

15q26 Deletion in a Patient with Congenital Heart Defect, Growth Restriction and Intellectual Disability: Case Report and Literature Review

Yahya BENBOUCHTA (✉ benbouchtayahya@yahoo.fr)

FSR

Nicole de Leeuw

Department of Human Genetics,Radboud university

Saadia Amasdl

Département de Genetique Médicale ,Institut National d Hygiène Rabat

Aziza Sbiti

Département de Genetique Médicale,Institut National d Hygiène Rabat

Dominique Smeets

Department of Human Genetics,Radboud University ,Medical Center NIGMEGEN

Abdelaziz Sefiani

Universite Mohammed V de Rabat Faculte de Medecine et de Pharmacie Rabat

Khalid Sadki

Université Mohammed V de Rabat Faculté des Sciences: Université Mohammed V de Rabat Faculte des Sciences

Case report

Keywords: 15q26 deletion, CHD, Array CGH, Case report

Posted Date: October 30th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-34129/v2>

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Version of Record: A version of this preprint was published at Italian Journal of Pediatrics on September 16th, 2021. See the published version at <https://doi.org/10.1186/s13052-021-01121-5>.

Abstract

Background 15q26 deletion is a relatively rare chromosomal disorder described in only few cases. Patients with this aberration display numerous symptoms particularly, pre- and postnatal growth restriction, microcephaly, intellectual disability, dysmorphic gestalt and various congenital malformations.

Case presentation We report on a girl, four years old, of consanguineous parents, with a de novo 15q26 deletion. Clinical manifestations included failure to thrive, microcephaly, dysmorphic facies with broad forehead, hypertelorism, narrowed eyelid slits and protruding columella. The patient also showed skeletal abnormalities, especially clinodactyly of the 5th finger, varus equine right foot and left club foot. Additionally, she had teething delay and divergent strabismus. Heart ultrasound displayed a left-to-right shunt, two atrial septal defects, enlarging the right heart cavities. Routine cytogenetic analysis revealed a shortened 15 chromosome with an abnormally short ended long (q) arm. Subsequent array analysis disclosed a terminal 9.15 Mb deletions detected in band 15q26.1-q26.3. Five candidate genes associated with 15q26 deletion phenotype were within the deleted region, i.e. *IGF1R*, *NR2F2*, *MEF2A*, *MCTP2*, and *CHD2*.

Conclusion 15q26 monosomy should be considered when growth retardation is associated with ear anomaly, clinodactyly and/or abnormal toe, heart defect mainly atrioventricular septal defects (AVSDs) and/or aortic arch anomaly (AAA).

Introduction

15q26 monosomy can occur either as a de novo event leading to a pure deletion or as a consequence of ring chromosome 15 formation and unbalanced translocation. Up to now, 58 cases of pure deletion have been documented in the literature (1, 2). The sub-bands involved in this rearrangement include many candidate genes responsible for common symptoms, especially pre and postnatal growth retardation (3), developmental delay, microcephaly. Others genes were involved in more particular features like Congenital Heart disease (CHD) (4), skeletal anomalies (5), diaphragmatic hernia (6), kidney anomalies (1) and seizures (7). This variability could be assigned to the difference in breakpoint location and the size of the deleted fragment. Recently, several authors focused on some particular regions especially the report of Klasseens et al. which restricted the critical region for congenital diaphragmatic hernia (CDH) to 4 Mb at 15q26.1-q26.3 Band. Thus two annotated genes namely *NR2F2* (MIM 107773) and *CDH2* (MIM 602119), were considered to be relevant for CDH (8). Other genes have been reported as playing crucial role in pathogenesis of 15q26 deletions, particularly *IGF1R*, *CHD2*, *NR2F2*, involved respectively in growth restriction (3), neurodevelopmental disorders (9), and CHD (4).

Herein we report a further patient with CHD, intellectual disability and failure to thrive. Array CGH displayed a terminal 9.15 Mb deletion spanning 15q26.1-q26.3, encompassing 36 annotated genes including

(*ASB9P*, *CHD2*, *RGMA*, *BCO37497*, *MCPT2*, *LOC440311*, *NR2F2*, *SPATA8*, *LINC00923*, *ARRDC4*, *FAM169B*, *IGF1R*, *SYNM*, *TTC23*, *LRR28*, *HSP90B2P*, *MEF2A*, *DNM1P46*, *A*, *TARSL2*, *BC101079*, *OR4F6*, *OR4F15*, *OR4F13P*). Five relevant disease genes, i.e. *IGF1R*, *NR2F2*, *MEF2A*, *MCTP2*, *CHD2* were involved and are directly related to the clinical presentation of our case.

Until now, no patient had a deletion of this exact size. There was also no similar work in the literature that had already focused on the types of CHD assigned to the 15q26 deletion with the different genotype-phenotype correlations.

Case Report

The proband, a four-year-old girl, came to our attention because of atypical face and heart malformation. She was the only child of healthy, consanguineous parents. There were no health problems in the family or a history of miscarriages. She was born at term by Cesarean section after a history of intrauterine growth restriction (IUGR) associated with oligoamnios. IUGR was noted since the fourth month of pregnancy without that maternal or placental causes have been identified. Her birth weight was 950 g (< 3rd centile). Clinical history was suggestive of psychomotor delay and congenital hypotonia. Upon clinical examination, her weight was 8 kg

(< 3rd centile), height 81 cm (< 3rd centile) and head circumference 43 cm (< 3rd centile). She had dysmorphic features including a broad forehead, hypertelorism, narrowed eyelid slits, low set ears, protruding columella, and a short neck. She also presented with skeletal abnormalities, especially clinodactyly of the 5th finger, right foot varus equine, left club foot, biphalangeal fifth finger, and widely-spaced toes. Additionally, she had teething delay and divergent strabismus. Chest X-ray showed a dorsal scoliosis and enlarged cardiac silhouette with a cardiothoracic ratio of 70%. An echocardiogram displayed a left-to-right shunt of good flow, presence of two atrial septal defects of 1 cm and 7 mm in width, dilating the right heart cavities and the pulmonary artery trunk with normal right pressures. Her bone age was two years at a chronological age of four years. Screening for endocrinological deficits showed normal serum concentrations of T4, TSH, GH, and IGF 1. Ocular assessment and brainstem acoustic potential evaluation revealed divergent strabismus and sensorineural hearing loss, respectively. Further investigations including calcemia, brain MRI, computed tomography of the brain and abdominal ultrasound were normal

Methods And Results

Cytogenetics

Chromosome slides were prepared from cultured peripheral blood lymphocytes of the proband and her parents after obtaining informed consent. RHG-banding and high resolution R-banded chromosome analysis was performed on the three samples according to standard procedures. Both parents displayed normal karyotypes.

Cytogenetic studies of the child showed an abnormal female karyotype with an apparently terminal deletion of the long arm of one chromosome 15 (Figure. 1). The patient's karyotype was designated as 46,XX,?del(15q)dn.

Array analysis

After disclosing the chromosomal aberration in the child, a genome wide array analysis was performed using the CytoScan HD SNP-based array platform (Affymetrix, Inc., Santa Clara, CA, USA) with an average resolution of approximately 20 kb following the manufacturer's protocols. Inherent to the structure of the human genome, this resolution is not achieved for all regions such as the centromeric regions and heterochromatic parts.

Genome wide array analysis confirmed the cytogenetic results and mapped the terminal deletion to a 9.15 Mb region encompassing 36 annotated genes with the proximal breakpoint at 93,275,228 Mb in band q26.1. (Figure. 2)

Based on these results, the final karyotype was designated as 46,XX,del(15)(q26.1)dn.arr[GRCh37] 15q26.1q26.3(93,275,228-102,429,113)x1

In addition to this terminal loss of chromosome 15, several homozygous regions were detected (164 Mb of the autosomal genome (~5.6 %)), which is in agreement with the indicated consanguinity of the parents.

Discussion And Conclusion

Here we report a further case of "pure" terminal deletion 15q26 associated with complex CHD. Fifteen other cases with such aberration and CHD were previously described. Table 1 summarizes clinical and cytogenetic data in these patients and ours.

Clinical findings	Our case	Dateki 2011 (13)	Poot 2007 (15)	Tönnies 2001 (30)	Nakamua 2011 (4)	Slavotinek 2006 (6)		Hengstschlagr 2004 (31)	Bhakta 2005 (32)	Rump 2008 (33)
						Patient 1	Patient 2			
Age	4y	13y 9m	8y 6m	19 m	33 weeks	newborn	newborn	newborn	newborn	6 m
Gender	F	F	F	F	F	F	F	F	F	M
Position of 15q26 deletion	15q26.1qter	15q26.2qter	15q26.2qter	15q26.1	15q26.2	15q26.2	15q26.2	15q26.1qter	15q26.1qter	15q26
Deletion size	9,15Mb	5 Mb	6,87Mb	NA	5,78 Mb	NA	NA	NA	NA	5.8 Mb
Origin	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	NA	<i>De novo</i>	NA	<i>De novo</i>	NA	<i>De novo</i>
IUGR	+	-	+	+	+	NA	NA	+	+	-
Microcephaly	+	-	+	+	+	+	+	-	+	+
Failure to thrive	+	+	+	+	+	+	+	+	+	+
Psychomotor delay	+	NA	+	+	+	NA	NA	NA	+	+
Intellectual disability	+	+	-	NA	NA	NA	NA	NA	NA	+
Facial dysmorphic features	+	-	+	+	+	-	+	+	+	+
Broad nasal bridge	+	-	-	+	NA	NA	+	NA	+	+
Micrognathia	+	-	+	+	+	NA	+	NA	NA	-
Ear anomaly	+	-	-	+	+	-	+	+	+	+
Eye anomaly	+	-	+	-	NA	NA	NA	NA	NA	+
Cardiac defect	+	+	+	+	+	+	+	+	+	+
Hypoplastic heart	-	-	-	-	-	+	-	-	-	-
Enlarged heart	+	-	-	-	-	-	-	-	-	-
Cardiac shunt	+	-	-	-	-	-	-	-	-	+
Aortic arch anomaly	-	-	-	+	-	+	+	+	+	-
Ventricular septal defect	-	+	-	+	+	+	+	+	+	-
Patent ductus arteriosus	-	-	-	+	-	-	+	-	+	-
Atrial septal defect	+	-	+	+	+	-	+	-	-	+
Valvular defect	-	-	+	-	-	+	+	-	+	-
Lung hypoplasia	-	-	-	-	-	+	+	-	+	-
Diaphragmatic hernia	-	-	-	-	-	+	+	+	-	-
Kidney anomalies	-	-	-	+	+	-	+	+	+	-
Skeletal anomalies	+	-	+	-	+	+	+	+	+	+
Clinodactyly	+	-	+	-	-	-	-	-	+	-
Foot deformity	+	-	-	-	-	+	-	+	+	+
Toe anomaly	+	-	+	-	+	-	-	-	+	+

Table 1: Clinical and cytogenetic data in patients with “pure” 15q26 deletion and CHD:

Our proband share many relevant symptoms with others especially pre and post natal growth retardation, developmental delay, skeletal anomalies, microcephaly, micrognathia and ear anomaly. In addition eye anomalies were observed less frequently. Less common features were found in some cases including kidney anomaly, CDH and lung hypoplasia; however this was lacking in our patient. Through this table, we also note that the CHD was most often complex with several concomitant abnormalities and so was our patient. among the major cardiac defect are ASD/VSD and aortic arch anomaly. Valvulopathy, patent ductus arteriosus, cardiac shunt and hypoplastic heart were irregularly described. Our patient shared some of this anomalies namely ASD and cardiac shunt, however she lacked VSD, AAA and valvular defect. Cardiomegaly was an unusual feature reported exclusively in our patient. Indeed the atrial septal defect resulted in the formation of significant shunts, which led to volume overload of the right atrium and ventricle and consequently our patient developed cardiomegaly.

Array analysis allowed us to characterize a *de novo* 9.15 Mb deletion within the 15q26.1-q26.3 region. Comparable aberrations are often reported as *de novo*. Most often, terminal 15q deletions are found in combination with a terminal duplication of another chromosome due to an unbalanced translocation. To the best of our knowledge and according to the DECIPHER database, a deletion of this specific size has not been reported previously. Based on the Genome Data viewer (<https://www.ncbi.nlm.nih.gov/genome/gdv/>), the deleted segment encompasses thirty six HGNC genes, nineteen of them are referenced in the OMIM database, among which only *IGF1R*, *MCTP2*, *NR2F2*, *CHD2* and *MEF2A* are consistent with the phenotype described in our proband: (Figure. 3)

NR2F2 (Nuclear *NR2F2* (Nuclear Receptor Subfamily 2, Group F, Member 2) (MIM 107773), located at 15q26.2 locus, is involved in angiogenesis and heart development (10). Indeed, *NR2F2* haploinsufficiency in patients with a 15q26 deletion appears to be associated with heart malformations (11). In addition, variants within the *NR2F2* gene were found to cause non-syndromic atrioventricular septal defects (AVSDs) and other heart defects as well (12). Moreover, this gene has been implicated to be involved in some patients with diaphragmatic hernia (6, 13), but this was not reported in others (14, 15) nor present in our patient.

MEF2A (Mads Box Transcription Enhancer Factor 2, Polypeptide A) (MIM 600660), mapped to the human chromosome 15q26.3 region, is member of the myocyte enhancer family of transcription factors (MEF2) (16). The sub unit *MEF2A* is expressed in endothelial and smooth muscle cells of coronary arteries. Subsequently *MEF2A* mutations can disturb the growth or differentiation of these cells, increasing the risk of developing coronary artery disease (CAD)/ myocardial infarction (MI) (17, 18). CAD/MI was not evident in patients with 15q26 deletion involving *MEF2A*. This could be explained by the relatively young age of these patients compared to others described by Wang and Bhagavatula whose age of diagnosis was between 36 and 80 years (17, 18). Therefore, regular checking up would be useful from the third decade onwards in these patients.

MCTP2 (Multiple C2 Domains-Containing TransmembraneProtein 2) (MIM 616297) is mapped to 15q26.2 and encodes a Multiple C2 domain and transmembrane region protein (TMRs) (19). Previous studies found that disruption of this gene was associated with congenital left heart obstructive cardiac defects in humans (20); this was observed in two half siblings with coarctation of the aorta (CoA) and a 15q26 deletion encompassing *MCTP2* gene (20). A further patient was described with an intragenic duplication of *MCTP2* in association with CoA and hypoplastic left heart (20).

IGF1R (insulin like growth factor 1 receptor) (MIM 147370) lies on the 15q26.3 locus. it is bound to the growth factor ligands IGF1 and IGF2 to play a key role in pre- and post-natal development (21, 22). The crucial impact of *IGF1R* on growth processes was underlined by the growth restriction found in individuals with pathogenic variants in the *IGF1R* gene (3, 23), in addition to patients with a 15q26 deletion leading to haploinsufficiency (24). To the best of our knowledge, no heart anomalies have ever seen in patients carrying IGF1 or *IGF1R* mutations nor in knockout mice lacking these genes. Therefore, it is unlikely that the onset of CHD is only caused by haploinsufficiency of the *IGF1R* gene (4).

CHD2 (Chromodaine helicase DNA-binding protein) belongs to a family of ATP-dependant chromatin remodeling proteins known for being important in chromatin regulation (25). Mutations in this gene were associated with severe non-syndromic intellectual Disability (26), as well as epileptic encephalopathy (27). Additionally, disruption of *CHD2* was associated with scoliosis in murine models (28). Interestingly, this anomaly was observed in our patient as well as a few in the literature (9, 15, 29). These findings together highlight the involvement of *CHD2* dysfunction in neurodevelopmental disorders and scoliosis.

To sum up .This work focused on the main genes whose haploinsufficiency could explain heart disease in patients with 15q26 monosomy, i.e. the *NR2F2* and *MCTP2* genes involved respectively in AVSDs and AAA/hypoplastic left heart. Scoliosis and mental retardation in our patient would be explained both by the *CHD2* gene disruption. The phenotype in our patient could also be ascribed to the high rate of homozygous regions outlined by the CGH array, without excluding the possible contribution of epigenetic and environmental factors as well. 15q26 monosomy should be considered when growth retardation is associated with clinodactyly and/or abnormal toe, heart defect mainly ASD/VSD and/or AAA. Care in patients with 15q26 deletion must be multidisciplinary with endocrinological follow-up and a possible GH therapy (30), cardiovascular surgery cure, regular heart assessment, Neurosurgical treatment for scoliosis, Orthopaedic care, Psychomotor follow-up, speech therapy, educational and behavioral therapy.

Abbreviations

CHD: Congenital Heart disease

CNV: Copy number variations

NR2F2: Nuclear Receptor Subfamily 2, Group F, Member 2

AVSDs: Atrioventricular septal defects

MEF2A: Mads Box Transcription Enhancer Factor 2, Polypeptide A

CAD/ MI: Coronary artery disease/ myocardial infarction

MCTP2 : Multiple C2 Domains-Containing Transmembrane Protein 2

CoA: Coarctation of the aorta

IGF1R: Insulin like growth factor 1 receptor

Wg : Week of gestation

IUGR: intrauterine growth restriction

Declarations

Ethics approval and consent to participate.

Ethical approval is considered unnecessary according to national provisions. This report was not presented as a research study as all family members were seen in a medical consultation for diagnostic purposes and they gave their written consent to participate and benefit from the this analysis

Consent for publication

This family gave written consent for clinical data to be published

Availability of data and materials

All data is contained in the manuscript

Competing interests

The authors declare that there are no conflicts of interest

Funding

Study has no funding source

Authors' contributions

YB and SA carried out the cytogenetic study and drafted the manuscript. NL and DS carried out the molecular cytogenetic study and revising the work critically for important intellectual content. AS participated in the cytogenetic study and revised the manuscript. KS and AS participated in the design of the study and in the draft of the manuscript. All authors read and approved the final manuscript..

Acknowledgements

We thank the patient's parents for their gracious participation and support

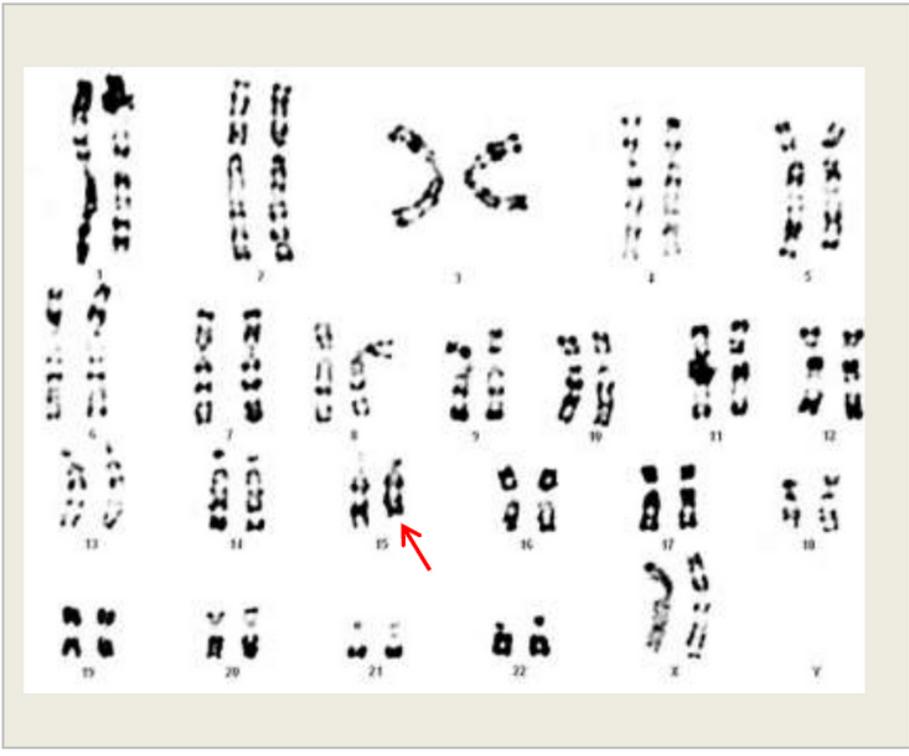
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Figures

a



b



c

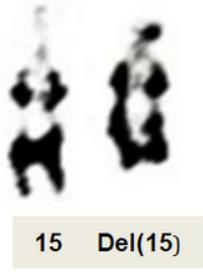


Figure 1

High-resolution R-banded karyogram (a,c), partial RHG (b) karyogram (c) showing deletion 15q chromosome with an abnormally short q-arm. (Red arrow)



Figure 2
 A. CGH-array data showing a terminal loss of 9.15 Mb in 15q26.1-q26.3 involving 93,275,228-102,429,113 breakpoints. B. UCSC genome browser assembly (GRCh37/hg19) highlighting genes involved in the loss segment

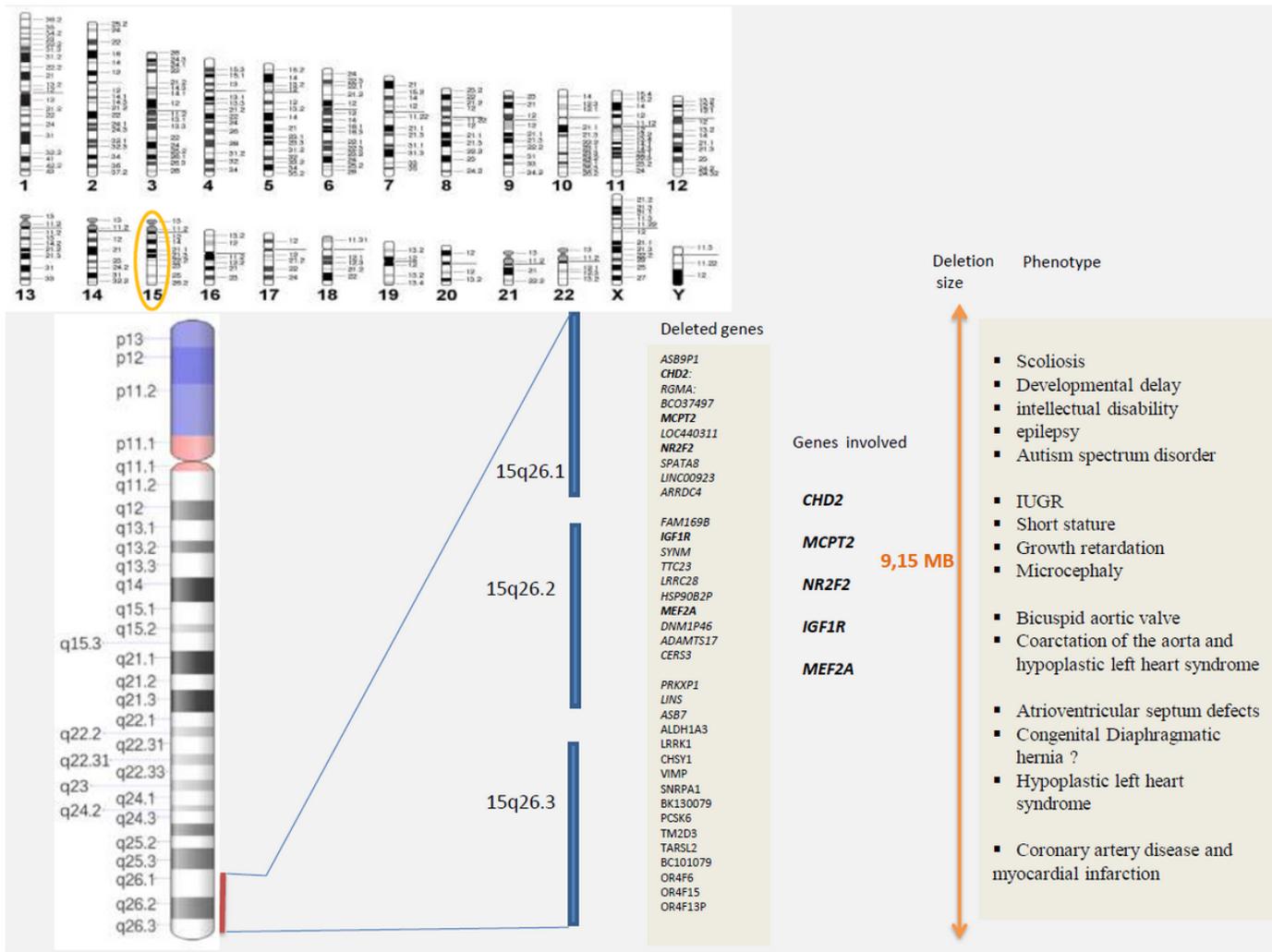


Figure 3

15q26.1-q26.3 deletions displaying the thirty-six missing genes together with the five genes involved in the Phenotype in our proband

Supplementary Files

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