dissociation curve of the haemoglobin. There was neither evidence of 2,3-bisphosphoglycerate deficiency nor of a haemoglobinopathy on chromatography and isoelectrofocusing. The serum erythropoietin was in the upper limit of normal (24 U/l, normal 15 - 30 U/l). The spleen size was normal. Measurement of red cell mass and plasma volume revealed an absolute erythrocytosis of 45 ml/kg (165 % of normal) with a reduced plasma volume of 36 ml/kg (83 % of normal).

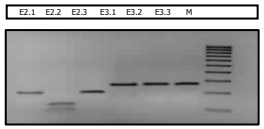
A further haematological evaluation was performed in 2000 with essentially the same results as described above. The serum erythropoietin was elevated (39 U/l, normal < 16 U/l) and because of a carbon monoxyhaemoglobin of 4.7 % (normal < 2 %) with a history of smoking a secondary erythrocytosis was postulated at that time.

The patient was referred to our division of haematology in 2005 for further diagnostic evaluation and disease management. In view of the young age at first diagnosis and of the previously documented serum erythropoietin levels in the upper limit of normal and above normal respectively with normal P_{50} values we evaluated the possibility of the occurence of Chuvash polycythemia as a rare cause of familial and congenital polycythemia.

Methods

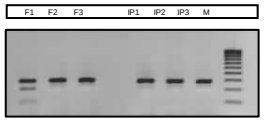
We performed an amplification of exons 2 and 3 of the von Hippel-Lindau (VHL) gene and screened for the single nucleotide polymorphisms (SNPs) G388C (exon 2) and C598T (exon 3) using polymerase chain reaction with restriction fragment length polymorphism analysis (PCR-RFLP). The mutations destroy the restriction site for Hpal enzyme (G388C) and BsrBI enzyme (C598T), which can be visualized by agarose gel electrophoresis.

Figure 1



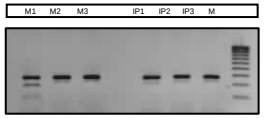
RFLP pattern of amplified exon 2 (E2.1-E2.3) and exon 3 (E3.1-E3.3), respectively, of the VHL gene of the index patient: Both amplification products were digested by the informative restriction enzymes for the pathognomonic SNPs (). Lane 1: *BsrBI* (C598T, exon 3), Lane 2: *Hpal* (G388C, exon 2), Lane 3: no digestion. Exon 2 reveales wild type at position 388 as indicated by intact *Hpal* restriction site (E2.2). Exon 3 contents the point mutation T598 as indicated by homozygous loss of *BsrBI* restriction site (E3.1). M: Molecular marker.

Figure 2



RFLP pattern of amplified exon 3 of the VNHL gene of the index patient (IP1-IP3) and his father (F1-F3): Lane 1: restriction product by *BsrBI*, Lane 2: restriction product by *Hpal*, Lane 3: undigested amplicon. The father carries the T598 mutation of exon 3 in heterozygous state as indicated by partial digestion of the amplicon (F1). The index patient carries the same mutation in homozygous state as shown by undigested amplicon (IP1). Mutation specificity of restriction enzymes is proven by lacking *Hpal* digestion of exon 3 in both probands (F2 and IP2, respectively).

Figure 3



RFLP pattern of amplified exon 3 of the VHL gene of the index patient (IP1-IP3) and his mother (M1-M3): There is an identical restriction pattern of exon 3 as it is found in the index patient's father (Figure 2), demonstrating the heterozygous carrier status of SNP T598 of the mother.

Results

The analysis of the patient revealed a homozygous pattern for the VHL C598T mutation in exon 3 (Figure 1). Additionally, the asymptomatic parents of the patient were identified as heterozygous carriers of the VHL C598T mutation in exon 3 (Figure 2 and 3).

Discussion

Chuvash polycythemia is an autosomal recessive disorder affecting the VHL gene and leading to the only known endemic form of erythrocytosis, which was discovered first in the central Russion region of Chuvashia among people of Asian Tatar-related ancestry (1). Recently, the VHL C598T mutation as well as other SNPs in exon 1, 2 and 3 leading to erythrocytosis have been recognized in other ethnic groups as well (2,3).

The VHL C598T mutation predicts an aminoacid exchange of arginine to tryptophan at position 200 of the VHL protein. This impairs the interaction of the VHL protein with hypoxia-inducible factor-1α, resulting in increased expression of downstream target genes including EPO encoding erythropoietin (4).

Recognition of Chuvash polycythemia is crucial because both thromboembolic and bleeding complications are common and treatment with phlebotomy should be introduced promptly.

References

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