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Chromosome 16p11.2 microdeletion syndrome with microcephaly and Dandy-Walker malformation spectrum: expanding the known phenotype

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Abstract

Background Chromosome 16p11.2 deletions and duplications were found to be the second most common copy number variation (CNV) reported in cases with clinical presentation suggestive of chromosomal syndromes. Chromosome 16p11.2 deletion syndrome shows remarkable phenotypic heterogeneity with a wide variability of presentation extending from normal development and cognition to severe phenotypes. The clinical spectrum ranges from neurocognitive and global developmental delay (GDD), intellectual disability, and language defects (dysarthria /apraxia) to neuropsychiatric and autism spectrum disorders. Other presentations include dysmorphic features, congenital malformations, insulin resistance, and a tendency for obesity. Our study aims to narrow the gap of knowledge in Saudi Arabia and the Middle Eastern and Northern African (MENA) region about genetic disorders, particularly CNV-associated disorders. Despite their rarity, genetic studies in the MENA region revealed high potential with remarkable genetic and phenotypic novelty.

Results We identified a heterozygous de novo recurrent proximal chromosome 16p11.2 microdeletion by microarray (arr[GRCh38]16p11.2(29555974_30166595)x1) [(arr[GRCh37]16p11.2(29567295_30177916)x1)] and confirmed by whole exome sequencing (arr[GRCh37]16p11.2(29635211_30199850)x1). We report a Saudi girl with severe motor and cognitive disability, myoclonic epilepsy, deafness, and visual impairment carrying the above-described deletion. Our study broadens the known phenotypic spectrum associated with recurrent proximal 16p11.2 microdeletion syndrome to include developmental dysplasia of the hip, optic atrophy, and a flat retina. Notably, the patient exhibited a rare combination of microcephaly, features consistent with the Dandy-Walker spectrum, and a thin corpus

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callosum (TCC), which are extremely infrequent presentations in patients with the 16p11.2 microdeletion. Additionally, the patient displayed areas of skin and hair hypopigmentation, attributed to a homozygous hypomorphic allele in the *TYR* gene.

Conclusion This report expands on the clinical phenotype associated with proximal 16p11.2 microdeletion syndrome, highlighting the potential of genetic research in Saudi Arabia and the MENA region. It underscores the importance of similar future studies.

Keywords de novo, Recurrent proximal chromosome 16p11.2 microdeletion syndrome, Saudi Arabia, Global developmental delay, Cognitive impairment, Optic atrophy, Microcephaly, Myoclonic epilepsy, Dandy-walker spectrum

Background

Copy Number Variations (CNVs) are structural variations defined as deletions/duplications of 50 base pairs or more [1]. They are considered a relatively common cause of human disease especially involved in the pathogenesis of developmental disabilities [2]. Large pathogenic CNVs have been linked to various phenotypic alterations in recent large population-based cohorts [1, 3]. [2]. CNVs associated with neurodevelopmental delay (NDD CNVs) were reported to occur in around 1 in 200 newborns (prevalence of 0.48%), with a third of these being de novo CNVs [4]. CNVs in the 16p11.2 region were linked to five rare disorders: 16p11.2p12.2 microdeletion [ORPHA:261211]/microduplication [ORPHA:261204], proximal and distal 16p11.2 microdeletion [ORPHA:261197 and ORPHA:261222], and proximal 16p11.2 microduplication syndromes [ORPHA:370079] [5, 6]. Chromosome 16p11.2 rearrangements (deletions/duplications) were found to be the second most commonly reported CNVs in cases with clinical features suggestive of chromosomal syndromes, with a frequency of 1 in 235 for the deletions and 1 in 404 for the duplications [2]. Overall, low expressivity and incomplete penetrance were observed in chromosome 16p11.2 deletions and duplications [7].

There are variations in the size and location of the deleted genomic region involved in the etiology of 16p11.2 microdeletion syndrome (OMIM #611913). However, deletions affecting the proximal 16p11.2 region are classically defined as a recurrent ~ 600 kb CNV between breakpoints (BP4 and BP5)] encompassing up to around 29 protein-coding genes [8, 9]. The syndrome has an incidence of around 1/2000 [10] with an estimated prevalence of 1–5/10,000 in the general population, whereas different studies reported a prevalence of 1.5% in cases of developmental or language delay, 1% of ASD, and 0.001% of cases presenting with psychiatric disorders [7, 10–13]. 75% of the cases were reported to occur de novo with only 7% being inherited [10, 12]. Phenotypically, it shows remarkable heterogeneity with extreme variability of presentation in line with its reported pleiotropy and the large number of phenotypic traits associated with it (mounting to 26) in numerous studies [3, 14, 15]. The presentation of patients with the 16p11.2- BP4-BP5 deletion syndrome ranges from normal development and cognition to severe phenotypes. Recent studies have provided compelling evidence of the pleiotropic effects associated with recurrent CNVs with 16p11.2 The spectrum of clinical manifestations associated with it spans neurocognitive delay, intellectual disability (ID), language impairment (dysarthria /apraxia), neuropsychiatric disorders, autism spectrum disorders (ASD), global developmental delay (GDD), dysmorphic features, congenital malformations, tendency for obesity, and more [7, 10, 13].

There is a notable scarcity of genetic studies in the Middle East and North Africa (MENA) region, especially of research on CNV-associated disorders and their impact on health, despite the demonstrated high potential of novel discoveries in this region that is attributed to the richness and novelty of genetic and phenotypic data. Our study aimed at expanding the knowledge about the genetic disorders in the MENA region and Saudi Arabia predicting a remarkable impact, not only locally and regionally, but also internationally. In this report, we expand the phenotypes associated with recurrent proximal chromosome 16p11.2 microdeletion syndrome, reporting a complex neurological phenotype in a Saudi girl that was associated with novel neurological features and areas of abnormal skin and hair pigmentation attributed to a concurrent homozygous hypomorphic allele in the *TYR* gene.

Method

Phenotyping

The patient and the two parents were phenotyped by the referring neuro-pediatrician and the clinical geneticist. A second standardized detailed phenotyping of the patient and the two parents was done by the research team. Specialized ophthalmological, auditory, cardiac, and orthopedic assessments were performed, and the patient's medical records were reviewed. The radiological assessments of the patient that were performed included magnetic resonance imaging (MRI) of the brain, X-rays, and

echocardiography. All necessary laboratory and neurophysiological investigations were also performed.

Genetics

DNA was extracted from blood using specialized DNA extraction kits according to the manufacturer's protocol (kit name, company, etc.).

Microarray

Genomic DNA was fragmented, amplified, and hybridized to the array according to the manufacturer's manual. Cytoscan HD array Affymetrix® which contained 2.7 million markers including 750,000 SNP markers was used. It enabled the detection of CNVs and/or large duplications / deletions. The chromosome analysis suite (ChAS Affymetrix) was used to analyze the results with CNVs larger than the size threshold of more than 200Kbs (for duplications) and 50Kbs (for deletions) reported. Although the choice of the cut-off sizes is usually influenced by the sensitivity and the specificity of the microarray platform, these sizes strike a balance between resolution, clinical relevance, and technological constraints, making them commonly used and effective thresholds for aCGH analysis in clinical and research settings [16–19].

Additionally, analysis was performed for all homozygous deletions which included aberrations of at least five aberrant markers (1Kb in size). Identified deletions below the above-given thresholds were only reported when a clear phenotypic overlap of affected genes was observed. Analysis was done based on the human genome assembly GRCh38 according to the preset pipeline, however, the GRCh37-based genomic positions were also identified using the University of California Santa Cruz (UCSC) Genomic Institute genome browser tool (LiftOver). Database of Genomic Variants (DGV) and Decipher database in addition to other available databases were used in result interpretation.

Whole exome sequencing (WES)

WES was performed on the patient and the two healthy parents (Trio WES). DNA was fragmented enzymatically. Target region enrichment was done using DNA capture probes. It included the human exome (the coding exons and the flanking -/+ 10 bases of the intronic regions of genes) covering more than 98% of the RefSeq coding sequence [human genome built GRCh37/hg19]) in addition to the mitochondrial genome. The generated library was sequenced via the Illumina platform and 20X depth was achieved for more than 98% of the targeted bases. The bioinformatics pipeline used for analysis included alignment with GRCh37/hg19 human genome assembly and revised Cambridge Reference Sequence of the mitochondrial DNA (NC_012920), followed by variant calling, annotation, and filtering [20]. All potential modes of inheritance were considered with all variants with a minor allele frequency of less than 1% in gnomAD v2.1 database and disease-causing variants reported in HGMD® Professional 2022.1, ClinVar, or in CentoMD® were evaluated. Variants were classified into five categories (pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, benign) along American College of Medical Genetics (ACMG) guidelines. Relevant variants related to the phenotype were reported and analyzed by PCR and sequencing of both strands of the entire coding region and the highly conserved exon-intron splice junctions.

We used an in-house pipeline for the detection of CNVs with a specific algorithm for the identification of uniparental disomy (UPD) screening. It includes the identification of the ROH in WES data via an H3M2-based algorithm, which uses the pileup format (https://en.wikipedia.org/wiki/Pileup_format) generated from BAM files [21] A CNV caller DECoN (Detection of Exon Copy Number) was used. It is specifically designed for targeted sequencing data and employs a Bayesian approach to distinguish biological differences from technical noise for each target region [22]. We annotate and rank structural variations (SV) using the tool AnnotSV [23].

Results

Clinical presentation

We present a 22-month-old Saudi girl with significant GDD, bilateral developmental dislocation and dysplasia of the hip more on the left side, myoclonic generalized epilepsy, impaired hearing, poor vision, and cutaneous hypopigmentation. She was the only child of healthy consanguineous parents in a family (PNU-NG3) with multiple consanguinity loops over generations originating from the south of Saudi Arabia. The patient's remarkable GDD was evidenced by her inability to accomplish the majority of the milestones that were expected at her age. She had limited recognition of her parents, poor visual fixation, and minimal interaction with her surroundings. She was capable of producing some non-comprehensive sounds and could roll from supine to prone positions but was unable to sit, even with support.

The myoclonic seizures were first observed by the neuro-pediatrician during consultation at the age of seven months. An electroencephalogram (EEG) confirmed generalized epileptic activity consistent with the diagnosis of myoclonic epilepsy and the patient was started on Levetiracetam as antiseizure medication. Although clinical seizures were controlled, follow-up EEGs showed the persistence of less frequent epileptic discharges.

At 22 months, clinical examination revealed microcephaly with a head circumference of 37 cm, failure to

thrive with a weight of 6.3 kg, and short stature with a length of 72 cm. All her growth parameters were far below the third percentile for age and sex. The patient displayed plaques and macules of hypopigmentation on her face and extremities, along with streaks of white hair and white eyelashes. The hypopigmentation appeared to progress slowly. Dysmorphic features included low-set ears, retracted forehead and chin, prominent maxillae and occiput, and high-arched palate were detected (Fig. 1) (Table 1). Orthopedic assessment indicated developmental dysplasia of the hips (DDH) with bilateral congenital hip dislocation that was more severe on the left side, accompanied by bilateral acetabular dysplasia and a smaller left femoral epiphysis. There were no signs of scoliosis, joint laxity, or other deformities. Cardiac assessment and echocardiography were normal excluding cardiac malformations.

Cognitive impairment was evident, characterized by limited interaction with her surroundings, corroborating parental observations. A formal cognitive assessment was challenging to perform. Neurological examination showed axial hypotonia with spasticity in both upper and lower limbs. Deep tendon reflexes were normal in the upper limbs but increased in both lower limbs with bilateral up-going plantar responses. The assessment of her power was affected by her disability; however, a minimum strength of 4 out of 5 was noted. Examination of the sensory, extrapyramidal, and cerebellar systems was not feasible due to her spasticity and marked disability. The ophthalmological assessment revealed poor visual fixation with response only to light only, normal anterior chamber, and a flat retina with optic atrophy, but no evidence of retinitis pigmentosa or retinal hypopigmentation.

Following an abnormal neonatal hearing screening (automated auditory brainstem response (AABR)), an auditory brainstem response (ABR) test revealed sensorineural hearing loss with absent Distortion Product Otoacoustic Emissions (DPOAE) and Transient Evoked Otoacoustic Emissions (TEOAE), normal middle ear and no evidence of conduction hearing loss. MRI of the brain showed mild thinning of the splenium of the corpus callosum. Additional features suggestive of the Dandy-Walker spectrum were identified. These included a small volume of the cerebellar vermis, cerebellum, and brain stem with enlargement of the retro-cerebellar subarachnoid space that communicates with the fourth ventricle. Moreover, pronounced Sylvian fissures and prominent frontal peri-cerebral cerebrospinal spaces were noted, likely attributable to microcephaly of the adjacent cerebral lobes (Fig. 1) (Table 1).

A prenatal onset of clinical presentation in our patient was hypothesized even though there were no ultrasound records documenting specific prenatal features. This hypothesis was supported by the presence of congenital microcephaly, bilateral DDH, as well as

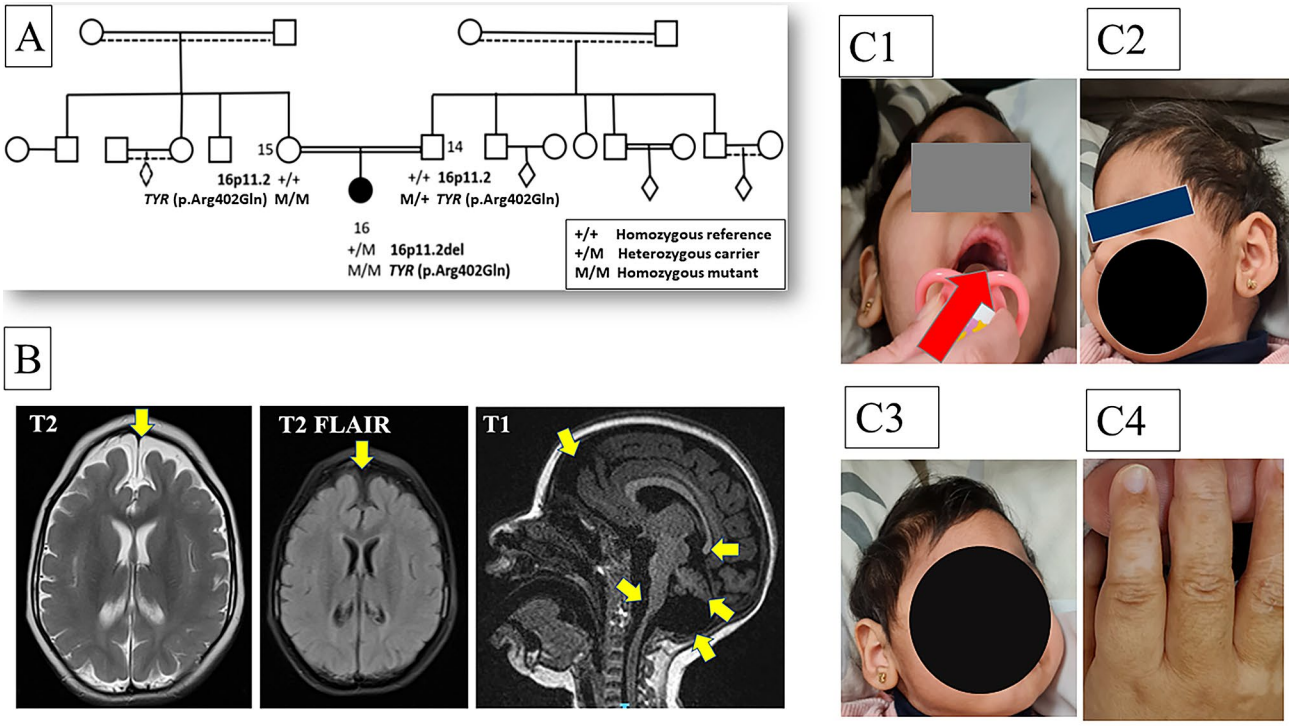

Fig. 1 16p11.2 deleted region identified by whole exome sequencing.30 genes are shown to be encompassed in the deleted region (Chr16:29635211–30199850) [UCSC genome browser: GRCh37]: (including two pseudogenes (in pink) and one divergent transcript RNA gene (in green)

Table 1 Previous and current reports of chromosome 16p11.2 deletion syndrome in the Middle East and North Africa (MENA) region

Reports	**[27] Al-Hassnan et al., 2018**	**[28] Al-Saud, 2013**	**[29] Chehbani et al., 2022**	**Current Report Elsayed et al.,**
Chromosome 16p11.2 deleted region	16p11.2; 29,567,295 – 30,321,320; ~754 Kb (hg19).	16p11.2 deletion of 659,635 bp (Exact genomic location was not provided)	16p11.2; 29,652,999 – 30,197,341; ~545 Kb (hg19).	Microarray: 16p11.2; 29,567,295 – 30,177,916; ~611 Kb (hg19) WES: 16p11.2; 29,635,211 – 30,199,850; ~565 Kb (hg19).
Concomitant CNVs/chromosomal rearrangement	Balanced translocation: the q-arm of chromosome 10 and the q arm of chromosome 12 (46,XX, t(10;12)(q22;q22) Deletion: chromosome 12 (12p12.1p11.21; 25,320,816–31,285,151; ~5.96 Mb)	-	-	-
Other variants	-	-	-	TYR gene Homozygous mutation [NM_000372.4:c.1205G > A (p.Arg402Gln)] Identified by WES
Number of patients reported	1	2	1	1
Patients Nationalities	Saudi	Saudi	Tunisian	Saudi
Gender	F	NDA	M	F
Inherited /De novo	Translocation chromosome 10/12) (probably inherited but not confirmed) Chromosome 16 del. (paternally inherited) Chromosome 12 del. (de novo)	NDA	NDA	De novo
Consanguineous parents	+	NDA	NDA	+
Onset of clinical manifestations	Prenatal	NDA	Mostly at birth	Likely prenatal
Age at examination	3 years	NDA	6 years	22 months
Prenatal /Delivery/Neonatal manifestations	In vitro fertilization (delivery at 34 weeks)	NDA	Birth complications	• Complicated delivery (cesarean section) due to fetal distress and meconium-stained liquor • Neonatal intensive care admission for three days
Intellectual disability/ neurocognitive delay	As part of the GDD	Mild mental retardation	+	As part of the GDD
Developmental delay	GDD	NDA	+	GDD
Language impairment	As part of the GDD	+	+	As part of the GDD
Epilepsy/Seizure	-	NDA	-	+
Neuropsychiatric disorders	-	Hyperactivity	Moderate ASD manifestations including severe social communication deficit and language delay with echolalia	No proper assessment could be done
Head size	< 5th percentile (microcephaly)	NDA	NDA	< 3rd percentile (microcephaly)
Other growth parameters (Height and weight)	< 5th percentile	Moderate Obesity	NDA	< 3rd percentile
Dysmorphic Features	Low-set ears, depressed nasal bridge, and long philtrum	NDA	-	Low-set ears, retracted forehead and chin, prominent maxillae and occiput, and high-arched palates
Congenital cardiac malformation	Septal defect (atrial & ventricular) Hypoplastic right upper pulmonary vein	NDA	-	-
Other (non-cardiac) congenital malformations	-	NDA	-	Skeletal: DDH with bilateral congenital hip dislocation (more severe on the left side)

Table 1 (continued)

Reports	[27] Al-Hassnan et al., 2018	[28] Al-Saud, 2013	[29] Chehbani et al., 2022	Current Report Elsayed et al.,
Hyperphagia/ Obesity/ Insulin resistance	-	Hyperphagia and Moderate obesity (BMIs of 34.5 and 35.1 kg/m^2)	-	-
Visual impairment	-	-	-	+
Macular/optic disc coloboma	Left-sided	-	-	-
Optic atrophy	-	-	-	+
Axial hypotonia	-	-	-	+
UL/LL pyramidal features	-	-	-	+
Auditory impairment	-	-	-	+
MRI findings	Normal	NDA	NDA	• Dandy-Walker spectrum • Mild thinning of the splenium of corpus callosum

CNV: copy number variation, GDD: global developmental delay, DDH: developmental dysplasia of the hip, UL: upper limb, LL: lower limb, MRI: magnetic resonance imaging. NDA: No data available, M: male, F: female, (+): present, (-): Absent OA

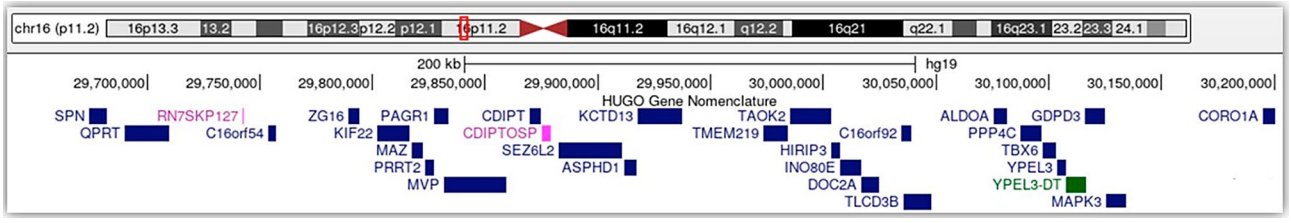

Fig. 2 Family pedigree, genetic, radiological, and clinical characterization of the patient. **A** Family pedigree showing the segregation of the chromosome 16p11.2 deletion identified by whole exome sequencing and microarray and *TYR* gene mutation [NM_000372.4:c.1205G > A (p.Arg402Gln)]. **B** MRI of the brain (T2 and T2 FLAIR axial and T1 sagittal views) showing a small volume of the cerebellum, and brain stem with enlargement of the retro-cerebellar subarachnoid space communicating with the fourth ventricle (suggestive of Dandy-Walker spectrum). Thin splenium of the corpus callosum, prominent Sylvian fissures, and frontal peri-cerebral cerebrospinal spaces are also evident.**C** High-arched palate (C1), low-set ears (C2), microcephaly (C1-C3), and hypopigmented macules and plaques on the dorsum hand (C4)

the Dandy-Walker spectrum, and the abnormal AABR detected shortly after birth. Further support to this suggestion was the complicated delivery (cesarean section) [due to fetal distress and meconium-stained liquor] followed by three days of admission to neonatal intensive care. In the 16p11.2 microdeletion syndrome, the prenatal onset of disease phenotype could be proposed in cases with congenital malformations and those with neonatal complications. However, a variety of fetal presentations were documented by ultrasonography including skeletal, cardiovascular, and neurological malformations among others [7, 24–26]. Detailed examination of the parents revealed no hypopigmentation or phenotypic features seen in the patient.

Genetic results

Microarray results

A heterozygous deletion of size 611 Kb was identified (arr[GRCh38]16p11.2 (29555974_30166595)x1) [(arr[GRCh37]16p11.2(29567295_30177916)x1)]. In addition, a significant absence of heterozygosity encompassing 5.97% of the autosomal genomic length (166,280 Kb) was detected indicating parental consanguinity (Supplementary Table S2).

WES results

A pathogenic interstitial one-copy loss of 565 Kb was detected using an NGS-based CNV analysis (arr[GRCh37]16p11.2(29635211_30199850)x1). The copy loss was within the chromosomal region 16p11.2 with 30 genes (including two pseudogenes and the entire *TBX6* gene) involved in the deleted area (Fig. 2) (Supplementary Table S1). This NGS finding confirmed the results obtained by the chromosomal microarray (CMA) analysis. The deletion was absent in both parents suggesting it was a de novo CNV (Fig. 1) (Table 1). The region reported is identified as pathogenic in both Decipher and ClinVar databases. Additionally, WES identified a homozygous mutation *TYR* gene [NM_000372.4:c.1205G > A (p.Arg402Gln)] (Fig. 1). WES identified that the mother was homozygous and the father heterozygous for the same *TYR* gene mutation. The variant was reported in

the literature as a hypomorphic allele associated with hypopigmentation. According to the criteria defined in the methods, no other putatively pathogenic variants (including structural variants) were found to segregate with the phenotype of the patient.

Discussion

Even though 16p11.2 microdeletion syndrome is relatively common among CNV-associated disorders, it was detected in only four studies from the MENA region collectively reporting 4 cases, with 3 cases from Saudi Arabia and one from Tunisia [27–29]. We are reporting the 8th case of 16p11.2 deletion in the region, a Saudi girl who presented with a complex neurological phenotype associated with loss of skin and hair pigmentation – probably due to an involvement of a *TYR* gene hypomorphic polymorphism.

Our report supports the deep effect of genetic studies conducted in the MENA region on the understanding of many disorders despite the relative insufficiency of the published data. Two of the Saudi patients had obesity, mild mental retardation, hyperphagia, language delay, and hyperactivity [28]. The last had a combination of two deletions on chromosomes 12 and 16 [a de novo 12p12.1p11.21 and inherited 16p11.2. deletion] presenting with a complex phenotype that partially overlaps with the phenotype observed in our patient [GDD, failure to thrive, dysmorphic features, macular and optic disc coloboma, septal defects] [27].

The clinical picture of our patient relatively matched the described 16p11.2 deletion syndrome phenotypic presentation with some unique features that expand the known phenotypic spectrum of the syndrome. Developmental delay at variable degrees and speech deficit are considered among the commonest presentations of the 16p11.2 deletion syndrome occurring in >90% and >70% of the patients, respectively. On the other hand, deafness is considered a rare manifestation of 16p11.2 microdeletion syndrome (<11%) with less than 10 cases reported to date [7, 10, 30–34].

Myoclonic seizures are extremely rare although seizures and epilepsy are reported in around 24–38% and 18% of individuals with chromosome 16p11.2 deletion, respectively [7, 35]. In a cohort of 129 individuals with 16p11.2 deletion syndrome, myoclonic jerks were found in one patient only whereas overall the focal seizures constituted 55% of the reported seizure cases with a predominance of focal tonic/tonic-clonic (29%). Additionally, tonic-clonic seizures of unknown onset were observed in 29% of cases. The onset of epilepsy during the first year of life was common, occurring in 61% of individuals, which aligns with our observations [12, 35]. The deleted region spans *PRRT2*, the loss of which predisposes to seizure and movement disorders [OMIM * 614386].

Although 16p11.2 has been strongly associated with obesity and hyperphagia, the failure to thrive and abnormally decreased weight that was observed in our patient match what has been described in some reports as well. However, our patient was younger than the age at onset (2 years) of hyperphagia and the consequent obesity that was described by Szelest et al. and a few other reports [7, 10, 12, 31, 36, 37].

A variety of congenital malformations was described in 16p11.2 deletion syndrome, with a relatively high overall average rate of occurrence of 30–31% with remarkable variations observed according to the type of the congenital anomaly and the system involved [7, 26, 33]. Remarkably, none of the commonly encountered malformations was detected in our patient who had instead bilateral DDH. DDH was not previously linked to chromosome 16p11.2 deletion which makes our patient the first case reported.

It is noteworthy that the combination of microcephaly and Dandy-Walker spectrum as a part of the presentation of 16p11.2 microdeletion syndrome is quite a rare incidence as both were very rarely described in association with the deletion in addition to the rarity of their combination. Microcephaly was very rarely described in patients with 16p11.2 deletion with our patient being the seventh case reported to present [26, 38, 39]. In previous cohorts, microcephaly was associated with 16p11.2 duplication with deletions significantly associated with absolute or relative macrocephaly [7, 10, 36, 40]. Although posterior fossa and cerebellar malformations, particularly, Chiari I/cerebellar tonsillar ectopia, were relatively commonly associated with 16p11.2 microdeletion syndrome in numerous previous reports [8, 32, 39, 41, 42], however; Dandy-Walker malformation was reported in one case only before our current report [26]. Moreover, the combination of microcephaly with Dandy-Walker spectrum malformation is remarkable since the latter was known to be more frequently associated with macrocrania and hydrocephalus [43]. The microcephaly associated with the 16p11.2 duplication and the macrocephaly associated with the deletion were attributed by Golzio et al. to the overexpression and the suppression of the *KCTD13* gene (one of the genes included in the deletion region) implying a dosage effect of the KCTD13 protein [44]. This contradiction with the classical presentation of macrocephaly and the proposed role of KCTD13 protein may be attributed to differences in background genetics and the presence of genetic modifiers. It can add up to the known phenotypic heterogeneity described in the 16p11.2 deletion and the extreme variability of its associated clinical presentations. Future functional studies may provide a molecular explanation of the occurrence of microcephaly and open a new area in research.

The 16p11.2 microdeletion syndrome is associated with a range of ocular manifestations, however, there were no previous records of its association with optic atrophy and flat retina [45, 46].

Limited dermatological features have been associated with chromosome 16p11.2 deletion, with café au lait spots being among the few reported pigmentary disturbances. The hypopigmentation and depigmentation observed in our patient may be attributed to the identified homozygous mutation *TYR* p.Arg402Gln [rs1126809]. This substitution has been frequently described as a hypomorphic allele resulting in a thermolabile tyrosinase enzyme. It produces a peptide that is subject to retention by the endoplasmic reticulum with consequent reduction of its catalytic activity to 25% of that of the wildtype enzyme at 37° C. It has been reported to contribute to the pathogenesis of albinism especially when associated with other heterozygous pathogenic mutations [47–49]. Given the mild phenotype observed in our patient, characterized by dispersed regions of hypopigmentation despite its progressive nature, we propose that the substitution may have played a role in the pathogenesis of the condition. [47–49]. However, the absence of hypopigmentation in the mother who was also homozygous for the same *TYR* variant contradicts the complete attribution of the pigmentary lesions to the variant only. Although further workup may be needed to understand the exact underlying mechanism, there may have been a contribution of an interaction of the p.Arg402Gln variant with the 16p11.2 deletion or any other modifier variant that might not have been detected.

Limitations

The origin of the patient consanguineous family with several loops of consanguinity over multiple generations and long runs of homozygosity identified upon genetic analysis might be associated with the presence of pathogenic mutations in a homozygous state that might not have been identified which is especially true for variants in non-coding/regulatory regions and for novel genes. This could have an important impact on the patient's phenotypic presentation since the population in which the patient originated is considered relatively genetically underexplored.

This is particularly evident when considering the pathogenesis of the hypo-pigmentary lesions. Both the healthy mother and the affected patient carry the same homozygous p.Arg402Gln variant, suggesting the presence of an unidentified genetic modifier. This reasoning may also extend to other rare manifestations observed in the patient. Thorough investigation of the medical history of the nuclear and extended family, along with comprehensive genetic data analysis, could help to address this challenge, at least in part.

Conclusions

In this report, we expand the clinical phenotype associated with proximal 16p11.2 microdeletion syndrome to include DDH, optic atrophy, flat retina, Dandy-Walker spectrum, and TCC. Furthermore, we are reporting one of the exceptionally scarce cases of microcephaly in association with 16p11.2 deletion. Our patient also exhibited other rare presentations, including myoclonic epilepsy and deafness. This case report further highlights the potential of genetic research in Saudi Arabia and the MENA region emphasizing the importance of further studies to explore the genetic background and understand the causes of the unique features observed in our patient.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-024-00662-0.

Supplementary Material 1

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Author contributions

LEOE, NAA, AMA, HEE, MAA, AMB, FAA, HMA, AMM, and OAA formulated and designed the study. LEOE, AMA, HEE, NMMM, MMA, and FAA granted funds. LEOE, NAA, AMA, HEE, NMMM, MMA, HIBZ, LMA, SAA, KA, SYA, HYA, FAA, HAR, HMA, AMM, and OAA contributed to the sampling, clinical, radiologic, and ethnological data collection and interpretation. LEOE, NAA, HEE, HAR, MAKO, AMM, and OAA contributed to the genetic data analysis, WES and microarray data bioinformatics analysis, and the drafting and revision of the manuscript. All authors read and approved the manuscript, assented to its submission, agreed to be responsible for all aspects of this work, and agreed to be personally accountable for their contributions.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Princess Nourah bint Abdulrahman University, Saudi Arabia (IRB Log Number: 20–0150) according to the recommendations of the Helsinki Declaration. Written informed consent to participate in this study was provided by all the adult participants and the legal guardian (father) of the child.

Consent for publication

Written informed consent was also obtained for the publication of the results and any potentially identifiable images or data included in this article.

Competing interests

The authors declare no competing interests.

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