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Clinical report

Interstitial 9p24.3 deletion involving only *DOCK8* and *KANK1* genes in two patients with non-overlapping phenotypic traits

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ABSTRACT

Chromosome 9p deletion represents a clinically and genetically heterogeneous condition characterized by a wide spectrum of phenotypic manifestations and a variable size of the deleted region. The deletion breakpoint occurs from 9p22 to 9p24 bands, and the large majority of cases have either terminal deletions or translocations involving another chromosome. Here we report on two patients with similar inherited interstitial 9p24.3 deletion involving only *DOCK8* and *KANK1* genes. Interestingly, the two patients showed non-overlapping phenotypic traits ranging from a complex phenotype in one to only trigonocephaly with minor dysmorphic features and hand anomalies in the other one. The factors underlying the phenotypic variation associated with seemingly identical genomic alterations are not entirely clear, even if smaller variants, single-nucleotide changes, and epigenetic or stochastic factors altering the expression of genes within functionally relevant pathways have been recently shown to contribute to phenotypic variation. We discuss the role of the two genes and propose possible explanations for the clinical heterogeneity of the phenotype of the two patients.

1. Introduction

Chromosome 9p deletion syndrome (MIM 158170) was first identified as a chromosomal disorder causing a distinctive clinical syndrome by Alfi et al. (1973). It represents a clinically and genetically heterogeneous condition characterized by a wide spectrum of phenotypic manifestations and a variable size of the deleted region. The main clinical features are trigonocephaly, moderate to severe mental retardation, low-set and malformed ears, abnormal genitalia, and dysmorphic facial features (Huret et al., 1988; Flejter et al., 1998; Christ et al., 1999). The deletion breakpoint occurs from 9p22 to 9p24 bands, and the large majority of cases have either terminal deletions or translocations involving another chromosome.

In recent years, high-resolution methods, including FISH, MLPA, and array-CGH, allowed the identification of a number of individuals with cryptic 9p deletions (Swinkels et al., 2008; Barbaro et al., 2009; Hauge et al., 2008). Most studies reported deletions located at 9p24.3, extending from *DMRT* genes (included) to the telomere (Calvari et al., 2000), while smaller telomeric 9p24.3 deletions including only *DOCK8* and *KANK1* genes were much more rarely described (Hauge et al., 2008; Griggs et al., 2008; Lerer et al., 2005; Vanzo et al., 2013).

Here we report on two patients with similar inherited interstitial 9p24.3 deletion involving only *DOCK8* and *KANK1* genes, but with non-overlapping phenotypic traits.

We compared our patients' clinical features with those of other cases reported in the literature. Our data can contribute to better define the critical region and involved genes and therefore facilitate subsequent genotype–phenotype correlations.

2. Clinical report

2.1. Case 1

The girl is the only child of non-consanguineous and healthy parents. She went to our attention at the age of 10 months. The family history revealed a second cousin with autism spectrum disorder. She was born full-term after an uneventful pregnancy. At birth, Apgar score was 9 and 10 at 1 and 5 min, respectively, and no perinatal complications were reported. Weight was 3250 g (50–75th centile), length 53 cm (75–90th centile), and head

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circumference 34 cm (25–50th centile). Because of facial dysmorphisms and delayed developmental milestones, extended metabolic investigations, including plasma and urine amino acid profiles, and organic aciduria, VLCFA were performed, as well as sialotransferrin profiles, which resulted normal. Abdominal and cardiac ultrasound examinations were normal. Brain MRI depicted slight thinning of corpus callosum and mild supratentorial ventricular dilatation. Auditory Brainstem Response (ABR) detected severe unilateral hearing loss. The patient started walking with support at 3 years of age and uttered her first words at 4 years, but afterwards she showed language regression associated with some stereotypic hand movements. Molecular genetic analyses for *MECP2*, *UBE3A* and *FOXG1* genes were performed with normal results, as well as DNA methylation studies for Prader–Willi/Angelman syndrome and genetic analyses for Fragile-X syndrome. Physical examination at 7 years of age showed normal auxological parameters. She had short and sloping forehead, horizontal eyebrows, small and deep set eyes, long nose with broad nasal base, wide mouth tending to be open, with downturned corners, thick and everted lips, big superior incisors, prominent chin, and hyperplastic helix of both ears (Fig. 1A, B). Furthermore, she presented broad thumbs, single transverse palmar crease in both hands, clinodactyly of 5th digit bilaterally, fetal pads, and self-injury signs on digits. Feet showed broad big toes, sandal gap sign, fetal pads, and cutaneous syndactyly of 2nd and 3rd toes. Due to overlapping of some of these features and those of Coffin-Siris syndrome, genes related to SWI/SNF (switch/sucrose non-fermenting) complex (*SMARCA2, SMARCA4, SMARCB1, SMARCE1, ARD1A, ARID1B*) were analysed without any positive results, while TCF4 gene analysis for Pitt Hopkins syndrome is currently undergoing. Neurological evaluation revealed severe intellectual disabilities with absent speech, behavioural disorders with stereotyped movements and self-harm traits, and clumsy ambulation and wide-based gait. Bruxism and profuse drooling were reported.

2.2. Case 2

The boy is the only child of non-consanguineous parents. His mother suffered from congenital scoliosis, autoimmune thyroiditis, and macrocytic anemia of unknown origin. In the maternal family history, an aunt had congenital scoliosis, a first cousin died at 40 years of age for aortic rupture, and the paternal uncle was affected by bipolar disorder. The boy was born at term after an uneventful pregnancy; caesarean section was performed. Apgar score was 8 at the 1st and 10 at the 5th minute, respectively. Birth weight was 3000 g (10th centile), length 48 cm (10th centile), and cranial circumference 35 cm (25–50th centile). He came to our Institute at the age of seven years. He had normal psychomotor development: he controlled his head at 5 months of age and walked at 13 months. At 10 months, he was surgically treated to repair trigonocephaly due to premature closure of the metopic suture (Fig. 1C, D). He further presented microcephaly, short frontal region, glabellar

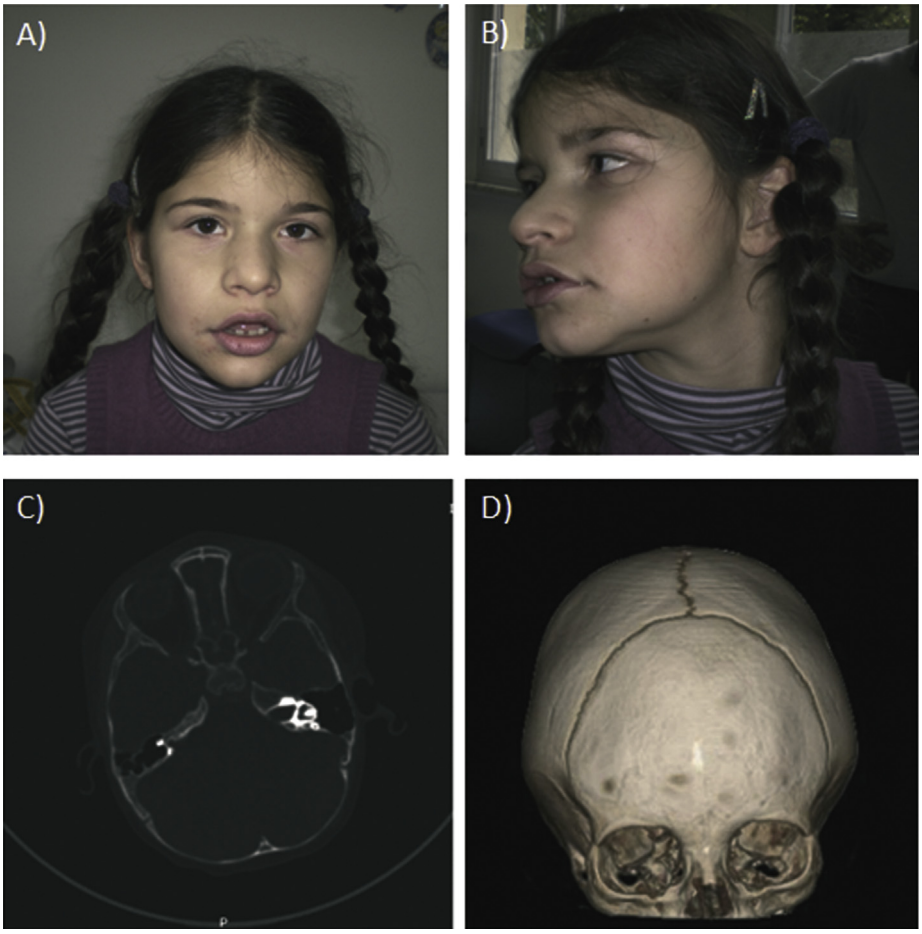

Fig. 1. Clinico-radiological features of patients 1 and 2. A-B) Clinical features of patient 1 with horizontal eyebrows, deep set eyes, long nose with broad nasal base, wide mouth held open with thick and everted lips, prominent chin, and hyperplastic helix of both ears. C) CT scan shows synostosis of the metopic suture with decreased interorbital distance in patient 2. D) The 3D Reformation of patient 2 gives the qualitatively clear impression of this dysmorphology: ossification of the metopic suture and medial orbital rim protrusion, led back of the lateral orbital rims and narrowed bitemporal width.