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# A Chromosomal Duplication Map of Malformations: Regions of Suspected Haplo- and Triplolethality—and Tolerance of Segmental Aneuploidy—in Humans

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## Summary

**The distribution of simple autosomal duplications associated with congenital malformations has been analyzed by means of data contained in the Human Cytogenetics Database. For each of the 47 malformations, the frequency of duplication of a given chromosome band associated with the malformation was compared with the overall frequency of duplication of that band recorded in the database. In total, there were 143 malformation-associated chromosomal regions (MACR); 21 of these contained at least one band with a highly significant ($P < .001$) association. The average number of bands per MACR was 3.1. Eight bands, representing 2.1% of haploid autosomal length, were not involved in any duplication, and we suggest that these are potentially triplolethal. This compares with 31 bands, representing 11% of haploid autosomal length, that were identified in the previously reported deletion map and that were not involved in any deletion and are potentially haplolethal. In both cases, approximately half of these bands are pericentromeric. The longest duplication involves 4.3% of haploid autosomal length, and the longest deletion involves 2.7%.**

## Introduction

Malformations are now the most common cause of neonatal death in full-term infants (Hogue et al. 1989). There is considerable evidence for a significant genetic component in the etiology of many common malformations (Chung and Myrianthopoulos 1968; Kalter and Waranky 1983; Hrubec and Robinette 1984; Khoury et al. 1988; Wilkie 1994). The present study was initiated to aid in the identification of genetic loci underlying birth defects. Elsewhere, we have presented data on the distribution of autosomal deletions associated with malformations, as a method for identification of causative genetic loci (Brewer et al. 1998). We have used an identical technique to examine the association between malformations and simple autosomal duplications, which occur at an incidence of 1:7,000 births (Jacobs et al. 1992). These data have been used to construct a map of duplications associated with human congenital malformations. We have also attempted to identify regions of the genome that are potentially haplo- or triplolethal, and we present the first large-scale analysis of the tolerance of segmental aneuploidy in the human genome.

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## Material and Methods

### *Case Ascertainment and Deletion Definition*

The Human Cytogenetics Database (see Schinzel 1994) is a commercially available computerized database of postnatally ascertained chromosome aberrations collected from the literature. Details of 1,621 cases of simple autosomal duplications were extracted. Only nonmosaic duplications involving a single contiguous region of autosomal DNA as the only karyotypic abnormality were used; this was done to avoid the known interactive effects in more-complex rearrangements (Lurie 1993). ISCN 400-band nomenclature (Mittelman 1995) was used to describe the duplications, and breakpoint bands were scored as duplicated. Duplications involving subbands were scored as were those for the whole band. This gave a total of 6,900 duplicated autosomal bands for analysis. The group of 47 malformations used was identical to that used in construction of the chromosomal deletion map and was chosen to cover a wide spectrum of developmental processes (table 1).

### *Statistical Analysis*

The distribution of duplicated bands in patients with 47 different congenital malformations was determined.

## Table 1

**MABs: Significance**

| Malformation (No. of Cases) | All Significantly ($P < .05$, $P < .01$, $P < .001$) Associated Bands | Highly Significantly ($P < .001$) Associated Bands Only |
|---|---|---|
| Craniofacial: | | |
| Cleft palate (218) | 3p24–23, 3p26, 3q23–25, 7q22–32, 8q21, 10p15–11, 14q11–21, 16p12–13, 22q12–13 | |
| Cleft lip (81) | 3p26–21, 10p15–11, 11p14–11, 13q22–34 | 3p26–21, 10p15–11 |
| Micrognathia (669) | 10q24, 18q12–23 | |
| Choanal atresia (20) | 6p25–21, 7p22–14, 8q22–24 | 7p22-15 |
| Cardiac: | | |
| Patent ductus arteriosus (110) | 1q25–41, 7p14, 16q11–24 | 16q22 |
| Atrial septal defect (131) | 1q25–41, 1q43, 3p26–23, 3q21–22, 5q31–32, 5q35, 7p14, 8q22–24 | |
| Ventricular septal defect (178) | 1q25–32, 3p26–21, 3q26–29, 8q22–24, 16q11–24 | 8q24 |
| Atrio-ventricular septal defect (13) | 4q11–13, 10q24–26, 11q23–25, 12q13, 20q11–12 | |
| Pulmonary stenosis (52) | 1q25–31, 36p25–21, 8q22–24 | 8q22–24 |
| Hypoplastic left heart (12) | 1p35–32, 8p12–11, 12p11, 16q11–24 | 16q11-12 |
| Aortic stenosis (18) | 17q25 | |
| Truncus arteriosus (10) | 1p35–33, 1q32–44 | |
| Tetralogy of Fallot (34) | 1p33–35, 8q22–24, 16p11 | 8q22-24 |
| Coarctation (24) | 6q21–22, 8p23–11, 16q22–24 | |
| Skeletal and limb: | | |
| Scoliosis (173) | 4p16–11, 10q24–26, 15q23–26 | 4p16–11, 10q25–26 |
| Pectus excavatum (95) | 2p25–24, 5p12, 5p15, 15q22–26, 18q21–23 | 15q23–26 |
| Talipes equinovarus (199) | 6q21–27, 10p15–11 | 6q25, 10p15-11 |
| Syndactyly of fingers (51) | 5q11, 5q13, 9p11–24 | 9p11–24 |
| Postaxial polydactyly (58) | 13q14–34, 17q23–25 | 13q14–34, 17q23–25 |
| Split hand (1) | 5q15–31 | |
| Absent sacrum (2) | 15q12–13, 17q23–25 | |
| Gastrointestinal: | | |
| Small-bowel atresia (2) | 12p13–11, 15q12 | 15q12 |
| Anal atresia (18) | 3q25–29, 22q11–12 | |
| Hirschsprung syndrome (4) | 17q21–23 | |
| Intestinal malrotation (33) | 3q21–29, 11p11–15 | 11p11–15 |
| Umbilical hernia (107) | 4q25–35, 11p15, 13q31–34, 14q11–13 1q11–22, 3q12–13, 11p13–11 | |
| Genitourinary: | | |
| Renal agenesis (22) | 10p12–11, 14q22 | |
| Multiple renal cysts (40) | 3q21–29, 10p15–11, 17q23–25 | |
| Hydronephrosis (65) | None | |
| Hypospadias (65) | 2q35–37, 8q12, 16q21–24 | |
| Cryptorchidism (308) | 1q41, 4q28–35, 8q24 | |
| Inguinal hernia (114) | 5q33–35, 13q22–34, 17p13 | |
| Ambiguous genitalia (5) | None | |
| Ocular: | | |
| Microphthalmia (116) | 1q31–41, 6p25–21, 10q24–26, 13q14–34, 14q11–13, 20q13, 22q11 | |
| Coloboma (46) | 1q31–41, 5p15–13, 10q21, 13q32–34, 17q21–22, 22q11 | |
| Cataract (36) | 3q21, 3q25–29, 6p25–22 | |
| Aniridia (2) | None | |
| Anophthalmia (2) | 4q11–21, 7q21 | |
| Glaucoma (18) | 3q21–29 | 3q22, 3q25-29 |
| CNS: | | |
| Microcephaly (prenatal) (196) | 5q31, 5q33, 5q35, 6q23–24, 9q11–12, 9q22, 16q11–21 | |
| Hydrocephalus (154) | 1q42–44, 5p12–11, 8p23–21, 12q24 | |
| Holoprosencephaly (30) | 3p26–23, 3q23, 5q31–33, 6p21 | |
| Agenesis corpus callosum (44) | 3q25, 8p23–11 | 8p23–21 |
| Lissencephaly (0) | None | |
| Craniosynostosis (18) | 2p11, 2q11–12, 6p25–21, 16q11–13 | |
| Trigonocephaly (24) | 6p11, 13q14–34 | 13q21–34 |
| Scalp defects (6) | 11q13, 13q11–14, 16q11–24 | |

For each malformation studied, the observed number of duplications of a particular band was compared with the expected number, calculated from the band distribution of all 6,900 band duplications. The number of duplications of any band was assumed to follow a Poisson distribution, because the number of duplications of any band was usually small. Confidence limits for the observed number of duplications, as well as the significance of any deviation from expected values, were calculated as described by Vasarhelyi and Friedman (1989). Chromosome bands found to be significantly ($P < .05$ or $P < .01$) or highly significantly ($P < .001$) associated with a given malformation were termed "malformation-associated bands" (MABs); the term "malformation-associated chromosomal regions" (MACRs) was used to describe groups of adjacent bands associated with the same malformation.

Duplication size was estimated by a count of the number of bands involved and by measurement of the length of each duplication on the ISCN karyotype and was expressed as a percentage of the total haploid autosomal length (HAL). The two estimates of size were highly significantly correlated (Spearman rank coefficient .88; $P < .001$). The resolution of the duplication map was compared with that of the deletion map by estimation of the average MACR size (in Mb), calculated by use of chromosome lengths in the physical human transcript map (Human Gene Map).

### *Duplication:Deletion Ratios*

The possibility that some malformations were particularly likely to result from duplication whereas others were likely to result from deletion was addressed by calculation of the deletion:duplication index (DDI). This is the proportion of cases of each malformation that are associated with deletions (DDI = $a/a + b$, where $a$ is the number of cases of the malformation that are associated with deletions and $b$ is the number of cases of the malformation that are associated with duplications). Malformations for which the DDI differed significantly from the proportion for the other malformations combined were identified, and correction was made for multiple testing (by the Bonferroni method)

## Results

### *Spectrum of Malformations*

There were approximately equal numbers of simple duplications (1,621) and deletions (1,753) in the Human Cytogenetics Database (see Schinzel 1994). For most of the malformations, there was a highly significant correlation between the number of cases associated with duplications and the number of cases associated with deletions ($r = .87$; $P < .001$), with a mean DDI of .57 (range .31–1). However, scoliosis ($P < .001$), postaxial polydactyly ($P < .01$), and pectus excavatum ($P < .05$) were significantly associated with duplications, whereas aniridia ($P < .01$), trigonocephaly ($P < .01$), hypospadias ($P < .001$), and lissencephaly ($P < .05$) were associated with deletions.

### *MACRs*

One thousand six hundred twenty-one cases of 331 different autosomal duplications were identified in the Human Cytogenetics Database (see Schinzel 1994). This gave a total of 6,900 duplicated bands. There were 450 MABs identified, of which 373 were significant ($P < .05$ or $P < .01$) and 77 were highly significant ($P < .001$) (table 1). MABs were distributed among 143 MACRs (fig. 1). The average number of MABs per MACR was 3.1 (range 1–9) (table 2). Twenty-one MACRs contained at least one highly significant MAB. The average number of MABs and of MACRs per malformation was 9.6 (range 0–23) and 3 (range 0–9), respectively. The only malformations that had no MABs identified were hydronephrosis, aniridia, and lissencephaly.

### *Map Resolution*

When the average size of the MACRs is calculated, that of a duplication MACR is 32.6 Mb, compared with 21.7 Mb for a deletion MACR (table 2). This reflects the pattern seen in the size distribution of duplications and deletions overall (fig. 2).

### *Regions of Possible Triplo- and Haplolethality*

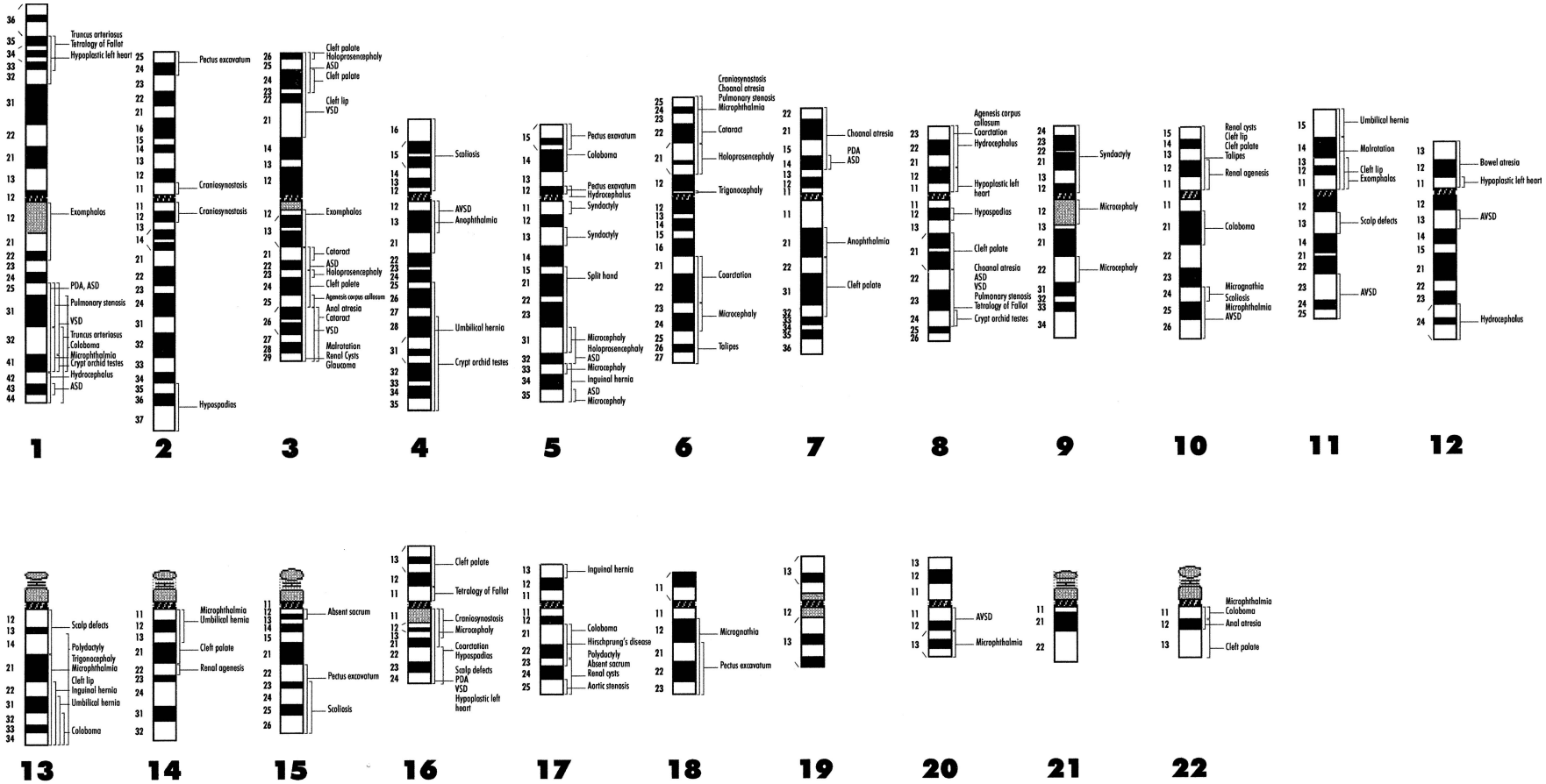
Only 8 of 289 possible autosomal bands were not involved in any duplication, which represents 2.1% of the total HAL. This compares with 11% of HAL (31 bands) not represented in the chromosome deletion map (Appendix).

### *Tolerance of Segmental Aneuploidy*

Neither duplication sizes nor deletion sizes were normally distributed (fig. 2). The longest duplication recorded in the database represented 4.3% of HAL and involved 15 bands, compared with 2.7% of HAL (7 bands) for the longest deleted region.

## Discussion

With few exceptions, partial autosomal hypoploidy results in malformation. The fact that many loss-of-function mutations result in specific malformation syndromes—for example, Holt-Oram syndrome (Li et al. 1997) and aniridia (Schedl et al. 1996)—suggests that the embryopathy associated with segmental hypoploidy




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 band duplications significantly associated with malformations

**Table 2**

**Estimation of Map Resolution**

| | Duplication Map | Deletion Map |
|---|---|---|
| No. of MABs | 450 | 283 |
| No. of MACRs | 143 | 137 |
| MAB:MACR ratio | 3.1 | 2.1 |
| Average MACR size (Mb) | 32.6 | 21.7 |

NOTE.—The average band size (in Mb) given in the Human Gene Map was multiplied by the average number of bands per MACR, to give the approximate resolutions of the duplication map and the deletion map.

is due to haploinsufficiency for a series of developmentally important genes. However, the mechanisms by which hyperploidy causes malformations are less apparent. There are examples of malformation-causing dominant-negative mutations in humans—for instance, dimerization of mutant *FGFR3* molecules, leading to activation of the receptor complex in achondroplasia and thanatophoric dysplasia (Tavormina et al. 1995; Naski et al. 1996). Both spontaneous and transgenic gain-of-function mutations cause malformations in laboratory animals, particularly in conserved genes involved in body-axis patterning (Pollock et al. 1995; Zachgo et al. 1998). However, neither of these would be expected to mimic a simple alteration in gene dosage. More interestingly, a site- and stage-specific increased *PAX6* gene dosage effect has been shown to cause eye malformations in transgenic mice (Schedl et al. 1996).

In theory, a point mutation could mimic the duplication of a gene by either promoter enhancement, repressor-element disruption, or amino acid substitution, thus increasing functional activity. However, we can find no examples of such mutations as a cause of malformations in mammalian developmental genes. Abnormalities of genomic imprinting mimicking a chromosomal duplication phenotype have been found in Beckwith-Wiedemann syndrome (BWS). However, although BWS is associated with overexpression of *IGF2* (Henry et al. 1991; Joyce et al. 1997), it is not clear that this overexpression results in the BWS phenotype (Hatada et al. 1996). Currently, it must be assumed that the deleterious effects of hyperploidy are due to overexpression of a series of dosage-sensitive developmental genes. Evidence that this effect may be relatively specific comes from the observation that much of the Down syndrome phenotype can be produced by duplication of a relatively small (~5 Mb) region of chromosome 21 (Delabar et al. 1993). Interestingly, in this study no MACRs for the malformations seen in Down syndrome were identified on chromosome 21. We reasoned that a whole-genome approach to segmental hyperploidy may provide a useful method for identification of dosage-critical developmental genes on other chromosomes, at least some of which may be genomically imprinted.

Given the differences outlined above, it might be expected that hypo- and hyperploidy would result in different spectrums of malformations. However, with a few exceptions, this does not seem to be the case (fig. 1). This is particularly intriguing, because, for a given malformation, there is almost no overlap in the genomic distribution of duplication MACRs, compared with that for deletion MACRs. This suggests that, in general, there are different groups of developmental genes that are sensitive to either increases or decreases in gene dosage. There are two interesting exceptions. First, structural eye defects are associated with both deletion and duplication of 13q32–34 and 1q41. Second, a range of cardiac defects is associated with 8p aneuploidy: atrio-ventricular septal defect, pulmonary stenosis, and tetralogy of Fallot with 8p deletions and coarctation, and hypoplastic left heart with 8p duplications. Such findings of apparent dosage sensitivity make these regions very good candidates for the identification of the genes responsible for these malformations.

Eight bands (2.1% of HAL) and 31 bands (11% of HAL) were not involved in any deletion or duplication, respectively. It is likely that these represent haplo- and triplolethal regions of the human genome. Half of these bands are pericentromeric. This may simply reflect the difficulty in an attempt to examine these regions by light microscopy. Other possibilities are that dosage-critical genes tend to be located close to the centromere or that these bands contain sequences critical for centromere

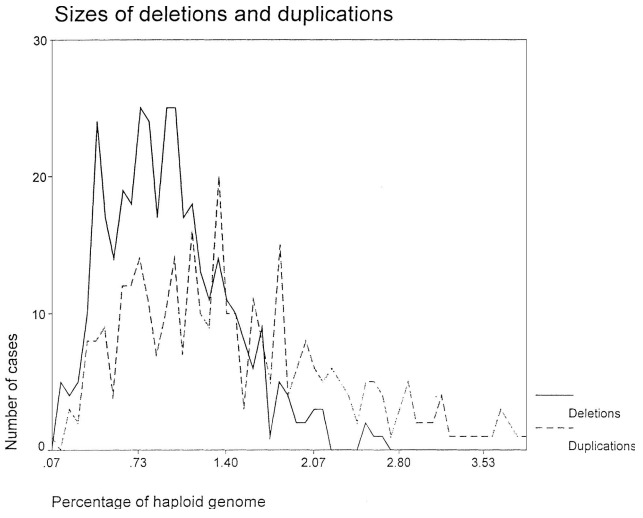



**Figure 2** Distribution of sizes of all simple autosomal deletions and duplications contained in the Human Cytogenetics Database (see Schinzel 1994). Sizes are expressed as percentage of HAL. The unbroken line represents deletions; the broken line represents duplications.

function. Indeed, molecular definition of these pericentromeric breakpoints may lead to insights into human centromere structure and function. It will be interesting to extend this work into prenatally ascertained aneuploidy, since the regions of haplo- and triplolethality in humans may be defined more precisely.

The maximum size of duplication presented in this study was 4.3% of HAL (15 bands), and the longest deletion was 2.7% of HAL (7 bands). Our findings are in accordance with previous reports of the tolerance of autosomal aneuploidy in humans (Hecht and Hecht 1987). The maximum reported tolerance of segmental hyperploidy is 6% (Sandler and Hecht 1973). For the purposes of comparison, trisomies 21, 18, and 13 result in hyperploidy of 1.3%, 2.9%, and 3.3% of HAL, respectively. Also, double trisomies that involve up to 4.6% of HAL have been reported elsewhere (Gagnon et al. 1961; Becker et al. 1963). There are remarkable similarities when these results are compared with the effects of segmental aneuploidy in *Drosophila melanogaster* (Lindsley and Grell 1968; Lindsley et al. 1972; Mange and Sandler 1973)—with, for any region of the genome, hyperploidy being tolerated better than the corresponding hypoploidy, with a maximum tolerance of 10% and 3%, respectively.

Some of the limitations of the statistical approach used to create the deletion map have been discussed elsewhere (Brewer et al. 1998), and these also apply to the duplication map. The statistical analysis assumes that each chromosome band can be treated independently. However, there are very few cases in which a single band is duplicated; more often, several adjacent bands are involved. It is also likely that the breakpoints involved in duplications are not randomly distributed, although a formal statistical analysis of this is not yet available. The effect of such "clustering" of duplicated bands is to reduce the resolution of the map, rather than to identify false loci. A larger data set with a greater number of overlapping duplications might help to alleviate this problem. A potentially more significant limitation of the method would be the possibility of chance associations, because of the large number of comparisons made: obviously, because 47 malformations were associated with a total of 143 MACRs in a sparse data set, some of these will be artifactual. However, the aim of the project is merely to identify chromosome regions where the search for malformation-causing loci might be most fruitful, and a conservative approach might be to concentrate on those bands for which a highly significant association was found.

In addition, the use of standard cytogenetic techniques can never be as reliable for identification of duplications as it is for identification of deletions, for, although the presence of a deletion can be recognized with certainty, this is not so with duplications. However, we hope that this map may aid in the choice of candidate genes for particular malformations and that it may allow specific regions of the genome to be targeted in linkage and association studies of particular malformations.

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## Appendix

The following list comprises bands in which, in the Human Cytogenetics Database (see Schinzel 1994), either no deletion or no duplication is reported—and that therefore are presumed to be haplo- or triplolethal, respectively.

Haplolethal bands:

1p12; 2p16, 2p12, 2p11, 2q11; 3p24, 3p23, 3p22; 4p11; 5p11; 6p12, 6p11; 9p11; 11q11, 11q12; 12q11, 12q12, 12q22, 12q23, 12q24; 14q12; 16p12, 16p11, 16q24; 17q11, 17q12; 19p12, 19p11, 19q11, 19q12, 19q13

Triplolethal bands:

1p23, 1q23; 6q11, 6q12; 11q11, 11q12; 19p12, 19p11

## Electronic-Database Information

The URL for data in this article is as follows:

Human Gene Map, http://www.ncbi.nlm.nih.gov/SCIENCE96

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