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Schaaf-Yang Syndrome: An Example of Genomic Imprinting and Expanding Phenotype

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Abstract

Schaf-Yang Syndrome is a rare genetic condition, produced by a mutation in the *MAGEL2* gene, located at the level of chromosome 15, in the Prader-Willi Syndrome region, with which it shares some physical similarity. The phenotype is variable and ranges from fetal akinesia to an important neurobehavioral phenotype and contractures of the small finger joints that are very characteristic. The gene has a maternal imprint and the phenotype will only be expressed when the mutated allele has been transmitted parentally. We present the case of a 2-and-a-half-year-old male from Ecuador, whose most prominent signs were in the beginning a marked macroglossia that gave a certain rough facial appearance, as well as bilateral camptodactyly of the 3rd and 4th fingers. The history of a previous sister who died at age 8 with a diagnosis of hypothyroidism, and clinical similarity to this new baby, led the clinical orientation to the screening of a potentially autosomal recessive condition. The genetic tests performed as part of the differential diagnosis where to pathologies such as Becwith-Wiedeman Syndrome, Mucopolysaccharidosis and Congenital Hypothyroidism. The clinical elements of this case are compared with those described in the literature with this rare genetic syndrome, and the clinical evolution of dysmorphic patterns in young children is emphasized in order to achieve a better diagnostic certainty. We emphasize the features of macroglossia as a probably expanding phenotype in this rare condition. The presentation of this clinical case shows that the factors that alter the segregation of simple mutations such as the case of the genetic imprint, found in this patient, constitute an event that hinders the interpretation of inheritance patterns and should always be taken into account in genetic counseling.

Keywords: Schaf-Yang Syndrome • Genomic imprinting • *MAGEL2* • Bilateral camptodactyly • Macroglossia

Abbreviations: SYS: Schaaf-Yang Syndrome • *MAGEL2* gene • PWS: Prader Willi Syndrome • IGF: Insulin like Growth Factor • HPV: Human Papiloma Virus

Introduction

Schaaf-Yang Syndrome (SYS, OMIM # 615447) is a rare genetic condition, produced by a mutation in the *MAGEL2* gene, located at the level of chromosome 15, in the region of Prader-Willi syndrome, with which it shares a certain physical similarity. Indeed, SYS was originally considered 'Prader-Willi-like syndrome', due to the location of the gene in the Prader-Willi domain and the phenotypic overlap between individuals with *MAGEL2* loss-of-function and those with Prader-Willi syndrome (PWS, OMIM # 176270) [1].

SYS phenotype is variable and ranges from fetal akinesia to an important neurobehavioral phenotype and contractures of the joints of the small fingers that are very characteristic. The gene has a maternal imprint and only the phenotype will be expressed when the mutated allele has been transmitted through the paternal route.

We made the presentation of clinical, metabolic and genetic results in diagnosis route that allowed us to reach the diagnosis in a male case of 2 and half years of age, from Ecuadorian highlands.

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Case Presentation

He is a 2-year-old male, second child of a young marriage, not blood related who was born by cesarean delivery due to previous maternal infection of HPV, at 39 weeks with birth weight of 3300 grams and a size of 49 centimeters. The cephalic perimeter was 33.5 centimeters. He got an Apgar score of 8/9. He presented precocious jaundice.

At family background is remarkable a history of a sister who died at 8 years of age with a clinical phenotype similar to this patient that was interpreted as congenital hypothyroidism (Figure 1).

On examination, the child had rough facial appearance, tendency to hirsutism, bulging eyes, macroglossia, bilateral camptodactyly of 3rd, 4th and 5th fingers, umbilical hernia (Figure 2).

Neurological examination reveals distal hypertonia with trunk hypotonia and good visual and auditory response. Also he had swallowing difficulties. Major delay in neurodevelopment and speech was evident because the patient at this age didn't seat alone and he pronounced any words.

In the clinical evolution of the measurements during the first and second year of age he kept between 50 and 75 percentiles, always with greater commitment of size than weight.

Regarding laboratory and radiographic research

Thyroid profile, blood biochemistry, glycemia, muscular enzymes, metabolic screens for Mucopolysaccharidosis, kidney and cardiac ultrasound were normal. X-ray of left carpus to see bone age showed retarded osseous maturation. Growth hormone deficiency accompanied by low IGF-1 (insulin-like growth factor) and IGF-binding protein 3 was detected. The determination of gonadotropic hormones considering that they are normal in the pre-puberal stage was not performed. Bone densitometry was postponed for an older age.

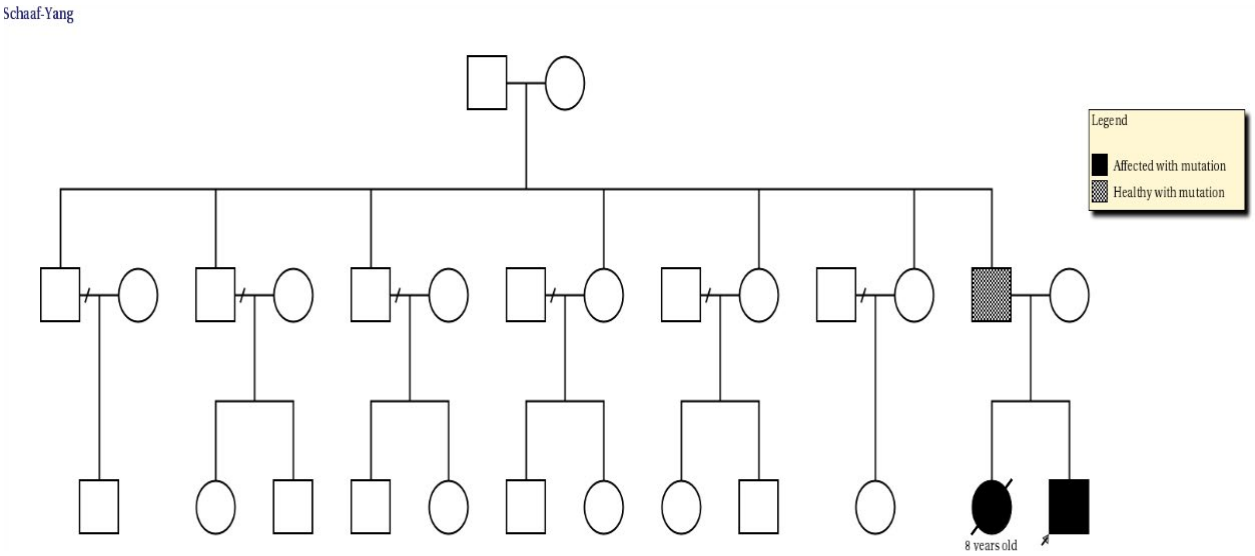

Figure 1. Pedigree of the family showing affected siblings with mutation and healthy father with the same mutation.

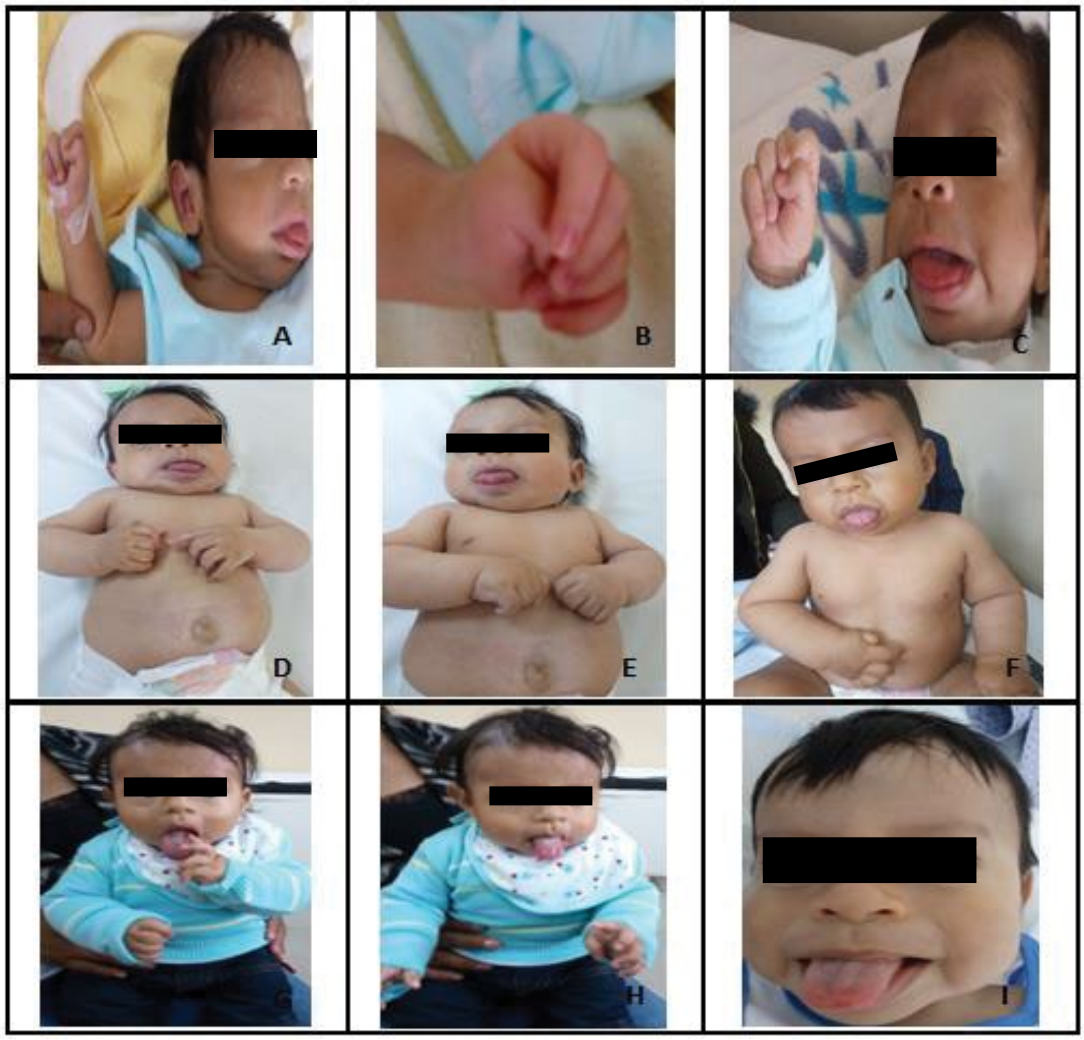

Figure 2. (A to I). Proband at the age of two months to one year; note rough facial appearance, tendency to hirsutism, bulging eyes, macroglossia, bilateral camptodactyly of 3rd, 4th and 5th fingers, umbilical hernia.

Genetics tests ordered were conventional karyotype, methylation study for Beckwith-Wiedeman Syndrome, array comparative genomic hybridization and clinical exome. The last one revealed heterocigotic variant c.3175_3176 dup p (leu 1059 phefs ter2) in *MAGEL2* gene (Figure 3).

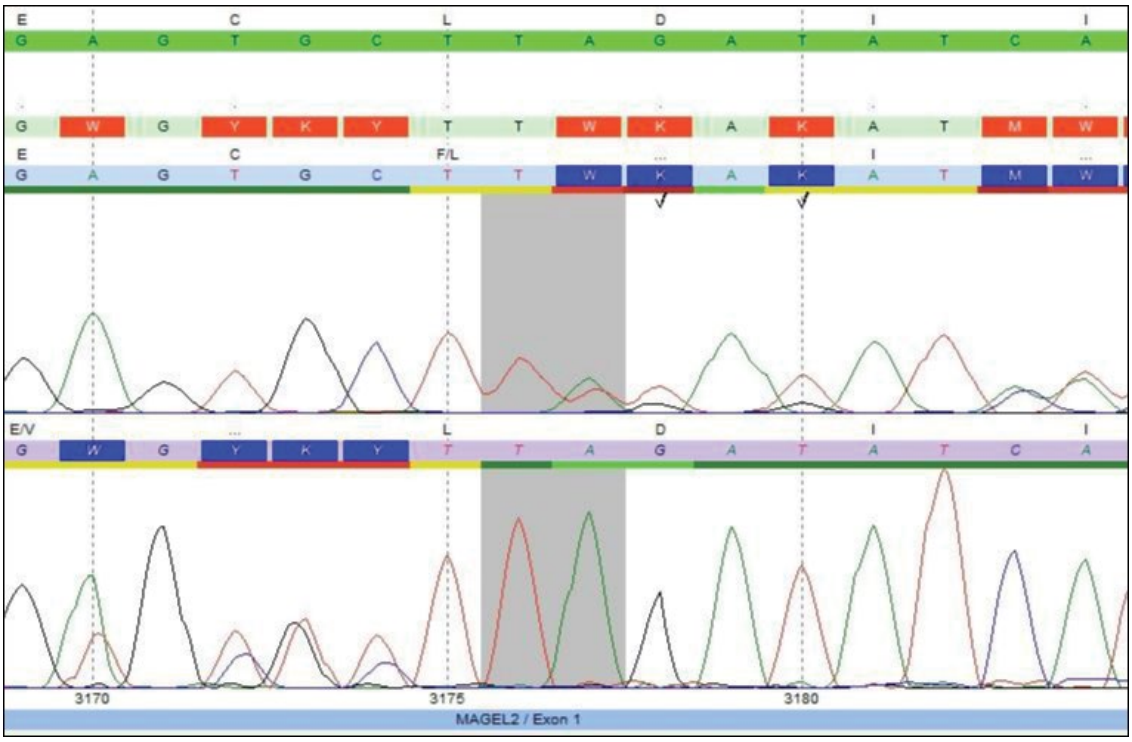

Figure 3. Sequence electropherogram that show heterocigotic variant c.3175_3176 dup p (leu 1059 phefs ter2) in *MAGEL2* gene.

Table 1. Cognitive, neurologic and physical profile of 78 patients with SYS previously described compared to our presented case.

Cognitive, neurologic, and physical profile of patients with SYS	Totals (N=78 patients with SYS) [2]	Our Case
Cognitive/Neurologic		
Global developmental delay	100%	X
ASD Diagnosis (+)	78%	X
Full Scale IQ (Avg.)		
Seizures	33%	
Sleep Apnoea	76%	
Temp. Instability	67%	X
Respiratory Distress	71%	
Intubation	58%	
Mechanical Ventilator	55%	
Tracheostomy	18%	
Feeding Problem	97%	
Poor Suck in Infancy	97%	X
Dysphagia	84%	X
Hyperphagia	25%	
Use of ng Tube	75%	
Use of g Tube	53%	
Excessive Weight Gain	22%	
Reflux-(GERD)	57%	
Chronic Constipation	71%	X
Neonatal Hypotonia	97%	X
Scoliosis	57%	
Exaggerated Kyphosis	32%	
Contractures	88%	X
Hypogonadysm	41%	X
Macroglossia	0%	X

The patient was therefore diagnosed with Schaaf-Yang Syndrome and genetic test looking for the same found mutation was done in his father. He had the same mutation of his child.

Discussion

Truncating mutations of *MAGEL2* gene were reported for the first time in Schaaf-Yang syndrome in 2013 [1]. To date, the most complete series of patients with SYS contains 78 cases and has been described by Mc Carthy et al. [2] and contemplated the previous descriptions of patients with SYS made by other authors [1,3-12]. In the description, the characteristics that mark this phenotype are joint contractures at the hand level and neurobehavioral disorders, however, within the facial dysmorphisms in no one case had macroglossia been indicated, which makes our case interesting and could mean the contribution of a new phenotypic trait of the SYS (Table 1).

We comment that macroglossia associated with psychomotor retardation and dysmorphisms was our first diagnostics presumptions in this case, so we consider some conditions like congenital hypothyroidism, Mucopolysaccharidosis and Becwkith-Wiedeman syndrome in differential diagnosis. After the first results and with the clinical evolution of the case we redirect the diagnosis and considering family history regarding previous affected sister and healthy parents we think of a possible autosomal recessive condition to rule out. However, we were facing a genomic imprinting phenomenon, which consists of differential gene marking according to parental origin and is a factor that alters the expression of simple mutations; in this case, the *MAGEL2* gene mutation was present in the healthy father of both affected children, however, because this gene has a maternal imprint, only the phenotype will be expressed when the mutated allele has been transmitted through the paternal route. Thus, in reality, an autosomal dominant condition is being segregated in the presented family, which was phenotypically omitted in first generation, due to the imprinting effect. The mutation is likely to reside on the paternal grandmother's chromosome (printed) (Figure 1) [3-12].

Conclusion

The genetic counseling offered was based on the high risk of recurrence for this couple, which is 50%, and the available reproductive options were discussed, also multidisciplinary clinical follow-up consisting of pediatric endocrinologist, neuropaediatrician, rehabilitator, geneticist and pediatrician was established. It is probable that this family contains other asymptomatic carriers of the mutation with risk of transmission; however this genetic study has not been completed in view of economic constraint of the family.

Genetic imprinting occurs in a case presented with Schaaf-Yang Syndrome constitutes an event that hinders the interpretation of inheritance patterns and should always be taken into account in genetic counseling.

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