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A novel SMARCAL1 missense mutation that affects splicing in a severely affected Schimke immunoosseous dysplasia patient

Jimena Barraza-García [a, b, c], Carlos I. Rivera-Pedroza [a, c], Alberta Belinchón [a, b, c], Carlota Fernández-Camblor [d], Blanca Valenciano-Fuente [e], Pablo Lapunzina [a, b, c], Karen E. Heath [a, b, c, *]

[a] Institute of Medical & Molecular Genetics (INGEMM), Hospital Universitario La Paz, Universidad Autónoma de Madrid, IdiPAZ, Madrid, Spain
[b] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto Carlos III, Madrid, Spain
[c] Multidisciplinary Skeletal dysplasia Unit (UMDE), Hospital Universitario La Paz, Madrid, Spain
[d] Dept. of Pediatric Nephrology, Hospital Universitario La Paz, Madrid, Spain
[e] Dept. of Pediatric Nephrology, Hospital Universitario Materno Infantil de las Palmas, Las Palmas, Canary Islands, Spain

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A B S T R A C T

Schimke immunoosseous dysplasia (SIOD) is an autosomal recessive disease characterized by skeletal dysplasia, focal segmental glomerulosclerosis, renal failure and immunodeficiency. In this work, we report the molecular studies undertaken in a severely affected SIOD patient that died at six years old due to nephropathy. The patient was screened for mutations using a targeted skeletal dysplasias panel. A homozygous novel missense mutation was identified, c.1615C > G (p.[Leu539Val]) that was predicted as mildly pathogenic by *in silico* pathogenicity prediction tools. However, splicing prediction software suggested that this variant may create a new splicing donor site in exon 9, which was subsequently confirmed using a minigene assay in HEK293 cells. Thus, the splicing alteration, c.1615C > G; r.1615c > g, 1615_1644del; (p.[Leu539_Ile548del]), results in the loss of 10 amino acids of the HARP-ATPase catalytic domain and the RPA-binding domain. Several studies have demonstrated a weak genotype-phenotype correlation among such patients. Thus, the molecular characterization has helped us to understand why a predicted weakly pathogenic missense mutation results in severe SIOD and should be considered in similar scenarios.

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1. Introduction

Schimke immunoosseous dysplasia (SIOD, MIM 242900) is an autosomal recessive multisystemic disorder with an estimated incidence of 1 in 1–3 million live births in the USA (Santangelo et al., 2014). The main clinical features include growth failure (which may be identified *in utero*, especially in patients with the severe form), spondyloepiphyseal dysplasia, progressive nephropathy, and poor cellular immunity. Transitory ischemic attacks due to vaso-occlusive processes (atherosclerosis) are also often present in patients with severe SIOD (Saraiva et al., 1999; Boerkoel et al., 2000; Elizondo et al., 2009; Clewing et al., 2007; Dekel et al., 2008; Baradaran-Heravi et al., 2008). Other reported features include thyroid dysfunction, enteropathy, bone marrow hypoplasia, migraine-like headaches and ocular abnormalities (Boerkoel et al., 2000). Phenotypic features are variable but may include broad nose, with low bridge and bulbous tip, disproportionate short stature with short neck and trunk, lumbar lordosis, and protruding abdomen. Many patients also have abnormally thin hair, small or absent secondary teeth, and hyperpigmented macules, most frequently located on the trunk (Saraiva et al., 1999; Boerkoel et al., 2000). Although normal intelligence is described in most cases, there are also reports of patients with microcephaly and cognitive, social, motor and language abnormalities (Deguchi et al., 2008).

Patients with severe SIOD have earlier clinical manifestations and usually die within the first 5–15 years whilst patients with milder forms have a later onset, with growth failure and renal disorders starting between ages 8–12 years, and they do not suffer from recurrent infections, hypothyroidism, or cerebrovascular disease. These patients often live into their second decade of life

* Corresponding author. Institute of Medical and Molecular Genetics (INGEMM), Bloque Quirúgica, Hospital Universitario La Paz, Pº Castellana 261, 28046 Madrid, Spain.
E-mail address: karen.heath@salud.madrid.org (K.E. Heath).

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(Saraiva et al., 1999; Elizondo et al., 2009; Santangelo et al., 2014). The principal causes of death, in decreasing frequency, are: severe opportunistic infections, cerebral vascular events, end-stage renal failure, pulmonary hypertension with congestive heart failure or lung disease, bone marrow failure, and complications from renal transplant or lymphoproliferative disease (Boerkoel et al., 2000; Elizondo et al., 2006; Clewing et al., 2007; Baradaran-Heravi et al., 2012b, 2013).

SIOD is caused by biallelic loss of function mutations in the *SMARCAL1* (SWI/SNF-related, matrix-associated, actin dependent regulator of chromatin, subfamily a-like 1) gene (Boerkoel et al., 2002). More than 68 different mutations, distributed throughout the gene, have been reported to date. The gene encodes SMARCAL1, a member of the SNF2 family of proteins that encodes a protein homologous to the Switching defective 2 (SWI2) or Sucrose Non-Fermenting 2 (SNF2) (SWI2/SNF2) family of ATP dependent chromatin remodelling proteins (Boerkoel et al., 2002). It is a multidomain protein, containing an ATPase catalytic domain in the carboxy terminal, a conserved RPA-binding domain in the N-terminal and two HARP domains (HARP1 and HARP2). HARP2 is the DNA binding domain, the ATPase domain for annealing helicase activity, and HARP1 may have a role of supporting or facilitating SMARCAL1 functions (Bétous et al., 2012; Mason et al., 2014; Feldkamp et al., 2014; Keka et al., 2015).

Increased DNA replication-associated damage and hypersensitivity to DNA-damaging agents that inhibit DNA replication are the main cellular effects related to *SMARCAL1* deficiency, leading to accumulation of single-strand DNA and double-strand breaks (Bansbach et al., 2010; Bétous et al., 2012; Couch et al., 2013; Mason et al., 2014; Feldkamp et al., 2014; Bhat et al., 2015; Keka et al., 2015; Poole et al., 2015). Thus, SMARCAL1 is a protein involved in avoiding genome DNA damage and when mutated this protection is loss. Thus, SIOD is considered as a genome maintenance disorder.

Here we report the case of a severely affected child with SIOD, molecularly confirmed using a targeted NGS skeletal dysplasia panel. The now deceased patient was found to be homozygous for a novel missense mutation in SMARCAL1, which was predicted as mildly pathogenic, but was shown to cause the creation of a new splice donor site in exon 9, affecting the HARP2 domain. This molecular mechanism can therefore be related with the severe SIOD phenotype observed in this case.

2. Patient data

The patient was the first son of healthy, non-consanguineous parents from a small town. He was diagnosed prenatally with oligoamnios and intrauterine growth restriction. An uneventful caesarean section was performed at week 31, with birth weight 1060 g and an Apgar score of 4/7. At 38 weeks his weight improved to 2300 g. The patient was hospitalized during the first two months of extrauterine life, due to prematurity, jaundice, leucopoenia and anaemia. Karyotype was normal. At 5 months, a right inguinal hernia was surgically repaired. He was fed through a nasogastric tube the first month of life, and during the first year of life he was diagnosed with chronic diarrhoea and oesophageal reflux that did not respond to conventional management. At two years old, Cockayne syndrome was considered.

At 3 years old, he was diagnosed with hypercholesterolemia and hyperlipidemia. Treatment with simvastatin was started. At the same age, right orchidopexia was performed. During this time, he presented with several episodes of chronic diarrhoea, vomiting and suppurative otitis media. Brain MRI did not indicate any abnormality. Psychomotor development was normal.

A dental abscess was detected and treated with dental extraction at 4 years of age. Due to severe growth delay, treatment with GH was started, but no response was observed. At the same age, nephrotic syndrome was diagnosed, along with limb asymmetry and mild spondyloepiphyseal dysplasia (horizontal acetabular roof, small femoral epiphyses with right coxofemoral subluxation, L2 vertebral deformity with sharpened of anterior segment, and S4–S5 spinal disc calcification), and the diagnosis of in SIOD was proposed. Renal biopsy showed diffuse and focal glomerulosclerosis, and chronic mild tubulointerstitial injury. He was treated with corticosteroids and cyclosporine, but failed to respond.

At 5.7 years, his height was 86.9 cm (−6.17 SDS), weight 11.4 kg (−2.72 SDS). Physical examination revealed lumbar hyperlordosis, short neck, barrel chest, relatively big hands, high-pitched voice, cafe-au-lait spots, hepatomegaly, absence of some permanent teeth, and dental primary dental structures. The patient presented a severe decompensation of his nephrotic syndrome that required haemodialysis for a month, during which he presented sepsis, acute respiratory distress syndrome, lobar atelectasis, and hypertension with mild left ventricle hypertrophy. He was diagnosed with severe lymphopenia due to a profound decrease of $CD3^+$ and $CD4^+$ lymphocytes, with normal values of B lymphocytes and NK cells. He started with temporary half-body paraesthesia and decreased strength, due to transient ischemic events associated to a prothrombotic state and arthritis (probable Moyamoya syndrome). He was diagnosed with end-stage renal failure, treated with hemodialysis and proposed as a candidate for a renal transplant, but he died at age six due to major metabolic disturbances and immune compromise.

3. Methods

3.1. NGS analysis

With the approval of the local ethics committee and the appropriate informed consent, a DNA sample was analyzed with a targeted Skeletal dysplasia Next-generation sequencing (NGS) panel (SKELETALSEQ.V3, n = 315 genes) using SeqCap EZ capture(Roche Nimblegen) and analyzed on a MiSeq (Illumina) platform. In house bioinformatic analysis was performed using Bowtie2 v2.0; Picard-tools v1.27; Samtools v0.1.19-44428cd; Bedtools v2.16.1; Genome Analysis TK v2.6-5 y SnpE 3.5e. *In silico* pathogenicity prediction was analyzed using Alamut 2.7 (Interactive Biosoftware, France).

3.2. Minigene assay

We undertook a minigene assay to determine if the identified variant affected splicing. The wild type and c.1615C > G mutant sequences were cloned into the pSPL3 exon trapping vector and the assay was performed as previously described (Paumard-Hernández et al., 2015).

4. Results and discussion

Using the SKELETALSEQ.V3 NGS custom designed targeted panel, we detected a previously undescribed homozygous variant, c.1615C > G (p. [Leu539Val]) in exon 9 of *SMARCAL1.* This missense change occurred at a moderately conserved amino acid with small physicochemical difference between amino acids in the ATPase catalytic domain (Fig. 1). *In silico* pathogenicity predictions classified the variant as tolerated (SIFT), disease causing (MutationTaster), possibly damaging (Polyphen) and likely pathogenic (CADD V3: 23.6). However, five splicing prediction tools (NNSPLICE, Human Splicing Finder, MaxEntScan, Splice Site Finder-like) predicted the creation of a novel splice donor site.

To confirm the pathogenicity of the identified variant, we subsequently undertook a minigene assay in HEK293 cells that

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