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Distal 15q Trisomy: Phenotypic Comparison of Nine Cases in an Extended Family

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SUMMARY

Nine related individuals have been identified as being trisomic for the distal part of the long arm of chromosome 15 (15q23 to 15qter). The physical characteristics, especially the facial features, of these nine cases are similar and distinctive. These include: facial asymmetry, downslanting palpebral fissures, ptosis, prominent nose, long philtrum, downturned mouth, midline crease in the lower lip, puffy cheeks, and micrognathia.

By comparing related individuals with the same translocation, the variability due to different breakpoints can be eliminated. Clinical similarities between unrelated individuals with similar duplicated 15q material, but differing second chromosomes, suggest that the phenotype is due to the extra distal 15q chromosomal material. We conclude that distal 15q trisomy produces a clinically recognizable syndrome.

INTRODUCTION

Nine related individuals have been identified as being trisomic for the distal part of the long arm of chromosome 15 (15q23 to 15qter). These individuals are part of a 6-generation family in which a reciprocal translocation t(7;15) (p22;q23) is segregating. The clinical findings of the nine affected individuals are presented and compared to 11 individuals reported in the literature.

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CYTOGENETIC STUDIES

Karyotypes were prepared by standard techniques from peripheral blood samples of affected and potential carrier members of this extended family. Q- and G-banding of prometaphase chromosomes from a balanced carrier revealed a reciprocal translocation between 7p and 15q (figs. 1 and 2), designated 46,XX,t(7;15)(7qter→7p22::15q23→15qter;15pter→15q23::7p22→7pter). The affected individuals have karyotypes designated as 46,XX(or XY),der(7),t(7;15) (p22;q23) derived by adjacent-1 segregation in a carrier parent.

RESULTS

Five members of this 6-generation family (fig. 3) were karyotyped and are trisomic for distal 15q. Four members are presumed affected on the basis of similarity of clinical findings to the proven affected individuals and because each has a parent who is a carrier of the balanced translocation. Individuals V-7 and VI-4 were examined but not karyotyped; both are presumed affected. The father and two siblings of V-7 are translocation carriers. VI-4 has a carrier mother and an affected brother by karyotype. Individuals IV-2 and V-10, now deceased, are presumed affected on the basis of photographs and medical records. IV-2 had three siblings who were karyotyped and found to be translocation carriers; her mother is an obligate carrier by pedigree. The mother and brother of V-10 are both carriers of this translocation by karyotype.

Approximately 80 members of this family were karyotyped; 24 individuals (fig. 3) were identified as being translocation carriers. There are five additional

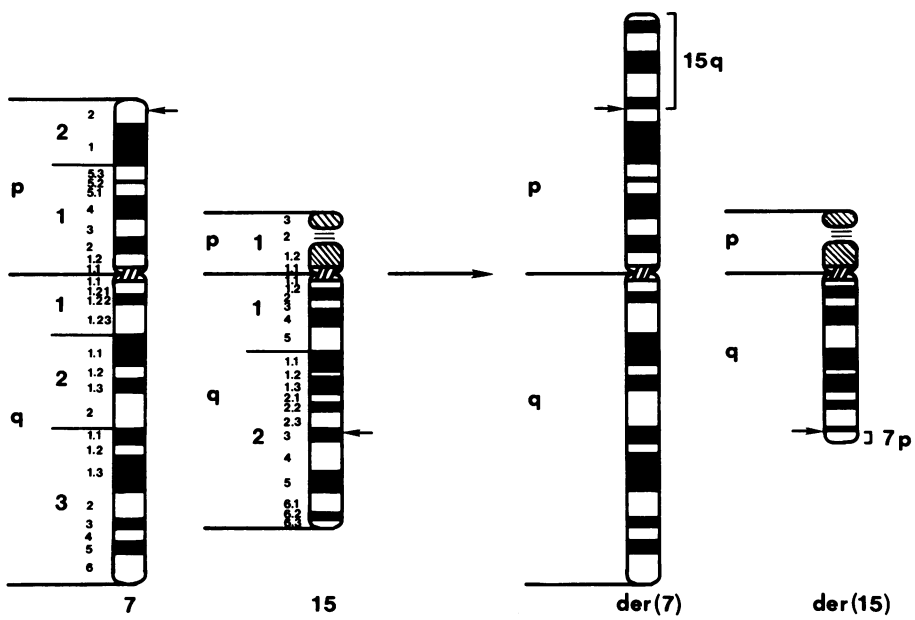

FIG. 1.—Idiogram of the normal chromosomes 7 and 15 *on the left* and the balanced translocation t(7;15) (7p22;15q23) *on the right*. *Small arrows* indicate breakpoints.

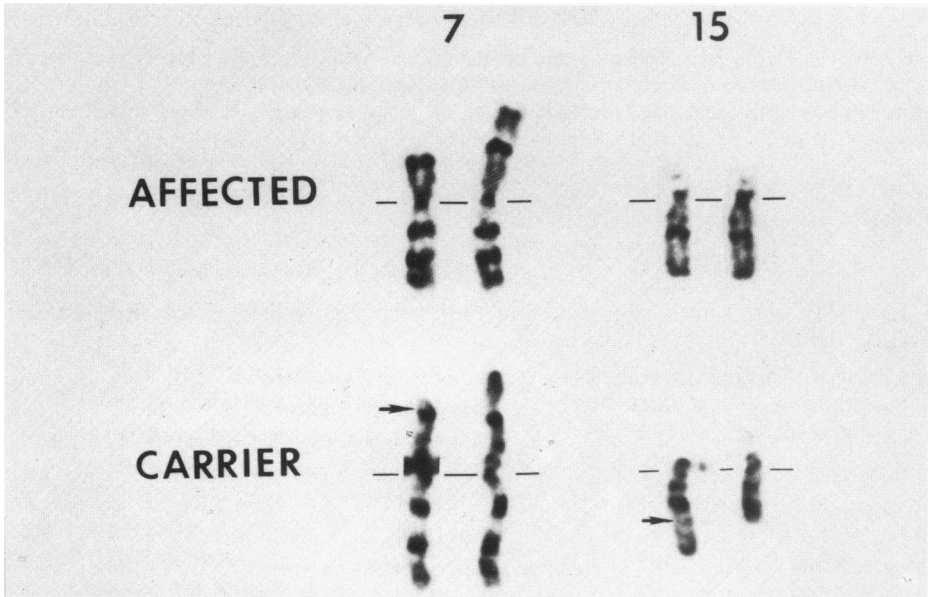

FIG. 2.—Prometaphase karyotypes of an affected individual and a balanced translocation carrier. *Small arrows on the normal chromosomes 7 and 15* indicate breakpoints.

deceased individuals in generations II and III who are obligate carriers by pedigree. One of the individuals in generation I is presumably an obligate carrier.

The clinical findings of each of the nine family members with distal 15q trisomy are listed in table 1. Four of the affected children from this family are depicted in figure 4*a–d*. In addition to the features listed in table 1, case VI-5 had accessory auditory canals and radiographic evidence of abnormalities of the cervical spine. Cases V-10 and VI-4 had a tentative diagnosis of "Seckel syndrome" made by their local physicians on the basis of their small size, microcephaly, and facial features. Case IV-2 was considered to have rickets.

The dermatoglyphics of affected individuals showed a combination of ulnar loops and arches. Only one of seven cases examined had single palmar creases; the others had normal creases. The palmar axial triradii were normally positioned. The fingers were slender and tapered, and the feet were slender with crowded toes.

DISCUSSION

Phenotype-karyotype correlations in unbalanced chromosome rearrangements have two inherent sources of variability: (1) the breakpoints in unrelated individuals are unlikely to be identical, and therefore different amounts of duplicated or deleted genetic material are likely involved; (2) the second chromosome involved in the translocation is usually different from family to family. Even though the breakpoint in the second chromosome is often in the terminal region, modifying effects of an undetectable deletion or duplication of genetic material involving

the second chromosome may still occur. By comparing affected individuals with the same translocation in a single family, the variability in the expression of the same chromosome abnormality can be more accurately defined.

A number of individuals have been reported who have duplication of the proximal portion of 15q [1–3]. Some of these patients have 47 chromosomes, with the extra chromosome being a de novo bisatellited number 15 chromosome. There is a second group of patients with 47 chromosomes in which the extra chromosome is a deleted 15 inherited as the result of 3:1 meiotic segregation in a balanced carrier mother. Three of these cases [4–6] have breakpoints at 15q22, which are similar to the breakpoints seen in many of the individuals with distal 15q trisomy. No affected individual with 47 chromosomes, and, therefore, no individual with proximal 15q trisomy, was found in the extended family reported here in spite of numerous pregnancies of balanced carriers.

In 1974 the first case of distal 15q trisomy was reported by Fujimoto et al. [7] (fig. 4*e*). Since that time there have been 10 more individuals with distal 15q trisomy reported in the literature [8–15]. Figure 4(*f*, *g*, and *h*) shows three of these individuals. The breakpoints in 15q were all between bands 15q21 and 15q23, except one at 15q25 [11] and one at 15q15 [15]. The second chromosome involved in the reciprocal translocations (nine of the 11 cases) varied from case to case. Table 2 summarizes the physical findings in the extended Virginia family and compares them to the previously reported cases. Tables of the individual characteristics of the previously reported cases may be found in Gregoire et al. [9], Howard-Peebles et al. [10], and Yip et al. [14]. The similarity of these cases

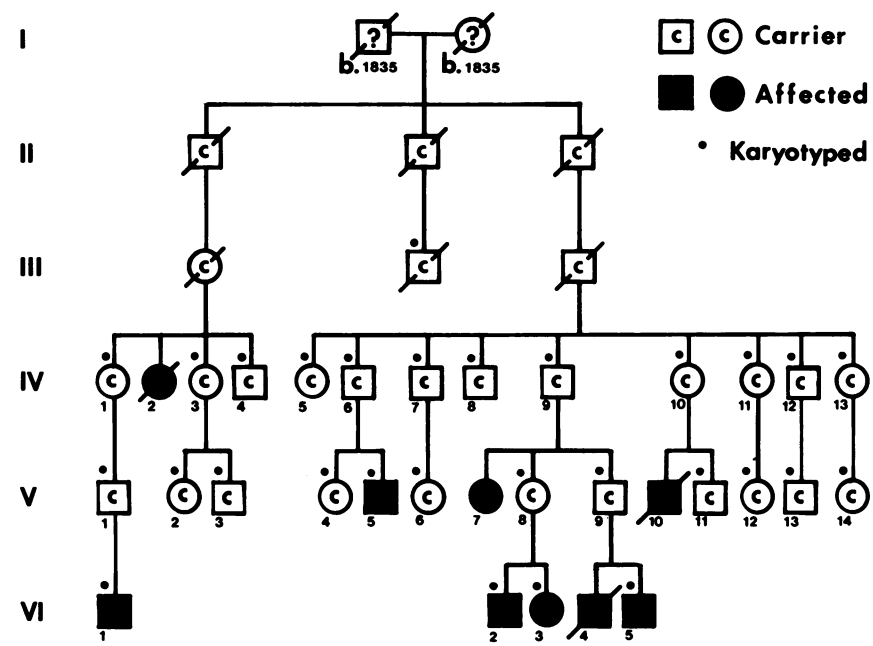

FIG. 3.—An abbreviated family pedigree showing the relationship of affected and carrier individuals.

TABLE 1

MAJOR CLINICAL FEATURES IN THE NINE FAMILY MEMBERS WITH DISTAL 15q TRISOMY

	VI-1	VI-2	VI-3	VI-4	VI-5	V-5	V-7	V-10	IV-2
Birth yr	1974	1976	1980	1976	1978	1955	1960	1959	1929
Age at death	—	—	—	10 days	—	—	—	12 yrs	8 yrs
Sex	M	M	F	M	M	M	F	M	F
Birth wt. (grams)	3,550	3,850	2,600	2,350	2,500	0	3,400	2,000	0
Mental retardation	+	+	+	0	+	+	+	+	+
Growth retardation	+	25th %ile	+	0	+	+	10th %ile	+	+
Microcephaly	+	−	−	+	+	−	+	+	0
Congenital heart disease	+	−	+	+	−	−	+	−	0
Seizures	+	−	+	+	−	−	−	−	0
Hypotonia	+	+	+	0	+	(hyper)	−	(hyper)	+
Facial asymmetry	+	+	+	0	+	+	+	0	+
Palpebral fissures (narrow)	−	+	+	0	+	0	+	−	0
Fissures (down-slanting)	+	+	+	0	+	0	−	−	0
Ptosis	+	+	−	0	+	+	−	−	+
Prominent nose	+	+	+	+	+	+	+	+	0
Long philtrum	+	−	−	0	+	+	−	+	+
Down-turned mouth	+	+	+	0	+	−	−	+	+
Midline V in lower lip	+	+	+	0	+	−	−	0	+
High palate	+	+	+	0	+	+	+	0	+
Micrognathia	+	+	+	0	+	−	−	0	0
Puffy cheeks	+	+	+	0	+	−	+	−	0
Preauricular pit	−	+	−	0	+	−	−	0	0
Pectus excavatum	+	+	+	−	+	+	+	+	0
Scoliosis	+	+	+	0	+	+	+	+	0
Short neck	+	−	−	+	+	−	+	+	+
Cryptorchidism	+	+	N.A.	+	+(R)	+	N.A.	+	N.A.
Hyperextensible thumbs	+	+	+	0	+	0	+	0	0

NOTE: Features are denoted as: present (+), absent (−), not known (0), or not applicable (N.A.).

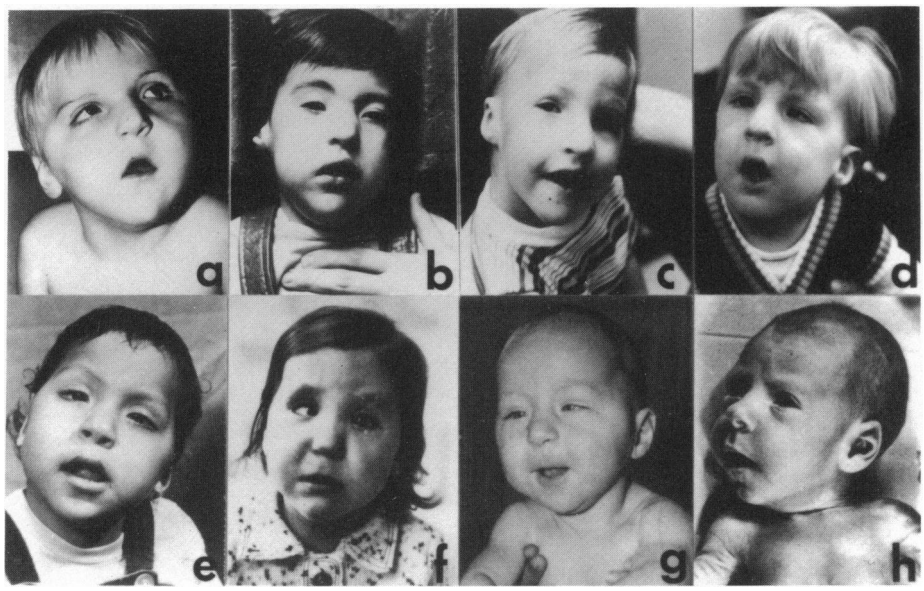

FIG. 4.—Individuals with distal 15q trisomy. *a*, Individual VI-1 in this report. *b*, Individual VI-3. *c*, Individual VI-2. *d*, Individual VI-5. *e*, Patient reported by Fujimoto et al. [7]. *f*, Patient reported by Gregoire et al. [9]. *g*, Patient reported by Tzancheva et al. [13]. *h*, Patient reported by Turleau et al. [12].

to the Virginia cases suggests that a phenotype due to the extra distal 15q chromosome material is distinguishable and that the effects of the deletion of the second chromosomes involved are minimal.

Distal 15q trisomy includes many of the common characteristics of unbalanced autosomal abnormalities, such as growth and mental retardation with microcephaly. Within this phenotype there is, however, variability in the degree of growth and mental retardation in spite of an identical karyotype. Several of the cases in this report and of the previously reported cases did not exhibit growth retardation. The presence of congenital heart disease and seizures also varied in both sets of patients.

The facial features are distinctive and include facial asymmetry, often with torticollis; down-slanting, narrow palpebral fissures; ptosis; a prominent nose with a broad nasal root; a long, well-defined philtrum; a down-turned mouth with a midline V-shaped crease in the lower lip; puffy cheeks; and micrognathia. These distinctive facial characteristics are consistent within a family and between unrelated affected individuals and produce a clinically recognizable phenotype.

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TABLE 2

COMPARISON OF THE CHARACTERISTICS OF THE NINE INDIVIDUALS IN THIS REPORT TO THE PREVIOUSLY REPORTED CASES

	This report	Literature
Mental retardation	8/8	7/7
Growth retardation	6/8	6/8
Microcephaly	5/8	6/7
Congenital heart disease	4/8	8/9
Seizures	3/8	3/5
Hypotonia	5/7	1/5
Facial asymmetry (+/− torticollis)	7/7	8/9
Down-slanting palpebral fissures	4/6	8/9
Ptosis	5/8	3/3
Prominent nose with broad nasal root	7/8	4/4
Long, well-defined philtrum	5/8	8/8
Down-turned mouth	6/8	4/4
Midline crease in lower lip	5/7	2/2
High palate	7/7	6/6
Micrognathia	4/6	8/8
Puffy cheeks	5/7	7/7
Preauricular pit	2/6	1/1
Pectus excavatum	7/8	4/4
Scoliosis	7/7	2/2
Short-neck (+/− vertebral anomalies)	6/9	5/7
Cryptorchidism	6/6	3/6
Hyperextensible thumbs	5/5	1/1

NOTE: The denominators consist only of those individuals for whom a determination as to the presence or absence of the particular feature could be established.

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MEDICAL GENETICS COURSE: Washington, D.C., May 10–12, 1984. The 3-day course, organized by members of the National Institutes of Health Inter-Institute Medical Genetics Program, will include didactic and problem-oriented sessions. Topics include: gene and chromosome structure and function; population genetics; dysmorphology; inborn errors of metabolism and the genetics of cancer; endocrine, neurologic and other common diseases; as well as prenatal diagnosis, counseling, and treatment. The course is intended, in part, as a review for candidates for the examinations of the American Board of Medical Genetics, but will not ignore the excitement of current research. The course is approved for AMA Category 1 credit. Further information is available from: Medical Genetics, c/o FAES, The National Institutes of Health, Building 10, Room B1-L-101, Bethesda, MD 20205. Telephone: (301)496-7976.