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A clinical report and further delineation of the 14q32 deletion syndrome

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Introduction

Deletions of the chromosome 14q32 region are rare but common clinical features indicate the presence of a cytogenetic syndrome. This condition is characterized by developmental delay, hypotonia, and a particular face (broad and flat nasal bridge, broad philtrum, thin upper lip, and prominent forehead). Further delineation of this syndrome is needed to clarify cognitive, physical, and behavioral aspects. A ring chromosome 14 defect produces a similar phenotype but often results in seizures, visual problems, and retinal abnormalities, and will not be discussed further in this report. We report our experience in examining the clinical, cognitive, and behavioral findings in an 18.5-year-old female studied with chromosomal microarray hybridization and reviewed earlier reported patients with 14q32 deletions.

Clinical report

Our patient was the first child born to nonconsanguineous parents after an uncomplicated pregnancy; however, premature labor led to delivery at 34 weeks of gestation. The Apgar scores were 7 and 9 at 1 and 5 min, respectively. Birth weight was 2200 g (< 3rd centile), birth length was 44.5 cm (<3rd centile), and head circumference was 29.5 cm (< 3rd centile). She was jaundiced and required mechanical ventilation for 1 day after the delivery, after which oxygen therapy was required for 6 months. A small-appearing jaw, large tongue, high-arched palate and a bifid uvula, horizontal nystagmus, and hypotonia were noted at birth. She had a weak cry and poor suck with feeding difficulties. A three-generation family history was negative for genetic disorders, psychiatric problems, birth defects, and miscarriages. Horizontal nystagmus noted at birth was secondary to optic nerve hypoplasia. Retinitis pigmentosa, seen in ring chromosome 14 syndrome patients, was not identified in our patient. She later manifested hyperopia, but nystagmus, optic nerve hypoplasia, and hyperopia were noted on subsequent annual eye examinations. Bilateral hearing loss was detected by 2 years of age. On account of chronic infections and excessive fluid buildup, tympanostomy and polyethylene tubes were placed. Narrow ear canals were also noted. Hearing aids were prescribed at 6 years of age for sensorineural deafness. Eye surgery was performed at an age of 5 years to correct strabismus. She was small for age during early

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childhood and developmentally delayed with walking at an age of 2 years and first words were said at 4 years of age. She learned sign language before she could speak her first words. She received physical, occupational, and speech therapies during infancy and early childhood. Other supports included individual educational plans and special education. Her full scale IQ was 74, verbal IQ was 71, and performance IQ was 81 at 18 years (Wechsler Adult Intelligence Scale-III). On the Global Assessment of Functioning Scale, used to determine an individual's overall level of functioning and carrying out activities of daily living (American Psychiatric Association, 2000), she had a score of 65, which is consistent with mild symptoms of depressed mood or difficulty with social functioning. She had an overall adequate level of functioning with meaningful interpersonal relationships.

She was diagnosed at an age of 8 years with attention-deficit hyperactivity disorder, depression, obsessive-compulsive disorder, and generalized anxiety disorder. She was impulsive and disruptive at times. She was found to be intrusive socially, with excessive touching and hugging. In the past, she was aggressive but interacted well with younger children. She was noted to be clumsy and teased by others in the school setting. There was no history of seizures nor head injuries. In the psychiatry specialty clinic, she received the diagnosis of pervasive developmental disorder, not otherwise specified based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision criteria (American Psychiatric Association, 2000). Her current psychiatric medications include atomoxetine, sertraline, and guanfacine after which she has shown much improvement. Earlier medication trials included methylphenidate, dextroamphetamine, mixed salts of dextroamphetamine, fluoxetine, and paroxetine, all of which produced agitation and behavioral worsening.

She began menstruation at approximately 15 years of age. Her stature increased more rapidly during early adolescence (12–15 years of age) when her height ranged from the 20th to the 80th centile. She achieved her maximum height at approximately 16 years of age.

Clinical examination at an age of 18 years, 6 months showed a pleasant, cooperative, tall-appearing white female in no acute distress. Her height was 170cm (85th centile), weight was 60.6kg (60th centile), and head circumference was 53 cm (10th centile). Inner canthal distance was 3.2 cm (75th centile), outer canthal distance was 7.6cm (< 3rd centile), interpupillary distance was 5.3cm (25th centile), and palpebral fissure length was 2.3 cm (5th centile). Her face was long and narrow with a high forehead and downslanting palpebral fissures. In addition, she manifested blepharophimosis, epicanthal folds, a flattened, wide nasal bridge, short nose with anteverted nares, and a large-appearing pointed chin (Fig. 1a). Bilateral hearing aids were in place. Horizontal nystagmus was noted. She had a bifid uvula, high-arched palate, and a tongue with a central fissure. She had medial flare of her eyebrows, low-set small-appearing ears (5.7cm, 25th centile), a low-posterior hair line with normal hair texture and pattern, and mild neck webbing. Her hand length was 18.2cm (75th centile) and middle finger length was 7.9cm (75th centile). Her hands and feet showed shortened fifth metacarpals and metatarsals with a wide space between the first and second toes bilaterally (Fig. 1b). Mild cubitus valgus was present. Her arm span was normal at 175 cm. She had no heart murmur. No pathological reflexes were identified and muscle strength of her upper and lower extremities were within normal range. There was no leg length asymmetry nor scoliosis.

Chromosome analysis carried out during infancy showed a terminal deletion of the 14q32.3 band. Both parents' chromosome studies were normal. To further define the size and location of the deletion on chromosome 14 earlier identified during infancy, a whole-genome array-based comparative genomic hybridization was performed commercially using the 105K CMDX Oligo HD Scan (Combimatrix Molecular Diagnostics, Irvine, California, USA). The array-based comparative genomic hybridization study showed a 4.16 Mb deletion (positioned at 102.21–106.37 Mb from the pterminus) extending from 14q32.32 to the qterminus. Approximately, 50 genes have been identified in this region on chromosome 14q (Fig. 2).

Results and discussion

The focus of our report was to describe an additional patient with a deletion involving the 14q32 band and to review the literature. Eleven patients ranging in age from 1 day to 33 years have been described in the literature with proximal and distal breakpoints within the 14q32 band (Hreidarsson and Stamberg *et al.*, 1983; Masada *et al.*, 1989; Teleford *et al.*, 1990; Wang and Allanson, 1992; Wintle *et al.*, 1995; Ortigas *et al.*, 1997; Van Karnebeek *et al.*, 2002; Schlade-Bartusiak *et al.*, 2005, 2009; Zollino *et al.*, 2009) excluding those with ring chromosome 14, unbalanced translocations, and mosaicism. Individuals with ring chromosome 14 were excluded as these patients frequently present with seizures, visual problems, and retinal abnormalities not generally seen in the patients with the 14q32 deletion. The following list of commonly occurring physical anomalies reported in patients with the 14q32 deletion, including our patient, in order of frequency is, broad philtrum (8/8), broad and flat nasal bridge (7/8 patients), telecanthus (8/10), hypotonia (8/10), high-arched palate (8/10), thin upper lip (4/5), blepharophimosis (6/8), pointed chin (5/9), malformed helices (4/7), small mouth (4/8), downslanting palpebral fissures (4/8), and strabismus (4/9).

Short fifth metacarpals and metatarsals, but otherwise long-appearing fingers, increased space between the first and second toes, optic nerve hypoplasia, nystagmus, bifid uvula, mild neck webbing, and low-posterior hair line seen in our patient are not in common with other reported cases. Cognitive, neurological, and behavioral findings were also reviewed from the reported patients with the 14q32 deletion in the literature and summarized in Table 1. Many phenotypic features observed in our patient with the 14q32 deletion also overlap with those reported in the literature, representing common features.

We researched genes in the deleted region using online access to genetic databases (i.e. Online Mendelian Inheritance in Man) that may play a role in our patient's phenotype or which may be significant clinically. For example in our patient, creatine kinase, brain type *(CKB)* is essential in the central nervous system and plays a crucial role in energy metabolism (Klein et *al.*, 1991). BCL2-associated athanogene 5 *(BAG5)* sensitizes dopaminergic neurons to injury-induced death and thus promotes neurodegeneration (Kalia et *al.*, 2004). Other genes in the deleted region include *CRIP1* involved with zinc transport, *PPP1R13B* involved in inducing apoptosis, and *JAG2* involved in the activation of the NOTCH signaling pathway and development of the nervous system (Deng *et al.*, 2000). Maurin *et al. (2006)* discussed a similar list of genes that may contribute to the 14q32 deletion syndrome phenotype. In addition, the immunoglobulin heavy chain genes (e.g.

IGHM, IGHE, IGHG1, IGHD) are located in the same deleted region of chromosome 14q. Deletion of these genes may cause impaired immune system function. Our patient had recurrent ear infections during infancy and early childhood with hearing loss. She now wears hearing aids.

High resolution techniques, such as chromosome microarray hybridization, allows for a more precise description of size, location, and genes involved in a specific chromosome region and are helpful in further characterizing the genetic lesion for genotype-phenotype correlations, genetic counseling, and medical management. The investigators encourage further reporting of individuals with the 14q32 deletion syndrome using newer high-resolution genetic techniques to better characterize the cytogenetic defect and better delineate the clinical and behavioral aspects of this cytogenetic syndrome.

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List of key features

Developmental delay/mental retardation

Broad philtrum

Broad and flat nasal bridge

Telecanthus

Hypotonia

High-arched palate

Thin upper lip

Blepharophimosis

Pointed chin

Malformed helices

Small mouth

Downslanting palpebral fissures

Strabismus

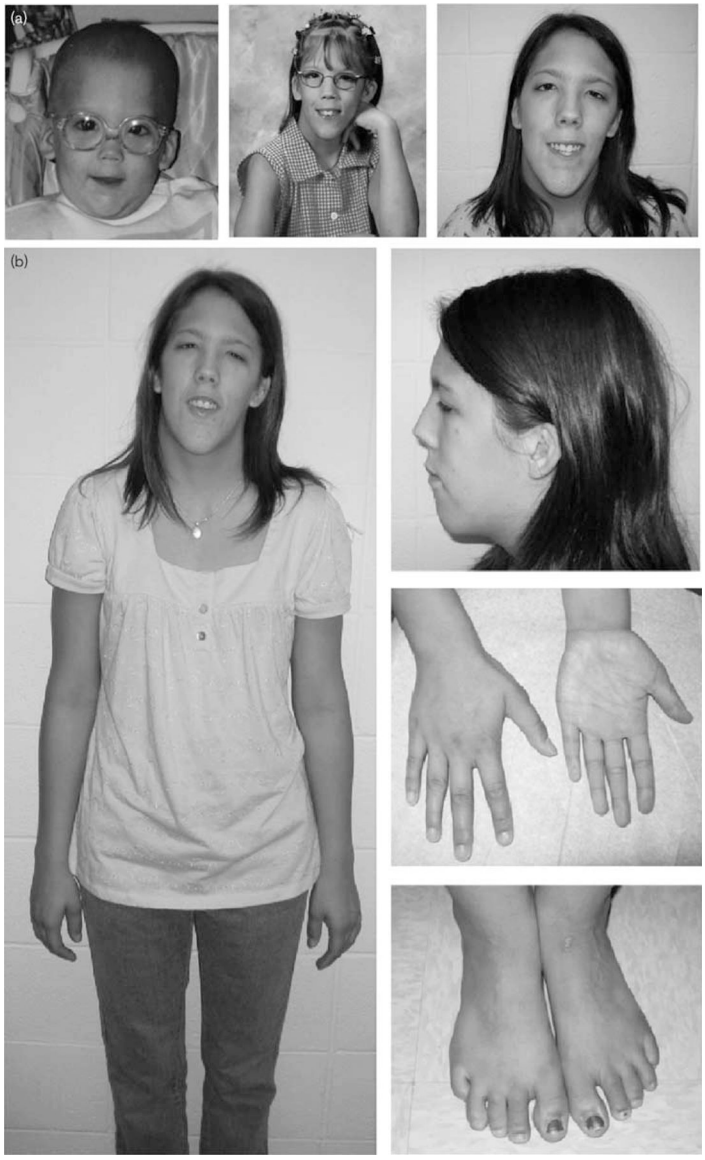

Fig. 1.

(a) Frontal facial views of our patient with the 14q32.32 deletion at 12 months, 10 years, and 18 years of age showing a broad philtrum, flat and broad nasal bridge, ptosis, high forehead, pointed chin, and low-set ears. (b) Longitudinal and profile views of our patient at 18 years of age. Hands and feet showing short fifth metacarpals and metatarsals and a wide space between the first and second toes.

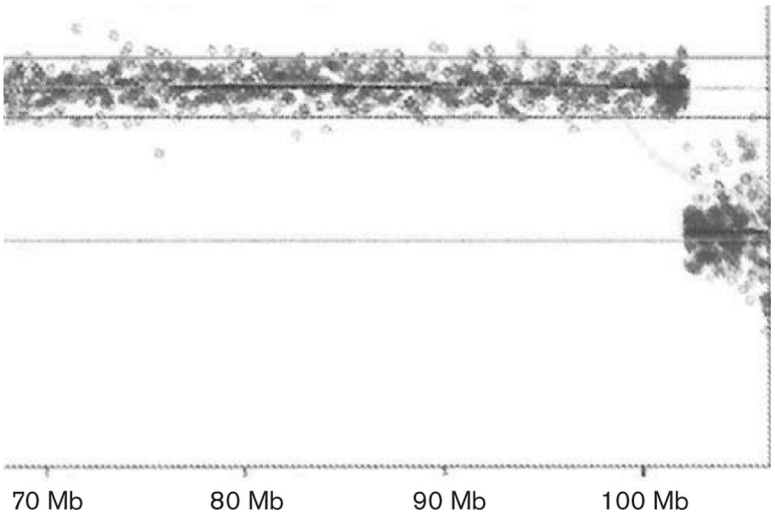

Fig 2.

Chromosome microarray hybridization showing the location of the 4.16Mb deletion of the 14q32.32 qter region occurring at 102.21 — 106.37 Mb from the pterminus including approximately 50 genes *(ADAM6, ADSSL1, AHNAK2, AKT1, AMN, BAG5, BRF1, BTBD6, CKB, C14orfl151, C14orfl172, C14orf180, C14orf2, C14orf73, C14orf79, C14orf80, CDC42BPB, CDCA4, CRIP1, CRIP2, EIF5, GPR132, INF2, JAG2, KIAA0284, KIF26A, KLC1, LOC374569, MARK3, MGC23270, MTA1, NUDT14, PPP1R13B, PACS2, PLD4, RCOR1, SIVA1, SNORA28, TDRD9, TMEM121, TMEM179, TNFAIP2, TRAF3, ZBTB42, ZFYVE21).*

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Table 1

Summary of clinical features and developmental/cognitive, neurological, and behavioral find[a]

	Hreidarsson and Stamberg *et al.* (1983)	Masada *et al.* (1989)	Teleford *et al.* (1990)	Wang and Allanson (1992)	Wintle *et al.* (1995)	Ortigas *et al.* (1997)	Van Karnebeek *et al.* (2002)	Schlade-Bartusiak *et al.* (2005)	Schlade-Bartusiak *et al.* (2009)	Zollino *et al.* (2009)	Zollino *et al.* (2009)	Our patient
Features												
Age at presentation/sex	12-year M	1-day M	26-month F	3 year F	3-month F	3-year F	9-month F	6-month F	14-day M	4-year F	33-year F	18-year F
Chromosome 14q proximal breakpoint	q32.3	q32.11	q32.3	q32.2	q32.3	q32.3	q32.31	q32.32	q32.32	q32.31	q32.2	q32.32
Chromosome 14q distal breakpoint	qter	qter	qter	qter	qter	qter	qter	qter	qter	qter	q32.3	qter
Intrauterine growth retardation	+	+	+	−	−	−	−	NR	NR	NR	NR	−
Microcephaly	−	−	−	−	−	+	+	−	+	NR	−	+
Strabismus	−	−	−	−	NR	+	+	NR	−	NR	+	+
Blepharophimosis	−	−	+	+	NR	+	+	NR	+	NR	NR	+
Ptosis	−	−	+	−	+	−	+	NR	−	NR	NR	+
Downslanting palpebral fissures	−	−	+	+	NR	−	−	NR	+	NR	NR	+
Telecanthus	−	+	+	+	+	+	+	+	−	NR	NR	+
Broad/flat nasal bridge	+	+	+	+	NR	+	+	NR	−	NR	NR	+
Philtrum abnormalities	+	+	+	+	NR	NR	+	+	+	NR	NR	+
Thin upper lip	NR	NR	−	NR	NR	+	+	NR	+	NR	NR	+
Small mouth	−	+	+	−	NR	−	−	NR	+	NR	NR	+
Highly-arched palate	+	+	+	+	+	+	−	+	−	NR	NR	+
Malformed helices	+	−	−	+	NR	NR	+	NR	+	NR	NR	−
Pointed chin	+	+	−	+	NR	+	−	−	−	NR	NR	+

	Hreidarsson and Stamberg *et al.* (1983)	Masada *et al.* (1989)	Teleford *et al.* (1990)	Wang and Allanson (1992)	Wintle *et al.* (1995)	Ortigas *et al.* (1997)	Van Karnebeek *et al.* (2002)	Schlade-Bartusiak *et al.* (2005)	Schlade-Bartusiak *et al.* (2009)	Zollino *et al.* (2009)	Zollino *et al.* (2009)	Our patient
Other	CHD	Coloboma of iris; esophageal atresia; scoliosis; cryptorchidism; hypospadias; finger-like thumbs; CHD	HL	Optic nerve coloboma; clinodactyly		Hirsutism			CHD; arthrogryposis; retinopathy of prematurity; midgut malrotation; HL; prematurity			Optic nerve hypoplasia; HL; bifid uvula
Developmental/cognitive												
Developmental delay/mental retardation	+	NA	+	+	+	+	+	+	+	NR	+	+
Sit unassisted	NR	NA	NR	NR	NR	NR	NR	NR	NA	NR	NR	NR
Crawled	NR	NA	NR	NR	NR	1 year	NR	NR	NA	NR	NR	NR
Walked	NR	NA	NR	NR	NR	2 year	NR	NR	NA	NR	NR	24 month
First words	NR	NA	NR	NR	NR	3 year	NR	NR	NA	NR	NR	4 year
Neurological												
Hypotonia	−	+	+	+	+	−	+	+	−	NR	+	+
Seizures	−	+	−	−	−		−	NR	+	NR	NR	−
Hearing loss	NR	NR	+	NR	NR	NR	NR	NR	+	NR	NR	+
Weak suck/ difficulty feeding	NR	NR	+	NR	NR	NR	−	NR	NR	NR	NR	+
Weak cry	NR	NR	NR	NR	NR	NR	−	NR	NR	NR	NR	+
Behavioral	NR	NA	NR	NR	NA	NR	NR	NA	NA	NR	Compulsive; hyperactivity	PDDNOS; ADHD; OCD; GAD; aggression; depression

ADHD, attention-deficit hyperactivity disorder; CHD, congenital heart disease; F, female; GAD, generalized anxiety disorder; HL, hearing loss; M, male; NA, not applicable; NR, not reported; OCD, obsessive-compulsive disorder; PPDD-NOS, pervasive developmental disorder-not otherwise specified.

[a]This table consists of those patients with the involvement of only the 14q32 band and excludes those individuals with other chromosome anomalies, translocations, or mosaicism.