A novel large alpha^0-thalassemia deletion found in a Portuguese 32 years old woman

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A Portuguese 32-year-old Caucasian woman was admitted to the Haematology Service in 2007 because of hypochromic and microcytic anemia, with Hb 9 g/dL, and a low ferritin level. The HbA2 value was normal. The colonoscopy and the high digestive endoscopy were normal and the search for *Helycobacter pillory* was negative.

The physical examination showed moderate pallor, no hepatosplenomegaly and the neurologic examination was normal.

Personal History: type I Diabetes Mellitus diagnosed when she was 8 years old.

Family History: father died at the age of 40 with cancer, mother without history of anemia and a healthy sister.

Therapy: she received therapy with ferrous iron given orally, with a good response of ferritin but not of Hb. Therefore, she started endovenous iron therapy with EPO and had a good response, with values of Hb over 12.0 g/dL until 2009. At this time her Hb level had decreased to 10.3 g/dL, with a MCV of 71.4 fL and a MCH of 22.9 pg and with normal values of iron and ferritin. The hypothesis of α–thalassemia was raised and her blood sent to a reference center for molecular biology.

Molecular biology analysis:
DNA was extracted from a peripheral blood aliquot. The common deletions of the α-globin gene cluster ($-\alpha^{3.7}$, $-\alpha^{4.2}$, $--^{MED-I}$, $--^{SEA}$ and $-\alpha^{20.5}$) were searched by Gap-PCR but negative results were obtained. Then, Multiplex Ligation-dependent Probe Amplification (MLPA) was performed to search for large deletions, using a commercial kit (SALSA MLPA kit P140-B2 HBA, MCR-Holland). The probe amplification profile revealed a deletion of structural genes as well as of the MCS-R2 (HS-40) regulatory element, in heterozygosity. Synthetic MLPA probes (flanking the gene cluster) were used in order to fine map deletion's breakpoints. Results show that it has at least 271.14 kb, removing three upstream regulatory sites (MCS-R2, -R3, and -R4), all α-like structural genes and a large region 3' from the globin gene cluster. The 5' breakpoint falls into a 4.9 kb uncertainty region, and the 3' breakpoint locates between TMEM8A and SOX8 genes, in a region with 610.6 kb. As well as we know it is a novel large α^0-thalassemia deletion.

The resulting genotype of the patient (--/αα) is in agreement with the hematological phenotype presented and the clinical features observed. As Portugal has a moderate prevalence of α–thalassemia, the patient's partner was tested to eliminate the possibility of their children having a Hemoglobin H disease or *hidrops foetalis.*

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