Am. J. Hum. Genet. 63:1153–1159, 1998

A Chromosomal Deletion Map of Human Malformations

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Summary

Malformations are common causes of pediatric morbidity and mortality, and genetic factors are a significant component of their etiology. Autosomal deletions, in almost all cases, cause a nonspecific embryopathy that presents after birth as growth failure, mental retardation, and multiple malformations. We have constructed a chromosome map of autosomal deletions associated with 47 different congenital malformations, using detailed clinical and cytogenetic information on 1,753 patients with nonmosaic single contiguous autosomal deletions. The 1,753 deletions involved 258 (89%) of 289 possible autosomal bands (by the use of ISCN 400-band nomenclature), giving a total of 4,190 deleted autosomal bands for analysis. We compared the band distributions of deletions associated with common major malformations with the distribution of all 1,753 deletions. We noted 283 positive associations between deleted bands and specific malformations, of which 199 were significant ($P < .05$, $P > .001$) and 84 were highly significant ($P < .001$). These "malformation-associated bands" (MABs) were distributed among 137 malformation-associated chromosome regions (MACRs). An average of 6 MABs in 2.9 MACRs were detected per malformation studied; 18 (6%) of 283 MABs contain a locus known to be associated with the particular malformation. A further 18 (6%) of 283 are in seven recognized specific malformation-associated aneuploid regions. Therefore, 36 (26%) of 137 of the MACRs contain an MAB coinciding with a previously recognized locus or malformation-associated aneuploid region. This map should facilitate identification of genes important in human development.

Received December 30, 1997; accepted for publication July 23, 1998; electronically published September 18, 1998.

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0002-9297/98/6304-0029$02.00

Introduction

In developed countries, malformations account for 21% of pediatric hospital admissions (Hall et al. 1978), 39% of pediatric intensive care–unit admissions (FitzPatrick et al. 1991), and 48% of deaths in full-term neonates (Hogue et al. 1989). Kalter and Warkany (1983) estimated that 6% of all congenital malformations are due to visible cytogenetic abnormalities. Several areas of investigation (twin studies [Hrubel and Robinette 1984], familial aggregation [Khoury et al. 1988], analysis of interracial crossing [Chung and Myrianthopoulos 1968], and rare Mendelian traits [Wilkie 1994]) provide evidence that genetic factors play a significant causative role in birth defects. Very few of these genes have, as yet, been characterized.

In humans, cytogenetically visible autosomal deletions have a live birth incidence of ~1 in 7,000 (Jacobs et al. 1992). Over the last 25 years, autosomal deletions have been used extensively in human gene mapping to order genes in contiguous gene defects (Ballabio 1991) and have provided the first clues to the map location of many genetic loci (Ferguson-Smith and Aitken 1982). As yet, no systematic approach to mapping the phenotypic associations of segmental hypoploidy has been undertaken in humans, although this approach has been suggested elsewhere (Lewandowski et al. 1977). Such an analysis may facilitate the identification of genes involved in human site-specific malformations. We present herein a first-generation chromosome-deletion map.

Material and Methods

Case Ascertainment and Deletion Definition

The Human Cytogenetics Database (HCDB) is a commercially available computerized catalog of postnatally ascertained, cytologically detectable human chromosomal aberrations (Schinzel 1994). We extracted cytogenetic and clinical data on individuals with nonmosaic uncomplicated deletions (those involving a single contiguous region of autosomal DNA). In view of the modifying influence of segmental trisomies on deletions (Lurie 1993), the presence of any other aneuploid region excluded individuals from further analysis. International System for Human Cytogenetic Nomenclature (ISCN)

400-band nomenclature (Mittelman 1995) was used to describe the deletions, and breakpoint bands were scored as deleted. Deletions involving subbands were scored as including the whole band. This gave a total of 289 whole autosomal bands. To assess how accurately the distribution of HCDB deletions represents that in the overall population, we compared it with cases of uncomplicated autosomal deletions presented in the Constitutional Chromosome Abnormality Database (CCAD). This database is funded by the Oxford and East Anglia Health Authority, and it catalogs all abnormal cytogenetic reports from ~70% of UK cytogenetic laboratories. The CCAD individuals had received diagnoses in postnatal life by analysis of metaphase chromosomes obtained from peripheral blood lymphocyte culture.

Statistical Analysis

The distribution of deleted bands in patients with 47 different congenital malformations was then determined. These specific malformations were chosen as common, major malformations that cover a wide spectrum of developmental processes. For some malformations—for example, gastroschisis, esophageal atresia, and radial ray defects—the numbers associated with simple deletions were too small to allow valid analysis. For each malformation studied, the observed number of deletions of a particular band was compared with the expected number calculated from the band distribution of all 4,190 band deletions. Confidence limits for the observed number of deletions and the significance of any deviation from expected were calculated as described by Vasarhelyi and Friedman (1989). The number of deletions in any band was taken to follow a Poisson distribution, since total deletions and the number of deletions in any band were usually small. Chromosome bands found to be significantly ($P < .05$, $P > .001$) and highly significantly ($P < .001$) associated with a given malformation were termed "malformation-associated bands" (MABs).

The analyses of sex ratios and the comparison of distribution of cases between HCDB and CCAD were simplified by grouping the deletions by the chromosome arm containing the deleted region (unless the number of deletions on that arm was <10, in which case they were grouped by whole chromosome). Chromosome 19 was excluded from analysis because of the very small number of reported deletions involving this chromosome (1/1,753), leaving a total of 33 chromosomal categories (deletion groups). The Spearman rank correlation coefficient was calculated between the number of deletions in each deletion group in the two databases. Comparisons were also made, between the two groups, of the proportions of all deletions in each of the 33 deletion groups, with correction for the number of tests carried out. We compared the sex ratios of individuals in the 33 deletion groups by comparing the proportion of males in each group with that in the rest of the groups combined and by correcting for the number of tests made.

The Wilcoxon rank sum test was used to compare the band size distribution in each malformation group with that for all other deletions considered together. In this analysis, the number of bands involved in each deletion was used as an estimate of deletion size. We also estimated deletion size by measuring the length of each deletion on the ISCN karyotype and expressing this as a percentage of the autosomal haploid genome. There was a highly significant correlation between these two values (correlation coefficient 0.69, $P < .001$).

Results

General Information

A total of 1,753 individuals with uncomplicated autosomal deletions were identified, representing approximately one-third of all cases in HCDB; 258 (89%) of the 289 possible autosomal bands were involved in one or more deletions. This gave a total of 4,190 band deletions that were used for analysis. No deletions were recorded in 31 (11%) of 289 autosomal bands.

MABs

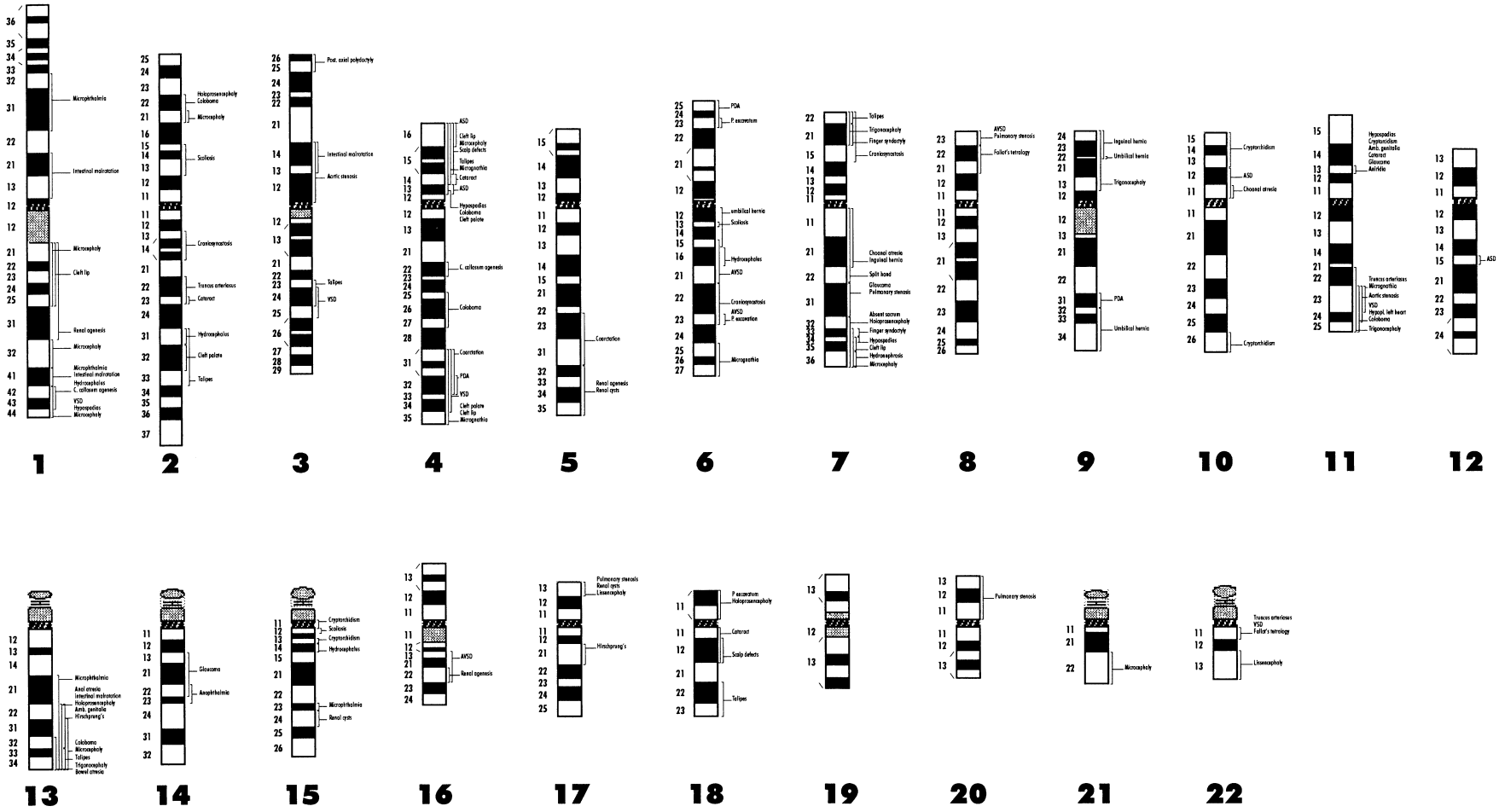
In the 47 malformations chosen for study, 283 MABs were identified (199 in which $P < .05$, $P > .001$, 84 in which $P < .001$) and 138 different bands were involved (fig. 1, table 1). The average number of associated bands detected per malformation was 6 (range 0–13), of which 4.3 were significant ($P < .05$, $P > .001$) and 1.8 were highly significant ($P < .001$). The chromosome regions containing no significant loci were 5p, 8q, 12p, 16p, 19, and 20q.

Deletion Size

Seven of the malformations (anal atresia, cleft lip, cleft palate, micrognathia, hydrocephalus, microphthalmia, and talipes) were associated with deletion sizes significantly larger than the rest of the group and two (aniridia and cataract) with deletions involving significantly fewer bands ($P < .01$).

Distribution of Deletions in HCDB

The deletion group distribution of HCDB individuals was compared with 937 individuals with uncomplicated autosomal deletions extracted from CCAD. The distribution of deleted chromosomal material across the genome was nonrandom in both HCDB and CCAD, and there was a highly significant correlation between the distributions in these two groups ($r = 0.665$, $P < .001$).



Key:
ASD Atrial septal defect
AVSD Atrio-ventricular septal defect
PDA Patent ducts arteriosus
VSD Ventricular septal defect

Figure 1 Diagrammatic representation of G-banded autosomal karyotype indicating locations of MABs

Table 1

Regions of Autosomal Hypoploidy Significantly Associated with Specific Malformations

Malformation	No. of Cases	All Significantly Associated Bands ($P < .05$, $P < .01$, $P < .001$)	Highly Significantly Associated Bands ($P < .001$)
Craniofacial:			
Cleft palate	269	2q32, 4p16-13, 4q31-35	4p16-14, 4q31-35
Cleft lip	95	1q21-25, 4p16-15, 4q31-35, 7q34-35	1q25,4q31-35
Micrognathia	653	4p16-14, 4q31-35, 6q25-27, 11q23	4p16-15
Choanal atresia	11	7q11-21, 10p11	
Cardiac:			
Patent ductus arteriosus	94	4q32, 6p25-23, 9q31	
Atrial septal defect	97	4p13, 4p16, 10p12-11, 12q15	
Ventricular septal defect	166	1q42-44, 3q24-25, 4q31-34, 11q23-25, 22q11	4q31, 22q11
Atrioventricular septal defect	16	6q15-21, 6q23, 8p23, 16q13-22	
Pulmonary stenosis	71	7q31, 8p23, 17p13, 20p13-11	20p13-11, 22q11
Hypoplastic left heart	14	11q23-25	11q23-25
Aortic stenosis	23	3p14-11, 11q23-24	11q23-24
Truncus arteriosus	15	2q22-23, 11q23, 22q11	2q22,22q11
Tetralogy of fallot	37	8p22-21, 22q11	
Coarctation	23	4q31-32, 5q23-31	
Skeletal and limb:			
Scoliosis	114	2p15-13, 6q13, 15q12	
Pectus excavatum	60	6p23, 18p11	
Talipes equina varus	176	2q31-33, 3q23-24, 4p16-14, 7p22, 13q33-34, 18q22-23	
Syndactyly of fingers	38	7p21, 7q33	7p21, 7q33
Postaxial polydactyly	27	3p26-25	3p25
Split hand	7	7q11-22	7q21-22
Absent sacrum	9	7q32-36	7q36
Gastrointestinal:			
Small bowel atresia	14	13q33-34	
Anal atresia	36	13q22-34	13q22-34
Hirschprung's syndrome	11	13q22-32, 17q21	
Intestinal malrotation	29	1p21-13, 1q41, 3p14-13, 13q22-34	
Umbilical hernia	112	6q12-15, 9p22, 9q32-34	
Genitourinary:			
Renal agenesis	19	1q21-32, 5q32-35, 16q22	1q31
Multiple renal cysts	18	5q32-35, 15q24, 17p13	
Hydronephrosis	40	7q36	
Hypospadias	152	1q42-44, 4p16-13, 7q34, 11p13	
Cryptorchidism	267	10p15-13, 10q26, 11p13, 15q11, 15q13	10p15-14, 11p13
Inguinal hernia	115	7q11-21, 9p24-22	7q11-12
Ambiguous genitalia	23	11p13,13q22-34	11p13, 13q31-34
Ocular:			
Microphthalmia	86	1p32-31, 1q41, 13q21-34, 15q23	13q22-34
Coloboma	81	2p22-21, 4p16-13, 4q25-27, 11q23-25, 13q31-34	4p16-14
Cataract	61	2q23, 4p14, 11p13, 18q11-12	11p13
Aniridia	54	11p13	11p13
Anophthalmia	3	14q22-23	14q22-23
Glaucoma	25	7q31, 11p13, 14q13-22	11p13, 14q13-21
CNS:			
Microcephaly (prenatal)	261	1q21-25, 1q32, 1q42-44, 2p21, 4p16-15, 7q33-36, 13q31-34, 21q22	4p16-15
Hydrocephalus	139	1q42-43, 2q31, 6q16, 15q14	
Holoprosencephaly	55	2p22-21, 7q32-36, 13q22-34, 18p11	2p21, 7q32-34, 7q36, 13q33-34, 18p11
Agenesis corpus callosum	64	1q42-43, 4q22	1q42-43
Lissencephaly	12	17p13, 22q13	17p13
Craniosynostosis	30	2q13-14, 6q22-23, 7p22-15	7p21-15
Trigonocephaly	103	7p22-21, 9p24-13, 11q22-25, 13q32-34	9p24-21, 11q23-25
Scalp defects	10	4p16-15, 18q12	

NOTE.—All bands for which $P < .05$ are included in the 3d column; of these, the highly significant associations, for which $P < .001$, are indicated in the 4th column.

It was noted that deletions involving 1q, 4p, 13, and 18p were significantly overrepresented in HCDB but deletions involving 5p and 15 were significantly underrepresented.

Sex Ratios

The male:female ratio was 0.85 (794:935), with 24 cases (1.37%) in which the phenotypic sex was ambiguous or not recorded. There were no significant differences in the male:female ratios in the deletion groups.

Known Malformation-Associated Loci

A search of the Online Mendelian Inheritance in Man database was then performed to look for known Mendelian loci associated with each malformation. Eighteen (6%) of 283 MABs contain a locus, identified by linkage or mutation analysis, associated with the particular malformation (table 2). Therefore, 18 (13%) of 137 MACRs contain a known corresponding locus. A further 18 (6%) of 283 are in regions of recognized aneuploid syndromes.

Table 2

MABs Containing Loci Identified by Linkage or Mutation Analysis

Malformation	MAB	Known Locus (MIM Number)
Holoprosencephaly	2p23-22	HPE type 2 (157170)
Atrial septal defect	4p13	Ellis–van Creveld (225500)
Craniosynostosis	7p21-15	Saethre Chotzen (101400)
Trigonocephaly	7p22-21	Saethre Chotzen (101400)
Split hand	7q11-22	EEC-1 syndrome (129900)
Choanal atresia	7q11-21	EEC-1 syndrome (129900)
Absent sacrum	7q32-36	Sacral agenesis (176450)
Holoprosencephaly	7q32-36	HPE type 3 (142945)
Cryptorchidism	11p13	WT-1 (137357)
Ambiguous genitalia	11p13	WT-1 (137357)
Cataract	11p13	AN-1 (106210)
Glaucoma	11p13	AN-1 (106210)
Aniridia	11p13	AN-1 (106210)
Hirschprung's syndrome	13q22-32	HSCR-2 (600155)
Renal cysts	15q24	Bardet-Biedl (209901)
Lissencephaly	17p13	LIS-1 (601545)
Holoprosencephaly	18p11	HPE type 4 (142946)
Pulmonary stenosis	20p13-11	JAG1 (601920)

Discussion

Remarkable similarities have been noted in the effects of segmental aneuploidy in species as diverse as humans and *Drosophila melanogaster* (Lindsley et al. 1972). A generally applicable rule is that phenotypes associated with deletions are more severe than those associated with duplications, with a maximum tolerance in viable organisms of 3% and 10% of the genome, respectively (Hecht and Hecht 1987). It is also generally accepted that human autosomal deletions produce certain nonspecific phenotypic effects, such as intrauterine growth retardation and mental handicap. However, the clinical recognition of deletion-specific syndromes (e.g., 4p [Wolf-Hirschhorn], 5p [cri du chat], and 11q [Jacobson]) supports the assumption that haploinsufficiency for at least some of the genes in the deleted region has a direct effect on specific developmental processes. If this assumption is correct, then the recognition of significant associations between a particular malformation and haploinsufficiency at a cytogenetic locus may facilitate the identification of causative mutations in cytogenetically normal individuals with that malformation. This approach is supported by several notable successes in the use of human constitutional autosomal deletions to localize or clone specific malformation-causing genes (Tommerup et al. 1992; Muenke et al. 1994; Lynch et al. 1995; Roessler et al. 1996).

Given this evidence, it is perhaps surprising that a systematic chromosomal deletion map in humans has not been attempted before. One reason for this may be the complex nature of many human aneuploidies with both trisomic and monosomic regions present in the same individual. We have chosen to discount such cases and limit our analysis to individuals with nonmosaic deletions of a single contiguous region of autosomal DNA. This was done to exclude the modifying action of trisomic regions on deletions (Epstein 1993) but, obviously, it cannot eliminate other genetic background effects that exist in such a complex genome. It should also be noted that we did not attempt to analyze parent-of-origin effects, since this information was not available for the majority of cases.

Several recent advances in human and other mammalian genomics have prompted this study. First, a gene map of the human genome has been constructed by regionally mapping ~20% of all human transcripts in the form of expressed sequence (ES) tags (Shuler et al. 1996). This resource enables investigators to identify candidate genes in any cytogenetic region of interest. Second, the recognition of regions of human-mouse synteny throughout the genome will allow the integration of the map locations of developmental mutations in both species. The ongoing projects to create an atlas of gene expression data in the mouse embryo (Ringwald et al. 1994) and targeted deletion mutants in mouse ES cells (Yun et al. 1997) may also improve candidate gene selection in humans. Third, the ability to use polymorphic genetic markers in mapping non-Mendelian traits involves powerful but expensive and time-consuming laboratory and computational techniques (Risch and Merikangas 1996). The deletion map may be useful in obviating the need for whole genome scans as a first approach to the identification of disease genes.

Several factors mean that this map must be interpreted

with care. First, the degree to which the ascertainment of uncomplicated deletions in the database is complete is unknown. Second, the deletions cataloged in HCDB are not completely representative when compared with deletions in CCAD. However, most of the underrepresentation in HCDB can be accounted for by specific deletions involving the Prader-Willi/Angelman (15q) and cri du chat (5p) loci. The reason that deletions involving 1q, 4p, 13, and 18p are apparently overrepresented is not clear. It is also interesting that seven malformations were associated with significantly larger deletions, and this may simply reflect a nonspecific embryopathy. Aniridia and cataract were associated with significantly smaller deletions on 11p, and this may reflect a high phenotypic penetrance of haploinsufficiency at this locus. Interestingly, PAX6, which maps to 11p13 and is mutated in individuals with aniridia (Jordan et al. 1992), shows exquisite developmental dosage dependence (Schedl et al. 1996). Third, a potential bias in HCDB is that a report of a particular malformation in a patient with a deletion is likely to lead to that malformation being specifically sought in future cases. This bias would apply particularly to asymptomatic internal malformations that may be difficult to detect on routine clinical examination (e.g., atrial septal defects). This may be a particular problem where the numbers of individuals with a specific malformation are small (e.g., choanal atresia) (table 1). Fourth, the accuracy of breakpoints recorded in HCDB is not known. Such inaccuracies mean that the MAB results should be seen as clues to particular chromosomal regions rather than specific significant bands. Fifth, the statistical method of identifying the MAB could be criticized when it is used with the whole group, rather than the whole group without the test cases, to define the "deletability" of each band. This approach was necessary, since an independent measure of deletability was not available. However, the approach we have taken should bias against finding MABs, since the individuals are being tested in part against themselves. This article should be seen as merely suggesting those chromosome regions where the search for loci involved in the etiology of the malformations is most likely to be fruitful.

Finally, although the association of a specified malformation with a particular chromosome deletion is evidence that haploinsufficiency of a gene (or genes) in that region is responsible, this method would not be expected to reliably identify the locations of recessive genes and would not identify disease genes acting via other mechanisms of genetic dominance (Wilkie 1994).

We plan to develop this map by searching the database for combinations of malformations, to identify candidate deletion groups for syndromes that involve multiple malformations. We are also in the process of developing a similar map for autosomal duplications.

Acknowledgments

We thank Maggie Fitchett and Neena Nirsimloo for information on the Constitutional Chromosome Abnormality Database and Veronica van Heyningen, Isobel Hansen, Mary Porteous, and David Bonthron for helpful comments on the manuscript. We also thank the anonymous reviewers for helpful suggestions regarding the statistical approach taken. We also thank the Hartmann Mueller Foundation, Zurich, and the Julius Klaus Foundation, Zurich, for their support of the Human Cytogenetics Database. This work was partially funded by Action Research and the Western General Hospital NHS Trust.

Electronic-Database Information

URLs for data in this article are as follows:

Constitutional Chromosome Abnormality Database, http://www.hgmp.mrc.ac.uk/local-data/ccad_form.html (for a catalog of all abnormal cytogenetic reports from ~70% of UK cytogenetic laboratories)

Human Cytogenetics Database, version 1.0. Oxford University Press Electronic Publishing, 1994

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for known malformation-associated loci)

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