European Journal of Medical Genetics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

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

ARTICLE INFO

Keywords:
15q24.1 BP4-BP1 microdeletion
Ventricular arrhythmia
Functional polymorphism
Distal 15q24.2q24.3 microduplication

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

https://doi.org/10.1016/j.ejmg.2018.03.005
Received 19 October 2017; Received in revised form 5 December 2017; Accepted 10 March 2018

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