

Concomitant 1q42.13-q44 Duplication and 14q32.33 Deletion: A Case Report and Review of Literature

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Duplications of 1q concomitant with other chromosomal deletions are rare conditions in association with compound phenotypes. We present a case with a duplication of 1q42.13-q44 and a deletion at 14q32.33 and perform a comprehensive review on relevant cases of simple or concomitant duplications involving distal 1q42-qter region. The patient was a 1-year-old boy with delayed mental development, relative macrocephaly, brain and facial deformities, hypotonia, and minor dilation of ascending aorta. Cytogenomic analyses revealed a derivative chromosome 14 with a 21.4 Mb duplication of 1q42.13-q44 and a 2.8 Mb deletion at 14q32.33. This derivative chromosome was inherited from his mother who is a carrier of a balanced translocation between 1q42.13 and 14q32.33. This patient presents compound phenotypes from the distal 1q42 duplication and 14q32.3 terminal deletion. Review of reported cases with duplications of 1q42-qter revealed that approximately 22% were de novo cases and 78% were familial cases from a maternal or a paternal carrier of a balanced translocation. Pedigrees from familial carriers of a balanced translocation involving 1q42 showed an increased risk up to 35% for spontaneous abortion. Thorough clinical assessment of compound phenotypes and follow up study on both parents are recommended for cases with concomitant 1q42-qter duplication and other chromosomal deletions.

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INTRODUCTION

Segmental duplications of 1q resulting from parental carriers of a balanced translocation had been recognized from malformed newborn infants or fetal loss by earlier cytogenetic analysis during 1970's.^{1,2} Since then, high resolution chromosome Giemsa-banding (G-band) analysis, fluorescence in situ hybridization (FISH), and array comparative genomic hybridization (aCGH) have been applied to define chromosomal abnormalities from G-band level to gene level.³⁻⁵ Segmental trisomies of 1q were classified to groups 1 to 4 based on G-band regions of 1q11-q25, 1q25-q41, 1q32-q42 and 1q42-qter, respectively.⁷ The group 4 trisomy of 1q42-qter represents an entity of distal 1q duplication. Simple duplications of 1q42-qter had been reported with a syndromic phenotype of intellectual disability, macrocephaly, dysmorphic facial features, and cardiac defects.^{8,9} Most cases of 1q42-qter duplication were concomitant with a deletion in another chromosome and thus showed variable phenotypes.¹⁰⁻

²⁸ Continuous efforts had been made to correlate compound phenotypes with concomitant cytogenomic imbalances.

In this study, we present clinical findings in a patient with a derivative chromosome 14 inherited from a mother carrying a balanced translocation. The genomic imbalances in the derivative chromosome 14 are characterized by aCGH analysis. A comprehensive literature review summarizes breakpoints, concomitant cytogenomic imbalances, and parental origin from relevant cases involving duplications of 1q42-qter. These results provide further information of genotype-phenotype correlation and familial history for cases with a distal duplication of 1q42-qter which could be helpful for genetic counseling and clinical management.

CASE REPORT

The patient was born to a 36-year-old G1P0 (pregnant but not yet delivered) mother by caesarean section. The pregnancy was complicated by early hyperemesis and later failure to progress. His birth weight was 2.81 kg (5-10th percentile), length was 49.5 cm (5-10th percentile), and head circumference was 36.2 cm (50-75th percentile). The family

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history was unremarkable and the parents was non-consanguineous.

At the age of 2-3 months, he was noted to have torticollis with his head constantly leaning towards his right side. At age of 4-8 months, the patient was noted with delayed motor skill development and hypotonia. At age of 10 months, he could sit alone for a few seconds and could keep his chest up on prone position. He was not able to crawl and could not pronounce specific words. Physical exam showed weight 7.14 kg (< 3rd percentile), height 67 cm (< 3rd percentile), and head circumference 46 cm (67th percentile). He had deformational plagiocephaly with the left forehead flatter than the right side, and left ear more posteriorly placed and rotated, relative macrocephaly, open fontanel, short and upturned nose, down turned corner of mouth, high arched palate, and a relatively small chin (**Figure 1A**). He also showed periotic noisy breathing. Brain MRI scan showed benign enlargement of the subarachnoid space. Mild dilation of the ascending aorta was observed via echocardiogram.

Biochemical testing detected normal creatinine phosphokinase level, long chain fatty acid proportion and plasma amino acid profile. His carnitine profile showed an elevation in acetylcarnitine without abnormalities of other acylcarnitine likely the result of fasting and an elevated lactate and pyruvate (at 3.9 and 0.21) likely due to difficult blood drawing. Urine organic acid and thyroid function tests were also reported normal. Fragile X DNA test was negative. Although there are a few mild abnormalities in these tests, none of them is indicative of a specific cause of this patient's hypotonic condition and developmental delay.

CYTOGENOMIC ANALYSIS AND RESULTS

Peripheral blood samples from the patient and his parents were collected for cytogenomic analysis. Routine chromosomal analysis was performed on cultured lymphocytes using laboratory standard procedures.⁴ Chromosome G-band analysis detected a derivative chromosome 14 with distal 1q42.13-qter segment joining at 14q32.33 in the proband. Follow up parental chromosome analysis detected a normal male karyotype in the father and a reciprocal balanced translocation between chromosomal bands 1q42.13 and 14q32.33 in the mother (**Figure 1B**). These results indicated that the derivative chromosome 14 in the patient, denoted as der(14)t(1;14)(q42.13;q32.33), was of maternal origin. The aCGH analysis using DNA extracted from the patient's blood leukocytes was performed as previous described.^{3,4} The detected genomic imbalances were designated per the GRCh37/hg19 assembly in the UCSC Human Genome browser (<http://genome.ucsc.edu/>). The result from aCGH

analysis defined a 21.4 Mb duplication of 1q42.13-q44 (chr1: 227,801,297-249,212,668) including genes from ZNF678 to PGBD2 and a 2.8 Mb deletion at 14q32.33 (chr14:104,491,726-107,287,505) including 17 genes (**Figure 1C**).

REVIEW OF LITERATURE

Studies of relevant cases with a distal 1q42 duplication were searched from PubMed using the following terms: "1q42, duplication, and partial trisomy" A total of 21 reports with 38 affected patients from 28 families were retrieved.⁸⁻²⁸ The results from G-band karyotyping, FISH, and microarray, parental studies and family history from these patients are summarized in **Table 1**. A simple intra-chromosomal 1q42-q44 duplication was noted in three cases.^{8,9,28} Concomitant 1q42-q44 duplication with a deletion in another chromosome were detected in 35 patients from 25 families.¹⁰⁻²⁸ Three cases with 1q42-qter segment translocated onto the short arm of chromosome 22 and 15 and the terminal 9q could be viewed as a simple duplication due to the absence of euchromatin loss in the partner chromosomes.^{13,22,25} Of the eight cases studied by FISH mapping or microarray analysis, the breakpoints at 1q42 were defined from 224.1 Mb at 1q42.11 to 234.6 Mb at 1q42.2. For parental carriers of a balanced translocation between 1q42 and a partner chromosome, the partner chromosomes from most frequent to less are 6q in three cases, 3p, 4p, 4q, and 18p each in two cases, as well as 6p, 13q, 14q, 15p, 15q, 21q and 22p each in one case. Results of parental studies available from 23 families showed that 22% were de novo, 30% were from a paternal carrier and 48% were from a maternal carrier of a balanced translocation. From the five reports with a three-generation pedigree, 13 spontaneous abortions (SAB) were noted in a total of 37 pregnancies in the third generation (**Table 1**). The empirical risk of SAB for carriers with a balanced translocation involving 1q42 is up to 35% even though this could be an over estimation due to the limited number of families.

DISCUSSION

It has been a challenge to correlate clinical phenotypes with concomitant segmental duplication and deletion due to the difficulty in dissecting gene-dosage effect, gene-gene interactions, modify gene effect, and epigenetic influence and their contributions to phenotypes.^{29,30} Mapping of overlapping deletions and duplications could define critical regions harboring dosage sensitive candidate genes for syndromic or distinctive phenotypes.^{31,32} A comparison of clinical findings between patients with simple and concomitant deletions or duplications had been used to differentiate distinct and overlapping manifestations.^{20,33}

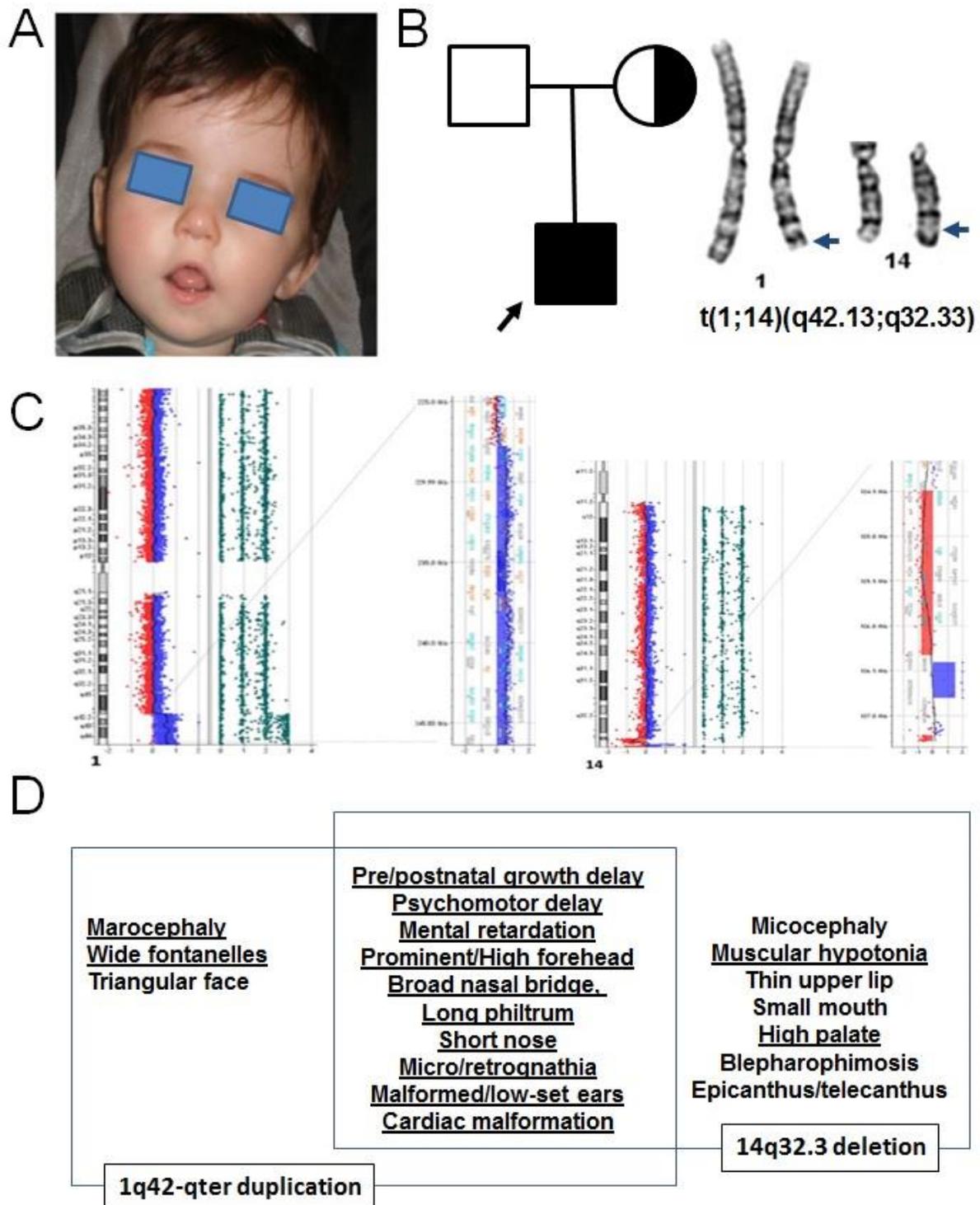


Figure 1. Clinical and cytogenomic findings in the patient. A. Facial picture shows short and upturned nose, down turned corner of mouth and a relatively small chin. B. Pedigree shows the affected proband (filled square) and carrier mother (half-filled circle). Chromosome image shows the reciprocal translocation observed in the mother (arrows point to the breakpoints). C. aCGH analysis detected a 21.411 Mb duplication of 1q42.13-q44 and 2.796 Mb deletion at 14q32.33 in the derivative chromosome 14 of the affected proband. For each chromosome, the left panel shows a chromosome view from copy number and single nucleotide polymorphism probes and the right panel shows a gene view. D. Distinct and overlapping manifestations found in the 1q42-qter duplication and the 14q32.3 deletion are outlined by a box. Clinical findings in our patient are underlined.

Table 1. Reported cases with a duplication of 1q42-1qter.*

Methods	1q41/q42-qter dup	Coordinates (in Mb by HG19)	Size	Concomitant del	Coordinates	Size	Affected	Pedigree	Parental karyotype	Ref
K, F	inv dup(1)(q42.2q44)	1q42.2q44(-234.6-249.2)x3	14.6				1F		nl	8
K, F	dup(1)(q42.2q44)	1q42.2q44(-232.5-249.2)x3	16.7				1F		nl	9
K	dup(1)(q42qter)			del(18)(p11pter)			1M, 3F	6SAB/13	mat, t(1;18)(q42;p11)	10
K	dup(1)(q42qter)			del(18)(p11pter)			1M, 1F		mat, t(1;18)(q42;p11)	10
K	dup(1)(q42qter)			del(4)(p16pter)			3M, 2F	2SAB/10	mat, t(1;4)(q42;p16)	11
K	dup(1)(q42qter)			del(4)(p14pter)			1M	2SAB/6	pat, t(1;4)(q42;p14)	12
K	dup(1)(q42qter)			del(22)(p12)			1M		mat, t(1;22)(q42;p12)	13
K	dup(1)(q42qter)			del(6)(q27qter)			1F		pat, t(1;6)(q42;q27)	14
K	dup(1)(q42qter)			del(4)(q35.1qter)			1F		pat, t(1;4)(q42;q35.1)	15
K	dup(1)(q42qter)			del(4)(q35qter)			1M		mat, t(1;4)(q42;q35)	16
K	dup(1)(q42qter)			del(13)(q34qter)			1F		mat, t(1;13)(q42;q34)	16
K	dup(1)(q42qter)			del(6)(q27qter)			1F		mat, t(1;6)(q42;q27)	17
K	dup(1)(q42qter)			del(6)(p23pter)			1F	2SAB/5	pat, t(1;6)(q42;p23)	18
K	dup(1)(q42.3qter)			del(3)(p26.3pter)			2M		mat, t(1;3)(q42.3;p26.3)	19
K	dup(1)(q42qter)			del(15)(qter)			1M		pat, t(1;15)(q42;qter)	20
K	dup(1)(q42qter)			del(15)(p11)			1F, 1M	1SAB/3	pat, t(1;15)(q42;p11)	21
K, F	dup(1)(q42.1qter)			del(8)(p23.3pter)			1F		nl	22
K, F	dup(1)(q42.3qter)			del(1)(p36.13pter)			1M		nl	23
K, F	dup(1)(q42.3qter)			del(21)(q22.3qter)			1F		mat, t(1;21)(q42.3;q22.3)	24
K, F, MA	dup(1)(q42qter)	1q42.11q44(-224.1-249.2)x3	25.1	9qter		0	1M		nl	25
K, MA	dup(1)(q42.13qter)	1q42.13q44(226.6-249.2)x3	22.6	del(6)(q27qter)	6q27(167.3-170.9)x1	3.6	1F		pat, t(1;6)(q42.13;q27)	26
K, MA	dup(1)(q42.13qter)	1q42.13q44(227.6-249.2)x3	23.5	del(3)(p25.3pter)	3p25.3(1-10.9)x1	11	1M		mat, t(1;3)(q42.13;p25.3)	27
K	dup(1)(q42.1q44)						1M		n.a	28
K	dup(1)(q42.3qter)			del(14)(q32.33qter)			1M		n.a	28
K	dup(1)(q42.1qter)			del(14)(q32.3qter)			1M		n.a	28
K, MA	dup(1)(q42.13qter)	1q42.13q44(228.7-249.2)x3	20.5	del(3)(p26pter)	n.a		1M		n.a	28
K, MA	dup(1)(q42.11qter)	1q42.11q44(224.1-249.2)x3	25.1	del(10)(q26qter)	n.a		1F		n.a	28
K, MA	dup(1)(q42.13qter)	1q42.13q44(227.8-249.2)x3	21.4	del(14)(q42.13qter)	14q32.33(104.5-107.3)					
							18F, 20M	13SAB/37	5 nl, 11 mat, 7 pat	18F, 20M

Clinical findings from cases with a simple or pure segmental duplication of 1q42-qter indicated a syndromic phenotype of prenatal and postnatal growth retardation, relative macrocephaly, triangular face, prominent forehead, broad nasal bridge, abnormal philtrum, micro/retrognathia, cardiac defects, and mental retardation.^{8,9,25} From cases with overlapping deletions of 1q43-q44, high resolution aCGH defined critical regions within a 1.5 Mb interval (chr1:243.5-245.0 Mb) and candidate genes for microcephaly, abnormalities of the corpus callosum, and seizure. A deletion of only the AKT3 gene in two cases implicates haploinsufficiency of this gene for the microcephaly phenotype.³¹ The opposite phenotype of macrocephaly in the 1q42-qter duplication may be caused by triple-sensitive of the AKT3 gene. Typical gene-dosage effect involving the GPC3 gene at Xq26 showed opposite phenotypes of overgrowth with a deletions and growth retardation with a duplication.^{34,35} A phenotype map for 14q32.3 terminal deletions revealed a 250 Kb critical region (chr14:105.7-106.0 Mb) correlating with typical clinical findings of intellectual disability, developmental delay, muscular hypotonia, postnatal growth retardation, microcephaly, congenital heart defects, genitourinary malformations, ocular coloboma, and several dysmorphic features.³⁴ Of the seven genes within this critical region, the MTA1, CIRP2, and TMEM121 genes are

considered most promising candidate genes for intellectual disability. A comparison of clinical findings in our patient with typical phenotypes from 1q42-qter duplication and 14q32.3 deletion is shown in Figure 1D. Our patient manifested multiple deformities of typical 1q42-qter duplication and his hypotonia likely resulted from 14q terminal deletion. However, concomitant 1q42-qter duplication with a 4p14-pter deletion showed phenotype of Wolf-Hirschhorn syndrome caused by the 4p deletion.¹² Caution should be exercised when interpreting the compound phenotypes with concomitant segmental duplication and deletion. Two cases with concomitant duplication of 1q42-qter and deletion 14q32-qter were detected by chromosome analysis.²⁸ The brief clinical description showed macrocephaly, low-set ear, polydactyly and overlapping toes in these two cases. However, lack of genomic analysis on these two cases made it difficult to compare the involved gene content and to correlate clinical phenotypes. Clinical findings from additional cases with similar concomitant imbalances and knowledge of gene functions within the involved regions are needed for accurate genotype-phenotype correlation.

The concomitant 1q42.13-q44 duplication and 14q32.33 deletion in our patient is the result from an unbalanced segregation of a maternal balanced translocation. Review of

reported cases with duplications involving 1q42 revealed that 22% were de novo cases and 78% were familial cases from a maternal or a paternal carrier of a balanced translocation. The observed balanced reciprocal translocations showed different breakpoints at 1q42 and different partner chromosomes. Examination of breakpoints at 1q42.13 and 14q32.33 in our case found an absence of inter-chromosomal segmental duplications. Further sequencing analysis on breakpoints is needed to understand the mutagenesis mechanisms for these reciprocal translocations. Carriers of a balanced reciprocal translocation could have an increased risk of SAB.^{2,33} Pedigrees from carriers of a balanced translocation involving 1q42 showed an increased risk up to 35% for SAB. This information could be helpful for genetic counseling and clinical management of patients with a duplication of 1q42-qter.

CONFLICT OF INTEREST

None.

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