


## ORIGINAL ARTICLE

# 8q21.11 microdeletion syndrome: Delineation of *HEY1* as a candidate gene in neurodevelopmental and cardiac defects

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## Abstract

**Background:** 8q21.11 microdeletion syndrome is a rare chromosomal disorder characterized by recurrent dysmorphic features, a variable degree of intellectual disability and ocular, cardiac and hand/feet abnormalities. To date, *ZFHX4* is the only candidate gene implicated in the ocular findings. In this study, we evaluated a patient with a de novo 8q21.13–21.3 deletion to define a new small region of overlap (SRO) for this entity.

**Methods:** We conducted a clinical evaluation and comparative genomic hybridization (CGH) 4x44K microarrays in a patient with de novo unbalanced translocation t(8;16)(q21; q11.2).

**Results:** The case, a 6-year-old boy, presented dysmorphic features including an elongated face, brachycephaly with a high forehead, an underdeveloped ala, thin upper lip, micrognathia, low-set ears, hypotonia, mild intellectual disability, cortical atrophy with thin corpus callosum defect, and an atrial septal defect. No ocular abnormalities were found. Microarray analysis revealed a 9.6 Mb interstitial 8q21.11–21.3 deletion, not including the *ZFHX4* gene. This microdeletion was confirmed in our patient through qPCR analysis, and both parents had a normal profile. Alignment analysis of our case defined a new SRO encompassing five genes. Among them, the *HEY1* gene is involved in the embryonic development of the heart, central nervous system, and vascular system. *Hrt1/Hey1* null mice show perinatal lethality due to congenital malformations of the aortic arch and its branch arteries. *HEY1* has also been linked to the maintenance of neural stem cells, inhibition of oligodendrocyte differentiation, and myelin gene expression.

**Conclusion:** *HEY1* is a candidate gene for both neurological and cardiac features of the 8q21.11 microdeletion syndrome and might, therefore, explain specific components of its pathophysiology.

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## KEYWORDS

8q21.11 microdeletion syndrome, cardiac defect, comparative genomic hybridization, *HEY1*, intellectual disability

## 1 | INTRODUCTION

De novo interstitial deletions of the 8q21.13–q21.3 chromosomal region are rare rearrangements that have been reported in only 18 cases so far (Africk, 2015; Belligni & Hennekam, 2010; Happ et al., 2016; Heide et al., 2017; McMullan et al., 2002; Palomares et al., 2011; Quintela et al., 2015; Vulto-van Silfhout et al., 2013; Wu et al., 2020). Palomares et al. (2011) reported the first large cohort, with eight patients, and suggested that the 8q21.11–q21.3 sub-microscopic deletions represent a clinically recognizable entity, referred to as 8q21.11 microdeletion syndrome (OMIM # 614230). Although the patient's phenotype was remarkably variable, common features were noted consisting of mild to moderate intellectual disability (ID), hypotonia, and abnormalities of the hands/feet, as well as a characteristic facial appearance. A round face with a high forehead, short palpebral fissures, wide nasal bridge, underdeveloped alae, micrognathia, short neck, small mouth with downturned corners, Cupid's bow of the upper lip, and prominent low-set ears are the most common dysmorphic features. Other anomalies have been described in most patients, such as developmental ocular abnormalities, including congenital ptosis, sclerocornea, and microphthalmia. Less common features include other systemic defects and comprise sensorineural hearing loss, cleft palate, congenital cardiac defects, and brain abnormalities, including dysgenesis of the corpus callosum, gyration abnormalities, and decreased myelination. Subsequently, the phenotypic spectrum of the 8q21.11 microdeletion syndrome was expanded to further include arthrogryposis and Peters anomaly (Happ et al., 2016; Hofmann et al., 2011).

Deletions with different sizes have been reported in all patients, ranging from 0.12 to 13.15 Mb without recurrent proximal and distal breakpoints. Therefore, the genotype–phenotype correlation is still confusing. Through the use of a high-density targeted oligonucleotide array, Palomares et al. (2011) defined a small region of overlap (SRO) of 539.77 kb, including three genes that were further reduced into one gene; the zinc finger homeobox 4 (*ZFH4*) (OMIM# 606940) (Vulto-van Silfhout et al., 2013). This gene has been proposed as a candidate gene for the ocular findings identified in this entity.

In this study, we identified, through comparative genomic hybridization (CGH) microarrays, a 9.6 Mb deletion within chromosome 8q21.13–q21.3 that does not include the *ZFH4* gene. Owing to these findings, we provide new

insights into the molecular cytogenetic and clinical features of 8q21.11 microdeletion syndrome by defining a new SRO and proposing *HEY1* (OMIM#602953) as a new candidate gene in both neurologic and cardiac defects.

## 2 | PATIENT AND METHODS

### 2.1 | Patient

Our patient, a 6-year-old boy suffering from dysmorphic features, psychomotor retardation, and a congenital heart defect, was referred for genetic counseling. Informed consent was obtained from the patient's parents, and institutional approval was given by the local medical ethical committee of the South of Tunisia (Accession number 28/2019).

### 2.2 | Peripheral blood karyotype

Peripheral blood lymphocytes were cultured in a growth medium according to the standard procedures. Analysis of the GTG-banded metaphase chromosomes at the resolution level of 400 bands was performed using Cytovision® Karyotyping software version 4.0, and karyotypes were classified according to the ISCN 2016 system.

### 2.3 | Fluorescence in situ hybridization (FISH)

A fluorescence in situ hybridization (FISH) study was performed using whole-chromosome painting (WCP) Kreatech™ probes for chromosomes 8 and 16. Chromosomes were observed using a LEICA DM2500 fluorescent microscope and analyzed using Cytovision® Karyotyping software version 4.0.

### 2.4 | Array comparative genomic hybridization

Genomic DNA was extracted from blood samples using a phenol–chloroform standard protocol. CGH 4x44K microarrays were performed using the Agilent platform. DNA denaturation, labeling, and hybridization steps were carried out according to Array-Based CGH for Genomic DNA

Analysis–ULS Labeling, version 3.5 protocol (Agilent Technologies). DNA labeling was carried out in a dye-swap design, and after hybridization and washing, the slide was scanned with an Agilent G2565CA Microarray Scanner (Agilent Technologies). Raw data were generated using the accompanying Feature Extraction software (v10.5). The raw data were visualized and analyzed by means of Cytogenomic 3.0.4. software (Agilent Technologies). The karyotype was designed according to the International System for Human Cytogenetic Nomenclature (ISCN 2016). Genomic coordinates were based on the GRCh38/hg38 build of the human genome. To further evaluate the called copy number variations (CNVs), in silico analysis of the unbalanced regions was explored using UCSC Genome Browser (<https://genome.ucsc.edu/>), the Database of Genomic Variants DGV (<http://dgv.tcag.ca/dgv/app/home>), and the Database of Chromosome Imbalance and Phenotype in Humans using Ensemble Resources DECIPHER (<https://decipher.sanger.ac.uk/>; Firth et al., 2009). Genes where loss of function is known to cause autosomal recessive disorders were excluded. Haploinsufficiency index predictions (HI) of all deleted genes were noted according to the DECIPHER database.

## 2.5 | Quantitative real-time PCR

To validate the CNV from the array CGH results, quantitative real-time PCR (qPCR) was performed for the patient, the parents, and the same run control sample. Two couples of primers were designed for both *HEY1* and *PMP2* genes. The ring finger protein 7 (*RNF7*) genes were used as an endogenous control for data calibration. Primers and thermal cycling conditions are described in Table S1. PCR experiments of target and control genes were carried out in triplicate using Syber Premix Ex Taq at 2x (Tli RNaseH Plus) (TakaRa). PCR amplification and melting curves were performed using a CFX96 real-time PCR detection system (Bio-Rad). Bio-Rad CFX Manager software (Bio-Rad, Redmond, WA, USA) was used for data interpretation. Quantification of target regions was normalized, and the relative copy number (RCN) was determined based on the comparative  $\Delta\Delta C_t$  method, with the normalized copy number =  $2^{-\Delta\Delta C_t}$ . A 0.5-fold RCN was considered for deletion and 1.5-fold for duplication (Livak & Schmittgen, 2001).

## 3 | RESULTS

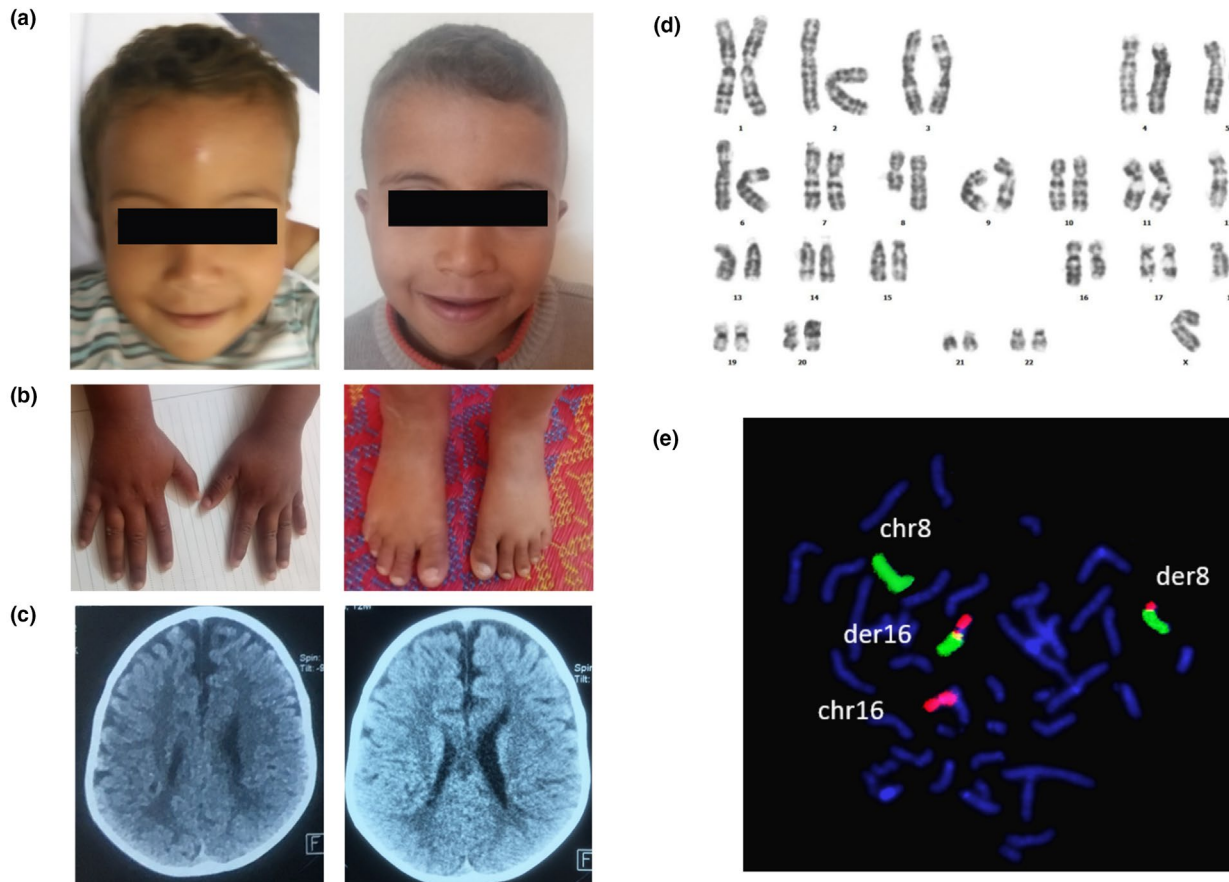
### 3.1 | Clinical report

The reported patient is the third child of an apparently healthy, non-consanguineous couple. Pregnancy was

uneventful; the mother denied any exposure to alcohol, radiation, or infectious agents. Our patient had developmental delay associated with failure to thrive. A Denver Developmental Screening Test II at 15 months of age revealed severe hypotonia associated with a delay in overall child development, including speech (12 months), motor (7 months), and personal–social skills (9 months). Physical examination at the age of 5 years noted low weight (–3DS), distinctive dysmorphic features including elongated face, brachycephaly with a high forehead, an underdeveloped ala, thin upper lip, micrognathia, low-set ears, preauricular tag, highly arched palate, and a short neck (Figure 1a). Anomalies in the fingers and toes were also reported, including brachydactyly, ungual hypoplasia, and flat feet (Figure 1b). Clinical evaluation noted a mild intellectual disability with poor speech and abnormal behavior with unusual pleasant. A brain scan at the age of 24 months showed cortical atrophy, predominant in bifrontal associated with a thin corpus callosum (Figure 1c). An echocardiogram performed at 30 months of age showed an atrial septal defect, ostium secundum, with hypertrophy of the right ventricular. The ophthalmological examination, VEP (visual evoked potentials), ABR (auditory brainstem response), EEG (electroencephalogram), EMG (electromyography), thyroid function, and standard metabolic exams were normal.

### 3.2 | Genetic results

The karyotype determined by GTG-banding showed an apparently unbalanced translocation between chromosomes 8 and 16 (Figure 1d). This result was further confirmed through painting FISH analysis (Figure 1e). Because both parents were found to have a normal karyotype, the patient's karyotype was reported as 46,XX,t(8;16)(q21.1;q12.13)dn. The aberrant array CGH analysis revealed an interstitial deletion at chromosome 8q21.13–21.3 (chr8: 79647725–88947344/hg 38) spanning 9.6 Mb. This deletion included 28 OMIM genes, 5 of which are disease causing, namely *CA2*, *CNGB3*, *IMPA1*, *RRPS28*, and *PMP2* (Figure 2a,b). All the genes included in the deleted region were annotated according to the Gene Ontology resource (to <http://geneontology.org/>; Table S2). According to the DECIPHER database, HI predictions revealed three genes *CA2*, *STMN2*, and *HEY1* with a high rank of HI [0–10%] (Huang et al., 2010), and six genes *WWP1*, *ZNF704*, *ZBTB10*, *STMN2*, *E2F5*, *MMP16*, and *RALYL* were found to have high pLI scores [0.92–1]. No additional clinically significant copy number change was identified on chromosome 16 or for any other chromosomes. The molecular karyotype of the patient, according to the ISCN 2016, was arr[GRCh38] 8q21.13–q21.3 (79647725–88947344×1)dn.



**FIGURE 1** Clinical findings, brain scan, karyotype, and FISH analysis of the reported patient. (a) Photographs of the patient taken at 2 years and 6 years of age. (b) Hands and feet abnormalities. (c) Brain scan images showing cortical atrophy, predominant in bifrontal. (d) G-banding karyotype of the patient: 46,XY,t(8;16)(q21.1;q12.13). (e) Fluorescence in situ hybridization (FISH) using probes for whole painting chromosome 8 (WCP8-green) and chromosome 16 (WCP16-red): WCP8 (green) paints only the normal chromosome 8 and a part of the der (16); WCP16 (red) paints only the normal chromosome 16 and a part of der (8)

This microdeletion was confirmed in our patient through qPCR analysis, and both parents, as well as control run samples, had a normal profile (Figure 2c,d).

## 4 | DISCUSSION

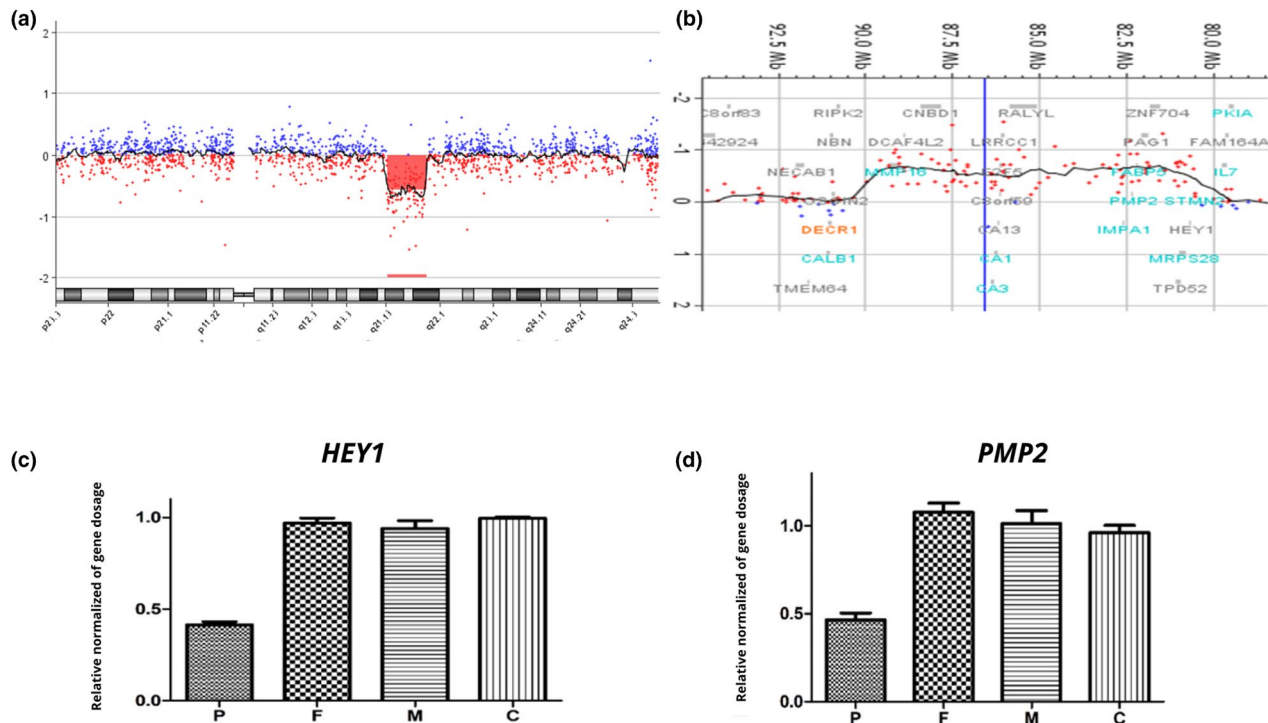
A total of 18 cases with chromosomal aberrations at chromosome 8q21.11–q21.3 region have been previously described. Despite the variable deletions' sizes, facial characteristics and intellectual disability/developmental delay are common features in all patients. Congenital ptosis, hypotonia, and abnormalities of the hands/feet were also noticed in most patients.

Most of the reported cases were de novo with a normal karyotype. However, some patients had de novo apparently balanced chromosome translocations involving 8q21. All deletions were diagnosed postnatally, and only one prenatal case has been recently reported in a fetus with growth restriction, coarctation of the aorta, and a ventricular septal defect (VSD; Wu et al., 2020).

In this study, we report a new case with a 9.6 Mb microdeletion in the 8q21.13–21.3 region caused by a de novo translocation t(8;16)(q21.1;q12.13) in a patient with hypotonia, mild intellectual disability, dysmorphic facial, behavior abnormalities, cardiac defect, cerebral atrophy, and a thin corpus callosum. Our patient shared several clinical features of the 8q21.11 microdeletion syndrome, providing interesting insights into the molecular cytogenetic and clinical features of this entity. To further refine the phenotype–genotype correlation, we collected all clinical and molecular data of the previously reported cases as well as those from the Decipher database presenting pathogenic CNVs (until April 2021) that overlap with the deleted region identified in our patient. Publications where conventional cytogenetic techniques have been used for the identification of 8q alterations were excluded. All genomic positions for the previously reported cases had been converted from GRCh37 or GRCh36 to GRCh38.

In total, we collected 19 cases carrying different sizes (3.7–18.27 Mb) with no recurrent breakpoints (Table 1). Previous sequencing studies, in three cases, revealed that





**FIGURE 2** Results of array CGH analysis and qPCR validation of the aberrant region. (a) Oligo array CGH profile of chromosome 8, showing decreased  $\log_2$  ratio intensity values within the 8q21.13–21.3. (b) Details of genes are presented within the deleted region. (c) Validation of the 8q21.13–21.3 microdeletion by SYBR Green-based real-time PCR, the patient (P) presented only one copy of *HEY1* and *PMP2* genes while both parents (father (F) and mother (M)), and the control (C) presented two copies

the breakpoints were located in unique sequences with no apparent homology. Hence, the non-allelic homologous recombination between clusters recurrent of flanking low-copy repeats or repetitive elements seems not to be the rearrangement mechanism underlying 8q21 microdeletions (Palomares et al., 2011).

Compared to these reported cases, our patient harbored the most common features, including hypotonia, mild ID, and unusual behavior. Moreover, he presented growth failure, brain abnormalities, and cardiac defects, all of which have been previously reported in some cases (Hofmann et al., 2011; Palomares et al., 2011). Focusing on the facial dysmorphia, our patient shared some features, including a high forehead, underdeveloped alae, micrognathia, and low-set ears. However, he presented other distinctive dysmorphic features because he had an elongated rather than round face, as reported by Quintela et al. (2015). His ears were not prominent, and he had neither a wide nasal bridge nor epicanthal folds. Interestingly, our patient, as well as two other patients in whom the identified deletions did not disrupt the *ZFHX4* gene, did not show ocular abnormalities (Decipher ID: 285918; Heide et al., 2017). These data provide further evidence for the implication of the *ZFHX4* gene in the ocular features of this syndrome (Happ et al., 2016; Heide et al., 2017; Palomares et al., 2011).

The alignment of our case with all 19 previously reported overlapping deletions that we collected delineated a new SRO in 8q21.13 region (chr8:79647725–80520882; Figure 3). This region contains five genes OMIM: *HEY1*, *MRPS28*, *STMN2*, *TPD52*, and *ZBTB10*. A higher rank of HI [0–10%] was noted within the *STMN2* and *HEY1* genes (Figure 3).

Based on the literature and expression data, we particularly focused on the *HEY1* gene. In fact, the hairy/enhancer of split related to the YRPW motif 1 (*HEY1*) gene (OMIM#602953) encodes a transcription factor belonging to the hairy and enhancer of split related (HESR) family of basic helix–loop–helix (bHLH) type. Numerous studies have demonstrated that *HEY1* plays a key role in Notch signaling as transcriptional repressors implicated in the development of various tissues, including bone, nerve, heart, muscle, and vascular tissues. It is also known to be linked to the maintenance of neural stem cells, inhibition of oligodendrocyte differentiation, and myelin gene expression (Fischer et al., 2004; Liu et al., 2006; Massari & Murre, 2000; Steidl et al., 2000). The Hey1 protein was highly expressed in the hypothalamus, hippocampus, thalamus, and cerebellum during embryonic and adult periods. It has been recently reported that Hey1 is expressed in radial glial cells under Notch3 control, maintains proliferating neural progenitors and controls neural stem

**TABLE 1** Clinical evaluation of our patient with a 9.6 Mb interstitial 8q21.11–21.3 deletion as well as of 19 cases that overlap with this region reported from the literature and Decipher database

ID	Palomares et al. (2011)						Quintela et al. (2015)	Happ et al. (2016)	Hofmann et al. (2011)
	P.1	P.2	P.3	P.5	P.6	P.7	Reported patient	P.1	Reported patient
Gender	M	F	M	M	F	F	M	F	M
Age (years)	7	6	6	16	13	15	9	6	12
Growth failure	ND	+	–	–	–	+	+	–	–
Neurologic findings									
Hypotonia	+	+	+	+	–	+	–	+	+
ID/DD	+	+	+	+	+	+	+	+	–
Behavior disorders	+	+	AU	–	UP	–	–	–	Timid
Cerebral abnormalities	UCC, GA	DM	UCC GA, DM	NI	NI	UCC	VA	UCC WML	ND
Dysmorphic features									
Round face	+	+	+	+	SQ	+	EL	–	+
High forehead	+	+	+	+	+	–	+	+	+
Hypertelorism	–	+	ND	–	+	–	–	–	+
Downslanting fissures	–	+	+	+	–	+	Upslanting	–	–
Short palpebral fissures	+	+	+	–	+	+	+	–	–
Epicanthus folds	+	–	+	+	+	+	–	–	+
Wide nasal bridge	+	+	+	–	+	–	–	–	+
Under-developed alae	+	+	+	+	+	–	+	–	+
Short philtrum	+	+	+	–	+	+	+	–	+
Cupid's bow	+	+	+	–	+	+	+	+	–
Down-turned corners mouth	+	+	+	+	+	–	ND	–	–
Highly arched palate	ND	+	–	–	+	–	–	–	+
Micrognathia	+	+	+	+	+	–	+	–	–
Prominent, low-set ears	+	+	+	+	+	+	+	+	+
Short neck	+	+	+	+	–	–	–	–	+
Cardiac malformations	CM	–	–	–	–	–	ASD, OS	PDA	SD
Ophthalmologic anomalies	Mi, SC, C, S	PR, S	Mi, SC	SC,S	+	D,S	MY, As	Mi, CO	S
Hands/feet anomalies	+	+	+	+	+	+	+	–	+

Abbreviations: Ab, abnormal; As, astigmatism; ASD, atrial septal defect; AU, autism; C, cataract; CA, cerebral atrophy; CM, cardiomyopathy; CO, corneal opacity; DCC, dysgenesis corpus callosum; DD, developmental delay; DM, decreased myelination; EL, elongated; F, female; ID, intellectual disability; M, male; Mi, microphthalmia; My, myopia; ND, not determinate; Ny, nystagmus; OS, ostium secundum; P, patient; PDA, patent ductus arteriosus; PR, pigmentary retina degeneration; RD, retinal detachment; S, strabismus; SC, sclerocornea; SQ, square; UCC, underdeveloped corpus callosum; UP, unusual pleasant; WML, white matter loss.

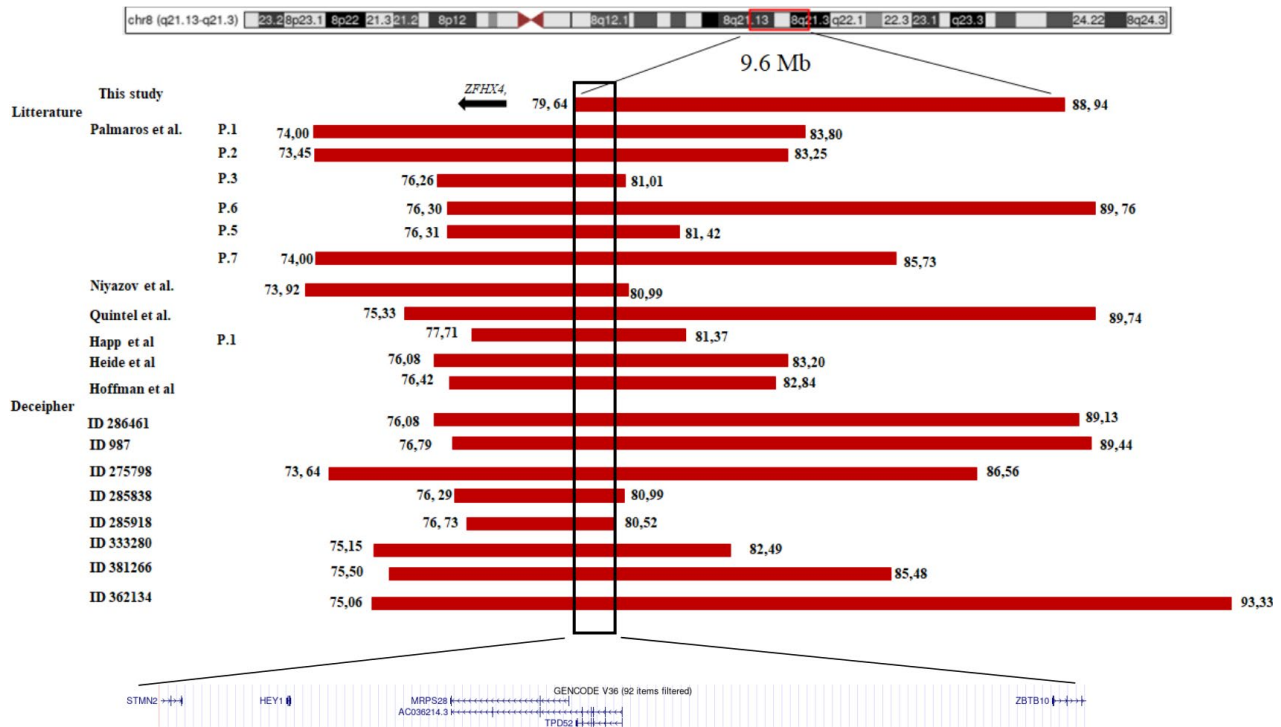
cells stemness in the vertebrate adult (Than-Trong et al., 2018). Heide et al. (2017) suggested that *HEY1* represents a candidate gene implicated in ID and corpus callosum abnormality. According to our comparative analysis with the 19 reported cases, we noted that almost all patients with *HEY1* deletion (18/19) presented variable degrees of

ID, and at least 11/19 patients presented agenesis/hypoplasia of the corpus callosum or other brain abnormalities such as gyration defects and decreased myelination. Furthermore, we observed that our patient, in addition to 5/20 patients, showed unusual behavior and/or autism spectrum disorder. In fact, *HEY1* was identified as one of

Heide et al. (2017))	Africk (2015)	Decipher ID								Our case
Reported patient	Reported patient	987	285918	333280	381266	285838	286461	275798	362134	Reported patient
M	F	F	M	F	F	M	F	F	M	M
ND	12	ND	ND	ND	ND	ND	ND	ND	ND	6
ND	+	ND	+	ND	ND	-	-	-	+	+
ND	+	ND	+	+	ND	-	+	+	ND	+
+	+	+	+	ND	+	+	+	+	+	+
ND		-	-	-	-	-	-	-	-	UP
UCC	CA	ND	UCC	ND	ACC	UCC	-	ND	ND	UCC, CA
ND	ND	ND	ND	ND	Ab. Shape face	-	+	ND	ND	EL
ND	ND	ND	+	ND	ND	+	ND	+	ND	+
ND	ND	ND	ND	ND	ND	hypothelormism	ND	-	ND	-
ND	ND	ND	+	ND	ND	-	ND	-	ND	-
ND	ND	ND	ND	ND	ND	+	ND	-	ND	-
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	-
ND	ND	ND	ND	ND	ND	ND	ND	-	+	+
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	-
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	-
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	-
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	+
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	+
ND	ND	ND	+	ND	ND	ND	ND	-	ND	+
ND	ND	ND	ND	ND	ND	ND	ND	-	ND	+
ND	+	CM	-	ND	ND	ND	ND	ASD	ND	ASD, OS
ND	ND	ND	-	ND	+	+	ND	Ny,	Mi,RD	-
ND	ND	ND	+	ND	-	ND	ND	+	+	+

the dysregulated genes in the autism spectrum disorder involved in the Notch signaling networks as well as in Williams syndrome, which is known to be associated with unusual pleasantness (Corley et al., 2016; Ghahramani Seno et al., 2011). Moreover, *Hey1* knockout mice exhibited behavioral alterations through the dopaminergic

nervous system, and previous studies suggested that *HEY1* plays a key role in the expression of the human dopamine transporter (*DAT1*) gene, which is involved in neuropsychiatric disorders and behavioral traits (Fuke, 2005; Fuke et al., 2006). Taken together, all these data provide further evidence that *HEY1* is an interesting candidate gene



**FIGURE 3** Schematic representation of deletions in our patient and 19 patients from the literature and Decipher database overlapping with the reported deletion. Red bars represent the deletion sizes. The smallest region of overlap (SRO) is marked by vertical lines (chromosome 8:79647725–80520882). The Ref Seq genes are shown using UCSC Genome Browser (GRCh38)

that can be implicated in the neurological defects of the 8q21.11 microdeletion syndrome.

In addition to the neurological development, our patient showed an atrial septal defect, as already reported in 7/19 cases. Interestingly, the gene ontology annotation (<http://geneontology.org/>) of all genes encompassed in the reported deletion showed that *HEY1* is the only gene implicated in both cardiac embryogenesis and neuron differentiation (Table S2). In fact, *HEY1* gene is required for embryonic vascular development, cardiac septum morphogenesis, circulatory system development, and cardiac epithelial to mesenchymal transition (Fischer et al., 2004; Rutenberg et al., 2006). Thereby, *HEY1* deletion can explain the cardiovascular defect in 8q21.11 microdeletion syndrome, as previously advanced by Hoffman et al. (Hofmann et al., 2011).

The *STMN2* gene (Stathmin 2, OMIM#600621), which codes for a neuronal growth-associated protein encoding a microtubule regulator, is overexpressed in all brain areas at embryonic and adult stages. *STMN2* loss accelerates a neuronal degeneration program; therefore, it has been proposed as an axonal maintenance factor (Graf et al., 2011; Mori & Morii, 2002; Riederer et al., 1997). For young adult stathmin knockout mice, no neurodevelopmental phenotype has been observed with no neurological or behavioral deficits (Schubart et al., 1996). However, aged stathmin mutant mice developed a late-onset axonopathy

of both the peripheral and central nervous system (Liedtke et al., 2002). Therefore, we suggest that *STMN2* haploinsufficiency does not contribute to the ID or behavioral abnormalities associated with the 8q21.11 microdeletion syndrome; however, it would be considered a risk factor for developing neurodegenerative diseases (Glass, 2020).

On the other hand, previous studies have shown that genes within the 8q21, but outside the critical region characterizing this syndrome, may be involved in dentition and bone metabolism. In fact, *STMN2*, together with *IL7* and *PAG1*, have recently been identified as being expressed in the periodontal ligament (Chang et al., 2015; Lee et al., 2013; Pinkerton et al., 2008). Interestingly, normal dentition was noted in our patient, suggesting that *IL7*, not included in our deletion, would be more likely to contribute to the occurrence of the dentition anomalies. In addition to genes involved in SRO, the *PMP2* (peripheral myelin protein 2, OMIM# 170715) gene is known to be implicated in demyelinating Charcot–Marie–Tooth neuropathy (CMT1). Despite previous studies showing that the overexpression of human *PMP2* wild type causes mild pathfinding errors of axons, suggesting dose sensitivity for *PMP2*, the correct implicated mechanism is currently unknown (Gonzaga-Jauregui et al., 2015). The last follow-up of our patient, at age 6, did not reveal an appropriate neurologic feature of CMT, whereas electromyography (EMG) studies provided a normal profile. Nevertheless,



our patient should have regular follow-up visits to allow early detection of difficulties in walking and distal sensory impairment.

In conclusion, 8q21.11 microdeletion syndrome is associated with a wide range of clinical presentations, with an extreme end presenting neurological, eye, cardiac, dentition, and hand/foot development defects. Here, we report the first case of deletion in 8q21.11–21.3 that does not encompass the *ZFHX4* gene, reporting all the clinical details of this patient. It is important to note that, to date, *ZFHX4* represents the only candidate gene of the 8q21.11 microdeletion syndrome, suggested to be implicated in the ocular findings. The alignment of our case with all previously reported overlapping deletions delineated a new SRO in the 8q21.13 region involving five genes, one of which is *HEY1*. According to our findings, and considering its expression profile and function, we suggest *HEY1* as a new candidate gene explaining both the neurological and cardiac features in 8q21.11 microdeletion syndrome. This study will help to better understand the specific components of the pathophysiology of this syndrome that have not been explained so far.

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## CONFLICT OF INTEREST

The authors declare whether or not there are any competing financial interests in relation to the work described.

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