Case Report

A 420 Kb Deletion within the Minimum Critical Region of the 15q24 Microdeletion Syndrome in a Female Infant

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Recurrent deletions of the chromosomal region 15q24 have recently been identified as the underlying cause of a novel microdeletion syndrome. A recent study comparing patients with 15q24 deletions of variable size defined a minimum critical deletion region of 1.7 Mb. The corresponding clinical phenotype includes intellectual disability, developmental delay, muscle hypotonia, dysmorphic facial features, skeletal anomalies, cardiac defects, and male genital anomalies. To date, 34 patients with a 15q24 deletion based on array CGH have been reported in the medical literature. Little is known about the genotype phenotype correlation for this genomic region. Case Report: We report a female newborn infant with a 420 Kb deletion within the reported 1.7 Mb critical region of the 15q24 deletion that was identified by array CGH. The infant had tetralogy of Fallot and dysmorphic facial features including a flat nasal bridge, hypertelorism, retro- and micrognathia. The 420 Kb deletion included 11 known genes: COMMD4, NEIL1, MIR631, MAN2C1, SIN3A, PTPN9, SNUPN, IMP3, SNX33, CSPG4, and ODF3L1. The 420 Kb deletion defines the minimum critical region of the 15q24 microdeletion syndrome. Conclusion: Thirty-one of 35 reported patients including the patient presented here, were classified phenotypically according to breakpoints and size. Haplo-insufficiency of the genes in the minimum region may contribute to the clinical phenotype observed in affected patients.
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INTRODUCTION

The advent of array Comparative Genomic Hybridization (CGH) has led to the identification of chromosomal imbalances in patients with overlapping clinical phenotypes.[1,2] Recurrent deletions of the chromosomal region 15q24 have recently been reported as the underlying cause of a new microdeletion syndrome.[3,4] To date, 34 patients with the 15q24 deletion syndrome diagnosed using array CGH are reported in the medical literature. The clinical phenotype includes varying degrees of developmental delay, dysmorphic features, growth failure including microcephaly, muscle hypotonia, digital abnormalities, congenital heart defects such as Tetralogy of Fallot (TOF), ventricular septum defect (VSD) and genital abnormalities in male patients.[3,5-8]

15q24 deletions range from 0.5 Kb to 6.1 Mb.[3-14] The majority of patients with 15q24 deletions share the same minimal deletion critical region of about 1.75 Mb, with breakpoints localized to LCR15q24B (BP1) and LCR15q24D (BP2).[13] Reciprocal duplications of the minimal region have been reported.[13,15] Non-Allelic Homologous Recombination (NAHR) was considered as the mechanism for the deletions in this region.[16] LCR15q24A (BP4) (70.6–70.8 Mb), LCR15q24B (BP1) (72.0–72.3 Mb), LCR15q24C (73.2–73.4 Mb), LCR15q24D (BP2) (73.7–73.9 Mb), and LCR15q24E (BP3) (75.8–76.1 Mb) were suggested to be the NAHR regions at 15q24.[6,8,13] A recent study comparing variable 15q24 deletions defined a minimum critical deletion region of 1.7 Mb that included 32 different genes.[7] Here we report a female newborn infant with a 420 Kb deletion within the 1.7 Mb region in 15q24 identified by array CGH. Thirty-one of 35 patients including the patient presented in this report were classified phenotypically based on breakpoints and size. These groups were assessed for genotype-phenotype correlation identifying a minimal critical deletion region.

CASE REPORT

The infant was born via C-section at 38 weeks of gestation to non-consanguineous, healthy Haitian parents following an unremarkable pregnancy. A prenatal ultrasound showed classic TOF without associated renal and/or skeletal anomalies. There was no family history of intellectual disability, developmental delay, cardiac disease, sudden or premature death. Birth parameters were as follows: Apgar scores were 7/8/8 at 1, 5 and 10 minutes, birth weight 2665g (25th centile for age), length 48 cm (50th cent), head circumference 31.5 cm (20th cent). On physical exam the infant exhibited prominent dysmorphic facial features

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including a flat nasal bridge, hypertelorism and micro- and retrognathia. No obvious skeletal anomalies, syndactyly or polydactyly were noted. The remainder of the physical exam was with the exception of a 3/6 pansystolic murmur on the left sternal border unremarkable. Ultrasound of the brain was without abnormal findings. The infant died at 25 days of age due to post-operative complications following open cardiac surgery at 8 days of age.

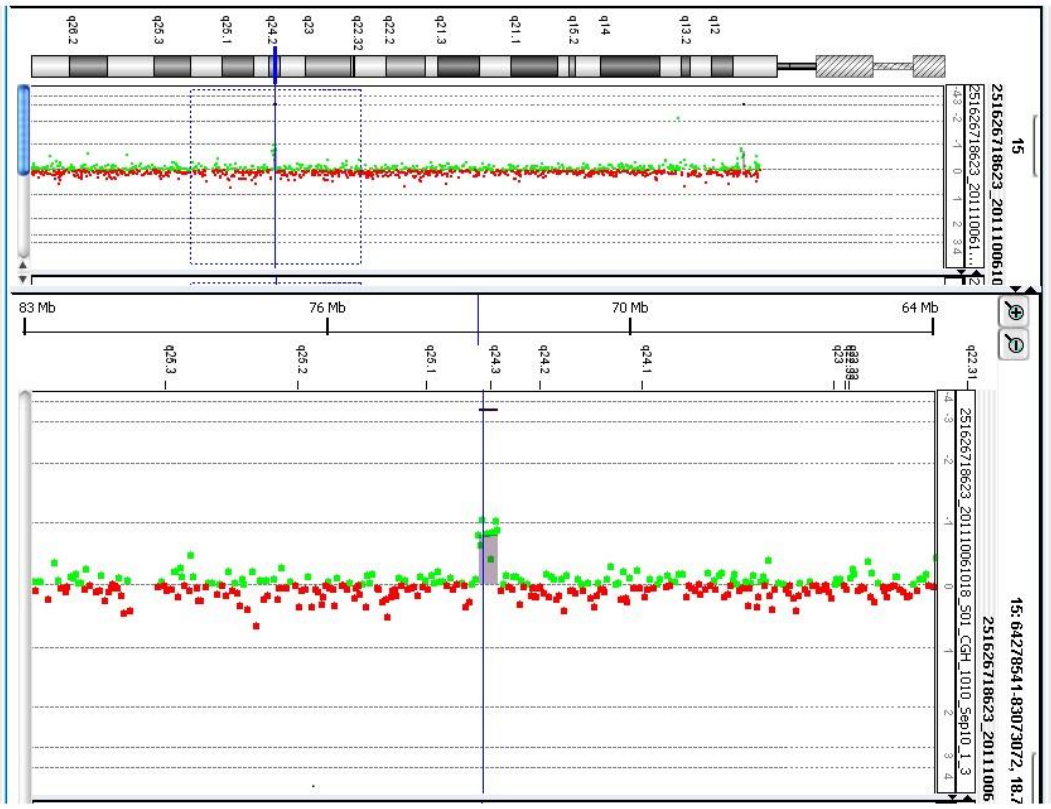

Figure 1: Result of Agilent array CGH 44k showing a 420 kb deletion at 15q24.2.

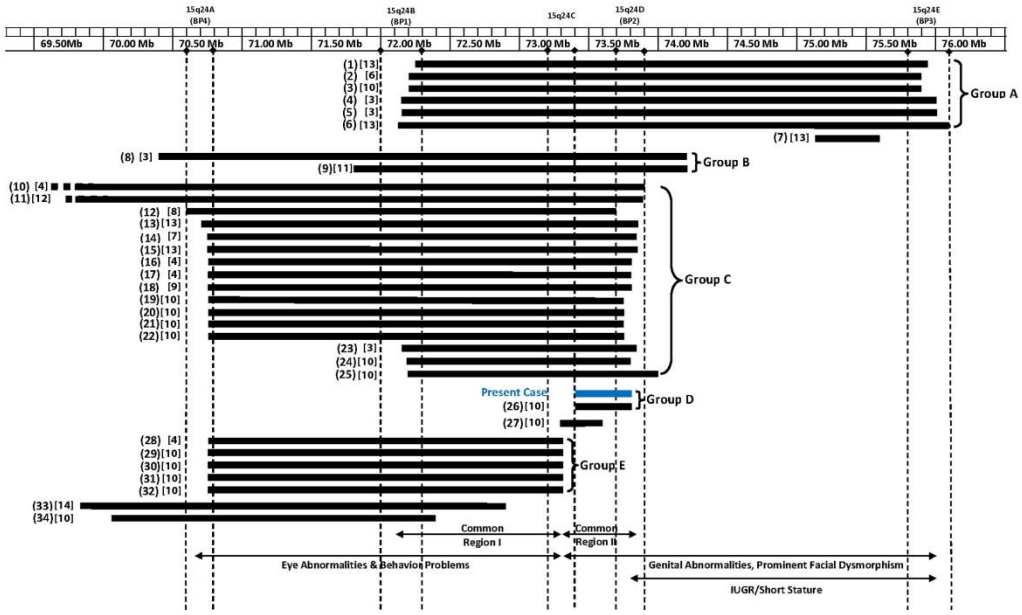

Figure 2: Schematic representation of the low copy repeat (LCR) and the deleted genomic regions on chromosome 15q24. The five LCR regions are represented by dotted lines: LCR15q24A (BP4) (70.6–70.8 Mb), LCR15q24B (BP1) (72.0–72.3 Mb), LCR15q24C (73.2–73.4 Mb), LCR15q24D (BP2) (73.7–73.9 Mb), and LCR15q24E (BP3) (75.8–76.1 Mb). The solid lines represent the deletions. The number (1) to (34) represent the cases. Number inside [ ] is the reference number.

Using a customized 44K cytogenomic array a 420 Kb deletion (ISCN: arr[hg18] 15q24.2(73,387,161-73,807,021)x1 or arr[hg19]15q24.2(75,600,108-76,019,966)x1) in chromosome 15q24.2 was detected (**Figure 1**). The proximal and distal breakpoints mapped to LCR15q24C and LCR15q24D (BP2), respectively (**Figure 2**). The 420 Kb deletion encompasses 11 genes: *COMMD4, NEIL1, MIR631, MAN2C1, SIN3A, PTPN9, SNUPN, IMP3, SNX33, CSPG4,* and *ODF3L1*. The parents refused microarray testing and/or FISH studies.

Thirty-four patients with 15q24 deletions diagnosed using array CGH were identified from the medical literature. We classified these patients including the patient reported here according to distinct phenotypic groups (A, B, C, D and E) based on breakpoints mediated by NAHR and deletion size. We identified two genomic regions (region I and II) that were commonly deleted in 31 patients. Review of all the reported patients with a 15q24 deletion including the size and location of deletions are summarized in **Figure 2**. Four of 35 patients including patients 7, 27, 33 and 34 respectively were not assigned to any group. Their break points were atypical and not located within common break points. It is thought that these deletions were random with low risk for recurrence.

We compared the reported clinical phenotype between groups and found that Intra Uterine Growth Retardation (IUGR) and/or postnatal short stature were mostly observed in patients of group A (5/6) but not seen in group B or E and only in very few patients in group C (3/16). Genital abnormalities including hypospadias, microphallus, and cryptorchidism in males are present in 2/2 of group B, in about half of male patients in group A and C, but were not reported in any of the 5 male patients in group E.

Prominent dysmorphic facial features, including high forehead/ hair line, down slanting palpebral fissures were mostly seen in patients in groups A and B and to some extent in group C but not in group E. It appears that abnormalities of the male genitalia and dysmorphic facial features are due to deletions that range from 15q24C to 15q24E. Eye anomalies, such as strabismus/nystagmus appear in about less than half of the patients of groups A, B and C, but are reported in all patients of group E (5/5). Behavioral abnormalities show a similar trend. Deletions from 15q24A to 15q24C may contribute more towards to the eye anomalies and behavioral abnormalities.

Table 1. Phenotypic anomalies in addition to developmental delay and/or intellectual disability.

phenotype besides DD and MR	A	B	C	D	E
high arched palate	1/5	1/2	4/15	0/1	0/5
high forehead/hair line	5/5	2/2	10/14	0/1	0/5
flared medial eyebrows	4/6	1/2	5/16	0/2	0/5
down-slanting eyes	3/5	2/2	8/15	0/1	0/5
epicanthus	2/6	1/2	8/16	1/2	0/5
strabismus/nystagmus	2/6	1/2	4/15	0/2	5/5
hypertelorism	3/5	1/2	3/13	2/2	1/5
long/smooth philtrum	4/5	2/2	6/14	0/1	0/5
broad nasal base	3/5	2/2	6/15	1/1	0/4
depressed nasal bridge	1/5	1/1	4/15	1/1	0/4
small mouth/micrognathia	1/5	2/2	6/14	1/1	1/5
ear malformation	3/6	1/2	8/14	nd	2/5
hearing loss	1/6	2/2	4/13	nd	2/5
hernia	1/5	1/2	3/15	0/2	0/5
cardiovascular defects	1/5	1/2	3/15	1/2	3/5
abnormal brain imaging	3/6	1/1	4/12	1/2	1/5
microcephaly	2/6	0/2	2/14	0/2	0/5
behavior problems	1/1	1/1	7/9	1/1	4/4
feeding difficulties	1/4	1/2	3/12	0/1	nd
hypotonia	4/5	1/1	8/10	0/1	4/4
skeletal abnormalities	5/6	2/2	9/15	0/2	4/5
digital abnormaities	4/5	2/2	11/14	1/2	2/5
IUGR/short stature	5/6	0/2	3/13	1/2	0/5

DISCUSSION

Patients reported with the 15q24 deletion syndrome have deletions with variable sizes, ranging from 500 kb to 6.1 Mb and most patients had developmental delay and/or intellectual disability. Although the clinical phenotype of the 15q24 deletion syndrome in 34 reported patients is heterogeneous, there is some clinical overlap between different groups of patients based on break points and deletion sizes (**Figure 2** and **Table 1**).[3,5-9,11-14,17] The reported deletion of our patient falls within common region II which was also deleted in 25 additional patients in groups A, B, and C. It represents the smallest reported deletion of 15q24 to date, although a similar 500 kb deletion in a 9 year old girl has been recently reported. The girl had global developmental delay and behavioral abnormalities including a short attention span. Minor facial dysmorphism was noted.[10] It also worth mentioning that an almost identical deletion in Decipher (case number 255342) was documented that a 3 year old girl had phenotypes of Intellectual disability and Microcephaly.

Individuals with deletions of common region II show mostly genital abnormalities in males, facial dysmorphism including high anterior hair line, flared medial eye brows, down-slanting eyes, epicanthus, long and smooth philtrum and retrognathia whereas eye anomalies and behavioral abnormalties are predominantly see in patients with deletions of common region I. There is no overall correlation between the size of the deletion and severity of phenotype. The main clinical finding in our patient was Tetralogy of Fallot (TOF) which was also reported in patients 5 and 28. Additional heart defects including Ventricle Septum Defect (VSD), pulmonic stenosis, persistent ductus arteriosus and right ventricular arrhythmia were identified in 5 patients.

The 420 Kb deletion in our case involves 11 genes with important biological functions including *COMMD4, NEIL1, MIR631, MAN2C1, SIN3A, PTPN9, SNUPN, IMP3, SNX33, CSPG4,* and *ODF3L1*. *NEIL1* is known to be involved in DNA repair, and is considered to be related to human cognitive performance.[18] Deletion of the gene may lead to intellectual disability and/or behavioral abnormalities. *MAN2C1* encodes α-mannosidosis 2C1, an enzyme involved in the catabolism of cytosolic oligosaccharides, which in turn play an important role cellular homeostasis and growth.[19]

SIN3A encodes a transcriptional regulatory protein, containing multiple protein-protein interaction domains. It is involved in DNA replication, protein localization, regulation of apoptosis and embryonic development. SIN3A forms complexes with the cell cycle apparatus and DNA damage response proteins in embryonic stem cells. It is essential for embryonic development around the time of implantation protecting the genomic integrity of pluripotent embryonic cells.[20] *PTPN9* is a member of the protein tyrosine phosphatase (PTP) family which as signaling molecules regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. Knockdown of *PTPN9* expression also enhances tyrosyl phosphorylation of the ErbB1/epidermal growth factor receptor (EGFR) in the MDA-MB-231 breast cancer cell line.[21] *PTPN9* deficient mice manifest growth retardation and evidence of neural tube defects, including craniofacial abnormalities, exencephaly, cerebral infarctions, abnormal bone development and high prenatal lethality.[22] *NEIL1, MAN2C1, SIN3A and PTPN9* are biologically important and are highly expressed in brain, thymus, lung and testis.

Haploinsufficiency of these genes in the deleted region contribute to the clinical phenotype of our patient although additional mechanism are likely to play a role. Most of the breakpoints of the patients with a 15q24 deletion map to clusters of highly identical LCR sequence, suggesting NAHR as the likely mechanism of recurrent microdeletions. Because the deletion in our case involves two LCR breakpoints, we expect more patients with this small 15q24 deletion to be identified, which will allow us to further delineate the clinical phenotype and phenotype-genotype correlation.

Clinical variability has frequently been reported in microdeletion/duplication syndromes, and it has been suggested that clinical diagnosis in some patients will be most readily achieved on the basis of genotype rather than phenotype.[17] Nevertheless, to our knowledge, this is the first patient reported to date with a deletion of less than 500 Kb in 15q24 caused by NAHR. We assume that this deletion represents the critical region of the 15q24 microdeletion syndrome although the clinical phenotype may vary to some extent based on deletion size and break points.

CONFLICT OF INTEREST

None.

ABBREVIATIONS

MRI: magnetic resonance imaging; TOF: Tetralogy of Fallot; VSD: Ventricular Septum Defect; FISH: Fluorescence In-Situ Hybridization; IUGR: Intrauterine Growth Restriction; CGH: *Comparative Genomic Hybridization;* NAHR: Nonallelic Homologous Recombination; LCR: Low-Copy Repeat.

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