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15q24.1 BP4-BP1 microdeletion unmasking paternally inherited functional polymorphisms combined with distal 15q24.2q24.3 duplication in a patient with epilepsy, psychomotor delay, overweight, ventricular arrhythmia

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ABSTRACT

15q24 microdeletion and microduplication syndromes are genetic disorders caused by non-allelic homologous recombination between low-copy repeats (LCRs) in the 15q24 chromosome region. Individuals with 15q24 microdeletion and microduplication syndromes share a common 1.2 Mb critical interval, spanning from LCR15q24B to LCR15q24C. Patients with 15q24 microdeletion syndrome exhibit distinct dysmorphic features, microcephaly, variable developmental delay, multiples congenital anomalies while individuals with reciprocal 15q24 microduplication syndrome show mild developmental delay, facial dysmorphism associated with skeletal and genital abnormalities. We report the first case of a 10 year-old girl presenting mild developmental delay, psychomotor retardation, epilepsy, ventricular arrhythmia, overweight and idiopathic central precocious puberty. 180K array-CGH analysis identified a 1.38 Mb heterozygous interstitial 15q24.1 BP4-BP1 microdeletion including *HCN4* combined with a concomitant 2.6 Mb heterozygous distal 15q24.2q24.3 microduplication. FISH analysis showed that both deletion and duplication occurred *de novo* in the proband. Of note, both copy number imbalances did not involve the 1.2 Mb minimal deletion/duplication critical interval of the 15q24.1q24.2 chromosome region (74.3–75.5 Mb). Sequencing of candidate genes for epilepsy and obesity showed that the proband was hemizygous for paternal A-at risk allele of *BBS4* rs7178130 and *NPTN* rs7171755 predisposing to obesity, epilepsy and intellectual deficits. Our study highlights the complex interaction of functional polymorphisms and/or genetic variants leading to variable clinical manifestations in patients with submicroscopic chromosomal aberrations.

1. Introduction

15q24 microdeletion and microduplication syndromes are rare genetic disorders. The 15q24 chromosome region is flanked by five segmental duplication blocks (SD) from centromere to telomere named LCR15q24A (BP4), LCR15q24B (BP1), LCR15q24C, LCR15q24D (BP2) and LCR15q24E (BP3) which have been implicated in the 15q24 chromosome rearrangements via non allelic homologous recombination. Submicroscopic deletions of 15q24 chromosome region were first described in a series of four patients with variable developmental delay, microcephaly, facial dysmorphism, abnormal growth, digital abnormalities, joint laxity and hypospasdias (Sharp et al., 2007). To date, more than thirty such cases have been reported (Samuelsson et al., 2015). Patients with 15q24 microdeletion share a common 1.2 Mb chromosome region, spanning from LCR15q24B to LCR15q24C, encompassing seven OMIM genes: *CYP11A1*, *SEMA7A*, *CPLX3*, *ARID3B*, *STRA6*, *SIN3A* and *CSK*. Such recurrent deletions occurred as a *de novo* event in most cases. Most individuals with 15q24 microdeletion had the typical 3.1 Mb deletion located between LCR15q24A and LCR15q24D while the remaining cases carried the smaller deletion of approximately 2.6 Mb extending from LCR15q24A to LCR15q24C. Moreover, rare atypical individual 15q24 losses with only one or no breakpoints within segmental duplications have also been recorded (Mefford et al., 2012). In addition, several cases with reciprocal 15q24 microduplication involving the minimal deletion critical region have been currently reported and the same 1.2 Mb SRO has been defined. Patients harboring 15q24 microduplication syndrome show some common clinical features including mild developmental delay, facial dysmorphism, skeletal and genital abnormalities. Recently, novel microduplications distal to the 15q24 minimal deletion critical region have been documented in individuals with neurodevelopmental disorders. Most duplications are inherited from an apparently normal parent (Table 1). To the best of our knowledge, only two families with distal 15q24 microduplication adjacent to minimal critical region presenting developmental delay, dysmorphic features and autistic traits have been reported (El-Hattab et al., 2009; Roetzer et al., 2010) (Supplemental Fig. S1). We report the first case of a 10 year-old girl who presented psychomotor retardation, cardiac arrhythmia, overweight, epilepsy and central precocious puberty, carrying a 1.38 Mb 15q24.1 BP4-BP1 microdeletion with a concomitant 2.6 Mb distal 15q24.2q24.3 microduplication. We compare the clinical and molecular data with a review of previously reported cases and discuss candidate genes in order to enhance the knowledge on genotype-phenotype correlation in the present index-patient.

2. Clinical report

This 10 year-old girl was born at 36 weeks of gestation to healthy non consanguineous parents after an uncomplicated pregnancy. Her birth weight was 2900 g (50-90th centile for age and gender), length 45 cm (10-50th centile) and OFC 35 cm (97th centile). The family history was unremarkable, the couple already had a healthy seventeen year-old boy. The proband had mild developmental delay. She started walking at 16 months and spoke the first word at 24 months. On last assessment at the age of 10, her weight, height and OFC were respectively 39.5 kg (75-90th centile), 134 cm (25th centile) and 55.2 cm (50th centile). She was overweight with

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Table 1
Phenotype details of 15q24 microdeletion and clinical manifestations in patients with 15q24 microduplication.

15q24 microdeletions involving the 1,2 Mb minimal deletion critical interval			15q24 microduplications involving the minimal deletion critical interval	15q24 microduplications not involving the minimal deletion critical interval
Inheritance	*De novo*		Inherited from one parent	Inherited from one parent
Developmental delay	Mildly to severe delayed		Midly delayed	Midly delayed
Growth	Short stature, obesity, microcephaly, IUGR		Short stature or normal growth	Normal
Facial dysmorphism	Face	High anterior hairline, broad forehead, frontal bossing, brachycephaly, asymmetry, round face, long narrow face	Long face, low posterior hairline	Round face, plat occiput, plagiocephaly
	Eye	Sparse eyebrows, broad medial eyebrows, hypertelorism, downslanting palpebral fissures, epicanthus, strabismus	Downslanting palpebral fissures, hypertelorism, epicanthus, full puffy hooded eyelids, ptosis, strabismus, high arched eyebrows, ptosis	Hypertelorism, epicanthus, strabismus, deep set eyes, thick eyebrows
	Nose	Depressed nasal bridge, broad upturned nasal tip, broad nasal base, hypoplastic nostrils, small nose	High or broad nasal bridge	Flat nasal bridge, bulbous nose tip
	Mouth	Long smooth philtrum, small mouth, full lower lip, thin upper lip, widely spaced teeth, high palate, cleft palate, bifid uvula	Smooth philtrum, full lower lip, triangular mouth	Full lower lip, smooth philtrum and dental problems
	Ear	Thick small ears, ear lobe pit, cup-shaped protruding ears, large ears, small everted ears, hearing loss	Low set posteriorly rotated ears	Prominent ears
Nervous system	Hypotonia, myelomeningocele, hydrocephalus, wide basal cisterna on brain MRI, cerebral atrophy, thick corpus callosum, focal cortical dysplasia, hypoplastic olfactory bulbs		Hypertonia, agenesis of corpus callosum	Truncal hypotonia, lower extremities hypertonia
Genital	Hypospadias, microphallus, cryptorchidism		Hypospadias	Normal
Skeletal	Clubfeet, joint laxity, scoliosis, pes planus, genua valga		Decreased joint range of motion, joint contractures	Joint hypermobility
Digital anomalies	Small hands, overriding second toes, clinodactyly, brachydactyly, broad thumb, long slender fingers, proximally implanted thumbs, hypoplastic right thumbs, toes syndactyly, bilateral short metacarpals		Broad thumbs, blunt finger tips, hyperconvex nails, broad feet, overlapping fingers, hypoplastic nails, broad finger pads	Tapering fingers, clinodactyly of the halluces, highly positioned second toes, syndactyly
Respiratory	Recurrent ear infections, nasal speech, low tone voice, high pitched voice, hoarse voice, soft nasal speech, asthma		//	Recurrent sinusitis, bronchitis, otitis
Other	Feeding difficulties, tetralogy of Fallot, café au lait spots, hepatosplenomegaly, skin laxity, autistic features, inguinal hernia, diaphragmatic hernia, aggressiveness, delayed puberty, attention deficit hyperactivity, epilepsy, dental problems, intestinal atresia, coloboma, imperforate anus, chronic constipation		Attention deficit hyperactivity disorder, Asperger syndrome	Gastro-oesophageal disease, autistic features, behavior problems

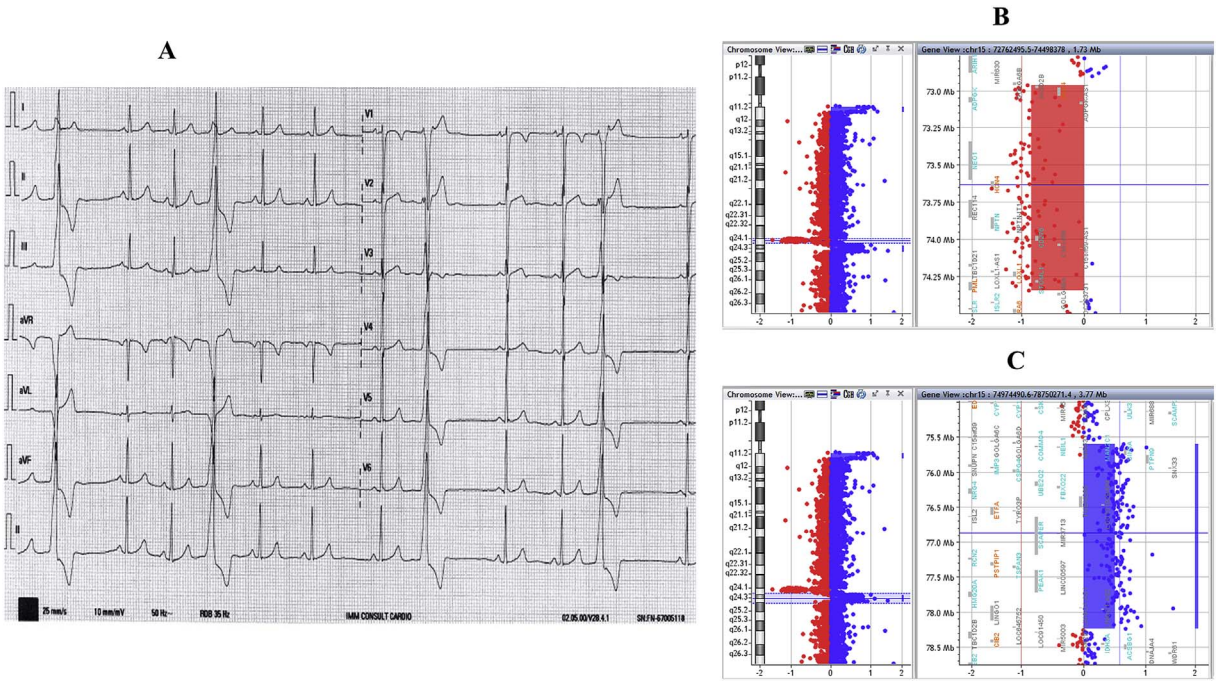

Fig. 1. A. ECG showed a pattern of premature ventricular beats with morphology of incomplete left bundle branch block, normal heart rate with 74 beats per minute and QRS axis. B. 180K array-CGH showed a 1.38 Mb heterozygous interstitial microdeletion at the 15q24.1 chromosome region with 98 probes, $\log_2$ratio = −0.84 encompassing 13 RefSeq genes and C. a 2.6 Mb heterozygous interstitial microduplication at 15q24.2q24.3 chromosome region with 201 probes, $\log_2$ratio = +0.51.

her BMI (Body Mass Index) 22 kg/m^2 (93rd centile). She also had learning difficulties, dyslexia and dysgraphia. Shortening of the fourth and fifth metacarpals was also noted. She began having her first seizure at the age of seven. Electroencephalogram (EEG) showed generalized slowdown of brain electrical activity, slow waves with high amplitude, diffuse cerebral patterns nonspecific. Her cerebral CT and MRI results were normal. Cardiac assessment revealed tachycardia with heart rate of 104 beats per minute, her arterial pressure was 112/55 mmHg, cardiac ultrasound showed a normal result. ECG (electrocardiogram) revealed frequent right premature ventricular contractions (PVC) with the morphology of incomplete left ventricular branch block (Fig. 1A). Holter ECG showed an abnormal pattern of frequent isolated, monomorphic premature ventricular contractions with 24315 PVCs per 24 hours. Idiopathic central precocious puberty with breast development and absence of pubic hair was also noticed. Endocrine assessment confirmed the diagnosis of precocious puberty with LH peak 74UI/L and FSH peak 18.2 UI/L.

3. Materials and methods

3.1. Conventional cytogenetic analysis

Blood lymphocytes were cultured in Chromosome kit P medium (EKAMT-500, Amplitech Sarl, France), metaphase chromosomes were harvested according to the laboratory protocol. Cytogenetic analysis was performed on G-banding metaphases at 400 band resolution.

3.2. Fluorescence in situ hybridization (FISH)

FISH analysis was performed on metaphases prepared from peripheral blood lymphocytes using three probes: RP11-435B9 (chr15:73,910,670–74,115,658) (FITC labeled probe) and control telomeric 15q Vysis probe (Cya3 labeled probe) for 15q24.1 microdeletion. Moreover, FISH analysis for 15q24.2q24.3 microduplication was carried out by using three probes: RP11-289H7 (Cya3 labeled centromeric probe) (chr15:76,467,873–76,669,536), RP11-338C8 (FITC labeled telomeric probe) (chr15:77,763,940–77,958,003) and control telomeric 15q Vysis probe (Cya3 labeled probe) (genomic coordinates GRCh37/hg19).

3.3. Array-CGH

180K array-CGH (Agilent technologies, Santa Clara, CA, USA) with 13 kb median probe spacing was carried out according to the manufacturer's protocol, chromosomal imbalances were detected considering a minimum of three consecutive probes with abnormal $\log_2$ ratio.

3.4. Microsatellite marker analysis

Markers for 15q24.1 microdeletion (D15S124, D15S980, D15S215 and D15S1026) and for 15q24.2q24.3 microduplication (D15S984) were amplified with corresponding primers. The amplified products were separated by capillary electrophoresis using the ABI 3130xl Genetic Analyzer (Life Technologies).

3.5. Candidate gene sequencing analysis

Mutation analysis of candidate genes in epilepsy and early childhood obesity-susceptibility locus was performed. Coding regions of *NPTN*, *C15orf59*, *NPTN* rs7171755, rs3743500, rs3826047, rs3840846, *BBS4* rs7178130 and *BBS6* rs2216667, rs6108572 were amplified with corresponding primers and sequenced on an ABI 3130xl Genetic Analyzer (Life Technologies).

4. Results

Conventional cytogenetic analysis in the proband showed a normal result 46,XX. Parental karyotypes were normal.

Array-CGH showed a 1.38 Mb heterozygous interstitial deletion at the 15q24.1 chromosome region with 98 probes, $\log_2$ratio = −0.84, containing 13 genes, arr[GRCh37] 15q24.1(72963970_74343898)x1 (Fig. 1B). In

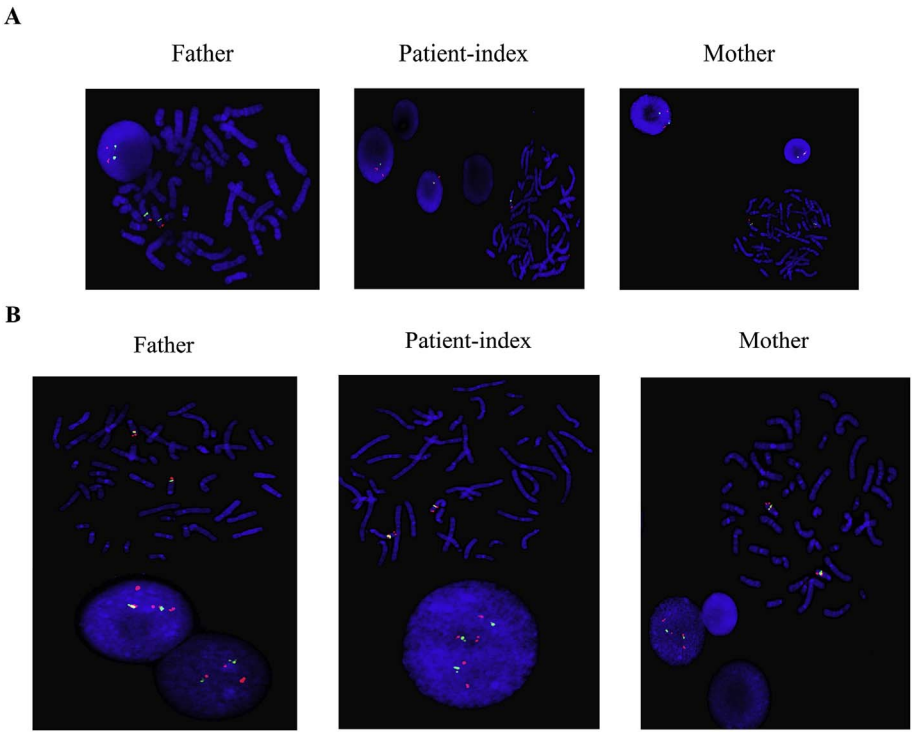

Fig. 2. A. FISH analysis with RP11-435B9 (green color) and control telomeric 15q Vysis probe (red color) showed that the deletion occurred *de novo* in the proband. B. FISH analysis with RP11-289H7 (red labeled centromeric probe), RP11-338C8 (green labeled telomeric probe) and control telomeric 15q Vysis probe (red labeled probe) showed that the duplication occurred *de novo* in the proband. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

addition, array-CGH analysis also identified a 2.6 Mb heterozygous interstitial duplication of chromosome 15q24.2q24.3, 201 probes, $\log_2$ratio = +0.51, arr[GRCh37] 15q24.2q24.3(75600108_78236552)x3 (Fig. 1C).

FISH analysis showed a *de novo* heterozygous deletion in 15q24.1 locus and *de novo* heterozygous tandem duplication in 15q24.2q24.3 chromosome region (Fig. 2A and B).

DNA marker analysis with D15S215, D15S980 and D15S1026 showed the deletion to be of maternal origin in the proband (Supplemental Fig. S2). The maternal contribution of the deletion was further confirmed by SNP marker analysis with *BBS4* rs7178130. Moreover, microsatellite marker analysis with D15S984 showed a maternal inheritance of the duplication (Supplemental Fig. S3).

Sequencing analysis showed that the index-patient was homozygous for *BBS4* rs7178130 c.-236G > A (ENST00000311755.3) and heterozygous for *BBS6* rs2216667 g.73151684T > C, rs6108572 c.-649 + 1997T > A. Additionally, the proband had a variant A-minor allele at *NPTN* rs7171755 c.637-1513G > A and haplotype T-G-G at *NPTN* rs3840846, rs3826047 and rs3743500 (Supplemental Fig. S4). Sequencing analysis of candidate gene for epilepsy showed no pathogenic mutations.

5. Discussion

Individual 15q24.1 BP4-BP1 microdeletions have never been recorded. Only one similar case (nssv579770) with the same 1.38 Mb microdeletion at 15q24.1 chromosome region was previously reported in the database dbVar but the complete clinical features have not been documented (Kaminsky et al., 2011). The proband had a *de novo* 1.38 Mb heterozygous deletion of chromosome 15q24.1, encompassing 13 RefSeq genes including *BBS4*, *NEO1*, *HCN4*, *LOXL1*, *C15orf59* and *NPTN*. *BBS4* (MIM *600374), a mutated gene in Bardet-Biedl syndrome 4, encodes a component of multiprotein BBSome complex required for ciliogenesis. Bardet-Biedl syndrome (BBS) is a pleiotropic autosomal recessive disorder associated with marked obesity and increased susceptibility to metabolic syndrome. *Bbs4*−/− and *Bbs6*−/− mouse models develop obesity associated with increased food intake. Recently, variants in *BBS4* and *BBS6* showed evidence of association with early-onset childhood obesity and common adult morbid obesity. Children homozygous for the minor A-allele of *BBS4* rs7178130 have a significant increased risk in early onset childhood obesity in a large cohort of 622 French-Caucasian obese children (Benzinou et al., 2006). The proband was hemizygous for the paternal at-risk A-allele of *BBS4* rs7178130 which confers high susceptibility for early-onset childhood obesity. *NEO1* encodes a cell surface protein, neogenin 1 which plays a pivotal role in cortical interneuron development. Homozygous *NEO1* mutations are associated with autism spectrum disorders (Siu et al., 2016). *LOXL1* (MIM *153456) is strongly expressed in all ocular tissues, *LOXL1* mutations cause autosomal dominant exfoliation syndrome with late onset characterized by severe chronic secondary open-angle glaucoma and cataract. *HCN4* predominantly expressed in heart ventricle, atrium and neurons encodes a hyperpolarization-activated channel that modulates the pacemaker potential in the sinoatrial node. Mutations of *HCN4* cause a wide spectrum of inherited arrhythmogenic diseases including Sick-sinus syndrome 2 and Brugada syndrome 8. Sick-sinus syndrome 2 (MIM #163800), an autosomal dominant inherited arrhythmic disorder characterized by atrial tachyarrhythmias, sinus bradycardia and sinus arrest (Raucci et al., 2017). Hitherto, the majority of reported *HCN4* missense variants are loss-of-function point mutations. The proband without apparent structural heart disease exhibits a significantly high right premature ventricular contraction burden of > 1000 per hour predisposing to ventricular tachyarrhythmia and PVC-induced cardiomyopathy (Latchamsetty and Bogun, 2015). Thus, we suggest that haploinsuffisance of *HCN4* can result in ventricular arrhythmia characterized by ectopic ventricular premature beats observed in the proband. Regular follow-up is mandatory and an echocardiogram should probably be performed once a year in order to detect early ventricular dysfunction or dilatation. Moreover, *C15orf59* and *NPTN* strongly expressed in brain are two potential candidate genes for epilepsy and intellectual deficits in 15q24.1 BP4-BP1 microdeletion because both of them play an important function in synaptic plasticity. A single polymorphism *NPTN* rs7171755 located less than 2 kb downstream associated with cortical thickness and intellectual abilities by modulation of *NPTN* expression was previously reported. Homozygous individuals for the minor A-allele at rs7171755 showed a reduced expression of the *NPTN* gene. The proband was hemizygous for the paternal A-at risk allele predisposing to many different types of

cognitive disorders (Desrivières et al., 2015). Additionally, sequencing of other *NPTN* SNPs (rs3743500, rs3826047, rs3840846) in the proband showed that the haplotype T-G-G of the remaining allele had slightly reduced *NPTN* transcriptional activity as compared to T-A-G haplotype (Saito et al., 2007). In addition to 15q24.1 BP4-BP1 copy number variation, the proband also had a *de novo* 2.6 Mb heterozygous microduplication at 15q24.2q24.3 chromosome region including some functionally relevant genes such as *SIN3A*, *LINGO1*, *CSPG4*, *PEAK1, ISL2* and *MAN2C1*. *SIN3A* encodes a transcriptional corepressor and mutations of *SIN3A* cause autosomal dominant Witteveen-Kolk syndrome. *SIN3A*, *LINGO1*, *CSPG4* and *PEAK1* highly expressed in brain are candidate genes for neurodevelopmental phenotype in patients with distal 15q24 microduplication. Moreover, *MAN2C1* encodes an alpha-mannosidase which plays a pivotal function in the protein glycosylation process. Overexpression of *MAN2C1* results in protein underglycosylation leading to misfolded proteins. These unstable and non-functional proteins are useless, even toxic to the cells and transported to the cytosols for Endoplasmic Reticulum associated degradation (ERAD) pathway (Bernon et al., 2011). To date, only two families with 15q24 microduplication distal to the minimal deletion/duplication critical region presenting neurodevelopmental disorders were reported, the distal 15q24 microduplications are frequently associated with reduced penetrance and variable clinical phenotype. The coexistence of both copy number changes involving 15q24.1 BP4-BP1 microdeletion and distal 15q24.2q24.3 microduplication might contribute to the neurodevelopmental delay observed in the proband. Of note, the proband did not exhibit facial dysmorphic features and both genomic copy number imbalances did not involve the minimal critical region in 15q24 microdeletion/microduplication syndrome. One could argue that other genes located in the minimal critical interval were responsible for dysmorphic facial features in patients with 15q24 microdeletion/microduplication syndrome. Patients with 15q24 microdeletion syndrome also show a wide range of digital abnormalities including brachydactyly, syndactyly, clinodactyly, proximal placement of thumbs, adducted thumbs, long slender fingers and hypoplastic thumbs … (Magoulas and El-Hattab, 2012) and the candidate critical interval for brachydactyly was assigned to the proximal 15q24 microdeletion (Mefford et al., 2012). Of interest, both the present case-index and one case carrying a 2.37 Mb deletion at proximal 15q24 chromosome region reported by Mefford et al. (2012) exhibited brachydactyly. Within a 1.38 Mb BP4-BP1 microdeletion region, *BBS4* and *NEO1* are two plausible candidate genes for digital abnormalities in patients with 15q24 microdeletion syndrome. *BBS4* sequence variants are associated with Bardet-Biedl syndrome and patients usually show digital abnormalities such as polydactyly, brachydactyly and syndactyly … Moreover, *NEO1* encodes a modifier of Sonic hedgehog (SHH) and GLI3 functions which play a role in the regulation of limb and digit patterning. Homozygous mice $Neo1^{Gt/Gt}$ display pre-axial polydactyly (Hong et al., 2012). Hence, haploinsufficiency of *BBS4* and *NEO1* might unmask recessive alleles and/or functional polymorphisms that could predispose to digital abnormalities in patients with proximal 15q24 microdeletion. In summary, we report the first case of 15q24.1 BP4-BP1 microdeletion associated with cardiac phenotype and expand the phenotype spectrum of *HCN4* haploinsufficiency with ventricular arrhythmia. Our report also highlights the important effects resulting from the unmasking of rare recessive alleles or functional polymorphisms as well as the interaction of multiple functional polymorphisms and/or genetic variants leading to the highly variable clinical phenotype in patients with submicroscopic chromosomal imbalances. We also suggest that *HCN4* was a causal gene for cardiac arrhythmia while *BBS4* and *NPTN* variants predisposed to obesity, epilepsy and intellectual deficits in patients with 15q24 microdeletion and propose that distal 15q24 microduplication was a potential high risk susceptibility locus for neurodevelopmental disorders. Identification of similarly affected patients should aid in the further elucidation of this syndrome.

Funding sources

None.

Disclosures

None declared.

Ethics statement

This work is not a clinical research and considered as routine clinical care.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2018.03.005.

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Minh-Tuan Huynh*
APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France
Faculté de Médecine Paris Sud, Université Paris-Sud, 94276 Le Kremlin-Bicêtre cedex, France
Pham Ngoc Thach Medical University, Ho Chi Minh city, Viet Nam
E-mail address: minhtuannia82@yahoo.it

Anne-Sophie Lambert
APHP, Service d'Endocrinologie et de Diabétologie Pédiatrique, Hôpitaux Universitaires Paris-Sud, Hôpital Kremlin-Bicêtre, 94275 Le Kremlin-Bicêtre, France

Lucie Tosca
APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France
Faculté de Médecine Paris Sud, Université Paris-Sud, 94276 Le Kremlin-Bicêtre cedex, France

François Petit
APHP, Laboratoire de Génétique Moléculaire, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France

Christophe Philippe
Laboratoire de Génétique Chromosomique et Moléculaire, Plateau technique de Biologie, CHU de Dijon, Dijon, France

Frédéric Parisot
APHP, Laboratoire de Génétique Moléculaire, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France

Virginie Benoît
APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France

Agnès Linglart
APHP, Service d'Endocrinologie et de Diabétologie Pédiatrique, Hôpitaux Universitaires Paris-Sud, Hôpital Kremlin-Bicêtre, 94275 Le Kremlin-Bicêtre, France

Sophie Brisset
APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France
Faculté de Médecine Paris Sud, Université Paris-Sud, 94276 Le Kremlin-Bicêtre cedex, France

Cong Toai Tran
Pham Ngoc Thach Medical University, Ho Chi Minh city, Viet Nam

Gérard Tachdjian
APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France
Faculté de Médecine Paris Sud, Université Paris-Sud, 94276 Le Kremlin-Bicêtre cedex, France

Aline Receveur
APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 92140 Clamart, France

* Corresponding author. APHP, Service d'Histologie, Embryologie et Cytogénétique, Hôpitaux Universitaires Paris-Sud, Hôpital Antoine Béclère, 157, Rue de La Porte de Trivaux, 92140 Clamart, France.