A Prospective Cytogenetic Study of 36 Cases of DiGeorge Syndrome

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Summary

Cytogenetic analysis was carried out in a prospective series of 36 children with DiGeorge syndrome. High-resolution banding (>850 bands/haploid set) was achieved in 30 cases. Monosomy 22q11.21→q11.23 was found in 9 of these 30 cases. In each of these cases monosomy 22q11.21→q11.23 resulted from an interstitial deletion and not from a translocation. No other chromosome abnormalities were seen.

Introduction

DiGeorge syndrome (DGS) is a congenital anomaly consisting of cardiac defects, aplasia or hypoplasia of the thymus and parathyroid glands, and dysmorphic facial features (Conley et al. 1979). The heart defects are usually abnormalities of the outflow tract and include interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot. The dysmorphic features include hypertelorism with short palpebral fissures, small mouth with short philtrum, micrognathia, and low-set, posteriorly rotated ears.

The first clue to the localization of genes disrupted in DGS came from four individuals in one family with the same unbalanced chromosome rearrangement. A balanced chromosome translocation, t(20;22)(q11; q11), was segregating in the family, and the unbalanced products in the four affected individuals resulted in monosomy 22pter→22q11 and trisomy 20pter→20q11 (de la Chapelle et al. 1981). Subsequent to the description of this family, there have been many reports of affected children with unbalanced translocations in-

volving chromosome 22 (Kelley et al. 1982; Faed et al. 1987; Schwanitz and Zerres 1987; Anneren et al. 1989; Dallapiccola et al. 1989; El-Fouly et al. 1991). More recently, affected children with interstitial deletions within 22q11 have been described (Moerman et al. 1987; Greenberg et al. 1988b; Mascarello et al. 1989).

In 1980 Bridgman and Butler (1980) described an affected child with a translocation causing both trisomy for the distal half of the long arm of chromosome 14 and monosomy for distal 10p, with breakpoints at 10p14 and 14q22. This child had tetralogy of Fallot, absent parathyroid glands, dysmorphic facies with low set ears, wide nasal bridge, and short palpebral fissures, with a narrow palpebral fissure on the left. There have been additional reports of children with hypocalcemia and depressed T-lymphocyte function in association with deletions of distal 10p (Herve et al. 1984; Greenberg et al. 1986; Monaco et al. 1991).

Other chromosome abnormalities have also been reported in children with features found in DGS. These include an 18q deletion (Greenberg et al. 1988b), a 17p13 deletion (Greenberg et al. 1988a), trisomy 8q (Townes and White 1978), a 5p13 deletion (Taylor and Josifek 1981), and a partial trisomy 1 (van der Berghe et al. 1973). However, all of these children had multiple congenital anomalies in addition to DGS features.

There has been one prospective study of children

with DGS that included high-resolution cytogenetic analysis (Greenberg et al. 1988b). In that study, 22 of 27 cases had a normal karyotype. Three of the 27 cases had rearrangements involving 22q11, two having unbalanced translocations, and one having an interstitial deletion. Two children in the study were found to have abnormalities of other chromosomes; interstitial deletions involving 10p13 and 18q21.33, respectively. From this study it appeared that cytogenetic interstitial deletions are rare in DGS. We have carried out a further prospective clinical and cytogenetic study of DGS to establish the incidence of cytogenetic abnormalities.

Subjects and Methods

Subjects

Ethical approval was obtained for the study. Children were recruited to the study by circulating a letter to members of the British Paediatric Association, pediatric cardiologists, and clinical geneticists. Thirty-six children were identified. Permission to contact the parents of children who were thought to have DGS was requested. When a child was seen at home the family practitioner was contacted prior to the visit.

Clinical details of each patient were obtained from the hospital notes. The cardiac status of each child had been assessed by a pediatric cardiologist and included either echocardiography, cardiac catheterization, or both. Aplasia or severe hypoplasia of the thymus (evident at operation or postmortem examination), low T-lymphocyte numbers, or poor T-lymphocyte response to phytohemagglutinin (PHA) stimulation were features indicating maldevelopment of the thymus. Prolonged or severe hypocalcemia was taken as evidence of parathyroid gland involvement. In eight cases, serum parathyroid hormone levels had been measured and shown to be low. Thirty children were visited at home or in the hospital and were assessed by D.I.W. Three patients did not live in Britain—NW23 and NW24, who were assessed by A.B., and NW18, who was assessed by the local pediatric team. Three patients (NW4, NW31, and NW32) living in Britain were assessed by the local team.

Children were considered to have DGS if they had at least three of the following four features: congenital heart disease (outflow-tract defects), evidence of thymic abnormalities, hypocalcemia, and a dysmorphic facial appearance compatible with the diagnosis. In every case the diagnosis was made on clinical grounds alone, prior to cytogenetic or molecular genetic investigation. Blood was obtained from each child, for chromosome studies and DNA analysis.

Cytogenetic Analysis

Chromosome preparations were made from 72-h PHA-stimulated cell cultures from peripheral blood. Cell division was synchronized by a pulse of thymidine (final concentration 0.4 mg/ml; GIBCO) administered 21 h prior to harvesting. The thymidine block was released by washing the cells in Dulbecco's PBS (Flow Laboratories) prewarmed to 37°C, followed by resuspending in fresh culture medium (RPMI 1640; GIBCO), also prewarmed to 37°C, for 4 h prior to harvesting. One culture was harvested using colcemid (final concentration 0.3 µg/ml; GIBCO) for 15 min prior to harvesting. One culture was harvested using colcemid for only 8 min prior to harvesting, in order to obtain chromosomes of sufficiently high resolution to visualize band 22q11.22 (i.e., at least 850 bands/ haploid set) (Standing Committee on Human Cytogenetic Nomenclature 1985). In the samples where this degree of resolution was not achieved, no comment was made on the presence or absence of an interstitial deletion.

In two cases (NW16 and NW17), the children had no mature T-lymphocytes at presentation. Pokeweed mitogen stimulation was attempted in one of these cases but failed to produce high-resolution preparations. In the other case, a further PHA-stimulated sample taken 2 mo later did produce adequate preparations for analysis.

Preparations were G-banded using trypsin and Leishman stain. The samples were analyzed independently by two cytogeneticists prior to the molecular investigation. This study was part of a wider investigation of individuals with congenital heart disease, in which the protocol included high-resolution chromosome analysis. The cytogeneticists analyzing these samples knew that they were part of the heart study but were not informed which samples were from DGS patients. At the end of the study, the 36 samples were allocated random numbers and were reexamined independently by two cytogeneticists who were not given previous results or clinical details.

Results

Thirty-six subjects who fulfilled the diagnostic criteria for DGS were ascertained. The clinical findings in these subjects are summarized in table 1. The karyo-

Table I

Clinical and Cytogenetic Details of 36 Cases of DGS

Subject	Thymus	Calcium	Cardiac Defect(s)[a]	Short Philtrum	Small Mouth	Low-set or Small Ears	Other Features	Karyotype
NW 1	Absent	Low	IAA (type B)	–	+	+	Small jaw	46,XY,del(22)(q11.21q11.23)
NW 2	Low T-cells	Low	PA, VSD	+	–	+	Sensorineural deafness	46,XY
NW 3	Low T-cells	Low	PA, VSD	+	+	+	Anteriorly placed anus	46,XX
NW 4	Low T-cells	Low	PA, VSD	+	+	+	Absent right kidney	46,XY
NW 5	Absent	Low	IAA (type B), VSD	+	+	+	Broad nasal bridge	46,XY (<850 bands)
NW 6	Normal	Low	Tetralogy of Fallot	–	–	+	Hypertelorism, broad nasal bridge	46,XX,del(22)(q11.21q11.23)
NW 7	Low T-cells	Low	Tetralogy of Fallot	+	–	+	Up-slanting palpebral fissures	46,XX,del(22)(q11.21q11.23)
NW 8	Absent	Low	Pulmonary valve stenosis	–	+	+	Down-slanting palpebral fissures, cerebral hypoplasia	46,XY
NW 9	Absent	Low	Right-sided IAA (type B), VSD	+	+	–		46,XY
NW 10	Absent	Low	Right-sided IAA (type C)	+	+	+		46,XY (<850 bands)
NW 12	Low T-cells	Low	Pulmonary valve stenosis	–	+	+	Down-slanting palpebral fissures	46,XY
NW 15	Absent	Low	IAA (type B), VSD	+	+	–	Broad nasal bridge	46,XX,del(22)(q11.21q11.23)
NW 16	No T-cells	Low	Truncus arteriosus	+	+	–	Bilateral cleft lip and palate, 7th cranial nerve palsy	46,XY (<850 bands)
NW 17	No T-cells	Low	Secundum ASD, PDA	–	–	+		46,XX (<850 bands)
NW 18	Low T-cells	Low	IAA	–	+	+	Up-slanting palpebral fissures	46,XX
NW 19	Normal	Low	AVSD, aortic coarctation	+	+	+		46,XY
NW 20	Absent	Low	IAA (type B), VSD	+	+	–	Small jaw	46,XX
NW 21	Low T-cells	Low	IAA (type B), VSD	+	+	–	Absent left kidney, talipes equino varus	46,XY
NW 22	Low T-cells	Low	IAA (type B), VSD	+	+	+	Malformed right ear, right 7th cranial nerve palsy	46,XX,del(22)(q11.21q11.23)
NW 23	PHA resp. low	Low PTH		–	–		Malformed left ear, left 7th cranial nerve palsy	46,XY
NW 24	Low T-cells	Low		–	–			46,XX
NW 25	Normal	Low	VSD	+	+	+	Small jaw, absent right kidney	46,XY,del(22)(q11.21q11.23)
NW 26	Low T-cells	Low	Truncus arteriosus	+	+	–	Up-slanting palpebral fissures, cleft soft palate	46,XY
NW 27	Absent	Low	Tetralogy of Fallot, DORV	–	+	+	Hypertelorism, hypothyroidism	46,XY
NW 28	Small	Low	IAA (type B)	+	–	–	Hypothyroidism	46,XX,del(22)(q11.21q11.23)
NW 29	Absent	Low	IAA (type B), VSD, hypoplastic tricuspid and aortic valves, ASD	–	–	+	Small jaw	46,XX
NW 30	Small	Normal	IAA (type B)	–	–	+	Hypertelorism, posteriorly rotated ears	46,XX
NW 31	Absent	Normal	IAA (type B), VSD	–	–	–		46,XY
NW 32	Absent	Low	IAA (type B)	+	+	–	Coronal synostosis	46,XY
NW 33	Low T-cells	Normal	Truncus arteriosus	+	+	+		46,XY (<850 bands)
NW 34	Low T-cells	Normal	IAA (type B), VSD	–	+	+	Down-slanting palpebral fissures	46,XX,del(22)(q11.21q11.23)
GOS 2	Absent	Low	PA, VSD, RAA	–	–	+		46,XY,del(22)(q11.21q11.23)
GOS 3	Normal	Low	Truncus arteriosus, RAA	–	–	+	Hypertelorism, submucous cleft palate	46,XX
GOS 4	Low T-cells	Low	Aberrant right subclavian artery	+	+	–		46,XX
GOS 5	Recurrent infections							46,XX
GOS 6	Absent	Low	PA, VSD, vascular ring	+	–	+	Broad nasal bridge	46,XY (<850 bands)
		Low	IAA (type B), VSD	–	–	+	Hypertelorism, broad nasal bridge, posterior cleft palate	46,XX

[a] IAA = interrupted aortic arch; RAA = right aortic arch; PA = pulmonary atresia; VSD = ventricular septal defect; ASD = atrial septal defect; AVSD = atrioventricular septal defect; PDA = patent ductus arteriosus; and DORV = double-outlet right ventricle.

type analyses by the two cytogeneticists were identical; these are summarized in table 1.

In six cases, despite a good PHA response, chromosome preparations did not achieve a resolution of 850 bands/haploid set, and no comment could be made about chromosome 22 band q11.22. Resolution of at least 850 bands/haploid set was achieved in 30 cases. In nine, an interstitial deletion within chromosome 22q was identified (del(22)(q11.21q11.23)) (fig. 1). No other cytogenetic abnormalities were detected in the DGS subjects.

Discussion

Cytogenetic interstitial deletions within chromosome 22q11 have been found in a higher proportion of DGS individuals in this study than in the prospective series of Greenberg et al. However, the majority of individuals with DGS do not have a visible cytogenetic abnormality. It is clear from the accompanying paper (Carey et al. 1992) that, within 22q11, less than half of the chromosome deletions causing DGS are detected by cytogenetic analysis.
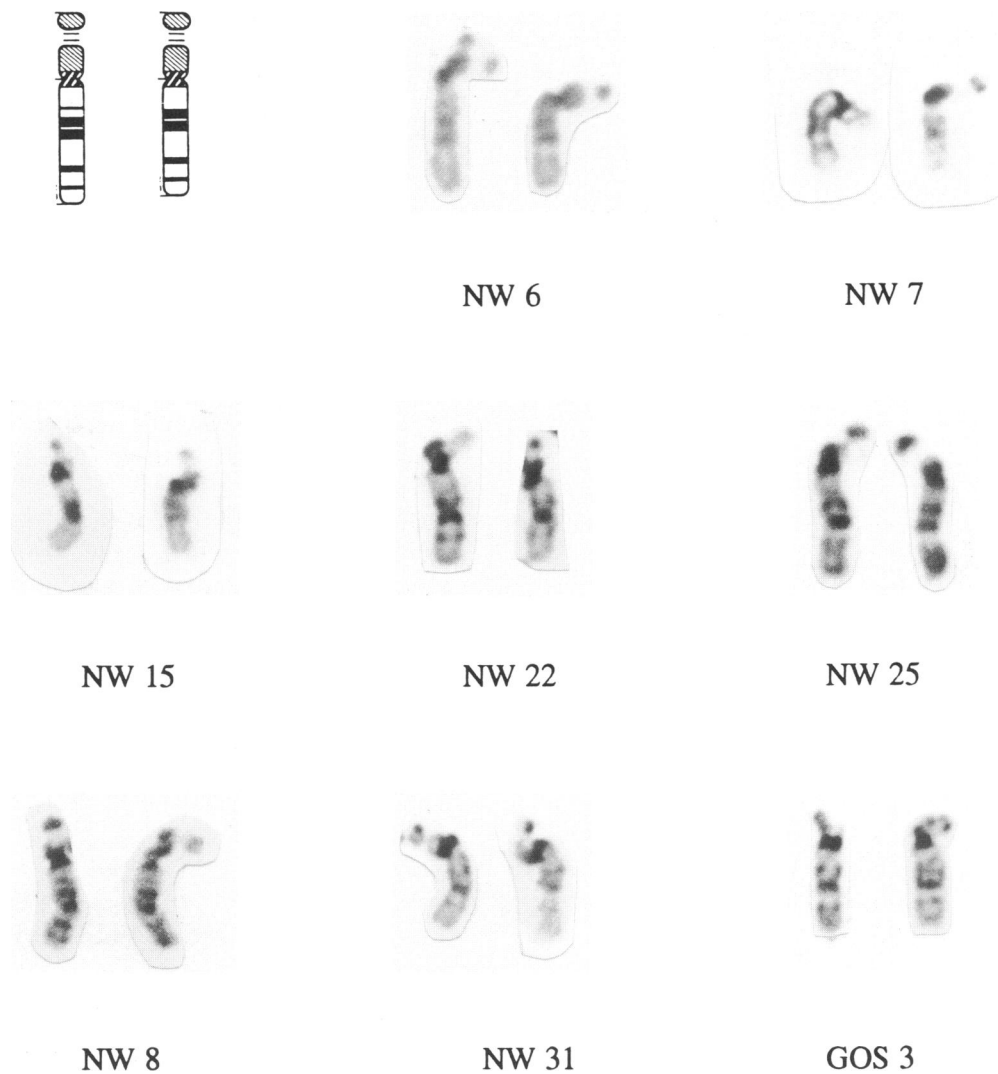
Figure I   Partial karyotypes showing five examples of patients with del(22)(q11.21q11.23)—NW 6, NW 7, NW 15, NW 22, and NW 25 (in all five cases, the deleted chromosome is on right)—and three examples of patients without visible cytogenetic abnormality—NW 8, NW 31, and GOS 3. An ideogram (*upper left*) is included for comparison (the deleted chromosome is on the right).

High-resolution chromosome preparations are dependent on PHA-stimulated T-lymphocytes. T-lymphocyte deficiency and poor response to PHA stimulation are features of thymic involvement in DGS; and, therefore, difficulty in obtaining adequate chromosome preparations is to be expected. In view of this, it may be more appropriate to carry out fluorescent in situ hybridization studies using probes from 22q11 in these cases and only proceed to further cytogenetic analysis, to look for other karyotypic abnormalities if no deletion is detected.

A spectrum of abnormalities has been described for DGS. In this prospective series, no correlation was found between the presence of a visible deletion and the clinical phenotype, whether the number of features or severity of features is considered. Case NW22 has inherited the chromosome 22 deletion from her mother, who does not have DGS. Two of her siblings have also inherited the deletion but do not fulfil the diagnostic criteria for DGS, as they have an isolated coarctation of the aorta and a membranous ventricular septal defect (VSD), respectively, along with a mildly dysmorphic appearance (Wilson et al. 1991).

The first indication that genes on chromosome 22 could be involved in the etiology of DGS was from the family with a translocation, reported by de la Chappelle et al. (1981), with breakpoints in 20q11 and 22q11. Four children in this pedigree had DGS; all had the same unbalanced translocation products resulting in monosomy for 22pter→22q11 and trisomy for 20pter→20q11 (de la Chapelle et al. 1981). The following year another three unrelated DGS patients were reported who were monosomic for 22pter→22q11 (Kelley et al. 1982). Two of these children had inherited unbalanced forms of familial translocations, and the third child had a de novo unbalanced translocation. There have been additional reports of affected children with unbalanced translocations with chromosome 22 involvement (Greenberg et al. 1984; Faed et al. 1987; Schwanitz and Zerres 1987; Anneren et al. 1989; Dallapiccola et al. 1989; El-Fouly et al. 1991). Most of these families were reported after the birth of a second affected child with features of DGS. Finding interstitial deletions has been the exception rather than the rule (Moerman et al. 1987; Greenberg et al. 1988b; Mascarello et al. 1989). It is therefore interesting that, in this prospective series, none of the cases result from unbalanced translocations.

A review of the literature reveals four children with features of DGS and partial deletions of 10p. Three of these are terminal deletions with the breakpoint at 10p13 and without involvement of other chromosomes (Herve et al. 1984; Greenberg et al. 1986; Monaco et al. 1991). These children had abnormalities of T-lymphocytes and hypocalcemia. The patients described by Monaco et al. and Greenberg et al. did not have heart defects, and the patient described by Herve et al. had a globular heart on chest X-ray, but further details were not given. The one other child with a 10p deletion also had 14q trisomy (Bridgman and Butler 1980). In this case the chromosome 10 breakpoint was at 10p14. This patient had classical dysmorphic features, tetralogy of Fallot, and absent parathyroids; no details are given of T-lymphocyte function, but the thymus appeared normal at postmortem. These four reports indicate that there is a second locus at or distal to 10p14 involved in the development of the third and fourth pharyngeal arches. In three of these four cases, the predominant clinical features were due to hypoplasia of the thymus and parathyroids. In our own series most of the cases were referred by cardiologists. We are now studying children presenting with T-lymphocyte immunodeficiency (where known causes have been excluded) and children presenting with hypoparathyroidism of unknown cause.

There are several single-case reports of children with abnormal karyotypes and features in common with DGS. Greenberg et al. (1988a) described a 34-wk stillbirth with a 17p13 deletion and features of DGS. Postmortem findings were intrauterine growth retardation, a hypoplastic left ventricle with mitral valve atresia and a large atrial septal defect, double-outlet right ventricle and pulmonary valve stenosis, thymic hypoplasia, and malrotation of the colon. Because of autolysis it was not possible to comment on the brain or parathyroids. The syndrome associated with 17p13 deletions is Miller-Dieker syndrome. The features of Miller-Dieker syndrome are lissencephaly and a characteristic dysmorphic appearance with prominent forehead, bitemporal hollowing, and a short upturned nose. Heart defects are found in approximately 50% of Miller-Dieker syndrome cases but do not usually involve the outflow tract. Thymic hypoplasia and hypoparathyroidism have not been reported in Miller-Dieker syndrome. The deletion described in this case deletes the whole of band p13 and is thus larger than previously reported in cases of Miller-Dieker syndrome.

A child has been described elsewhere (Taylor and Josifek 1981) with thymic dysplasia, atrial and ventricular septal defects with pulmonary valve atresia, and a deletion of 5p13. This child had multiple addi-

tional malformations. In the many other reports of 5p⁻, thymic dysplasia has not been recorded, and heart defects are present in only 30% of 5p⁻ cases.

Chromosome analysis in one child with a VSD, absent thymus gland at operation, and functional abnormalities of T-lymphocytes showed monosomy for 22pter→22p11.2 and trisomy for 18qter→18q12.2 (Bowen et al. 1986). In addition one of the children in Greenberg et al.'s (1988*b*) prospective series had an 18q deletion. This child had the characteristic 18q⁻ phenotype and also had tetralogy of Fallot and persistent hypocalcemia.

van der Berghe et al. (1973) described a child with partial trisomy 1, enlarged cystic kidneys, complex congenital heart defect, absent thymus, but a bilateral lymph node–like organ posterior to the thyroid gland. The karyotype suggested an unbalanced translocation between chromosomes 1 and 12. Townes and White (1978) described a child with multiple congenital anomalies including a VSD, anomalies of the aortic and pulmonary trunk, and agenesis of the thymus, with an unbalanced translocation, t(8;15), resulting in trisomy 8q22→qter.

From the reports of cytogenetic abnormalities found in association with aplasia of the thymus and parathyroids, and with outflow-tract defects of the heart, all of which have been discussed above, it is clear that many genes are required for normal development of these structures. However, deletions of 10p13 and 22q11 have been reported on more than one occasion in children with features of DGS but with no other malformations. Three of the four children with 10p13 deletions have presented with signs of hypoparathyroidism and thymic aplasia rather than with cardiac problems. A locus or loci on chromosome 22 may be particularly involved with cardiac morphogenesis. In this series of patients, ascertained largely through cardiologists, the only cytogenetic abnormality seen was interstitial deletion of 22q11.21→q11.23. This deletion was visible in 9 of 36 cases of DGS, and, as shown in the accompanying paper (Carey et al. 1992), deletions within 22q11 appear to be present in the majority of DGS cases. Our conclusion from this study is that the sensitivity of high-resolution banding in the investigation of DGS is low and that, in the future, the investigation of choice in these cases should be molecular cytogenetic analysis by in situ hybridization.

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