Report of a Second Lebanese Family with Basel-Vanagaite-Smirin-Yosef Syndrome: Possible Founder Mutation?

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Keywords

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Abstract

Basel-Vanagaite-Smirin-Yosef syndrome (OMIM 616449) is a rare autosomal recessive genetic disorder characterized by severe developmental delay and variable craniofacial, neurological, cardiac, and ocular anomalies in the presence of variants in the *MED25* gene. So far, only a handful of patients have been reported with this condition globally. Here, we report an additional Lebanese family with 2 affected siblings presenting with severely delayed psychomotor and language development as well as craniofacial anomalies. By whole-exome sequencing (WES), a homozygous variant was found in the *MED25* gene, c.518T>C, predicted to result in a p.Ile173Thr change in the MED25 protein. This change has recently been reported in another Lebanese family. Review of the literature, the importance of this mutation in the Lebanese population, and the possibility that this condition may be underdiagnosed and only effectively detected using molecular techniques such as WES are discussed.

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Basel-Vanagaite-Smirin-Yosef syndrome (OMIM 616449) is an extremely rare autosomal recessive genetic disorder characterized by severe developmental delay and variable craniofacial, neurological, cardiac, and ocular anomalies in the presence of variants in the *MED25* gene. So far, only a handful of patients have been reported with this condition globally. The disorder was described in 4 families originating from the same Israeli village [Basel-Vanagaite et al., 2015]. In addition, 7 affected adults in a consanguineous Brazilian family were also reported [Figueiredo et al., 2015]. Recently, we described an affected Lebanese family with a p.Ile173Thr variant in the *MED25* gene [Nair et al., 2018]. Here, we report an additional Lebanese family with 2 affected siblings carrying the same homozygous variant as the previously reported Lebanese family.

Case Report

The proband (Fig. 1c; II.1) is a male child born with normal growth parameters: OFC 38 cm (>97th centile), length 50 cm (50th centile), and weight 3.28 kg (50th centile). At birth, a cleft palate was noted. Cardiac evaluation revealed coarctation of the aorta

Fig. 1. Dysmorphic facial features. **a** Proband. **b** Sister. Note the high forehead, sparse scalp hair and eyebrows, flat nasal bridge with a broad nasal tip, hypertelorism, and the short philtrum. **c** Family pedigree. The arrow denotes the proband.

Fig. 2. Chromatogram of the proband. Arrow shows the c.518T>C mutation.

and a ventricular septal defect. At the age of 5 months, the child's parents noted a delay in developmental milestones. At the age of 16 months, he was able to sit with help. Language was absent. His growth parameters were at the 50th centile.

At 3 years of age, he presented with severely impaired psychomotor and language development. His OFC was 50 cm (85th percentile), his length 95 cm (50th percentile), and his weight was 12.1 kg (50th percentile). Upon examination, he had several craniofacial anomalies, including large anterior fontanel, high forehead, sparse scalp hair and eyebrows, flat nasal bridge with a broad nasal tip, hypertelorism, short philtrum, a large mouth with a thin upper lip, and a cleft palate (Fig. 1a). In addition, there was a bilateral

single palmar crease. He showed muscular hypotonia. There was no history of seizures. Ophthalmological examination, brainstem auditory evoked response, and brain MRI were normal (Table 1).

His younger sister (Fig. 1b, c; II.2) was born 2 years later after a normal pregnancy. According to the parents, she had the same clinical course as her affected brother. She was examined at the age of 1 year. Her OFC was 45.5 cm, length 76 cm, and her weight was 9.5 kg (all at the 50th percentile). She had severe psychomotor delay, hypotonia, and nearly similar facial features as her brother. However, in her case, cardiac abnormalities were not seen (Table 1).

Methods and Results

The patients, a boy and a girl, from healthy nonconsanguineous parents were referred to our clinic in Beirut, Lebanon. Genomic DNA was extracted from peripheral blood leukocytes using standard methods. Whole-exome sequencing was performed on DNA from the proband. The Nextera Rapid Capture Exome kit was used to create the enriched library which was sequenced on an Illumina platform to an average coverage depth of 70–100×. An end-to-end bioinformatics pipeline, including base calling, primary filtering of low-quality reads, and possible artefacts as well as annotation of variants was applied. All variants reported in HGMD, ClinVar, or CentoMD as well as all variants with minor allele frequency (<1% in the ExAC database) were considered.

Table 1. Clinical comparison between the present case and other reported patients with *MED25* mutations

	Basel-Vanagaite et al., 2015	Figueiredo et al., 2015	Nair et al., 2018	Present study	
				case 1	case2
Age at examination	NA	33–51 years	5 years	3 years	1 year
Congenital hip luxation	–	NA	+	–	–
Developmental delay	+	+	+	++	+
Absence/delayed speech	+	+	+	+	+
Short stature	–	NA	+	–	–
Seizures	+	NA	+	–	–
Hypotonia	+	NA	+	+	+
Wide fontanelles	NA	NA	NA	+	+
Microcephaly	+	NA	+	–	–
High forehead	–	+	–	+	+
Sparse hair	+	–	+	+	+
Sparse eyebrows	+	–	–	+	+
Nevus flammeus	+	–	–	–	+
Ptosis	+	–	–	–	–
Hypertelorism	+	–	+	+	+
Epicanthus	+	–	+	–	–
Cataract	+	NA	–	–	–
Microcornea	+	NA	–	–	–
Strabismus	+	NA	+	–	–
Downslanting palpebral fissures	+	–	–	–	–
Flat nasal bridge	NA	NA	–	+	+
Broad nasal tip	–	+	+	+	+
Short philtrum	+	+	+	+	+
Large mouth	–	–	+	+	–
Cleft palate	+	–	–	+	–
Prominent chin	NA	+	–	–	–
Wide cupid bow	+	–	–	–	+
Thin upper lip	+	+	+	+	–
Brain malformations	+	NA	–	–	–
Heart malformations	+	NA	+	+	–
Abnormal genitalia	+	NA	–	–	–
Mutation (NM_030973.3)	c.116A>G	c.418C>T	c.518T>C	c.518T>C	c.518T>C

NA, not available; +, present; –, absent.

For the younger patient, the relevant regions of the *MED25* gene were amplified by PCR and analyzed by direct sequencing.

Molecular Findings

Filtering of whole-exome sequencing variants relevant to the phenotype of the proband narrowed down the variants to a homozygous single base pair substitution in the *MED25* gene. This NM_030973.3:c.518T>C variant is predicted to result in a p.Ile173Thr change in the *MED25* protein [Nair et al., 2018]. Direct sequencing of the *MED25* gene in both affected sibs confirmed the presence of the variant in a homozygous state (Fig. 2). This variant was present in the gnomAD database at a very low frequency (0.00003470) and only in heterozygous state. Interestingly, the variant was not found in the Saudi Human Genome Program Variant Database which contains more than 14,000 variants detected in the Arab population [Abouelhoda et al., 2016].

Discussion

We recently described a Lebanese patient with a complex phenotype of ataxia, seizures, congenital hip luxation, microcephaly, sparse hair, and elevated serum lactate and pyruvate [Nair et al., 2018]. In that case, the analysis of the child was complicated by the fact that she carried 2 potentially pathogenic homozygous variants: one in the *MED25* and the other in the *ADCK3* gene. We speculated that the complex phenotype evinced by the patient was due to a synergistic effect of the 2 disparate variants. We now report a second Lebanese family with the same homozygous *MED25* variant (p.Ile173Thr). The

phenotype of the patients described in this study is very similar to the cases reported previously with Basel-Vanagaite-Smirin-Yosef syndrome (Table 1). Our previous in silico analysis of the pathogenicity of the variant had shown that it was predicted to be probably damaging by PolyPhen-2, deleterious by PROVEAN, and disease causing by MutationTaster.

As most other countries in the Arab World, rates of consanguinity in Lebanon are relatively high, reaching overall levels of up to 42% [Tadmouri et al., 2009]. In such highly consanguineous populations, it is not unusual to see rare genetic disorders appearing in multiple ostensibly unrelated families with the same underlying causal variant [Alkuraya, 2012; Romdhane et al., 2012]. In such cases, it is assumed that the variant under consideration is a founder mutation that either arose sporadically as a de novo event, or was introduced from a closely related population [Zlotogora et al., 2007]. However, the 2 families we report here and in our previous study belong to different religious communities and are clearly unrelated. In addition, haplotype analysis around the variant in both the families revealed that although the variant occurs

within a run of homozygosity in the previously reported patients from the consanguineous family, this is not so in the case of the probands reported here: the variant seems to have an independent origin in the 2 alleles, ruling out the presence of a founder mutation.

In conclusion, we report the second occurrence of the c.518T>C variant in the Lebanese population resulting in Basel-Vanagaite-Smirin-Yosef syndrome. Comparison with previously reported cases of the condition seems to point to the paucity of specific features that can be used for clinical diagnosis of the condition. Although there is overlap between the clinical phenotype of the patients, only developmental delay, absence of speech, and a short philtrum are present in all cases reported so far. Thus, there is a possibility that the condition may be underdiagnosed and only effectively detected using molecular techniques such as whole-exome sequencing.

Disclosure Statement

The authors declare no conflicts of interest.

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