Published in final edited form as:
Am J Med Genet A. 2009 August ; 149A(8): 1661–1677. doi:10.1002/ajmg.a.32896.

Chromosome 8p23.1 Deletions as a Cause of Complex Congenital Heart Defects and Diaphragmatic Hernia

Margaret J. Wat[1], **Oleg A. Shchelochkov**[1], **Ashley M. Holder**[2], **Amy M. Breman**[1], **Aditi Dagli**[3], **Carlos Bacino**[1], **Fernando Scaglia**[1], **Roberto T. Zori**[3], **Sau Wai Cheung**[1], **Daryl A. Scott**[1], and **Sung-Hae Lee Kang**[1,*]

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

[2]Department of Surgery, Washington University School of Medicine, Saint Louis, MO, USA.

[3]Department of Pediatrics, University of Florida, Gainesville, FL, USA

Abstract

Recurrent interstitial deletion of a region of 8p23.1 flanked by the low copy repeats 8p-OR-REPD and 8p-OR-REPP is associated with a spectrum of anomalies that can include congenital heart malformations and congenital diaphragmatic hernia (CDH). Haploinsufficiency of *GATA4* is thought to play a critical role in the development of these birth defects. We describe two individuals and a monozygotic twin pair discordant for anterior CDH all of whom have complex congenital heart defects caused by this recurrent interstitial deletion as demonstrated by array comparative genome hybridization. To better define the genotype/phenotype relationships associated with alterations of genes on 8p23.1, we review the spectrum of congenital heart and diaphragmatic defects that have been reported in individuals with isolated *GATA4* mutations and interstitial, terminal, and complex chromosomal rearrangements involving the 8p23.1 region. Our findings allow us to clearly define the CDH minimal deleted region on chromosome 8p23.1 and suggest that haploinsufficiency of other genes, in addition to *GATA4*, may play a role in the severe cardiac and diaphragmatic defects associated with 8p23.1 deletions. These findings also underscore the importance of conducting a careful cytogenetic/molecular analysis of the 8p23.1 region in all prenatal and postnatal cases involving congenital defects of the heart and/or diaphragm.

Keywords

Congenital heart defects; 8p23.1 deletion syndrome; Diaphragmatic hernia; Array comparative genomic hybridization; *GATA4*; Prenatal diagnosis

INTRODUCTION

Published deletions involving chromosome 8p23.1 range from large terminal deletions that are easily detectable by routine chromosome analysis to small interstitial deletions which are best identified using fluorescence in situ hybridization (FISH) or molecular techniques such as array comparative genomic hybridization (aCGH) [Paez et al., 2008; Reddy 1999; Devriendt et al., 1999]. Recurrent deletions of a region of 8p23.1 flanked by low copy repeats 8p-OR-REPD (distal) and 8p-OR-REPP (proximal) are associated with a spectrum of anomalies including congenital heart malformations, congenital diaphragmatic hernia

*Corresponding Author: Sung-Hae L. Kang, Ph.D. Department of Molecular and Human Genetics Baylor College of Medicine Houston, TX, USA. Phone: 713.798.8793 Fax: 713.798.4187 skang@bcm.edu.

(CDH), developmental delay, and neuropsychiatric findings [Digilio et al., 1998; Ciccone et al., 2001; Shimokawa et al., 2005; Ciccone et al., 2006; Zuffardi et al., 2006].

This region contains the transcription factor gene *GATA4* which is known to play a key role in heart development in humans [Garg et al., 2003; Okubo et al., 2004; Sarkozy et al., 2005]. Disruption of *Gata4* in mice has also been shown to cause heart defects and anterior CDH [Molkentin et al., 1997; Kuo et al., 1997; Jay et al., 2007]. Mice homozygous for a *Gata4* null allele failed to form a heart tube and died between E7.0 and E9.5 [Kuo et al., 1997; Molkentin et al., 1997]. More recently, Jay et al. reported that a significant fraction of C57BL/6 mice heterozygous for a *Gata4* deletion in exon 2—which removed the translation start site and the N-terminal activation domain—died within 1 day of birth, and that developmental defects in these heterozygotes included atrial septal defects (ASD), ventricular septal defects (VSD) and atrioventricular septal defects (AVSD) [Jay et al., 2007].

In this report, we describe two individuals and an identical twin pair discordant for anterior CDH all of whom were diagnosed prenatally with complex congenital heart defects and were subsequently shown to have interstitial 8p23.1 deletions. We review the spectrum of congenital heart and diaphragmatic defects that have been reported in individuals with isolated *GATA4* mutations and interstitial, terminal, and complex chromosomal rearrangements involving 8p23.1 and discuss the implications of this data on our understanding of the gene(s) within this region which may play a role in heart and diaphragm development.

CLINICAL REPORTS

Patient 1

Patient 1 is a male born at 39 3/7 weeks gestation to a 26-year-old G2P1→2 mother. Both parents were Hispanic and nonconsanguineous. Prenatal ultrasound revealed pulmonary and tricuspid atresia. No amniocentesis was performed. Birth weight was 2.82 kg (10th centile), length was 48.5 cm (50th centile) and frontooccipital circumference (OFC) was 31.5 cm (25th centile). In the neonatal period he was noted to have a two-vessel umbilical cord, a very large anterior fontanelle, downslanting palpebral fissures, mild micrognathia, a short neck, slender fingers, and proximally implanted thumbs. Head ultrasound revealed normal anatomy with possible thinning of the corpus callosum.

Shortly after birth he was admitted to the neonatal intensive care unit for respiratory distress and tachypnea. Postnatal cardiac evaluation revealed a complex single ventricle anatomy consisting of a double outlet right ventricle, unbalanced complete atrioventricular septal defect (AVSD) with left atrioventricular (AV) valve atresia and left ventricular hypoplasia, pulmonary atresia, and D-transposition of the great vessels. Despite stenting of his ductus ateriosus, he continued to have limited pulmonary outflow. During surgery to create a systemic-to-pulmonary artery (Blalock-Taussig) shunt and to ligate the stented patent ductus arteriosus (PDA), he was found to have bilateral superior vena cavae with absence of a bridging innominate vein.

Approximately 6 weeks after birth, he experienced a cardiopulmonary arrest requiring resuscitation and emergent use of extracorporeal membrane oxygenation (ECMO). While on ECMO he developed seizures. He was weaned, decannulated and maintained for a short period of time on high-dose inotropic support before dying at age one month.

Patient 2

Patient 2 is a female born via cesarean at 35 weeks to a G2P1→3 mother as part of a twin gestation. Prenatal ultrasound showed complex congenital heart disease and intra-uterine growth retardation. No anomalies were identified in the male twin. No amniocentesis was performed.

The family history was significant for postaxial polydactyly in father, paternal half brother and maternal half sister. A paternal half brother had aortic insufficiency but this was felt to be secondary to rheumatic heart disease.

Birth weight was 1320 gm (<5th centile), length was 39 cm (<5th centile) and frontooccipital circumference (OFC) was 27 cm (<5th centile). His weight, length, and OFC were at approximately the 50th centile level for a 29-30 week gestation infant, consistent with symmetric intra-uterine growth retardation. Postaxial polydactyly of the left hand was noted along with prominent heels. No facial dysmorphic features were noted.

Shortly after birth, the patient developed respiratory distress requiring intubation and mechanical ventilation. Cardiac evaluation by ECHO and cardiac angiography revealed a complex cardiovascular malformation consisting of an unbalanced AVSD, left AV valve atresia, hypoplastic left ventricle, severe tricuspid regurgitation, absent intrahepatic inferior vena cava and hemiazygos continuation to a left superior vena cava. Head and abdominal ultrasounds were normal.

Considering the severity of the cardiac condition, life-support was withdrawn with parental consent and the patient died at 88 days of life.

Patient 3

Patient 3 is a male infant born at 34 5/7 weeks via cesarean to a 33-year-old G1P0→2 mother as part of a monozygotic twin gestation (see Patient 4). Prenatal ultrasound at 20-weeks gestation revealed an AVSD with a large inlet ventricular septal defect (VSD) extending to the perimembranous septum, aortic hypoplasia, a dominant pulmonary artery, and mild tricuspid regurgitation. An amniocentesis was performed and aCGH and chromosome analyses revealed a deletion on chromosome 8p.

Birth weight was 1835 grams (25th centile), length was 44.5 cm (50th centile), and frontooccipital circumference (OFC) was 29 cm (10th centile). At birth, examination revealed a holosystolic murmur, mild dysmorphic facial features, minor digital anomalies, and a sacral dimple. Spinal cord tethering was ruled out by spinal ultrasound.

Postnatal cardiac evaluation revealed a balanced type A complete AVSD with mild AV regurgitation, moderate atrial septal defect (ASD), hypoplastic aortic arch, a narrow left ventricular outflow tract, a large PDA, and good biventricular function. At surgery, he was found to have a right atrium with two appendages and absence of a bridging innominate vein.

Shortly after birth, the patient was transferred to the neonatal intensive care with tachypnea and desaturations. Further evaluation revealed evidence of a large anterior congenital diaphragmatic hernia with herniation of the liver, levoposition of the heart and a hypoplastic, posteriorly rotated left lung.

The patient remained hospitalized until approximately 12 weeks of age and is presently 5-months-old.

Patient 4

Patient 4 is the male monozygotic twin of patient 3. Prenatally, he was found to a balanced complete AVSD, a small aortic arch, and a large PDA. An amniocentesis was performed and aCGH and chromosome analyses revealed a deletion on chromosome 8p.

He was born at 2020 grams (25th centile), with a length of 44.8 cm (30th centile), and frontooccipital circumference (OFC) of 29.5 cm (10th centile). Additional findings on postnatal cardiac evaluation included a small aortic valve, bilateral peripheral pulmonary stenosis, and mild right ventricular dilatation. He was also found to have a small right choroid plexus cyst and a sacral dimple. Spinal cord tethering was ruled out by spinal ultrasound.

He was discharged home on day of life 38, with a discharge weight of 2960 g, a length of 48.5 cm and an OFC of 33 cm.

MATERIALS AND METHODS

Patients

All four patients were referred for clinical cytogenetic testing. Institutional review board approved informed consent was obtained for high-resolution studies.

Clinical Cytogenetic Tests

Standard laboratory procedures were used for metaphase preparations. G-banded chromosome analysis and FISH analysis were performed in either Medical Genetics Laboratories at Baylor College of Medicine or by the referring center. DNA was extracted from peripheral blood [Ou et al., 2008] and amniotic fluid samples [Bi et al., 2008] as previously described. Patients 1 and 2 were examined in the neonatal period and Patients 3 and 4 in the prenatal period. In the case of Patients 1, 3, and 4, aCGH testing and chromosome analysis were performed concurrently at the Medical Genetics Laboratories at Baylor College of Medicine. For Patient 2, aCGH analysis was performed following normal chromosome analysis results. All clinical aCGH analyses were performed using Baylor College of Medicine (BCM) Chromosomal Microarray version 6 (CMA V6) manufactured by Agilent Technologies (Santa Clara, CA) according to the manufacturer's instructions with modifications [Ou et al., 2008].

High-Resolution aCGH Analysis

DNA from Patients 1 and 4 was further evaluated by high resolution genome-wide aCGH using Human Genome CGH 244K Oligo Microarray Kits G4411B (Agilent Technologies, Santa Clara, CA) according to the manufacturer's protocol version 2.0. Arrays were scanned using an Agilent DNA Microarray Scanner (Agilent Technologies, Santa Clara, CA). Data extracted using Feature Extraction Software Version 9.1.3 (Agilent Technologies, Santa Clara, CA) was analyzed using CGH Analytics 3.4.40 Software (Agilent Technologies, Santa Clara, CA) with copy number changes identified with the assistance of the Aberration Detection Method 2 algorithm (threshold 6.0). Control DNA consisted of DNA from a healthy gender-matched reference individual with no personal or family history of heart or diaphragm defects.

Sequencing Analysis

PCR amplification of genomic fragments was performed using previously described primer pairs [Okubo et al., 2004]. PCR-fragments were cleaned and sequenced commercially (Agencourt Bioscience, Beverly, MA) and DNA changes were identified by comparing the

published *GATA4* sequence to sequence data obtained from patient samples using Sequencher 4.5 software (GeneCodes, Ann Arbor, MI).

RESULTS

Visible deletions of 8p were identified on the chromosome analysis for Patients 1, 3 and 4 (Fig 1). Chromosome analysis and FISH for 22q11.2 deletions performed on a peripheral blood sample from Patient 2 at an outside facility were reported as normal.

Clinical aCGH detected an identical 8p23.1 deletion in all four patients with a minimal deletion size of 2.945 Mb (8,850,913 to 11,796,333) and a maximal deletion size of 6.352 Mb (6,436,314 to 12,788,647) (Fig 1). Parental studies confirmed that all of the deletions were de novo.

High resolution aCGH analyses confirmed the deletions previously seen in the clinical studies. In each case the deletion was flanked by the low copy repeats 8p-OR-REPD and 8p-OR-REPP with differences in apparent deletion size between Patients 1 and 4 being attributable to known copy number variant regions within and/or directly adjacent to the low copy repeats. The minimal deleted interval encompassed twenty-two known genes/open reading frames including *GATA4* (Fig 2).

To determine whether disruption of both *GATA4* alleles could explain the severe cardiac defects and CDH seen in our patients, we screened the entire *GATA4* coding sequence and intron/exon boundaries of the remaining GATA4 allele in Patients 1 and 4. No variations from the published *GATA4* reference sequence were identified in the coding sequence or the intron/exon boundaries of these DNA samples.

DISCUSSION

We have described the phenotype associated with the recurrent deletion of 8p23.1 in four patients with prenatally diagnosed complex congenital heart defects. The *GATA4* gene resides within this recurrently deleted interval and has been implicated as the gene responsible for heart defects associated with 8p23.1 deletions. The role of *GATA4* in heart development is supported by mouse models [Kuo et al., 1997; Molkentin et al., 1997; Jay et al., 2007] and studies of patients with *GATA4* gene mutations.

Some of the most compelling evidence that mutations in *GATA4* are associated with heart defects in humans come from studies of seven families in which ASD was found to segregate with heterozygous *GATA4* mutations with varying levels of penetrance (Table I) [Garg et al., 2003;Hirayama-Yamada et al., 2005;Sarkozy et al., 2005;Okubo et al., 2004]. The *GATA4* gene has also been screened in individual patients with ASD, VSD, AVSD, and tetralogy of Fallot (TOF). Although a number of non-synonymous changes were identified in these studies, it was often difficult to conclude whether these changes were causal due to a lack of parental/population controls and/or functional studies. This is particularly true of changes that are inherited from a non-affected parent. The most convincing of these changes include a de novo E216D missense mutations in two individuals with TOF that was shown to have reduced transcriptional activity in a reporter assay, and a frameshift mutation (Pro226fs) and a premature stop codon mutation (Arg266Ter)—which severely truncate the protein—each found in a patient with atrioventricular septal defects (AVSD) (Table II) [Nemer et al., 2006;Reamon-Buettner et al., 2007].

The complex cardiac phenotypes seen in our patients led us to question whether the spectrum of heart defects associated with 8p23.1 deletions was more severe than that seen in patients with *GATA4* mutations. With this in mind we reviewed previous reports of

interstitial, terminal and complex deletions of 8p23.1 (Table III) to determine the spectrum of cardiac phenotypes associated with these deletions. Previously reported patients with interstitial deletions were found to have a spectrum of cardiac defects that included ASD, VSD, AVSD, pulmonary stenosis, pulmonary valve stenosis, tetralogy of Fallot, and/or combinations of these defects. Cardiac defects in patients with terminal deletions extending to at least 8p23.1 included AVSD, hypoplastic left heart, hypoplastic right ventricle, pulmonary atresia/stenosis, pulmonary valve stenosis, partial anomalous pulmonary venous return, subaortic stenosis, transposition of the great arteries, double inlet/double outlet right ventricle, double inlet left ventricle and tetralogy of Fallot.

When combined with data from the four patients described in this report, it would appear that the spectrum of heart defects is more severe in interstitial and terminal deletions involving 8p23.1 when compared to defects seen in patients with heterozygous *GATA4* mutations. Although this increase in severity could be due to deleterious mutations in the remaining *GATA4* allele, we did not detect such mutations in Patients 1 and 4. A similar evaluation carried out by Paez et al. also failed to identify mutations in the remaining *GATA4* allele in two patients with 8p23.1 deletions involving *GATA4* who also presented with heart defects [Paez et al., 2008].

An alternative explanation for the increase in severity would be the existence of another gene(s) in the recurrent 8p23.1 deletion region that impact heart development. Of the genes deleted along with *GATA4*, *SOX7* is one of the most likely candidate genes. *SOX7* is expressed in mouse and human adult heart, and in the early cardiogenic region of *Xenopus* embryos [Takash et al., 2001; Taniguchi et al., 1999; Zhang et al., 2005]. *SOX7* mRNA injection induced cardiogenic marker expression in *Xenopus* animal cap explants whereas knockdown of *SOX7* using morpholinos decreased the expression of cardiogenic markers *MHCα* and *Nkx2.5*; and marker expression was rescued by injection of RNA encoding a *SOX7* transcript [Zhang et al., 2005]. Interestingly, silencing of *Sox7* in mouse F9 embryonal carcinoma cells blunts the increase in *Gata4* mRNA levels seen after treatment with all trans-retinoic acid/dibuterol cAMP [Futaki et al., 2004]. In contrast, silencing of *Gata4* did not result in decreased *Sox7* expression in the same system. This suggests that *Sox7* lies upstream of *Gata4*, and that haploinsufficiency of *SOX7* may exacerbate the cardiac phenotype of individuals with *GATA4* deletions.

Genes outside the *GATA4* region may also be involved in abnormal cardiac development based on reports of patients with inverted duplication deletion events involving 8p. The mechanism involved in creation of the most common inverted duplication deletion events of 8p has been well described [Ciccone et al., 2006]. These events typically result in loss of copy number (deletion) of 8p distal to 8p-OR-REPD, normal copy number of the *GATA4* region between 8p-OR-REPD and 8p-OR-REPP, and a variable region of increased copy number (duplication) proximal to 8p-OR-REPP. The number of cardiac malformations associated with patients carrying the inverted duplication deletion 8p was 11/39 (28.2%), a much lower proportion than 17/18 (94.4%) and 45/60 (75%) associated with interstitial and terminal deletions, respectively (Table III). In general, the spectrum of cardiac malformations in these cases is also milder but still includes ASD, VSD, right aortic arch, and pulmonary stenosis (Table III). If we assume normal expression of *GATA4* and other genes between 8p-OR-REPD and 8p-OR-REPP, we are left to conclude that decreased expression of one or more genes distal to 8p-OR-REPD and/or over expression of one or more genes proximal to 8p-OR-REPP can also contribute to the development of some heart defects.

Congenital diaphragmatic hernia is also common in patients with a deletion encompassing 8p23.1 with, at least, nine previously reported cases [Holder et al 2007]. CDH is associated

with 4/18 (22.2%) of reported interstitial deletions and 5/60 (8.3%) of terminal deletions but has not been described in patients with inverted duplication deletions. This is, presumably, due to the fact that terminal deletions may not always include the CDH minimal deleted interval and that this interval has a normal copy number in individuals with inverted duplication deletions.

The majority of CDH patients with 8p23.1 deletions have been described as having left sided (assumedly-posterior) CDH. Indeed, Patient 3 is the only individual described to date with an anterior CDH associated with an 8p23.1 deletion. This is surprising since the heterozygous *Gata4* mice described by Jay et al. have anterior CDH similar to that seen in our patient [Jay et al., 2007]. Using array data presented here and previously reported molecularly-defined deletions associated with CDH, the minimal deleted region for CDH on 8p can be defined as the region bounded by 8p-OR-REPD distally and 8p-OR-REPP proximally (Fig 3) [Faivre et al., 1998; Slavotinek et al., 2004; Shimokawa et al., 2005].

Although the use of array comparative genome hybridization can aid in the identification of 8p23.1 deletions in patients with heart and/or diaphragm defects, caution must be used in the interpretation of these findings. Chromosome 8p contains many copy number variant regions whose potential contribution to the development of birth defects has not been adequately studied. Recently Chen et al. [2007] described a patient with a Fryns-like phenotype including congenital diaphragmatic hernia, macrocephaly, brachytelephalangy, nail hypoplasia, short webbed neck with redundant posterior nuchal skin, coarse face, flat and broad nasal bridge, hypertelorism, macrostomia, microretrognathia, and low-set ears. The patient's phenotype was attributed to a de novo 0.7 MB deletion within 8p23.1 [Chen et al., 2007]. However, this deletion lies entirely within a known copy number variant region making it difficult to determine if this deletion is causal. Without careful evaluation, physicians may erroneously quote sibling and offspring recurrence risks that are either too low or too high based on an incorrect assumption of causality.

When used properly, aCGH detects detrimental submicroscopic changes that can be easily missed on routine chromosomal analysis especially in prenatal samples where the band resolution may be compromised [Pecile et al., 1990; Wu et al., 1996; Faivre et al., 1998]. This is illustrated well in Patient 2 where chromosome analysis failed to identify an 8p deletion which was easily detected by aCGH. This, and the high frequency of cardiac and diaphragmatic defects associated with 8p23.1 interstitial deletions, leads us to recommend that aCGH be performed on all prenatal and postnatal cases with congenital cardiac and/or diaphragm defects. At the present time we do not recommend that the GATA4 gene be sequenced in patients with cardiac defects since the percentage of cases with protein-altering changes in GATA4 is likely to be small— approximately 1% based on the articles reviewed —and the clinical significance of the majority of GATA4 changes remains unclear.

Acknowledgments

The authors thank the patients and family members who participated in this study and Zhiyin Yu for her technical assistance. This study was funded in part by NIH grant HD-050583 (DAS).

REFERENCES

Baynam G, Goldblatt J, Walpole I. Deletion of 8p23.1 with features of Cornelia de Lange syndrome and congenital diaphragmatic hernia and a review of deletions of 8p23.1 to 8pter? A further locus for Cornelia de Lange syndrome. Am J Med Genet A. 2008; 146A:1565–1570. [PubMed: 18470924]

Bhatia SN, Suri V, Bundy A, Krauss CM. Prenatal detection and mapping of a distal 8p deletion associated with congenital heart disease. Prenat Diagn. 1999; 19:863–867. [PubMed: 10521847]

Blennow E, Brondum-Nielsen K. Partial monosomy 8p with minimal dysmorphic signs. J Med Genet. 1990; 27:327–329. [PubMed: 2352261]

Borys D, Taxy JB. Congenital diaphragmatic hernia and chromosomal anomalies: autopsy study. Pediatr Dev Pathol. 2004; 7:35–38. [PubMed: 15255033]

Bosse K, Eggermann T, Van der Ven K, Raff R, Engels H, Schwanitz G. Unbalanced translocation 8;Y (45,X,dic(Y;8)(q11.23;p23.1)): case report and review of terminal 8p deletions. Ann Genet. 2004; 47:191–197. [PubMed: 15183753]

Brocker-Vriends AH, Mooij PD, van Bel F, Beverstock GC, van de Kamp JJ. Monosomy 8p: an easily overlooked syndrome. J Med Genet. 1986; 23:153–154. [PubMed: 3712390]

Brocker-Vriends AH, van de Kamp JJ, Geraedts JP, Bos SE, Nijenhuis TA. Unbalanced karyotype with normal phenotype in a family with translocation (8;13)(p21;q22). Clin Genet. 1985; 27:487–495. [PubMed: 4006274]

Chen CP, Wang TH, Chen YJ, Chang TY, Liu YP, Tzen CY, Chern SR, Wang W. Prenatal diagnosis of Fryns syndrome associated with a microdeletion at 8p23.1. Prenat Diagn. 2007; 27:967–969. [PubMed: 17602449]

Ciccone R, Mattina T, Giorda R, Bonaglia MC, Rocchi M, Pramparo T, Zuffardi O. Inversion polymorphisms and non-contiguous terminal deletions: the cause and the (unpredicted) effect of our genome architecture. J Med Genet. 2006; 43:e19. [PubMed: 16648372]

Claeys I, Holvoet M, Eyskens B, Adriaensens P, Gewillig M, Fryns JP, Devriendt K. A recognisable behavioural phenotype associated with terminal deletions of the short arm of chromosome 8. Am J Med Genet. 1997; 74:515–520. [PubMed: 9342203]

Devriendt K, De Mars K, De Cock P, Gewillig M, Fryns JP. Terminal deletion in chromosome region 8p23.1-8pter in a child with features of velo-cardio-facial syndrome. Ann Genet. 1995; 38:228–230. [PubMed: 8629811]

Devriendt K, Matthijs G, Van Dael R, Gewillig M, Eyskens B, Hjalgrim H, Dolmer B, McGaughran J, Brondum-Nielsen K, Marynen P, Fryns JP, Vermeesch JR. Delineation of the critical deletion region for congenital heart defects, on chromosome 8p23.1. Am J Hum Genet. 1999; 64:1119–1126. [PubMed: 10090897]

Devriendt K, Van Schoubroeck D, Eyskens B, Gewillig M, Vandenberghe K, Fryns JP. Prenatal diagnosis of a terminal short arm deletion of chromosome 8 in a fetus with an atrioventricular septal defect. Prenat Diagn. 1998; 18:65–67. [PubMed: 9483642]

Digilio MC, Marino B, Guccione P, Giannotti A, Mingarelli R, Dallapiccola B. Deletion 8p syndrome. Am J Med Genet. 1998; 75:534–536. [PubMed: 9489800]

Digilio MC, Marino B, Toscano A, Giannotti A, Dallapiccola B. Atrioventricular canal defect without Down syndrome: a heterogeneous malformation. Am J Med Genet. 1999; 85:140–146. [PubMed: 10406667]

Dill FJ, Schertzer M, Sandercock J, Tischler B, Wood S. Inverted tandem duplication generates a duplication deficiency of chromosome 8p. Clin Genet. 1987; 32:109–113. [PubMed: 2888552]

Dobyns WB, Dewald GW, Carlson RO, Mair DD, Michels VV. Deficiency of chromosome 8p21.1----8pter: case report and review of the literature. Am J Med Genet. 1985; 22:125–134. [PubMed: 3901750]

Engelen JJ, de Die-Smulders CE, Fryns JP, Hoovers JM, Albrechts JC, Loots WJ, Jacobs ME, Hamers AJ. Partial trisomy and monosomy 8p due to inversion duplication. Clin Genet. 1994; 45:203–207. [PubMed: 8062440]

Faivre L, Morichon-Delvallez N, Viot G, Narcy F, Loison S, Mandelbrot L, Aubry MC, Raclin V, Edery P, Munnich A, Vekemans M. Prenatal diagnosis of an 8p23.1 deletion in a fetus with a diaphragmatic hernia and review of the literature. Prenat Diagn. 1998; 18:1055–1060. [PubMed: 9826897]

Fryns JP, Kleczkowska A, Vogels A, Van den Berghe H. Normal phenotype and slight mental retardation in de novo distal 8p deletion (8pter----8p23.1). Ann Genet. 1989; 32:171–173. [PubMed: 2573313]

Futaki S, Hayashi Y, Emoto T, Weber CN, Sekiguchi K. Sox7 plays crucial roles in parietal endoderm differentiation in F9 embryonal carcinoma cells through regulating Gata-4 and Gata-6 expression. Mol Cell Biol. 2004; 24:10492–10503. [PubMed: 15542856]

Garg V, Kathiriya IS, Barnes R, Schluterman MK, King IN, Butler CA, Rothrock CR, Eapen RS, Hirayama-Yamada K, Joo K, Matsuoka R, Cohen JC, Srivastava D. GATA4 mutations cause human congenital heart defects and reveal an interaction with TBX5. Nature. 2003; 424:443–447. [PubMed: 12845333]

Giglio S, Graw SL, Gimelli G, Pirola B, Varone P, Voullaire L, Lerzo F, Rossi E, Dellavecchia C, Bonaglia MC, Digilio MC, Giannotti A, Marino B, Carrozzo R, Korenberg JR, Danesino C, Sujansky E, Dallapiccola B, Zuffardi O. Deletion of a 5-cM region at chromosome 8p23 is associated with a spectrum of congenital heart defects. Circulation. 2000; 102:432–437. [PubMed: 10908216]

Giglio S, Broman KW, Matsumoto N, Calvari V, Gimelli G, Neumann T, Ohashi H, Voullaire L, Larizza D, Giorda R, Weber JL, Ledbetter DH, Zuffardi O. Olfactory receptor-gene clusters, genomic-inversion polymorphisms, and common chromosome rearrangements. Am J Hum Genet. 2001; 68:874–883. [PubMed: 11231899]

Gilmore L, Cuskelly M, Jobling A, Smith S. Deletion of 8p: a report of a child with normal intelligence. Dev Med Child Neurol. 2001; 43:843–846. [PubMed: 11769273]

Guo WJ, Callif-Daley F, Zapata MC, Miller ME. Clinical and cytogenetic findings in seven cases of inverted duplication of 8p with evidence of a telomeric deletion using fluorescence in situ hybridization. Am J Med Genet. 1995; 58:230–236. [PubMed: 8533823]

Henderson KG, Dill FJ, Wood S. Characterization of an inversion duplication of the short arm of chromosome 8 by fluorescent in situ hybridization. Am J Med Genet. 1992; 44:615–618. [PubMed: 1481820]

Hirayama-Yamada K, Kamisago M, Akimoto K, Aotsuka H, Nakamura Y, Tomita H, Furutani M, Imamura S, Takao A, Nakazawa M, Matsuoka R. Phenotypes with GATA4 or NKX2.5 mutations in familial atrial septal defect. Am J Med Genet A. 2005; 135:47–52. [PubMed: 15810002]

Holder AM, Klaassens M, Tibboel D, de Klein A, Lee B, Scott DA. Genetic factors in congenital diaphragmatic hernia. Am J Hum Genet. 2007; 80:825–845. [PubMed: 17436238]

Hutchinson R, Wilson M, Voullaire L. Distal 8p deletion (8p23.1----8pter): a common deletion? J Med Genet. 1992; 29:407–411. [PubMed: 1619636]

Jay PY, Bielinska M, Erlich JM, Mannisto S, Pu WT, Heikinheimo M, Wilson DB. Impaired mesenchymal cell function in Gata4 mutant mice leads to diaphragmatic hernias and primary lung defects. Dev Biol. 2007; 301:602–614. [PubMed: 17069789]

Johnson MC, Hing A, Wood MK, Watson MS. Chromosome abnormalities in congenital heart disease. Am J Med Genet. 1997; 70:292–298. [PubMed: 9188669]

Kuo CT, Morrisey EE, Anandappa R, Sigrist K, Lu MM, Parmacek MS, Soudais C, Leiden JM. GATA4 transcription factor is required for ventral morphogenesis and heart tube formation. Genes Dev. 1997; 11:1048–1060. [PubMed: 9136932]

Lopez I, Bafalliu JA, Bernabe MC, Garcia F, Costa M, Guillen-Navarro E. Prenatal diagnosis of de novo deletions of 8p23.1 or 15q26.1 in two fetuses with diaphragmatic hernia and congenital heart defects. Prenat Diagn. 2006; 26:577–580. [PubMed: 16700088]

Macmillin MD, Suri V, Lytle C, Krauss CM. Prenatal diagnosis of inverted duplicated 8p. Am J Med Genet. 2000; 93:94–98. [PubMed: 10869109]

Marino B, Reale A, Giannotti A, Digilio MC, Dallapiccola B. Nonrandom association of atrioventricular canal and del (8p) syndrome. Am J Med Genet. 1992; 42:424–427. [PubMed: 1609823]

Mattei JF, Mattei MG, Ardissone JP, Coignet J, Giraud F. Clinical, enzyme, and cytogenetic investigations in three new cases of trisomy 8p. Hum Genet. 1980; 53:315–321. [PubMed: 7372335]

Minelli A, Floridia G, Rossi E, Clementi M, Tenconi R, Camurri L, Bernardi F, Hoeller H, Previde Re C, Maraschio P, et al. D8S7 is consistently deleted in inverted duplications of the short arm of chromosome 8 (inv dup 8p). Hum Genet. 1993; 92:391–396. [PubMed: 7901142]

Molkentin JD, Lin Q, Duncan SA, Olson EN. Requirement of the transcription factor GATA4 for heart tube formation and ventral morphogenesis. Genes Dev. 1997; 11:1061–1072. [PubMed: 9136933]

Nemer G, Fadlalah F, Usta J, Nemer M, Dbaibo G, Obeid M, Bitar F. A novel mutation in the GATA4 gene in patients with Tetralogy of Fallot. Hum Mutat. 2006; 27:293–294. [PubMed: 16470721]

Okubo A, Miyoshi O, Baba K, Takagi M, Tsukamoto K, Kinoshita A, Yoshiura K, Kishino T, Ohta T, Niikawa N, Matsumoto N. A novel GATA4 mutation completely segregated with atrial septal defect in a large Japanese family. J Med Genet. 2004; 41:e97. [PubMed: 15235040]

Orye E, Craen M. A new chromosome deletion syndrome. Report of a patient with a 46,XY,8p- chromosome constitution. Clin Genet. 1976; 9:289–301. [PubMed: 1261067]

Ostergaard GZ, Tommerup N. The 8p-syndrome. Ann Genet. 1989; 32:87–91. [PubMed: 2667457]

Ozkinay F, Kanit H, Onay H, Cogulu O, Gunduz C, Ercal D, Ozkinay C. Prenatal diagnosis of de novo unbalanced translocation 8p;21q using subtelomeric probes. Genet Couns. 2006; 17:315–320. [PubMed: 17100200]

Paez MT, Yamamoto T, Hayashi K, Yasuda T, Harada N, Matsumoto N, Kurosawa K, Furutani Y, Asakawa S, Shimizu N, Matsuoka R. Two patients with atypical interstitial deletions of 8p23.1: mapping of phenotypical traits. Am J Med Genet A. 2008; 146A:1158–1165. [PubMed: 18393291]

Patil SR, Hanson JW. Partial 8p- syndrome. J Genet Hum. 1980; 28:123–129. [PubMed: 7205196]

Pecile V, Petroni MG, Fertz MC, Filippi G. Deficiency of distal 8p--report of two cases and review of the literature. Clin Genet. 1990; 37:271–278. [PubMed: 2190718]

Pehlivan T, Pober BR, Brueckner M, Garrett S, Slaugh R, Van Rheeden R, Wilson DB, Watson MS, Hing AV. GATA4 haploinsufficiency in patients with interstitial deletion of chromosome region 8p23.1 and congenital heart disease. Am J Med Genet. 1999; 83:201–206. [PubMed: 10096597]

Pettenati MJ, Rao N, Johnson C, Hayworth R, Crandall K, Huff O, Thomas IT. Molecular cytogenetic analysis of a familial 8p23.1 deletion associated with minimal dysmorphic features, seizures, and mild mental retardation. Hum Genet. 1992; 89:602–606. [PubMed: 1511976]

Poirier O, Nicaud V, McDonagh T, Dargie HJ, Desnos M, Dorent R, Roizès G, Schwartz K, Tiret L, Komajda M, Cambien F. Polymorphisms of genes of the cardiac calcineurin pathway and cardiac hypertrophy. Eur J Hum Genet. 2003; 11:659–664. [PubMed: 12939651]

Posch MG, Perrot A, Schmitt K, Mittelhaus S, Esenwein EM, Stiller B, Geier C, Dietz R, Gessner R, Ozcelik C, Berger F. Mutations in GATA4, NKX2.5, CRELD1, and BMP4 are infrequently found in patients with congenital cardiac septal defects. Am J Med Genet A. 2008; 146A:251–253. [PubMed: 18076106]

Rajagopal SK, Ma Q, Obler D, Shen J, Manichaikul A, Tomita-Mitchell A, Boardman K, Briggs C, Garg V, Srivastava D, Goldmuntz E, Broman KW, Benson DW, Smoot LB, Pu WT. Spectrum of heart disease associated with murine and human GATA4 mutation. J Mol Cell Cardiol. 2007; 43:677–685. [PubMed: 17643447]

Reamon-Buettner SM, Borlak J. GATA4 zinc finger mutations as a molecular rationale for septation defects of the human heart. J Med Genet. 2005; 42:e32. [PubMed: 15863664]

Reamon-Buettner SM, Cho SH, Borlak J. Mutations in the 3'-untranslated region of GATA4 as molecular hotspots for congenital heart disease (CHD). BMC Med Genet. 2007; 8:38. [PubMed: 17592645]

Reddy KS. A paternally inherited terminal deletion, del(8)(p23.1)pat, detected prenatally in an amniotic fluid sample: a review of deletion 8p23.1 cases. Prenat Diagn. 1999; 19:868–872. [PubMed: 10521848]

Rodewald A, Stengel-Rutkowski S, Schulz P, Cleve H. New chromosomal malformation syndromes. I. Partial monosomy 8p. An attempt to establish a new chromosome deletion syndrome. Eur J Pediatr. 1977; 125:45–57. [PubMed: 870324]

Sarkozy A, Conti E, Neri C, D'Agostino R, Digilio MC, Esposito G, Toscano A, Marino B, Pizzuti A, Dallapiccola B. Spectrum of atrial septal defects associated with mutations of NKX2.5 and GATA4 transcription factors. J Med Genet. 2005; 42:e16. [PubMed: 15689439]

Sarkozy A, Esposito G, Conti E, Digilio MC, Marino B, Calabro R, Pizzuti A, Dallapiccola B. CRELD1 and GATA4 gene analysis in patients with nonsyndromic atrioventricular canal defects. Am J Med Genet A. 2005; 139:236–238. [PubMed: 16278904]

Scarbrough PR, Carroll AJ, Finley WH, Bridges DR. A de novo 3p;8p unbalanced translocation resulting in partial dup(3p) and partial del(8p). J Med Genet. 1987; 24:174–177. [PubMed: 3573002]

Schluterman MK, Krysiak AE, Kathiriya IS, Abate N, Chandalia M, Srivastava D, Garg V. Screening and biochemical analysis of GATA4 sequence variations identified in patients with congenital heart disease. Am J Med Genet A. 2007; 143A:817–823. [PubMed: 17352393]

Sherr EH, Owen R, Albertson DG, Pinkel D, Cotter PD, Slavotinek AM, Hetts SW, Jeremy RJ, Schilmoeller G, Schilmoeller K, Wakahiro M, Barkovich AJ. Genomic microarray analysis identifies candidate loci in patients with corpus callosum anomalies. Neurology. 2005; 65:1496–1498. [PubMed: 16275846]

Shimokawa O, Kurosawa K, Ida T, Harada N, Kondoh T, Miyake N, Yoshiura K, Kishino T, Ohta T, Niikawa N, Matsumoto N. Molecular characterization of inv dup del(8p): analysis of five cases. Am J Med Genet A. 2004; 128A:133–137. [PubMed: 15214003]

Shimokawa O, Miyake N, Yoshimura T, Sosonkina N, Harada N, Mizuguchi T, Kondoh S, Kishino T, Ohta T, Remco V, Takashima T, Kinoshita A, Yoshiura K, Niikawa N, Matsumoto N. Molecular characterization of del(8)(p23.1p23.1) in a case of congenital diaphragmatic hernia. Am J Med Genet A. 2005; 136:49–51. [PubMed: 15937941]

Slavotinek A, Lee SS, Davis R, Shrit A, Leppig KA, Rhim J, Jasnosz K, Albertson D, Pinkel D. Fryns syndrome phenotype caused by chromosome microdeletions at 15q26.2 and 8p23.1. J Med Genet. 2005; 42:730–736. [PubMed: 16141010]

Slavotinek AM, Moshrefi A, Davis R, Leeth E, Schaeffer GB, Burchard GE, Shaw GM, James B, Ptacek L, Pennacchio LA. Array comparative genomic hybridization in patients with congenital diaphragmatic hernia: mapping of four CDH-critical regions and sequencing of candidate genes at 15q26.1-15q26.2. Eur J Hum Genet. 2006; 14:999–1008. [PubMed: 16736036]

Takash W, Canizares J, Bonneaud N, Poulat F, Mattei MG, Jay P, Berta P. SOX7 transcription factor: sequence, chromosomal localisation, expression, transactivation and interference with Wnt signalling. Nucleic Acids Res. 2001; 29:4274–4283. [PubMed: 11691915]

Taniguchi K, Hiraoka Y, Ogawa M, Sakai Y, Kido S, Aiso S. Isolation and characterization of a mouse SRY-related cDNA, mSox7. Biochim Biophys Acta. 1999; 1445:225–231. [PubMed: 10320775]

Tomita-Mitchell A, Maslen CL, Morris CD, Garg V, Goldmuntz E. GATA4 sequence variants in patients with congenital heart disease. J Med Genet. 2007; 44:779–783. [PubMed: 18055909]

Weleber RG, Verma RS, Kimberling WJ, Fieger HG Jr. lubs HA. Duplication-deficiency of the short arm of chromosome 8 following artificial insemination. Ann Genet. 1976; 19:241–247. [PubMed: 1087853]

Wu BL, Schneider GH, Sabatino DE, Bozovic LZ, Cao B, Korf BR. Distal 8p deletion (8)(p23.1): an easily missed chromosomal abnormality that may be associated with congenital heart defect and mental retardation. Am J Med Genet. 1996; 62:77–83. [PubMed: 8779331]

Yenamandra A, Perrone R, McLaughlin J, Mehta L. Inverted duplication/deletion of chromosome 8p: mild clinical phenotype. Am J Med Genet. 1999; 82:91–93. [PubMed: 9916851]

Zahed L, Der Kaloustian V, Batanian JR. Familial complex chromosome rearrangement giving rise to balanced and unbalanced recombination products. Am J Med Genet. 1998; 79:30–34. [PubMed: 9738865]

Zhang C, Basta T, Klymkowsky MW. SOX7 and SOX18 are essential for cardiogenesis in Xenopus. Dev Dyn. 2005; 234:878–891. [PubMed: 16193513]

Zuffardi, O.; Ciccone, R.; Giglio, S.; Pramparo, T. Inversion Chromosomes. In: Lupski, JR.; Stankiewicz, P., editors. Genomic Disorders: The Genomic Basis of Disease. Springer; New York: 2006. p. 289-299.

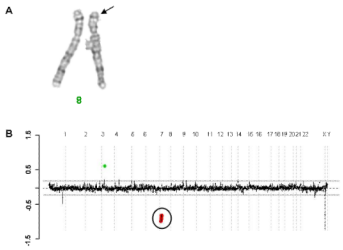

Figure 1.

Partial karyotype and clinically based array comparative genomic hybridization results for Patient 4. A) Chromosome 8 partial karyotype showing an interstitial deletion of 8p23.1. B) Prenatal clinical array (BCM CMA V6) confirming deletion of chromosome 8p23.1 with the oligonucleotide probes detecting the copy number loss marked in red. This array also detected a gain in copy number of four genes (*SLC2A9*, *WDR1*, *ZNF518B*, *MIST*) on chromosome 4 (marked in green) all of which are lie partially or completely within known copy number variants.

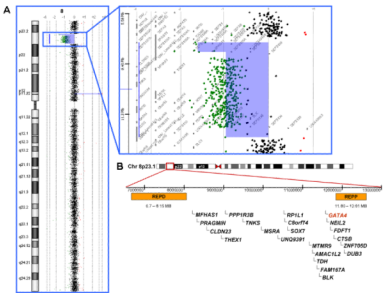

Figure 2.

A) High resolution array comparative genomic hybridization analysis of Patient 4 showing an interstitial deletion of chromosome 8p23.1. B) Graphical representation of unique genes (RefSeq reviewed or validated) located between segmental duplications 8p-OR-REPD and 8p-OR-REPP which are deleted in all of the patients reported in this study. Defensin genes, which are present in multiple copies within segmental duplications, are not shown.

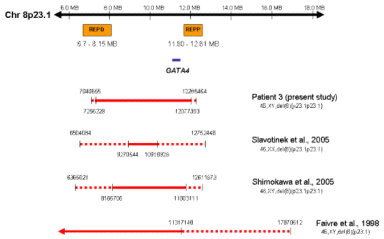

Figure 3.

Molecularly defined deletions of 8p23.1 associated with CDH. Solid and dashed red lines indicate the minimally and maximally deleted regions, respectively, for each patient. The approximate location of the segmental duplications 8p-OR-REPD and 8p-OR-REPP are represented by green bars. *GATA4*, represented by the blue bar, is located within the minimal deleted region for CDH.

Table I

GATA4 Alterations in Familial Heart Defects

Reference	Alteration (AA change)	Phenotype	Penetrance	Families	Control chromosomes	Functional studies
Garg et al., 2003	Gly296Ser	Non-syndromic ASD (+/- VSD, PVS, cardiac valve insufficiency, AVSD)	100% of clinically evaluated affected individuals	1 Family	0/6000 (and 0/10 evaluated unaffected family members)	Disrupted interaction with *TBX5*, decreased DNA binding affinity, hypomorphic transactivation ability
	Glu359fs	Non-syndromic ASD	100% of evaluated affected individuals	1 family	0/6000 (and 0/2 evaluated unaffected family members)	Transcriptionally inactive
Okubo et al., 2004	Ser358fs	ASD +/- PS	100% of clinically evaluated affected individuals	1 family	0/200 (and 0/13 evaluated unaffected family members)	Frameshift & premature STOP codon at amino acid 403, likely results in haploinsufficiency, similar to 1075delG described by Garg et al., 2003
Sarkozy et al., 2005b	Gly296Ser	ASD, PVS, no conduction abnormalities	2/2 Affected individuals (family 1), 3/3 clinically evaluated affected individuals (family 2)	2/16 Families total	NR	See Garg et al., 2003
Hirayama-Yamada et al., 2005	Glu359fs	ASD (5 individuals) dextrocardia (1 individual)	6/7 Affected individuals (family 1)	1 Family/16 families	NR	
	Ser52Phe	ASD (3 individuals)	3/3 Affected individuals (family 2)	1 Family/16 families	0/202 Control chromosomes from healthy Japanese individuals	Decreased transcriptional activity (Schluterman et al., 2007), normal subcellular localization & DNA binding activity, Ser52 located in transactivation domain 1 (TAD1)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; NR, not reported; PS, pulmonary stenosis; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.

Table II

GATA4 Alterations in Sporadic Heart Defects

Reference	Nucleotide Change[¥]	AA Change	Phenotype	Frequency	Inheritance pattern	Control Chromosomes	Functional studies
Poirier et al., 2003	NR	Ala411Val[§]	Cardiac hypertrophy	Unclear (95 individuals screened)	NR	NR	NR
Poirier et al., 2003	NR	Ser377Gly	Cardiac hypertrophy	Unclear (95 individuals screened)	NR	NR	NR
Reamon-Buettner et al., 2005	874T>C	Cys292Arg	VSD, ASD, AVSD		NR	0/40	NR
	687G>T	Arg229Ser	VSD, ASD, AVSD		NR	0/130	NR
	631T>C	Phe211Leu	VSD, AVSD		NR	0/130	NR
	731A>G	Tyr244Cys	VSD, AVSD		NR	0/130	NR
	743A>G	Asn248Ser	ASD, AVSD		NR	0/2	NR
	782T>C	Leu261Pro	VSD, ASD		NR	NR	NR
	677delC	Pro226fs	AVSD		NR	0/2	NR
	700G>A	Gly234Ser	AVSD		NR	0/4	NR
	755G>C	Arg252Pro	AVSD		NR	0/4	NR
	796C>T	Arg266Ter	AVSD		NR	0/2	NR
	818A>G	Asn273Ser	AVSD		NR	0/2	NR
	830C>T	Thr277Ile	AVSD		NR	NR	NR
	848G>A	Arg283His	AVSD, overriding aorta, ASD		NR	0/2	NR
	855T>G	Asn285Lys	AVSD		NR	NR	NR
	905A>G	His302Arg	AVSD		NR	NR	NR
	622T>C	Phe208Leu	VSD		NR	0/2	NR
	640G>A	Gly214Ser	VSD		NR	NR	NR
	668T>C	Met223Thr	VSD		NR	0/2	NR
	715A>G	Asn239Asp	VSD		NR	NR	NR
	716A>G	Asn239Ser	VSD		NR	NR	NR
	779G>A	Arg260Gln	VSD		NR	NR	NR
	779G>A	Ile255Thr	ASD		NR	NR	NR
	881C>T	Ala294Val	ASD		NR	NR	NR

Reference	Nucleotide Change[¥]	AA Change	Phenotype	Frequency	Inheritance pattern	Control Chromosomes	Functional studies
Nemer et al., 2006	648C>G	Glu216Asp	TOF	2/26 Patients with TOF	De novo in both patients	0/446	Reduced transcriptional activity in reporter assay
Reamon-Buettner et al., 2007	1288C>G	Leu430Val	AVSD		NR	NR	NR
	1081A>G	Met361Val	VSD		NR	NR	NR
	1130G>A	Ser377Asn	VSD		NR	NR	NR
	1324G>A	Ala442Thr	VSD		NR	NR	NR
	1295T>C	Leu432Ser	ASD		NR	NR	NR
	1288C>G	Leu430Val	ASD		NR	NR	NR
Rajagopal et al., 2007	487C>T	Pro163Ser	ECD	1/43 Patients with ECD	Paternal, unaffected father	0/600	NR
	1037C>T	Ala346Val	ECD	1/43 Patients with ECD	Maternal, unaffected mother	0/600	NR
	886G>T	Gly296Cys	Secundum ASD, PVS	1/8 Patients with septal defects	Paternal, affected father (persistent left superior vena cava)	0/500	NR
	1207C>A	Leu403Met	Hypoplastic RV, sinus venosus ASD	1/9 Patients with RV hypoplasia	Unknown, no parental DNA available	0/500	NR
Tomita-Mitchell et al., 2007	278G>C[§]	Gly93Ala[§]	Secundum ASD	1/222 ASD patients	Mother carrier, father unknown	0/318	NR
	946C>G[§]	Gln316Glu[§]	ASD, small muscular VSDs, mild PVS	1/137 VSD patients	Both parents unknown	0/318	NR
	1232C>T[§]	Ala411Val[§]	VSD	1/137 VSD patients	Both parents unknown	0/318	NR
	1273G>A[§]	Asp425Asn[§]	ASD	1/222 ASD patients	Mother carrier, father not carrier	0/528	NR
	1273G>A[§]	Asp425Asn[§]	TOF	1/201 TOF patients	Both parents unknown	0/528	NR
Posch et al., 2008	1232C>T[§]	Ala411Val[§]	Cribriform ASD and PAPVR	1/205 patients with congenital septal defects	unknown	0/600	NR

ASD, atrial septal defect; AVSD, atrioventricular septal defect; ECD, endocardial cushion defect; NR, not reported; PAPVR, partial anomalous pulmonary venous return; PVS, pulmonary valve stenosis; RV, right ventricle; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

[§]Documented in SNP database but no further details available.

[¥]Nucleotide +1 is the A of the ATG translation initiation codon.

TABLE III

Summary of Reported Cases Involving Deletion of 8p23.1

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
		INTERSTITIAL DELETIONS		
Present study, Patient 1	46,XY,del(8)(p23.1p23.1)	Complete AVSD (unbalanced), complex single ventricle, double outlet right ventricle, pulmonary atresia, left atrioventricular valve atresia, hypoplastic LV, D-transposition of the great vessels		Possible thinning of corpus callosum, large anterior fontanelle, dysmorphic features, 2-vessel umbilical cord
Present study, Patient 2	46,XY,del(8)(p23.1p23.1)	AVSD (unbalanced), left atrioventricular valve atresia, hypoplastic LV, severe tricuspid regurgitation, absent intrahepatic inferior vena cava, hemiazygos continuation to left SVC		Symmetrical intrauterine growth retardation, familial postaxial polydactyly of the left hand
Present study, Patient 3	46,XY,del(8)(p23.1p23.1)	Complete AVC (balanced type A), mild AV regurgitation, hypoplastic aortic arch, narrow left ventricular outflow tract	Large anterior CDH with left lobe of liver in anterior mediastinum, left lung hypoplasia	Small sacral dimple but no evidence of spinal abnormalities
Present study, Patient 4	46,XY,del(8)(p23.1p23.1)	Complete AVSD (balanced), small aortic valve, bilateral peripheral pulmonary stenosis, mild right ventricular dilatation		Small sacral dimple but no evidence of spinal abnormalities
Orye and Craen, 1976	46,XY,del(8)(pter→p23::p21→qter)*			MR, slow growth, dysmorphic features, broad chest, puffy hands and feet
Hutchinson et al., 1992; Giglio et al., 2000	46,XY,del(8)(pter→p23.2::p22→qter)	PS, PFO		Partial agenesis of corpus callosum
Digilio et al., 1998	del(8)(p21p23)	AVSD, subaortic stenosis, persistent left SVC		Slow growth, microcephaly, MR, dysmorphic features, broad chest, hypospadias
Digilio et al., 1998	del(8)(p21p23)	Complete AVSD, PS, persistent left SVC		
Digilio et al., 1998, 1999	del(8)(p21p23)	AVSD, PS, dextrocardia, persistent left SVC, hypoplastic RV		Slow growth, microcephaly, MR, dysmorphic features, broad chest, hypospadias, cryptorchidism
Pehlivan et al., 1999	46,XX,del(8)(p23.1p23.2)	Secundum ASD, PVS, left SVC, cardiomyopathy		Basal ganglia calcification, arched palate, hypothyroidism, atrophic pancreas, lordosis, renal artery stenosis
Pehlivan et al., 1999	46,XX,del(8)(p23.1p23.2)	AVSD, TOF		Language delay, MR, dysmorphic features, esotropia, scoliosis
Reddy, 1999	46,XY,del(8)(p23.1p23.1) or add(8)(p23.1)[20]	ASD, VSD, PS		Hepatosplenomegaly, feet deformity
Reddy, 1999	46,XY,del(8)(p23.1p23.1). ish del(8)(p23.1p23.1)(wcp8+, 8ptel+)	ASD		Developmental delay, behavioral disorder
Shimokawa et al., 2005	46,XY,del(8)(p23.1p23.1)	ASD	Left CDH with herniation of abdominal organs into left thorax, left pulmonary hypoplasia	Bilateral cryptorchidism
Slavotinek et al., 2005; 2006	46,XY,del(8)(p23.1p23.1)	Large ASD, VSD	Left CDH, pulmonary hypoplasia, pleural effusions	Ascites, polyhydramnios

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
Lopez et al., 2006	46,XY,del(8)(p23.1p23.1)	AVSD	Left CDH, severe pulmonary hypoplasia, Incomplete lobation of right lung	Dysmorphic features, intestinal malrotation
Paez et al., 2008	del(8)(p22p23.3)	Ebstein anomaly, hypoplastic RV, PVS, mild regurgitation of mitral valve due to stenosis, pulmonary artery HTN, ASD, VSD		Mild MR, microcephaly
Paez et al., 2008	del(8)(p23.1p23.1)	ASD, PVS, VSD, AVSD, persistent left SVC		Gonadotropin-dependent early expression of puberty, moderate MR, mild microcephaly, facial dysmorphic features, developmental delay
Totals for this subgroup		**Heart defects: 17/18 (94.4%)**	**CDH: 4/18 (22.2%)**	
		TERMINAL DELETIONS		
Lubs and Lubs 1973; Digilio et al., 1998	del(8)(p21)	ASD, VSD, persistent left SVC		
Tallemite et al., 1975; Digilio et al., 1998	del(8)(p21)	VSD, PS		
Guanti et al., 1976; Digilio et al., 1998	del(8)(p21)	Single ventricle, PS, transposition of great arteries		
Leisti and Aula 1977; Digilio et al., 1998	del(8)(p21)	VSD		
Rodewald et al., 1977; Digilio et al., 1998	46,XY,del(8)(p21)	PS, ASD		MR, behavior anomalies, craniofacial dysmorphic features, barrel chest, phalangeal abnormalities, clinodactyly
Reiss et al., 1979; Digilio et al., 1998	46,XY,del(8)(p22)	AVSD with L-R shunt and pulmonary HTN		Developmental delay, dysmorphic features, bilateral inguinal hernias
Patil and Hanson, 1980	del(8)(p21)			CNS and craniofacial abnormalities, spasticity with hyperreflexia
Marino et al 1982; Digilio et al., 1999	de(8)(p21)	Complete AVSD, pulmonary stenosis		
Dobyns et al., 1985; Digilio et al., 1998	del(8)(p21)	AVSD, PS, persistent left SVC, double-orifice mitral valve		
Brocker-Vriends et al., 1986; Digilio et al., 1998	(half of 8p deleted)**	TOF, double-outlet RV, left persistent SVC		Dysmorphic features
Brocker-Vriends et al., 1986; Digilio et al., 1998	del(8)(p21)	Complete AVSD, double-outlet RV, PDA, persistent left SVC		Dysmorphic features
Kiss and Osztovics, 1987	46,XY,del(8)(p21)			Craniofacial dysmorphic features
Fryns et al., 1989; Devriendt et al., 1989	46,XY,del(8)(p23.1)			Delayed psychomotor and speech development, behavioral problems, two truncal café-au-lait spots, cryptorchidism
Ostegaard and Tommerup, 1989	46,XY,del(8)(p21.3)	TOF		Microcephaly, facial dysmorphic features, puffy feet, cryptorchidism
Blennow and Brondum-Nielsen, 1990	46,XX,del(8)(p23)			Developmental delay, moderate MR, strabismus
Pecile et al., 1990; Digilio et al., 1998	46,XY,del(8)(p22)	SM		Dysmorphic features, talipes equinovarus, puffy hands and feet
Pecile et al., 1990; Digilio et al., 1998	46,XX,del(8)(p23.1)	AVSD, PS	Left CDH	Dysmorphic features, puffy hands and feet
Fraer et al., 1992	46,XY,del(8)(p23.1)	AVSD	Left CDH, pulmonary hypoplasia	Dysmorphic features

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
Hutchinson et al., 1992	del(8)(p23)			Premature adrenarche, aggressive behavior, visual abnormalities, dysmorphic features
Hutchinson et al., 1992	del(8)(p23)			Esophageal atresia/tracheoesophageal fistula, dysmorphic features, preaxial polydactyly, 13 pairs of ribs and extra thoracic vertebrae, left cryptorchidism, horseshoe kidneys
Hutchinson et al., 1992; Digilio et al., 1998	del(8)(p23)	PFO, mild PS		CNS abnormalities, dysmorphic features
Hutchinson et al., 1992; Digilio et al., 1998	del(8)(p23)	VSD's, Ebstein's anomaly, PDA, pulmonary hypertension		Developmental delay, strabismus, dysmorphic features, right hydronephrosis
Hutchinson et al., 1992; Digilio et al., 1998	del(8)(p23)	Complete AVSD, common AV valve, double-outlet RV, small LV, severe PS		Dysmorphic features
Marino et al 1992; Giglio et al., 2000	46,XY,del(8)(p21)	PS, Persistent left SVC, AVSD, dextrocardia, hypoplastic RV		Severe MR, craniofacial dysmorphic features, finger anomalies, hypospadias, cryptorchidism
Digilio et al, 1993	46,XY,del(8)(p21)	Complete AVSD, PS, hypoplastic RV		Microcephaly, dysmorphic features, scrotal hypoplasias
Digilio et al., 1993, 1999	del(8)(p23)	Complete AVSD, pulmonary stenosis		
Digilio et al., 1993; Giglio et al., 2000	46,XY,del(8)(p21)	PS, AVC		Slight MR, scrotal hypospadias
Devriendt et al., 1995; Digilio et al., 1998	46,XX,del(8)(p23.1)	ASD, PS		Aggressive behavior, mild MR, immobile soft palate, facial dysmorphic features
Wu et al., 1996; Digilio et al., 1998	del(8)(p23.1)	ASDs, PVS, AV regurgitation		Mild MR, speech delay, behavioral and attention disorders, post-traumatic seizures, abnormal EEG, craniofacial dysmorphic features
Wu et al., 1996; Digilio et al., 1998	del(8)(p23.1)	HLHS, mitral/aortic stenosis, hypoplastic aortic arch		Dysmorphic features, puffy feet, bilateral hydroureternephrosis
Wu et al., 1996	del(8)(p23.1)			Mild motor delays, speech delay, behavioral problems
Claeys et al., 1997	46,XX,del(8)(p22.1)			Hypotonia, mild MR, delayed development, corpus callosum hypoplasia, dysmorphic features, puffy lower limbs
Claeys et al., 1997; Devriendt et al., 1999	46,XY,del(8)(p23.1)	AVSD, isomerism with azygos continuation, hypoplastic RV, PS, AS		Absence epilepsy, mild MR, microcephaly, hyperactivity, dysmorphic features, partial small bowel malrotation, bilateral cryptorchidism
Claeys et al., 1997; Devriendt et al., 1999	del(8)(p23.1)	ASD, PS		Mild MR, microcephaly, aggression, hypernasal speech
Claeys et al., 1997; Devriendt et al., 1999	46,XY,del(8)(p23.1)	AVSD, univentricular heart with hypoplastic LV, double inlet RV, double outlet RV, PS, dominance of right coronary artery		Developmental delay, dysmorphic features, hypertrichosis (forehead and arms), mildly swollen hands and feet
Claeys et al., 1997; Devriendt et al., 1999	del(8)(p23.1)			Mild MR, behavioral problems, epilepsy, cryptorchidism
Johnson et al., 1997	46,XX,del(8)(p23.1)	TOF, AVSD		Developmental delay, scoliosis
Johnson et al., 1997	46,XY,del(8)(23.1)	ASD, VSD		Developmental delay
Devriendt et al., 1998	46,XY,del(8)(p21.3)	AVSD, hypoplastic right ventricle, double-outlet RV, malposition of large vessel side to side, associated PVS		Growth retardation, delayed psychomotor development, hypospadias
Devriendt et al., 1998; 1999	del(8)(p21.3)	AVSD, double-outlet RV, hypoplastic RV, PS, left isomerism		IUGR, delayed development, hypospadias

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
Digilio et al., 1998	del(8)(p21)	AVSD, PS, hypoplastic RV		Slow growth, microcephaly, MR, dysmorphic features, hypospadias
Digilio et al., 1998	del(8)(p23)	ASD, VSD, PAPVR, persistent left SVC		Microcephaly, MR, dysmorphic features, broad chest, hypospadias
Digilio et al., 1998	del(8)(p23)	ASD, absent left mediastinal pleura and pericardium		MR, seizures, dysmorphic features, broad chest, hypospadias
Digilio et al., 1998	del(8)(p23)	AVSD, PS		Microcephaly, MR, dysmorphic features, broad chest
Digilio et al., 1998	mos del(8)(p23pter)	ASD, VSD, PS		Slow growth, MR, seizures, dysmorphic features, broad chest
Digilio et al., 1998	del(8)(p21)	AVSD, subaortic stenosis		Microcephaly, MR, dysmorphic features, broad chest, hypospadias, cryptorchidism
Faivre et al., 1998	del(8)(p23.1)	AVSD, ASD	Posterior left CDH, hypoplastic left lung	Dolichocephaly, edematous eyelids
Pehlivan et al., 1999	46,XY,del(8)(p23.1)	Secundum ASD, VSD		Language delay, microcephaly, abnormal facies
Pehlivan et al., 1999	46,XX,del(8)(p23.1)	Secundum ASD, PVS, mitral valve abnormalities		MR, scoliosis
Pehlivan et al., 1999	46,XX,del(8)(p23.1)			Microcephaly, dysmorphic features
Bhatia et al., 1999	46,XX, del(8)(p23.1)	AVSD, persistent left SVC, hypoplastic right ventricle, pulmonary atresia, tricuspid atresia		Mildly dysmorphic features, nuchal edema
Devriendt et al., 1999	del(8)(p23.1)	ASD, PS		Mild MR, behavioral problems, epilepsy, external ear anomaly
Devriendt et al., 1999	del(8)(p23.1)	ASD, PS		Mildly delayed development, slight microcephaly, behavioral problems
Reddy, 1999	46,XY,del(8)(p23.1)[22]. ish del(8)(p23.1)(8ptel-)			Normal adult
Reddy, 1999	46,XX,del(8)(p23.1)[15 colonies]. ish del(8)(p23.1)(8p tel-)			Normal at birth
Reddy, 1999	mos 46,XX,del(8)(p23.1)[11]/46,XX[39]. ish mos del(8)(p23.1)(8p tel-)[12/25]			Recurrent spontaneous abortions as an adult
Reddy, 1999	46,XX,del(8)(p23.1)[20]			Hypotonia, cerebral palsy, microcephaly, developmental delay, craniofacial abnormalities, eye abnormalities, pectus excavatum
Gilmore et al., 2001	del(8)(p23)			Gross motor development delay, moderate delays in language and social skills until 6 years old
Borys and Taxy, 2004	46,XX,del(8)(p23.1)	ASD	Left CDH, pulmonary hypoplasia	Accessory spleen
Baynam et al., 2008	46,XY,del(8p23.1)	ASD	Left sided CDH and pulmonary hypoplasia, persistent pulmonary hypertension	Cornelia de Lange-like features, CNS abnormalities, dysmorphic features, chylothorax, reduced muscle bulk, cryptorchidism
Totals for this subgroup		**Heart Defects: 45/60 (75%)**	**CDH: 5/60 (8.3%)**	
		INVERTED DUPLICATION DELETION		
Weleber et al., 1976	inv dup del(8)(p11.2→23.1::p23.1→qter)			CNS abnormalities, lacrimal sac fistula, dysmorphic features
Mattei et al., 1980	inv dup del (8)(p11→p23.2::p23.2→qter)			Hypotonia, slow growth, corpus callosum agenesis, dysmorphic features

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
Jensen et al., 1982	46,XY,inv dup del(8)(p21.2→p23.1::p23.1→qter)			Cerebral atrophy, dysmorphic features, asymmetric chest, restricted articular function in all major joints, thoracolumbar scoliosis
Jensen et al., 1982	46,XX,inv dup(8)(p21.1→23.3::p23.3→qter)			Spastic paraparesis, epilepsy, abnormal EEG, dysmorphic features, coloboma, umbilical hernia, supernumerary finger
Dill et al., 1987	46,XX,inv dup del(8)(p12→p23.1::p23.1→qter)			Profound MR, hypotonia, dysmorphic features, scoliosis, long & hyperextensible fingers and toes, partial 2-3 syndactyly of toes
Henderson et al., 1992	46,XX,inv dup del(8)(p12→p23.1::p23.1→qter)			Severe MR
Minelli et al., 1993	inv dup del(8)(p12→p22::p22→qter)			Hypotonia, brain anomalies, MR, dysmorphic facies
Minelli et al., 1993	inv dup del(8)(p12→p22::p22→qter)	Heart malformation		Hypotonia
Minelli et al., 1993	inv dup del(8)(p21.1→p22.1::p22.1→qter)			Hypotonia, brain anomalies, dysmorphic facies
Minelli et al., 1993	inv dup del(8)(p12→p22::p22→qter)			Hypotonia, brain anomalies, MR, dysmorphic facies
Minelli et al., 1993	inv dup del(8)(p12→p22::p22→qter)			Hypotonia, brain anomalies, MR, dysmorphic facies
Minelli et al., 1993	inv dup del(8)(p12→p22::p22→qter)			MR, short stature, dysmorphic facies
Minelli et al., 1993	inv dup del(8)(p12→p22::p22→qter)			Hypotonia, MR, dysmorphic facies
Minelli et al., 1993	inv dup del (8)(p12→p22::p22→qter)			Hypotonia, brain anomalies, MR, short stature, dysmorphic facies
Minelli et al., 1993	inv dup del (8)(p12→p22::p22→qter)			Brain anomalies, MR, dysmorphic features
Minelli et al., 1993	inv dup del (8)(p12→p22::p22→qter)			Hypotonia, brain anomalies, MR, dysmorphic facies
Engelen et al., 1994; de Die-Smulders et al., 1995	inv dup del(8)(p12→p23.1::p23.1→qter)			Hypotonia, psychomotor retardation, facial dysmorphic features
Engelen et al., 1994; de Die-Smulders et al., 1995	inv dup del(8)(p21.1→p22::p22→qter)	Dextrocardia		Severe psychomotor retardation, dysmorphic facies, left kidney hypoplasia
Engelen et al., 1994; de Die-Smulders et al., 1995	inv dup del(8)(p12→p23.1::p23.1→qter)			Severe MR, dysmorphic facies, contractures of extremities, severe scoliosis, left cryptorchidism
Engelen et al., 1994; de Die-Smulders et al., 1995	inv dup del(8)(p12→p23.1::p23.1→qter)			Profound MR, dysmorphic features, severe scoliosis, contractures of lower extremities
Mitchell et al., 1994	46,XY,inv dup del(8)(p12→p23.1::p23.1→qter)			CNS abnormalities, MR, dysmorphic features, bilateral clinodactyly of fifth fingers
de Die-Smulders et al., 1995	inv dup del(8)(p21.1→p22::p22→qter)			CNS abnormalities, dysmorphic features, hearing loss
de Die-Smulders et al., 1995	inv dup del(8)(p11.2→p23.1→p23.1 →qter)	ASD		Agenesis of corpus callosum, psychomotor delay, dysmorphic features
de Die-Smulders et al., 1995	inv dup del(8)(p12→p23.1::p23.1→qter)			Hypotonia, severe MR, developmental delay, facial dysmorphic features
Guo et al., 1995	inv dup del(8)(p11.2→p23.1::p23.1→qter)	ASD, VSD		MR, hypotonia, agenesis of corpus callosum, facial dysmorphic features, umbilical hernia, hydronephrosis
Guo et al., 1995	inv dup del(8)(p11.2→p23.1::p23.1→qter)			MR, hypotonia, developmental delay, partial agenesis of corpus callosum, dysmorphic facies
Guo et al., 1995	inv dup del(8)(p11.2→p23.1::p23.1→qter)			MR, developmental delay, hypotonia, agenesis of corpus callosum, cranial asymmetry, dysmorphic facies

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
Floridia et al., 1996; Giglio et al., 2000	46,XX,dic inv dup del(8)(cen→p23.1::p23.1→qter)			Agenesis of corpus callosum, severe MR
Floridia et al., 1996; Giglio et al., 2000	46,XY,inv dup del(8)(p21→p23.1::p23.1→qter)			Hypoplasia of corpus callosum, severe MR
Yenamandra et al., 1999	46,XX,inv dup del(8)(p12→p23.1::p23.1→qter)			Mild motor delays, speech and language delay, corpus callosum hypoplasia, dysmorphic features, hypoplastic distal phalanges of first toes
Giglio et al., 2000	46,XX,inv dup del(8)(p11.2→p23.1::p23.1→qter)			Severe MR
Macmillin et al., 2000	inv dup del(8)(p11.2→23.1::p23.1→qter)	Limited heart exam: frequent bradycardia		Lumbar and sacral spinal abnormalities, Dandy-Walker variant, bladder distension with bilateral hydronephrosis
Macmillin et al., 2000	inv dup del(8)(p11.2→23.1::p23.1→qter)	Small ASD, multiple small VSDs, mildly depressed LV function, aortic coarctation		CNS abnormalities, Dandy-Walker variant, hypotonic with poor suck, possible gastrointestinal malrotation
Shimokawa et al., 2004	inv dup del(8)(p11.22→23.1::p23.1→qter)	cardiac anomalies		MR, craniofacial, ocular, skeletal anomalies
Shimokawa et al., 2004	inv dup del(8)(p11.1→23.1::p23.1→qter)	cardiac anomalies		MR, craniofacial, ocular, skeletal anomalies
Shimokawa et al., 2004	inv dup del(8)(p11.23→23.1::p23.1→qter)	cardiac anomalies		MR, craniofacial, ocular, skeletal anomalies
Shimokawa et al., 2004	inv dup del(8)(p?12→23.1::p23.1→qter)	cardiac anomalies		MR, craniofacial, ocular, skeletal anomalies
Shimokawa et al., 2004	inv dup del(8)(p12→23.1::p23.1→qter)	cardiac anomalies		MR, craniofacial, ocular, skeletal anomalies
Sherr et al., 2005	46,XX, der(8)del(8)(p23.1)dup(8)(p23.1p12)			Hypotonia, global developmental delay, CNS abnormalities, cerebral palsy
Totals for this subgroup		**Heart Defects: 11/39 (28.2%)**	**CDH: 0/39 (0%)**	
COMPLEX CHROMOSOMAL REARRANGEMENTS				
Mattei et al., 1980	t(8;14)(8pter→8p11→8p23.1::8p23.1→8p11::14q13→14qter)			Hypotonia, CNS abnormalities, dysmorphic features, phalangeal abnormalities
Brocker-Vriends et al., 1985	46,XY,der(8),t(8;13)(p21;q22),t(2;19)(q21;q13)			Mild dysmorphic features, laryngomalacia (infant)
Brocker-Vriends et al., 1985	46,XX,der(8),t(8;13)(p21;q22)			Pyloric stenosis, elbow hyperextensibility
van Balkom et al., 1992	46,XX,del(8)(p21)/46,XX,dup(8)(p21pter)			Agenesis of corpus callosum, short first metacarpals, short first metatarsal
Scarbrough et al., 1987	46,XX,der(8),t(3;8)(p21;p23)	2/6 systolic murmur		Hypotonia, dysmorphic features, long trunk, camptodactyly
Sujansky et al., 1993; Giglio et al., 2000	46,XX,rec(8)(qter→q22::p23.1→qter)	PS, PDA, ASD, VSD		MR
Digilio et al., 1994; Ciccone et al., 2006	mos 46,XX,psu dic(8)(p23.2)/46,XX,del(8)(p23.1)			Severe MR, dysmorphic features, kyphoscoliosis, globous abdomen, premature grey hair (at 14 years old)
Zahed et al., 1998	46,XX,rec(8)t(8;9)(p23.1;q34)mat			Hypotonia, developmental delay, hyperactivity, dysmorphic features
Giglio et al., 2000	46,XY,der(8)t(1;8)(q42;p23.1)pat	PS, PFO		MR, seizures, pyloric stenosis
Giglio et al., 2000	46,XY,der(8)t(8;16)(p21.3;q24)	PS, VSD, right aortic arch		Slight MR
Giglio et al., 2000	46,XY,der(8)t(8;16)(p21.3;q24)	PS		Slight MR
de Vries et al., 2001	46,XY.ish der(8)t(8;20)(p23;p13) (D8S2333-)	Murmur but no structural abnormalities		Delayed speech & language, dysmorphic features, blocked tear ducts, cryptorchidism

Reference	Cytogenetic findings	Heart	Diaphragm/Lungs	Other
de Vries et al., 2001	46,XY.ish der(8)t(8;20)(p23;p13) (D8S2333-)			Mild MR, behavioral disturbances, slightly delayed motor development, dysmorphic features
Bosse et al., 2004	45,X,dic(Y;8)(q11.23;p23.1)			Mild MR, psychomotor delay, speech delay, aggression, dysmorphic features, talipes planus
Ozkinay et al., 2006	46,XY,der(8)t(8p;21q)dn			IUGR, CNS abnormalities, pelvicaliectasis
Totals for this subgroup		**Heart Defects: 6/15 (40%)**	**CDH: 0/15 (0%)**	

ASD, atrial septal defect; AVC, atrioventricular canal; AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CNS, central nervous system; EEG, electroencephalogram,; HLHS, hypoplastic left heart syndrome; HTN, hypertension; IUGR, intrauterine growth retardation; LV, left ventricle; L-R, left-right; MR, mental retardation; PFO, patent foramen ovale; PDA, patent ductus arteriosus; PS, pulmonary stenosis; PVS, pulmonary valve stenosis; RV, right ventricle; SVC, superior vena cava; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

* interstitial deletion, but insufficient resolution to determine if it deletes region of interest.

** karyotype nomenclature not provided.