FIG4-Associated Yunis-Varon Syndrome: Identification of a Novel Missense Variant

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Established Facts

- Yunis-Varon syndrome (YVS) is a severe autosomal recessive disorder characterized by skeletal defects, including cleidocranial dysplasia and digital anomalies, and severe neurological involvement with neuronal loss. Enlarged cytoplasmic vacuoles are found in neurons, muscles, and cartilage.
- YVS is caused as a result of homozygous or compound heterozygous variants in the *FIG4* gene.

Novel Insights

- We characterized a Saudi proband and identified a novel homozygous missense variant (c.968A>G; p.Gln323Arg) in the *FIG4* gene causing YVS.
- Our study expands the molecular and genetic spectrum of *FIG4*-associated mutations.
- This is the first reported case of YVS from the Saudi population.

Keywords

Yunis-Varon syndrome · Whole-exome sequencing · Cleidocranial dysplasia · *FIG4* · Novel variant

Abstract

Yunis-Varon syndrome (YVS; OMIM 216340) is a rare heterogeneous autosomal recessive disorder with easy recognition of characteristic severe neurological and skeletal abnormalities involving skeletal muscles and cartilages. This cleidocranial dysplasia is characterized by bone and tooth disorders;

it also affects the cardiovascular system and tissues from ectoderm with very poor outcomes. Rarely, mutations of the *FIG4* gene, encoding a 50-phosphoinositide phosphatase have been identified as the cause for YVS. We report a neonate born to a consanguineous couple with typical clinical manifestations of YVS. Using whole-exome sequencing, we identified a novel homozygous missense variant (c.968A>G; p.Gln323Arg) in the *FIG4* gene. Thus, our study expands the molecular and genetic spectrum of *FIG4*-associated mutations. To our knowledge, this is the first reported case of YVS from the Saudi population.

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Introduction

Yunis-Varón syndrome (YVS; OMIM 216340) is a very rare heterogeneous disorder, described for the first time in 5 infants, originated from Columbia. YVS patients exhibit clinical features such as cleidocranial dysplasia, distal aphalangia, absent halluces and thumbs, and ectodermal anomalies. Along with neurological features, the patients also present severe skeletal abnormalities. Up to date, only 26 patients with YVS from 20 families have been reported [Corona-Rivera et al., 2011; Reutter et al., 2012; Nakajima et al., 2013]. The clinical spectrum of YVS has been extended to severe limb defects with aplasia and/or hypoplasia of nails and phalangeal bones, heart defects, earlobe dysplasia, brain malformations, retinopathy, and facial dysmorphisms [Corona-Rivera et al., 2011; Campeau et al., 2013; Nakajima et al., 2013].

Mutations in *FIG4* have been associated with 4 different neurological disorders, such as autosomal recessive bilateral temporooccipital Polymicrogyria (OMIM 612691), autosomal dominant amyotrophic lateral sclerosis 11 (OMIM 612577), recessive Charcot-Marie-Tooth disease, type 4J (OMIM 611228), and recessive YVS (OMIM 216340).

Herein, we investigated a proband showing hallmark features of YVS. Whole-exome sequencing (WES) followed by Sanger sequencing identified a novel biallelic missense variant in the *FIG4* gene located on chromosome 6q21.

Case Presentation

The single affected individual (II-1) in the family presented here was diagnosed having YVS on the basis of the phenotypic presentation, and molecular diagnosis. The male proband (II-1) was a product of consanguineous marriage, born at 35 weeks of gestation by cesarean section due to severe oligohydramnios to a G3P1+1 mother (Fig. 1a). The proband's (II-1) weight was 1.5 kg, and apart from oligohydramnios, the antenatal period was normal. However, he required minimal recovery at birth and developed mild respiratory distress. The APGAR score was 6 and 8 at 1 and 5 min, respectively.

Anthropometric data were <3rd centile for gestational age. The proband had membranous skull bones with wide confluent fontanels and sutures. The proband had a high forehead, alopecia, sparse hairs, absent eyelashes/eyebrows, malformed ears, anteverted nostrils, proptosis, micrognathia, and hypertelorism (Fig. 1b, c). The pro-

band had a narrow thoracic cage, which resulted in breathing difficulties and having rudimentary nipples. Features such as short limbs with absent terminal phalanges, hypoplastic thumbs, absent left big toe, and bilateral nail hypoplasia were also observed. The scrotum was empty as of undescended testis bilaterally, and there was associated hypospadias (Fig. 1b, c).

The radiological examination revealed hypoplastic calvarium, bilaterally hypoplastic thin clavicles having abnormal curvature and a small thorax. Ultrasound of cranium revealed dilatation of all ventricles; these features were suggestive of mild hydrocephalus. Sonography of the abdomen revealed normal liver, spleen, and kidneys. Echocardiogram revealed biventricular hypertrophy with good left ventricular function.

The neonate was managed with oxygen support via high-flow nasal cannula for the first 2 months of life; intermittently he remained in room air only twice for about 24 h. He had right-sided pneumothorax at 2 months of age and remained intubated for about 9 months with failed trials of extubation 8 times. At 9 months of age, a tracheostomy was carried out, and since then he is intermittently on CPAP/PS mode but mostly on synchronized intermittent mechanical ventilation support. Detail clinical description is presented in Table 1.

Molecular Examination

DNA Extraction

Blood samples were obtained from the proband and other family members. DNA extraction and quantification were performed via standard methods using commercially available genomic DNA extraction kit and a NanoDrop-1000 spectrophotometer.

Whole-Exome Sequencing

WES was performed by CENTOGENE (CentoGenome®, Germany) a well-known German commercial lab. RNA capture baits against approximately 60 Mb of human exome (99% target) was used to enrich the regions of interest using the fragmented DNA, using Agilent Sure-Select Human All Exon V6 kit. Using the Illumina platform the library was sequenced (coverage/depth approx. 100×). Total, 97% of the bases were covered at >10×. An in-house pipeline was used for base calling, alignment, and thus filtering low quality reads and artifacts. Standard annotation of the variants was applied according to the pedigree and clinical description [Asiri et al., 2020; Umair et al., 2020]. Autosomal

Fig. 1. **a** Pedigree of the family showing consanguineous union and autosomal recessive inheritance pattern. **b** Image of the proband (IV-3), taken immediately after birth showing typical dysmorphic facial features and limb abnormalities corresponding with Yunis-Varon syndrome. **c** Current image of the proband (IV-3) on ven-

tilator support and exhibiting severe developmental delay. **d, e** Schematic representation of the *FIG4* exons and protein domains showing the position of the variant identified in the present study. **f** Partial sequence of *FIG4*, showing Gln (Q) 323 amino acid conservation across different species.

recessive mode of inheritance was focused, homozygous, compound heterozygous variants, were given priority. All disease-causing variants with minor allele frequency of less than 1% in the gnomAD were considered.

After filtering WES data, we identified a novel homozygous missense variant (c.968A>G; p.Gln323Arg) in exon 9 of the *FIG4* gene (NM_014845.6), located in chromosome 6q21 (Fig. 1d). The identified variant (c.968A>G) was not observed in 1000 Genomes, dbSNP, ExAC, gnomAD, or 2000 in-house exomes.

Segregation Using Sanger Sequencing

The identified homozygous missense variant (c.968A>G; p.Gln323Arg) was Sanger sequenced in all the available family members using standard methods [Umair et al., 2016]. Primers were designed using Primer3 software (<http://bioinfo.ut.ee/primer3-0.4.0/>). Primer sequence can be provided upon request.

In silico Analysis

To evaluate the effect of the variants, various online protein prediction tools were used including MutationTaster, SIFT, PolyPhen-2, Varsome, Mutation assessor, and FATHMM-MKL, etc (Table 2). The variant p.(Gln323Arg) was conserved across several species (Fig. 1f).

Discussion

YVS is a severe and a rare autosomal recessive disorder characterized by severe skeletal defects, including digital anomalies, cleidocranial dysplasia, and severe neurological malformations. Affected individuals reveal enlarged cytoplasmic vacuoles in muscle, neuron, and cartilage, and the disorder is usually lethal in infancy. The condition was first reported in 5 children from 3 families with sparse hair, cleidocranial dysostosis, micrognathia, bilateral absent thumbs and first metatarsal, distal aphalangia,

Table 1. Clinical description of the proband

Clinical description	IV-3
Sex	Male
Origin	Saudi
Consanguinity	+
Pregnancy event	Normal full term
Head and Neck examination	
Wide fontanelle/sutures	+
Sparse scalp hair	+
Protruding eyes	+
Anteverted nostrils	+
Dysplastic ears	+
Microcephaly	+
Global developmental delay	+
Mild-intellectual disability	+
Hypotonia	–
Poor sleep	+
Loose skin in neck region	+
Limbs examination	
Short fingers/toes	+
Hypoplastic thumbs	+
Hypoplastic halluces	+
Hypoplastic nails	+
Dysmorphic facial features	+
MRI brain	Normal
Skeletal survey	Abnormal
Hearing test	Normal
Echocardiogram	Normal
Genetic results	Homozygous missense variant (c.968A>G; p.Gln323Arg) in <i>FIG4</i>

and bilateral hip dislocation [Yunis et al., 1980]. None of these children could survive beyond 10 weeks of age [Yunis et al., 1980]. Due to the involvement of both male and female gender and consanguinity of parents in 2 families, the authors suggested an autosomal recessive inheritance pattern. The dysmorphic features observed in our case were similar to those reported previously [Yunis et al., 1980; Campeau et al., 2013; Nakajima et al., 2013].

The features which were invariably present in all the cases reported in the literature to date include severe growth retardation, absent or hypoplastic thumbs and nails, short pointed fingers, abnormal/malformed ears, wide fontanelle with diastasis of cranial sutures, sparse scalp hairs and cleidocranial dysplasia. Other frequently reported associations were microcephaly with prominent eyes, anteverted nostrils, ectodermal abnormalities including absent or minimal eyebrows/eyelashes and hypodontia, bilateral dislocation of hips, bone fractures, and genital abnormalities including hypospadias and undescended testes. Several CNS abnormalities

Table 2. Details of the identified variant in *FIG4* gene

Gene	<i>FIG4</i>
Transcript ID	NM_014845.6
Chromosomal location	6q21
MIM number (<i>FIG4</i>)	609390
MIM number (YVS)	216340
Chromosomal position	110064404
Nucleotide change	c.968A>G
Protein change	p.Gln323Arg
dbSNP	rs1583671246
1000G_ALL	–
ExAC_Freq	–
gnomAD	–
Varsome	Likely pathogenic
MutPred	Pathogenic
MutationTaster	Disease causing
PROVEAN	Damaging
SIFT	Damaging
REVEL	Pathogenic
FATHMM-MKL	Damaging
FATHMM-XF	Damaging
DANN	0.9969-damaging
Mutation assessor	Medium
ACMG classification	Variant of uncertain significance (Class3)

have been reported frequently, which include Dandy-Walker malformation, agenesis of the corpus callosum, hydrocephalus, and hypoplastic vermis. Cardiovascular abnormalities are uncommon, but biventricular hypertrophy, cardiomyopathy and cardiomegaly have been reported with one reported case having tetralogy of Fallot. Other unique reported associations include pyloric stenosis with severe hearing impairment and papillomacular atrophic chorioretinopathy with “salt-and-pepper” appearance in 2 Mexican sisters with YVS [Yunis et al., 1980; Corona-Rivera et al., 2011; Philippe et al., 2012; Campeau et al., 2013; Nakajima et al., 2013; Wright et al., 2020].

After the advent of next-generation sequencing such as whole-genome sequencing and WES, it is apparent that single mutated genes exhibiting multiple phenotypes can cause a broad phenotypic spectrum. Phenotypic overlaps have been observed in many different disorders and also in cases of YVS. In the present study, using WES, we identified a novel homozygous missense variant (c.968A>G; p.Gln323Arg) in exon 9 of the *FIG4* gene (Fig. 1d). The variant causes an amino acid change from Gln to Arg at position 323. The identified variant is present in a highly conserved catalytic domain of the FIG4 protein (Fig. 1e, f). So, far only 6 variants in the *FIG5* gene have been as-

Table 3. Mutation update reported in the *FIG4* gene with autosomal recessive inheritance pattern

Description	Mutation type	hgvsAll	Disease
Deletion <0.94 Mb incl exon 2	Gross deletion		Charcot-Marie-tooth disease, type 4J
Deletion incl. exon 2	Gross deletion		Charcot-Marie-tooth disease, type 4J
Deletion exons 8–10	Gross deletion		Charcot-Marie-tooth disease, type 4J
Insertion incl. exon 17	Gross deletion		Charcot-Marie-tooth disease, type 4J
Leu17Pro	Missense	50TtoC L17P	Charcot-Marie-tooth disease, type 4J
IVS1 as G-T –1	Canonical-splice	67minusrs1487542191GtoT	Amyotrophic lateral sclerosis
Ile41Thr	Missense	122TtoC I41T	Charcot-Marie-tooth disease, type 4J
Asp48Gly	Missense	143AtoG D48G	Primary lateral sclerosis, adult, 1
Asp53Tyr	Missense	157GtoT D53Y	Amyotrophic lateral sclerosis
Gly82Arg	Missense	244GtoA G82R	Amyotrophic lateral sclerosis
Gly94Asp	Missense	281GtoA G94D	Peripheral neuropathy
IVS3 as A-T –2	Canonical-splice	290minusrs1487542192AtoT	Charcot-Marie-tooth disease
Del 1 bp codon 97	Frameshift	294delT 294delI 294del	Charcot-Marie-tooth disease, type 4J
Gly104Asp	Missense	311GtoA G104D	Yunis-Varon syndrome
Tyr106Cys	Missense	317AtoG Y106C	Charcot-Marie-tooth disease, type 4J
Ile107Thr	Missense	320TtoC I107T	Amyotrophic lateral sclerosis, sporadic
Ile133Val	Missense	397AtoG I133V	Amyotrophic lateral sclerosis, sporadic
IVS5 as G-A –1	Canonical-splice	498minusrs1487542191GtoA	Peripheral neuropathy
Tyr169Ser	Missense	506AtoC Y169S	Leukoencephalopathy
Leu175Pro	Missense	524TtoC L175P	Yunis-Varon syndrome
Arg183Term	Nonsense	547CtoT R183*	Charcot-Marie-tooth disease, type 4J
Ile220Val	Missense	658AtoG I220V	Amyotrophic lateral sclerosis
Trp246Term	Nonsense	737GtoA W246*	Charcot-Marie-tooth disease
Del 1 bp codon 253	Frameshift	759delG 759delI 759del	Charcot-Marie-tooth disease, type 4J
Del 4 bp/ins 14 bp codon 264	Frameshift	790_793delGGACinsTTCCAAGAGCTGTT 790_793del4ins14 790_793delins	Charcot-Marie-tooth disease, type 4J
Arg265Term	Nonsense	793CtoT R265*	Peripheral neuropathy
Del 8 bp codon 277	Frameshift	831_838delTAAATTG 831_838del8 831_838del	Charcot-Marie-tooth disease, type 4J
Phe279Leu	Missense	837TtoG F279L	Amyotrophic lateral sclerosis
Gly281Asp	Missense	842GtoA G281D	Left ventricular obstruction with extracardiac anomalies and neurodevelopmental disorder
Gly288Val	Missense	863GtoT G288V	Charcot-Marie-tooth disease, type 4J
IVS8 as A-C –2	Canonical-splice	877minusrs1487542192AtoC	Charcot-Marie-tooth disease, type 4J
Glu302Lys	Missense	904GtoA E302K	Charcot-Marie-tooth disease, type 4J
Asp307Asn	Missense	919GtoA D307 N	Amyotrophic lateral sclerosis
ins 1 bp codon 345	Frameshift	1032dupT 1032dup1 1032dup	Amyotrophic lateral sclerosis
Del 8 bp codon 347	Frameshift	1043_1050delATCAGGCA 1043_1050del8 1043_1050del	Charcot-Marie-tooth disease, type 4J
His360Tyr	Missense	1078CtoT H360Y	Amyotrophic lateral sclerosis
Arg381Term	Nonsense	1141CtoT R381*	Charcot-Marie-tooth disease, type 4J
Lys383Gln	Missense	1147AtoC K383Q	Amyotrophic lateral sclerosis, sporadic
Del 2 bp/ins 1 bp codon 383	Frameshift	1147_1148delAAinsT 1147_1148del2ins1 1147_1148delins	Charcot-Marie-tooth disease, type 4J
Del 2 bp/ins 1 bp codon 383	Frameshift	1149_1150delAAinsT 1149_1150del2ins1 1149_1150delins	Charcot-Marie-tooth disease
Arg388Gly	Missense	1162AtoG R388G	Primary lateral sclerosis, adult, 1
Del 3 bp codon 395	Inframe	1184_1186delTTG 1184_1186del3 1184_1186del	Charcot-Marie-tooth disease, type 4J
Gln403Term	Nonsense	1207CtoT Q403*	Amyotrophic lateral sclerosis
Thr410Pro	Missense	1228AtoC T410P	Amyotrophic lateral sclerosis
Ile411Val	Missense	1231AtoG I411V	Amyotrophic lateral sclerosis
Del 3 bp/ins 3 bp codon 413	Inframe	1239_1241delTATinsATA 1239_1241del3ins3 1239_1241delins	Charcot-Marie-tooth disease
Del 2 bp codon 427	Frameshift	1280_1281delGT 1280_1281del2 1280_1281del	Yunis-Varon syndrome
Arg432Term	Nonsense	1294CtoT R432*	Charcot-Marie-tooth disease, type 4J
ins 1 bp codon 458	Frameshift	1373dupT 1373dup1 1373dup	Charcot-Marie-tooth disease, type 4J
IVS12 ds G-T +5	Canonical-splice	1388plus5GtoT	Amyotrophic lateral sclerosis
Arg492Pro	Missense	1475GtoC R492P	Leukoencephalopathy

Table 3 (continued)

Description	Mutation type	hgvsAll	Disease
Del 2 bp codon 530	Frameshift	1589_1590delTT 1589_1590del2 1589_1590del	Amyotrophic lateral sclerosis
Thr540Ile	Missense	1619CtoT T540I	Amyotrophic lateral sclerosis
ins 1 bp codon 556	Frameshift	1666dupA 1666dup1 1666dup	Charcot-Marie-tooth disease, type 4J
Lys559Term	Nonsense	1675AtoT K559*	Charcot-Marie-tooth disease, type 4J
Del 1 bp noncoding DNA	Noncoding	1750+1delG 1750+1del1 1750+1del	Yunis-Varon syndrome
Pro637Gln	Missense	1910CtoA P637Q	Amyotrophic lateral sclerosis
Tyr647Cys	Missense	1940AtoG Y647C	Amyotrophic lateral sclerosis
IVS17 as T-G -10	Splice	1949minusr14875421910TtoG	Charcot-Marie-tooth disease, type 4J
ins 1 bp codon 663	Frameshift	1986dupG 1986dup1 1986dup	Charcot-Marie-tooth disease, type 4J
Asp688Gly	Missense	2063AtoG D688G	Amyotrophic lateral sclerosis
ins 1 bp codon 689	Frameshift	2065dupA 2065dup1 2065dup	Peripheral neuropathy
Met694Val	Missense	2080AtoG M694V	Amyotrophic lateral sclerosis
Arg699Cys	Missense	2095CtoT R699C	Amyotrophic lateral sclerosis
Arg699His	Missense	2096GtoA R699H	Amyotrophic lateral sclerosis
ins 1 bp codon 718	Frameshift	2151dupA 2151dup1 2151dup	Charcot-Marie-tooth disease, type 4J
Del 2 bp codon 762	Frameshift	2285_2286delCT 2285_2286del2 2285_2286del	Yunis-Varon syndrome
ins 1 bp codon 767	Frameshift	2299dupG 2299dup1 2299dup	Charcot-Marie-tooth disease
Asp783Val	Missense	2348AtoT D783V	Epilepsy with polymicrogyria
Gln796Term	Nonsense	2386CtoT Q796*	Charcot-Marie-tooth disease
Del 3 bp codon 813	Inframe	2439_2441delAGA 2439_2441del3 2439_2441del	Leukoencephalopathy
Phe815Ser	Missense	2444TtoC F815S	Amyotrophic lateral sclerosis
IVS21 ds G-A +1	Canonical-splice	2459plus1GtoA	Charcot-Marie-tooth disease
Gln823Term	Nonsense	2467CtoT Q823*	Charcot-Marie-tooth disease, type 4J
IVS22 as G-A -1	Canonical-splice	2547minusr1487542191GtoA	Charcot-Marie-tooth disease
Ser853Leu	Missense	2558CtoT S853L	Amyotrophic lateral sclerosis
Arg899Term	Nonsense	2695CtoT R899*	Charcot-Marie-tooth disease, type 4J
Ile902Thr	Missense	2705TtoC I902T	Amyotrophic lateral sclerosis

sociated with YVS, and this is the first case from the Saudi population (Table 3).

FIG4 encodes phosphatidylinositol-3,5-bisphosphatase, essential for endosome/lysosome function, and is involved in vesicle trafficking [Wright et al., 2020]. Improper function of *FIG4* leads to endocytic trafficking obstruction, resulting in accumulation of vesicles in the fibroblast and peripheral neurons [Martyn and Li, 2013; Wright et al., 2020]. *FIG4* binds with Fab1/PIKfyve and Vac14/ArPIKfyve, thus making a complex on the endosomal membranes known as PIKfyve-ArPIKfyve-Sac3 complex [Martyn and Li, 2013]. The complex helps in the conversion of endosomal phosphatidylinositol 3-phosphate (PI3P) to phosphatidylinositol 3,5-bisphosphate (PI (3,5) P2), which is essential for protein trafficking, sorting of late endosomes to lysosomal degradation compartment [Huotari and Helenius, 2011]. Mutations or improper *FIG4* function results in reducing the PI (3, 5) P2, which leads to malfunctioning of the endolysosomes/endosomes/lysosomes [Martyn and Li, 2013]. Homozygous null *FIG4* mice revealed impaired growth and reduced body weight. In addition, 50% reduction was ob-

served in the volume fraction of bones, trabecular number, bone surface, and connectivity density compared to the wild type. However, the trabecular separation in the *FIG4* null mice increased 3-fold. The femoral cortical thickness of the *FIG4* null mice was also reduced to less than 50% compared to the normal, thus suggesting abnormal vacuolized osteoblasts and ossification [Campeau et al., 2013].

In conclusion, we revealed a novel biallelic sequence variant in the *FIG4* gene associated with autosomal recessive YVS. Our finding increases the mutational spectrum of *FIG4* associated with YVS. The identification of additional YVS patients will delineate the full spectrum of the disorder, expand phenotypic manifestations and the molecular mechanisms involved in the disease course.

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Statement of Ethics

All procedures were approved by the research committee of King Abdullah International Medical Research Centre (KAIM-RC), Riyadh, Saudi Arabia and were performed in accordance with the Helsinki declarations. Informed consent for publication of this case report, presentation of images, and conducting research study was obtained from the parents.

Author Contributions

M.A.: Clinical evaluation, data analysis, responsible for conception, study design, and editing the manuscript. S.S., T.M.A.: Performed clinical evaluation. M.U.: Wrote the manuscript, performed genetic evaluation, and data analysis. All the authors read and approved the final manuscript.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

The supporting data on the findings of this study can be provided by the corresponding author on reasonable request.

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