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Minute Supernumerary Ring Chromosome 22 Associated with Cat Eye Syndrome: Further Delineation of the Critical Region

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Summary

Cat eye syndrome (CES) is typically associated with a supernumerary bisatellited marker chromosome (inv dup 22pter-22q11.2) resulting in four copies of this region. We describe an individual showing the inheritance of a minute supernumerary double ring chromosome 22, which resulted in expression of all cardinal features of CES. The size of the ring was determined by DNA dosage analysis and FISH analysis for five loci mapping to 22q11.2. The probes to the loci D22S9, D22S43, and ATP6E were present in four copies, whereas D22S57 and D22S181 were present in two copies. This finding further delineates the distal boundary of the critical region of CES, with ATP6E being the most distal duplicated locus identified. The phenotypically normal father and grandfather of the patient each had a small supernumerary ring chromosome and demonstrated three copies for the loci D22S9, D22S43, and ATP6E. Although three copies of this region have been reported in other cases with CES features, it is possible that the presence of four copies leads to greater susceptibility.

Introduction

Cat eye syndrome (CES) is highly variable in phenotype, but criteria for diagnosis include ocular coloboma (of the iris and/or retina); anal atresia (with or without fistula); preauricular skin tags and pits; heart defects (especially total anomalous pulmonary venous return); dysmorphic features, such as hypertelorism and downslanting palpebral fissures; urogenital defects; and mental retardation (mild to moderate) (Schinzel et al. 1981). Typically, cytogenetic analysis of these patients reveals the presence of a supernumerary bisatellited marker chromosome derived from an inverted duplication of the short arm and proximal long arm of chromosome 22 (inv dup 22pter-22q11.2) (McDermid et al. 1986). This results in the presence of four copies of this region. The size of these marker chromosomes in 10 CES patients was previously analyzed using five loci mapping to 22q11.2 (Mears et al. 1994). The order of these loci, proximal to distal, is D22S9–D22S43–D22S57–D22S36–D22S75 (Fibison et al. 1990; Driscoll et al. 1992). The marker chromosomes were shown to vary in size, with the critical region (smallest common duplication required to produce features of CES) spanning from the centromere to above locus D22S36 (Mears et al. 1994), representing a maximum distance of 3.1 Mb (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data). More recent work has determined that locus D22S181, which maps between D22S57 and D22S36 (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data), is also duplicated in all markers tested (Mears 1995). Therefore D22S181 marks the most distal probe mapped to the critical region in these marker chromosomes.

In this study, three generations of a family were found to carry a minute supernumerary ring chromosome derived from 22q11.2 (El-Shanti et al. 1993). We show that the proband's ring chromosome is smaller than the typical CES marker chromosome and therefore redefines the distal limit of the CES critical region. In addition, the affected proband has four copies of this region, whereas the unaffected father and grandfather have three copies. The likelihood of a threshold model being applicable to this syndrome is discussed in the context of other reported cases.

Material and Methods

Clinical and Cytogenetic Evaluation

Clinical information was obtained from the referring physician. Peripheral blood leukocytes were cultured and harvested by standard procedures. Metaphase spreads were stained and examined using a variety of techniques, including GTG-banding, C-banding, and NOR-silver staining (Benn and Perle 1992).

Cell Lines

Lymphoblastoid cell lines were established for all three individuals with a ring chromosome: the proband

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(CM15), father (CM14), and grandfather (CM13). Three control cell lines were obtained from the Coriell Institute for Medical Research at the National Institute of General Medical Science. GM03657 is a normal lymphoblastoid line, GM07106 is a trisomy 22 chronic villus sampling line, and GM02325 is a fibroblast line with partial trisomy 22 (47,XX,+der[22]t [16,22]-[p13.3;q12.2]) (Sutherland et al. 1989). A fourth control cell line (NC1) was a previously established normal lymphoblastoid line.

Probes

The 22q11.2 probes used in this study have been described elsewhere. D22S9 (p22/34) was isolated from a chromosome 22–enriched library and localized by in situ hybridization (McDermid et al. 1986). D22S43 (H32) and D22S57 (H98) were isolated from flow-sorted chromosome 22 library LL22NS01 from American Type Cell Culture/National Institutes of Health (Budarf et al. 1991). D22S181 and ATP6E (XEN61) were isolated by Lekanne Deprez et al. (1991) and Baud et al. (1994), respectively. The reference probes used in this study were to the chromosome 21–specific loci D21S110 (Spinner et al. 1989), D21S15 (Stewart et al. 1985*a*), and D21S19 (Stewart et al. 1985*b*).

The relative order and distances between the loci were determined by pulsed-field gel electrophoresis (PFGE) and YAC contigs to the region (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data). A summary of the physical map is shown in figure 1. The order of the loci, proximal to distal, is D22S9–D22S43–ATP6E–D22S57–D22S181.

D22S9 detects a *Taq*I polymorphism with alleles of 5.8 or 3.2 kb. D22S43 detects a *Taq*I polymorphism with alleles of 5.0, 4.0, or 3.5 kb. D22S57 detects an *Msp*I polymorphism with alleles of 2.5 or 1.5 kb. D22S181 detects a *Taq*I polymorphism with alleles of 2.9 or 2.2 kb.

For FISH analysis, the plasmid p22/34 (D22S9) or the cosmid specific to D22S9 (cosS9, address 107D6) and cosmids to ATP6E (cosATP6E, address 4D9), D22S181 (cosS181, address 54G12), and D22S39 (cosS39, address 108A7) were used. All four cosmids were isolated from the LL22NC03 library (Human Genome Center, Lawrence Livermore National Laboratory). D22S39 (Budarf et al. 1991) maps to the distal tip of the long arm of chromosome 22 and was sometimes used as a control locus, to identify the normal chromosomes 22.

DNA Studies

Detailed protocols of DNA extraction, digestion, electrophoresis, transfer, hybridization, and analysis that were used in this study are described elsewhere (Mears et al. 1994).

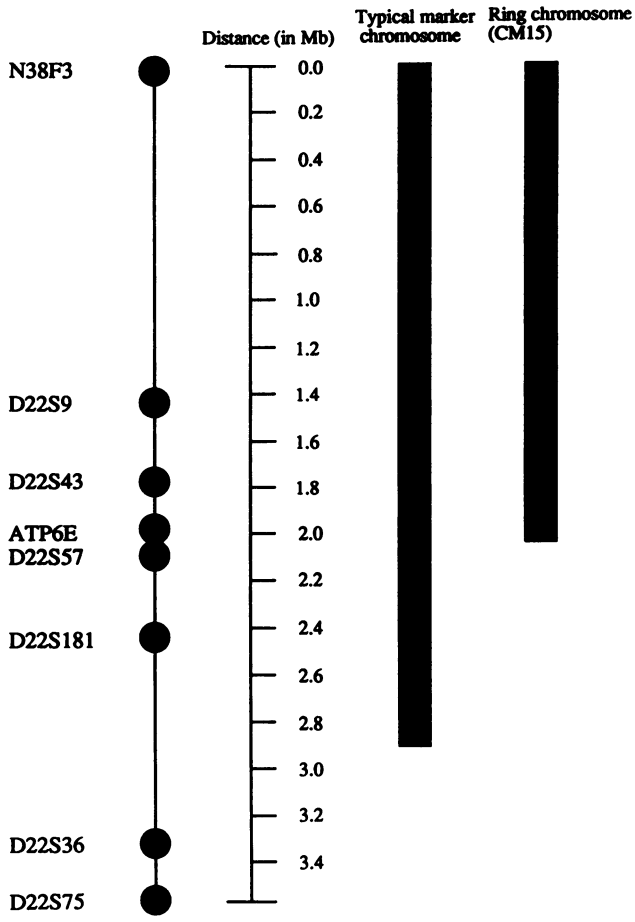

Figure 1 Physical map of some of the loci identified in the CES region. Loci (represented by blackened circles) are identified to the left. The scale bar indicates the maximum distances of the 22q11.2 loci from the N38F3 locus, as determined by PFGE and YAC contigs (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data). The locus designation N38F3 refers to the cosmid address of the most proximal 22q locus to the centromere. It was isolated from the chromosome 22–specific cosmid library LL22NC03 (Human Genome Center, Lawrence Livermore National Laboratory), by several cosmid walks away from the α-satellite-rich region of the chromosome 22 centromere (Xie et al. 1994). The bars on the right demonstrate the region duplicated in a typical marker chromosome (Mears et al. 1994 and Mears 1995, for D22S181) and by comparison the region duplicated in the ring chromosome (CM15). A maximum estimate of the size of the duplication for the marker chromosome is 3.3 Mb and for the ring chromosome, 2.1 Mb.

Dosage Analysis

Two methods were used to determine copy number of the 22q11 probes: RFLP dosage analysis and quantitative dosage analysis. A detailed account of both methods of analysis has been described elsewhere (Mears et al. 1994). In this study, hybridization signals were quantified from autoradiograms by using the BioRad GS670 scanning densitometer and the associated software, Molecular Analyst (version 1.1.1).

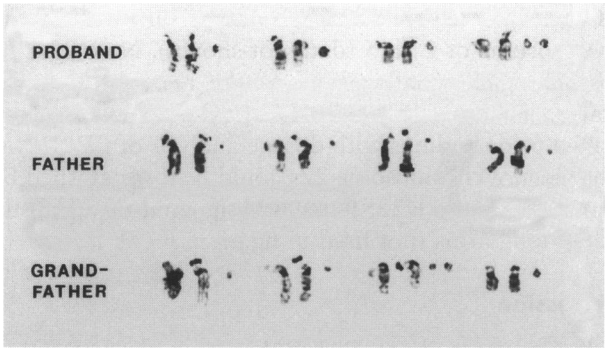

Figure 2 Partial karotypes of the proband, his father and grandfather, showing a minute ring chromosome 22 from four different cells. A small proportion of cells contain two rings (see table 1). Notice the size difference of the rings between the proband and the other family members.

RFLP dosage analysis.—RFLP analysis was performed with the polymorphic probes for the loci D22S9, D22S43, D22S57, and D22S181. In each case three replicates of CM13, CM14, CM15, a normal disomic control, and a trisomic control were used. The ratios were calculated for the band intensities when individuals were heterozygous and were then compared with the ratios of the heterozygous controls in order to determine copy number.

Quantitative dosage analysis.—This analysis was performed for the nonpolymorphic locus ATP6E and for the noninformative polymorphic loci tested (D22S57). Standardized ratios of the 22q11.2 test loci were determined by comparison of the hybridization signal relative to a reference probe. These ratios were then statistically compared with those obtained for the control DNAs, and copy number was calculated accordingly (Mears et al. 1994).

FISH.—Metaphase spreads were prepared from the lymphoblastoid cell lines CM13, CM14, and CM15. They were then hybridized with biotinylated (11-dUTP or 14-dATP) test probes. The test probes were cosS9, cosS181, and cosATP6E. Cohybridization was sometimes performed with the control probe (cosS39). Detection and visualization was achieved using the avidin–fluorescein isothiocyanate/antiavidin antibody system described elsewhere (Lichter et al. 1990; Driscoll et al. 1993).

Results

Clinical and Cytogenetic Evaluation

The proband was born at full term with length, weight, and head circumference well within the normal range. Right iris coloboma and left corneal opacity were noticed, as were bilateral ear pits, a left preauricular skin tag, and considerable micrognathia. A cleft in the soft palate was found, on examination. Both testes were undescended, the anus was imperforate, and the umbilical cord had only two vessels. An echocardiogram showed an interrupted aortic arch, total anomalous pulmonary venous return, ventricular septal defect, and atrial septal defect. The right kidney was polycystic and lacked function, and there was left-sided hydronephrosis and hydroureter. A voiding cystourethrogram showed severe reflux and demonstrated a rectovesical fistula. The patient was diagnosed with cat eye syndrome on the basis of the clinical picture. The family history was unremarkable until the cytogenetic analysis was performed. The father and grandfather were examined and were phenotypically normal.

Conventional GTG-banding, C-banding, and NOR-silver staining of lymphocyte chromosomes of the proband (CM15), father (CM14), and paternal grandfather (CM13) showed a variable-sized, supernumerary ring chromosome (fig. 2). The cytogenetic findings for blood, skin, and lymphoblastoid cell samples are summarized in table 1.

Dosage Analysis

Genomic DNA samples from the CM13, CM14, and CM15 cell lines were analyzed with the polymorphic probes to D22S9, D22S43, D22S57, and D22S181. Copy number was determined for heterozygous individuals for the respective probes. Quantitative dosage analysis was performed for the nonpolymorphic locus ATP6E and also for the loci D22S57 and D22S181. The cell lines showed a negligible level of mosaicism (table 1). A summary of the results is given in table 2.

All three individuals were informative for D22S9, and the ratio of signal intensities of the alleles were determined and compared with the ratios obtained for heterozygous controls. Both CM13 and CM14 showed a 2:1 allele ratio, indicating three copies of this locus. CM15, however, showed a 3:1 allele ratio, therefore indicating four copies.

All three were informative for the three-allele poly-

Table 1

Presence of a r(22) in Peripheral Blood, Skin, and Lymphoblastoid Cell Samples

	Blood	Skin	Cell Line
Proband (CM15)	72/80 (9)	NS	50/50 (1)
Father (CM14)	73/80 (1)	10/20 (2)	50/50 (1)
Grandfather (CM13)	80/80 (1)	16/20 (0)	50/50 (0)

NOTE.—Fractions indicate the number of cells, of the total studied, in which there was at least one ring chromosome observed. Numbers in parentheses are the numbers of cells in which two rings were observed. NS = not studied.

Table 2

Dosage Analysis of 22q11.2 Loci

Locus and Analysis	Grandfather (CM13)	Father (CM14)	Proband (CM15)
D22S9:			
RFLP	3	3	4
D22S43:			
RFLP	3	3	4
ATP6E:			
Dosage	3	3	4
D22S57:			
RFLP	2/4	2/4	NI
Dosage	2	2	2
D22S181:			
RFLP	2/4	2/4	2/4
Dosage	2	2	2

NOTE.—Copy number was determined for the five loci listed on the left. Loci are shown proximal to distal (top to bottom) on the basis of the study by H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell (unpublished data). NI = not informative for RFLP analysis. The designation "2/4" refers to heterozygotes revealing two bands of equal intensity, indicating an even copy number.

morphic probe to D22S43 (fig. 3). CM13 showed a 2:1 allele ratio (three copies), CM14 a 1:1:1 allele ratio (three copies), and CM15 a 3:1 allele ratio (four copies).

The nonpolymorphic locus ATP6E was tested by quantitative dosage analysis. Hybridization signals were quantified for this locus and were compared with the signal for the reference probe D21S110. CM13 and CM14 showed three copies for this locus, CM15 four copies.

D22S57 was informative for only CM13 and CM14. Both demonstrated a 1:1 allele ratio, indicating two or four copies of this locus. To determine copy number for all three cases, the allele signal intensity obtained for D22S57 was compared with a reference-probe signal (D21S19). The results indicated that this locus was in two copies in all cases.

The locus D22S181, which maps distal to D22S57, was informative for all three individuals, and all showed a 1:1 allele ratio, indicative of two or four copies. Comparison of the D22S181 allelic signals to the signal of the D21S15 reference probe indicated that this locus was in two copies in all cases.

FISH

To confirm the localization of the duplicated sequences on the ring, FISH analysis was performed. In all three cases, the D22S9 probe signal was present on the ring chromosome. A brighter, or dual, signal was observed on the ring of CM15, when compared with that of CM14, as would be predicted from dosage analysis (fig. 4). The ATP6E signal was present on the ring chromosome of CM15 (data not shown). No D22S181 cosmid signal was localized to the ring chromosome (data not shown; only CM14 tested). These results confirmed prior findings with dosage analysis of the DNAs. The normal chromosome 22s could be distinguished by the presence of a D22S39 cosmid signal at the distal tip of the long arms (not used in fig. 4).

Discussion

A previous study of marker chromosomes determined that the critical region for CES included the loci D22S9, D22S43, and D22S57, proximal to distal, but not D22S36 (Mears et al. 1994). The advent of a physical map of the region, generated from PFGE and YAC contigs (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data), and the availability of more probes to loci in the region, have enabled a more detailed analysis (fig. 4). The locus D22S181, which maps distal to D22S57, was found to be duplicated in all marker chromosomes tested (Mears 1995). As such, D22S181 represented the most distal locus of the cat eye syndrome critical region (CESCR), as defined by bisatellited marker chromosomes. The critical region is estimated to cover $\leqslant\sim 3.3$ Mb between the centromere and D22S36 (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data).

The proband described in this study represents one of

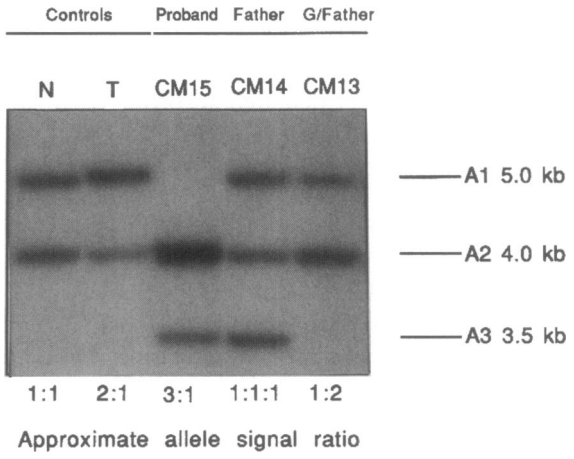

Figure 3 Autoradiogram of a Southern blot of *Taq*I-digested DNA samples, including normal (NC1, lane N) and trisomic (GM02325, lane T) controls and the three family members, CM15 (proband), CM14 (father), and CM13 (grandfather), hybridized to D22S43, a probe that reveals three alleles. Signal ratios between polymorphic bands in heterozygous individuals were compared with heterozygous controls in order to determine copy number. CM13 demonstrated a 2:1 allele ratio (A2:A1), CM14 a 1:1:1 allele ratio (A1:A2:A3), and CM15 a 3:1 ratio (A2:A3). Hence, CM13 and CM14 have three copies of the D22S43 locus, and CM15 has four copies.

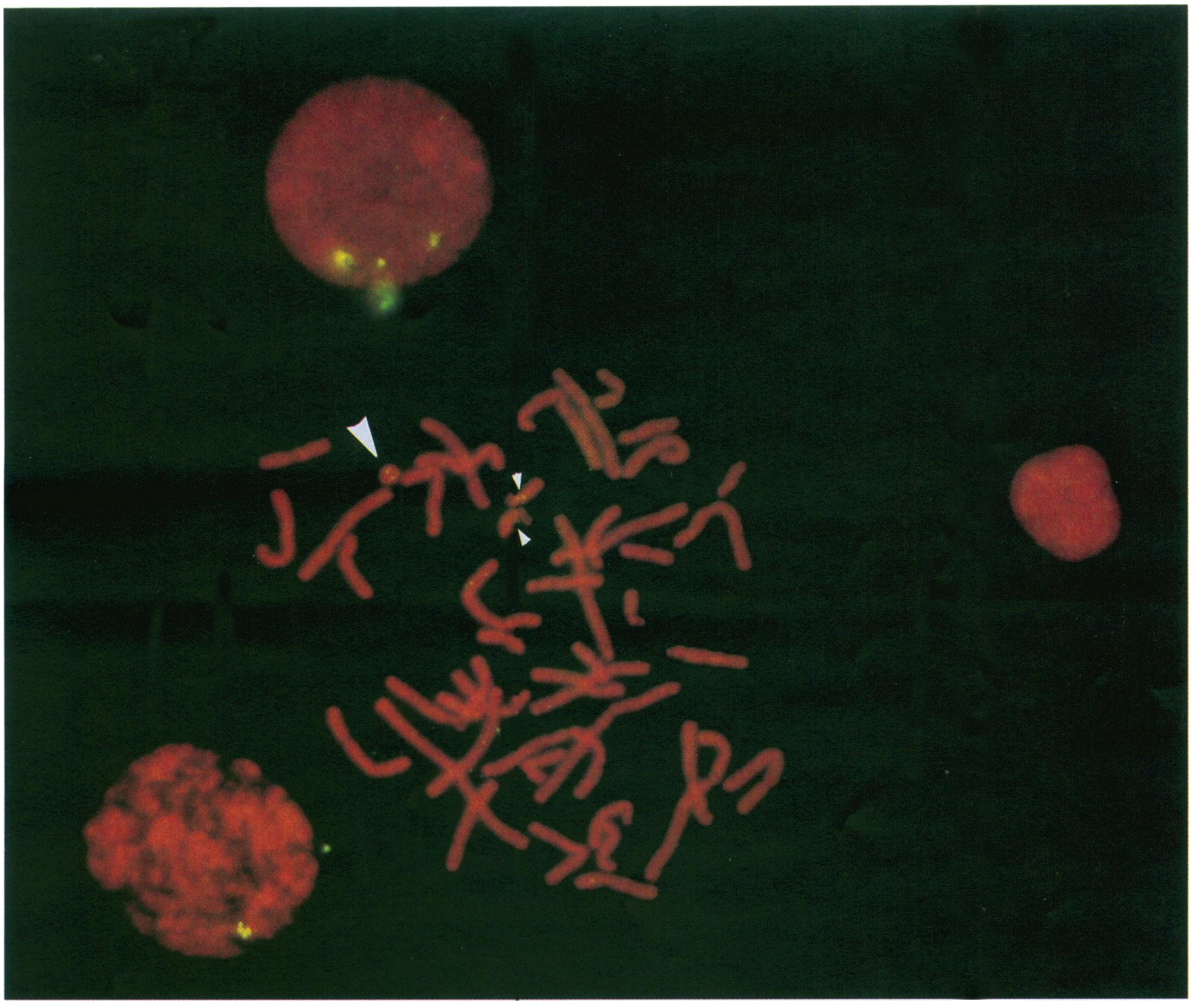

Figure 4 A metaphase cell of proband CM15 after in situ hybridization with the biotinylated D22S9 probe (cosS9). There are two distinct signals on the ring (large arrow), each signal with an apparently similar intensity to those of the normal chromosomes 22 (small arrow), indicative of the doubled-ring structure present in CM15.

the first reports of CES associated with a supernumerary ring chromosome derived from duplications of 22q11.2 (47, XY, + r(22)) (this family, El-Shanti et al. 1993; Ohashi et al. 1993). Dosage revealed that this duplication included the loci D22S9, D22S43, and ATP6E but did not include D22S57 or D22S181. Since the proband showed all the cardinal features of CES, the region between D22S57 and D22S36 can be excluded from the CESCR. ATP6E, the only gene currently localized to the CES region (Baud et al. 1994), is therefore still a potential candidate gene. A maximum physical estimate of the distance spanned by the CESCR, as defined by the pericentromeric probe N38F3 to D22S57, is 2.1 Mb. This compares with the prior estimate of $\leq$3.3 Mb (N38F3 to D22S36). Our study also confirms the physical mapping of ATP6E as being proximal to D22S57 (H. E. McDermid, M. A. Riaza, T. J. Hudson, M. L. Budarf, B. S. Emanuel, and C. J. Bell, unpublished data). Between these two loci, which were estimated to be $\leq$100 kb apart, lies the breakpoint associated in the original formation of the ring chromosome. This breakpoint maps to a different location than the majority of breakpoints involved in marker formation, which map between D22S181 and D22S36 (Mears et al. 1994; Mears 1995). Models for ring chromosome formation are usually associated with deletions rather than duplications (McGinniss et al. 1992). Because of the supernumerary nature of this ring chromosome and the novel position of the breakpoint (ATP6E-D22S57), it is hypothesized that this supernumerary ring chromosome may be a derivative product from an unstable dicentric CES marker chromosome. Derivative structures of CES marker chromosomes have been reported in the literature, such as smaller dicentrics (Ing et al. 1985), monocentrics, and even ring chromosomes (Urioste et al. 1994). Furthermore, other acrocentric rearrangements

have been associated with the presence of ring chromosomes of the same acrocentric. There are a number of individuals reported who are mosaic for acrocentric isochromosomes or homologous Robertsonian translocations and presumably a derivative ring chromosome (Orye and Craen 1974; Dallapiccola et al. 1982; Pangalos et al. 1984; Cantu et al. 1989; Jalal et al. 1990; Duckett et al. 1992). In other cases, parents carrying acrocentric isochromosomes or homologous Robertsonian translocations have been known to produce offspring with a ring chromosome apparently derived from the parental abnormality (de Almeida et al. 1983; Neri et al. 1983). In the family reported here, it is assumed that the ring chromosome observed in this family was formed in an ancestor of CM13, whereby an unstable marker chromosome broke between ATP6E and D22S181. One of the monocentric fragments then fused to form a supernumerary ring chromosome which was subsequently inherited by the descendants.

The dosage data determined that the grandfather (CM13) and father (CM14) had three copies of the loci D22S9, D22S43, and ATP6E, although they displayed none of the cardinal phenotypic features of CES. In contrast, the proband (CM15), who demonstrated four copies of the aforementioned loci, had severe CES and displayed all of the cardinal features of this syndrome. The results for this family would suggest a threshold model for CES, where four copies of the region are necessary to produce the syndrome phenotype. However, variability within familial cases of CES is common, with the same marker chromosome resulting in a very different phenotype in different generations (Schachenmann et al. 1965; Noël et al. 1976; Schinzel et al. 1981; Ing et al. 1985; Mears et al. 1994). For instance, Luleci et al. (1989) described one such case where the marker was passed from a normal mother to two daughters, with only one daughter affected. Furthermore, three copies of the cat eye region have been shown to be sufficient to result in a CES phenotype, as in the interstitial duplications of L.W. (Reiss et al. 1985) and S.K. (Knoll et al. 1994). L.W. presented with coloboma, preauricular pits, dysmorphic features, and developmental delay. S.K. presented with preauricular pits, total anomalous pulmonary venous return, dysmorphia, absent right kidney and testicle, and developmental delay. L.W. was shown to have three copies of D22S9 (McDermid et al. 1986), and S.K. three copies of the immunoglobulin light-chain locus (Knoll et al. 1994). In both cases, three copies of the CESCR were sufficient to produce a CES phenotype, although they differ in terms of the spectrum of features expressed. Thus, a simple threshold model is not sufficient to explain the phenotypic variability of CES.

There are numerous factors that may be hypothesized to contribute to this phenotypic variability. Although tissue-specific mosaicism leading to a normal phenotype cannot be ruled out in CM13 or CM14, the ring was present in 90% of blood cells over the three generations of this family. Genetic background differences and stochastic factors are more likely possibilities to explain the variation in this syndrome, since mosaicism of the marker chromosomes is not universal among CES patients. However, the presence of four rather than three copies of the CESCR may increase the susceptibility of an individual to express the CES phenotype, within the parameters of other influencing factors. This considered, copy number of the CESCR is unlikely to be useful in phenotypic prediction.

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