American Journal of Medical Genetics 116A:268–271 (2003)

Clinical Report

Interrupted Aortic Arch in a Child With Trisomy 5q31.1q35.1 due to a Maternal (20;5) Balanced Insertion

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Complex congenital heart defects (CHD) are associated with a variety of single gene abnormalities and chromosomal rearrangements. Of the various forms of CHD, aortic arch interruption, a conotruncal heart defect, is relatively uncommon. Here we report a male neonate with aortic arch interruption type B, secundum atrial septal defect, perimembranous ventricular septal defect, patent ductus arteriosus, aortic and subaortic stenosis, and trisomy 5q31.1q35.1 resulting from a maternal balanced insertion (20;5). Chromosomal deletions, including deletion 22q11, have been reported with interrupted aortic arch (IAA); however, to our knowledge this is the first report of a trisomy of distal chromosome 5q associated with aortic arch interruption. Here we compare this child's features to other cases of trisomy 5q31.1q35.1, and review other causes of IAA. We conclude that gene dosage in this chromosomal region likely influences aortic arch development. © 2003 Wiley-Liss, Inc.

KEY WORDS: **trisomy 5q; aortic anomalies; ventricular septal defect; atrial septal defect; chromosomal duplication**

INTRODUCTION

Interrupted aortic arch (IAA) is a rare and often lethal form of conotruncal congenital heart defect with an estimated population prevalence of 5.8 per 100,000 live births [Loffredo, 2000]. There are three main types of IAA (A, B, and C), defined in 1959 by the anatomical site of the aortic interruption [Celoria and Patton, 1959]. Type B is the most common form of IAA, and presents as an aortic interruption between the left carotid and left subclavian arteries. Infants with type B IAA who survive have an obligatory ventricular septal defect (VSD) and a patent ductus arteriosus which allows shunting of deoxygenated blood to the systemic circulation [Loffredo et al., 2000]. In addition, infants with IAA type B often have a secundum atrial septal defect (ASD) and subaortic stenosis. IAA type B is thought to arise from a defect in neural crest cell development within the aortic arch system [Kirby et al., 1983], and occurs in association with DiGeorge syndrome and deletions of chromosome 22q11 [Driscoll et al., 1993]. Other chromosomal regions implicated in IAA type B include chromosome 18, and regions 4q21q25, and 8p23 [Fukushima et al., 1992; Driscoll et al., 1993; Wu et al., 1996; Loffredo et al., 2000]. In this report, we describe a child with IAA type B and trisomy 5q31.1q35.1 whose chromosomal trisomy was due to a maternal (20;5) balanced insertion. This observation suggests that genes within 5q31q35 contribute in a dosage-sensitive manner to aortic development.

CLINICAL REPORT

A 2-day-old male infant was referred for evaluation of complex congenital heart defects (CHD) and a

Grant sponsor: March of Dimes-Birth Defects Foundation; Grant number: 6-FY99-425; Grant sponsor: National Institutes of Health; Grant number: HD34446.

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Received 27 February 2001; Accepted 23 February 2002
DOI 10.1002/ajmg.a.10064

prenatal diagnosis of partial trisomy 5q. Parents were nonconsanguineous, and family history included a healthy 20-month-old sister and two prior spontaneous first trimester abortions. His mother and father were 33 and 34 years old, respectively. Further information about the spontaneously aborted fetuses was not available. Prenatal history revealed intrauterine exposure to phenytoin as treatment for a maternal seizure disorder. There was no intrauterine exposure to isotretinoin. Antenatal ultrasound demonstrated a complex congenital heart defect (abnormal aortic arch, aortic stenosis) and a two-vessel umbilical cord. Amniocentesis showed extra chromosomal material on chromosome 20. The patient was born at 36 weeks gestation by vaginal delivery. Apgar scores were eight at both 1 and 5 min.

At 2 days of life, growth parameters were at the 25th centile: weight 2.295 kg, length 44 cm, and OFC 32 cm. Mildly dysmorphic facial features were present, including apparent hypertelorism, broad nasal root, and bitemporal narrowing. Nails were hyperconvex, and hands were broad. No other physical abnormalities were noted; specifically, the palate was intact, the ears were normally formed, there were no preaxial anomalies, and there was no distal digital hypoplasia. Echocardiogram demonstrated type B IAA, moderate sized secundum ASD, perimembranous VSD, patent ductus arteriosus, and aortic and subaortic stenosis.

A peripheral blood karyotype at 2 days of age revealed trisomy 5q31.1q35.1: 46,XY, der(20)ins(20;5)-(p13;q31.1q35.1) (Fig. 1A). Maternal peripheral blood karyotype revealed a balanced insertion of chromosome 5q material into the short arm of chromosome 20, with karyotype: 46, XX, ins (20;5) (p13;q31.1q35.1) (Fig. 1B). The paternal karyotype was normal. This indicated germline inheritance in the child of a paternal normal chromosome 20, and a maternal derivative chromosome 20 resulting in trisomy 5q31.1q35.1. Fluorescence in situ hybridization with a Tuple 1 probe revealed no deletion of chromosome 22q11 (the DiGeorge/velocardiofacial critical region). Chest radiographs revealed a thymic shadow; there was no hypocalcemia or lymphopenia.

The child's hospital course was complicated by apnea on day of life three requiring intubation. Cardiac repair with a Rastelli procedure on day of life nine was followed by severe hypotonia, acidosis, and anuric renal failure requiring support by extracorporeal membrane oxygenation (ECMO). On the third day of ECMO therapy, diffuse anoxic central nervous system (CNS) injury was apparent. Further worsening of his CNS injury resulted in removal from ECMO support on day of life 13, and the child died shortly thereafter.

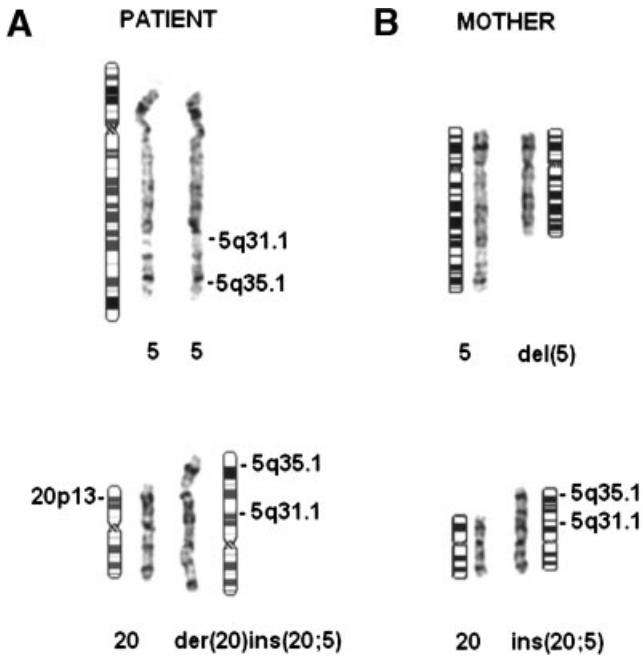

Fig. 1. Peripheral blood chromosome analysis of the patient (**A**) by high-resolution (850-band) karyotype at 2 days of life shows the derivative chromosome 20 with trisomy of 5q31.1.35.1, and (**B**) his mother's peripheral blood standard karyotype indicates deletion of chromosome 5q31q35 with insertion into chromosome 20p13. The locations of the breakpoints on the normal chromosome 5 and 20 are indicated. Images were straightened by the Cytovision computer program.

DISCUSSION

We report here, a male infant with IAA type B, secundum ASD, perimembranous VSD, PDA, and trisomy 5q31.1q35.1 resulting from maternal inheritance of a balanced insertion of 5q31.1q35.1 into chromosome 20p13. The patient's mother was unaffected, suggesting that the t(20;5) chromosomal breakpoints were not causative in the development of the observed cardiac anomalies. Instead, trisomy 5q31.1q35.1 more likely contributed to his complex CHD. To our knowledge, this is the first documented case of IAA with trisomy 5q31.1q35.1.

IAA is a rare form of conotruncal CHD [Loffredo et al., 2000]. Only a few cases of IAA have been reported in association with chromosomal rearrangements (Table I). As a component of DiGeorge syndrome, chromosome 22q11.2 deletions commonly involve IAA and complex CHD, and were ruled out in this patient by normal fluorescence in situ hybridization studies [Driscoll et al., 1993]. Despite reports of children with IAA and chromosome 22q11 deletions, other chromosomal regions are likely to contribute to the development of aortic arch anomalies [Brewer et al., 1998, 1999]. Deletion 10p syndrome shares significant phenotypic overlap with DiGeorge syndrome; however, there are no reports in the literature of 10p deletion in association with aortic arch anomalies [Van Esch et al., 1999]. Single case

TABLE I. Chromosomal Rearrangements Associated With Interrupted Aortic Arch

Chromosomal rearrangement	Reference
del 22q11	[Driscoll et al., 1993]
del 4q21.3q25	[Fukushima et al., 1992]
del 8p23.1	[Wu et al., 1996]
Trisomy 18	[Loffredo et al., 2000]
Trisomy 5q31.1q35.1	This report

reports of interrupted and hypoplastic aortic arch are associated with del 4q21.3q25 [Fukushima et al., 1992] and del 8p23.1 [Wu et al., 1996], respectively. Chromosome 8p23 is particularly noteworthy, since deletions also result in atrioventricular septal defect, pulmonary stenosis, and tetralogy of Fallot, while duplications of this region are associated with coarctation of the aorta and hypoplastic left heart syndrome [Brewer et al., 1998, 1999]. In contrast to these reported cases of IAA and chromosomal deletions, there is only one report in the literature of chromosomal duplication with IAA, that of a child with trisomy 18 and an unspecified form of IAA [Loffredo et al., 2000]. This is somewhat surprising, given the large collection of chromosomal duplications that contribute to other types of CHD [Brewer et al., 1999]. One family was reported that had a brother and sister with IAA type B1 [Pankau et al., 1990]; a different family had two double cousins, one with IAA and the other with truncus arteriosus and atrioventricular canal [Digilio et al., 2000]. These rare familial cases suggest that a variety of genetic causes may contribute to the etiology of aortic anomalies. The observation that several different chromosomal abnormalities are associated with IAA type B is consistent with the hypothesis that IAA type B is genetically heterogeneous [Loffredo et al., 2000].

In addition to chromosomal rearrangements, other causes of IAA have also been identified. Isotretinoin embryopathy is associated with IAA [Lammer et al., 1985]; however, this is unlikely in our patient given the absence of intrauterine exposures. In mice, mutations in several different genes cause IAA [Srivastava and Olson, 2000]. However, human single gene mutations with IAA are rare; only one family is reported to have type B IAA and VSD with contractural arachnodactyly and a missplicing mutation in the fibrillin gene *FBN2* [Wang et al., 1996].

Partial duplication of distal chromosome 5q has been considered a clinical multiple malformation syndrome since 1979 [Curry et al., 1979]. Duplication 5q is rare, with fewer than 40 cases reported thus far, most commonly involving the distal one-third of 5q (5q31-ter) [Fryns et al., 1987; Elias-Jones et al., 1988; Genuardi et al., 1992]. Most cases of trisomy 5q31q35 arise from unbalanced segregation of a familial balanced translocation, and are associated with monosomy or trisomy of other chromosomal regions [Fryns et al., 1987; Elias-Jones et al., 1988]. High-resolution (850 band) karyotype analysis showed no associated monosomy 20p13 in this child, reducing the likelihood that other chromosomal disruptions contributed to his anomalies. Among previously reported cases of trisomy 5q31qter, four are reported to have atrial and/or VSDs [Elias-Jones et al., 1988], as did our patient. Interestingly, our patient did not exhibit the intrauterine growth retardation and microcephaly seen in some cases of trisomy 5q31qter, suggesting that these features may be caused in other patients by associated aneuploidy of other chromosomal regions, or may develop beyond the postnatal period. Review of duplication maps from the Human Cytogenetics Database demonstrated significant associations between duplication of several regions within 5q31q35 and ASD, prenatal microcephaly, and inguinal hernia [Brewer et al., 1999].

The high frequency of cardiac malformations in individuals with trisomy 5q31qter indicates a role for gene dosage effects in this region. *CSX*, the gene for cardiac specific homeobox, is located on 5q34 and is a suitable candidate gene for dosage sensitivity during cardiac development since *CSX* mutations in humans cause ASDs [Schott et al., 1998]. Further evaluation of genes and associated birth defects in 5q31.1.35.1 will improve our understanding of the relative contribution made by this region to aortic and cardiac development, and allow for better genotype–phenotype correlations.

ACKNOWLEDGMENTS

DMM is a Fellow in the Medical Genetics Residency Program. JLG is supported by grants from the March of Dimes-Birth Defects Foundation (6-FY99-425) and the National Institutes of Health (HD34446).

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