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Enhanced Maternal Origin of the 22q11.2 Deletion in Velocardiofacial and DiGeorge Syndromes

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Velocardiofacial and DiGeorge syndromes, also known as 22q11.2 deletion syndrome (22q11DS), are congenital-anomaly disorders caused by a de novo hemizygous 22q11.2 deletion mediated by meiotic nonallelic homologous recombination events between low-copy repeats, also known as segmental duplications. Although previous studies exist, each was of small size, and it remains to be determined whether there are parent-of-origin biases for the de novo 22q11.2 deletion. To address this question, we genotyped a total of 389 DNA samples from 22q11DS-affected families. A total of 219 (56%) individuals with 22q11DS had maternal origin and 170 (44%) had paternal origin of the de novo deletion, which represents a statistically significant bias for maternal origin ($p = 0.0151$). Combined with many smaller, previous studies, 465 (57%) individuals had maternal origin and 345 (43%) had paternal origin, amounting to a ratio of 1.35 or a 35% increase in maternal compared to paternal origin ($p = 0.000028$). Among 1,892 probands with the de novo 22q11.2 deletion, the average maternal age at time of conception was 29.5, and this is similar to data for the general population in individual countries. Of interest, the female recombination rate in the 22q11.2 region was about 1.6–1.7 times greater than that for males, suggesting that for this region in the genome, enhanced meiotic recombination rates, as well as other as-of-yet undefined 22q11.2-specific features, could be responsible for the observed excess in maternal origin.

Velocardiofacial (MIM 192430) and DiGeorge (MIM 188400) syndromes, also known as 22q11.2 deletion syndrome (22q11DS), are congenital-malformation disorders most often associated with a de novo 3 Mb hemizygous 22q11.2 deletion.[1,2] Smaller nested deletions occur in 5%–10% of individuals, and all have similar phenotypes.[3,4] The frequency of the syndromes is estimated to be 1/4,000 live births, making them among the most

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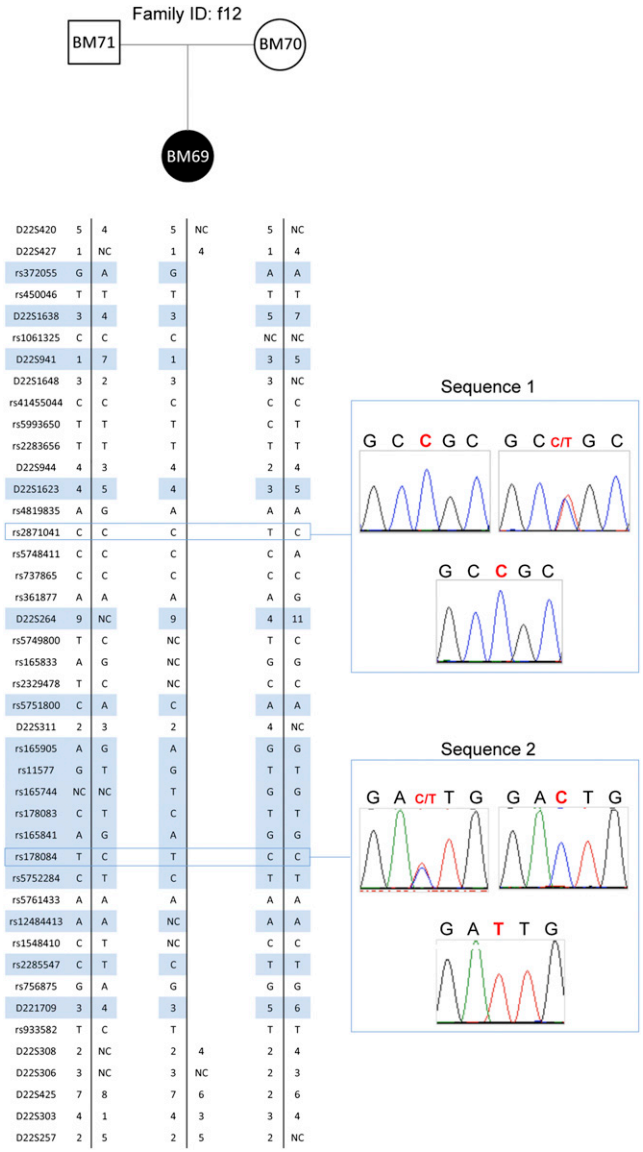


Figure 1. Haplotype Analysis for Family 12
Both microsatellite and SNP genotype analysis was performed on DNA from the female proband (BM69), her mother (BM70), and her father (BM71). The vertical lines represent the 22q11.2 region. Informative markers are highlighted in blue. Images of sequences 1 and 2 are from Sanger-sequencing chromatograms of markers rs2871041 and rs178084, respectively. Sequence 1 illustrates noninformative genotypes, whereas sequence 2 confirms informative genotypes. For example, for rs178084, the genotypes indicate that the paternal genotype is T/C and the maternal genotype is C/C. The child displays a T allele, which was inherited through the father, identifying the deletion as being maternal in origin. The following abbreviation is used: NC, no SNP call (failed genotype).

common congenital-malformation syndromes in humans.[5–10] The de novo 22q11.2 deletion usually results from nonallelic homologous recombination (NAHR) events between flanking low-copy repeats (LCRs), also known as segmental duplications (SDs), termed LCR22s.[3,4,11,12] NAHR-frequency-altering genetic risk factors, such as parent-of-origin bias or maternal age, have not been defined for 22q11DS. This might partly be because such factors are infrequent and tend not to be apparent within individual nuclear families. In addition, previous studies were all of small sample size. If gender bias did occur, it might suggest particular vulnerabilities in meiotic machinery.

In this study, we isolated or obtained DNA samples from 451 individuals with 22q11DS and their healthy parents after receiving their informed consent (internal review board 1999-201). All procedures were in accordance with the ethical standards of the Albert Einstein College of Medicine Committee on Clinical Investigation. The 22q11.2 deletion size was determined by multiplex ligation-dependent probe amplification (MLPA) testing (SALSA MLPA Kit P250 DiGeorge probemix, Medical Research Council Holland, the Netherlands) or microsatellite-marker analysis.[11,13,14] We used several molecular biological methods to detect the parent from whom the de novo deletion originated. Initially, we performed haplotype analysis by using microsatellite markers on 115 families.[11,13,14] We subsequently performed SNP-based genotyping with SNPs spanning the 3 Mb 22q11.2 region by using Sequenom MassArray technology (Tables S1and S2, available online). A representative example of results obtained with both microsatellite and SNP markers is shown in Figure 1. The map positions of the microsatellite and SNP genetic markers spanning the 3 Mb interval are shown in Figure 2. A subset of the SNP genotypes was validated with traditional Sanger sequencing (Figure 1 and Figure S1).

There were examples where the genotyping data were uninformative or only one SNP was informative as to parental origin of the de novo 22q11.2 deletion (Table S2). In these cases, we used Sequenom data that were available from the *TBX1* (MIM 602054) locus on 22q11.2[15] (Table S3). In addition, we performed Sanger sequencing to correct genotypes in 40 of the 45 probands with heterozygous SNP miscalls (Table S2; primers are indicated in Table S4).

Using this combination of approaches, we were able to obtain informative results for 389 (86.2%) of 451 families. The main reason for the lack of informative genetic data for the remaining 62 subjects was either missing parental DNA samples or poor DNA quality.

We found that the de novo deletion was of maternal origin in 219 (56.3%) of the probands and of paternal origin in 170 (43.7%) of the probands. We performed the binomial test for equal proportions to compare the actual parental origin of the deletion with the null hypothesis (proportion equal to 50%). There was a statistically significant maternal bias for the parent of origin of the 22q11.2 deletion ($p = 0.015$; "Current study" in Figure 3).

Previous studies of parent of origin of the de novo 22q11.2 deletion were relatively small in size (<100 probands; Table S5) and hence might have been underpowered. We used Fisher's combined probability test to calculate the combined p value from these previous

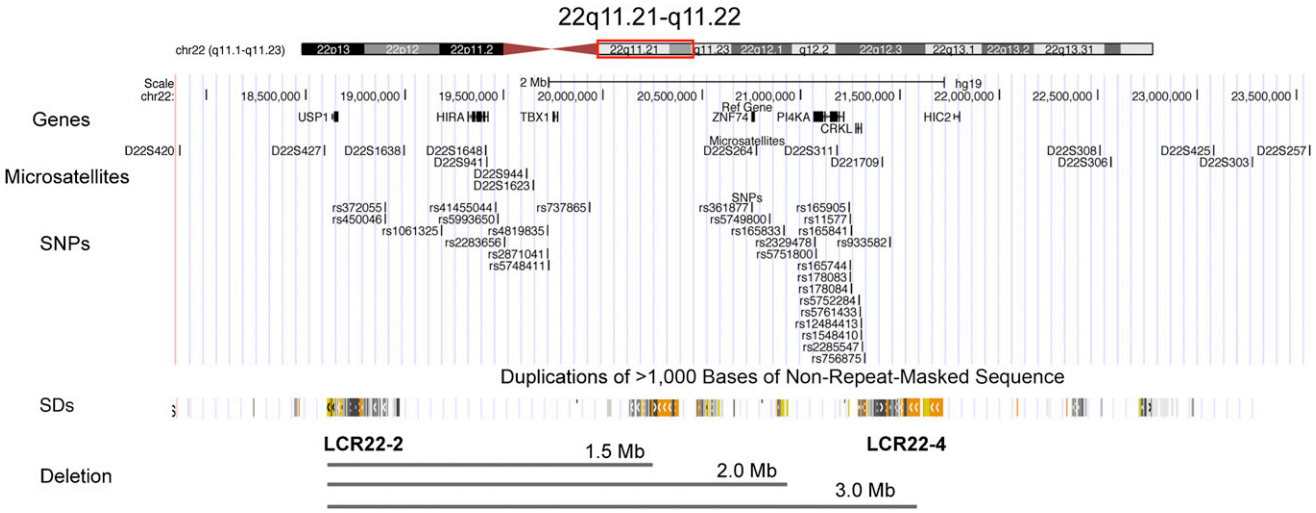
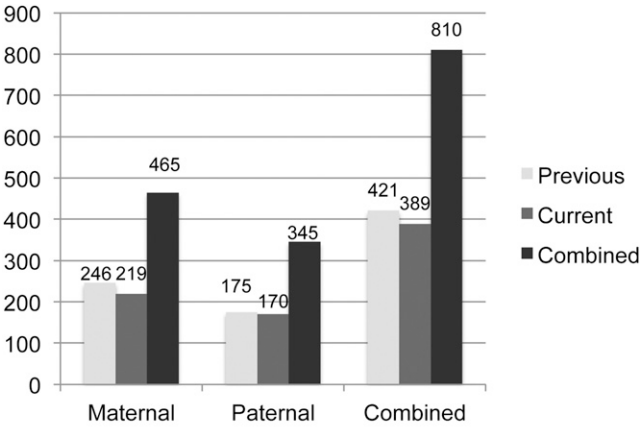


Figure 2. Genetic Markers Used for Genotyping 22q11DS Trios
A UCSC Genome Browser (hg19) image of the 22q11.21–q11.22 genomic region relevant to this study. The image displays representative genes spanning the region for orientation, as well as 15 microsatellite and 28 SNP markers used for our study. The positions of LCRs, or SDs, taken from the SD track and 1.5, 2.0, and 3.0 Mb deletions in 22q11.2 are also illustrated.

studies. We ensured that these comprised different DNA samples to those used in our current studies (exceptions are noted in Table S5). When we combined our data with those from these previous studies, we found that there were 465 (57.4%) individuals in whom the de novo deletion was of maternal origin and 345 (42.6%) in whom the deletion was of paternal origin (two-tailed binomial test, $p = 0.00065$; Figure 3). The combined results were highly significant with the use of Fisher's combined probability test ($p = 0.000028$)—the ratio of maternal to paternal origin was 1.35 to 1.00, corresponding to a 35% increase in risk for maternal compared to paternal origin of the de novo 22q11.2 deletion.

A possible limitation of this and other similar studies is a sampling bias in which DNA samples from fathers might be disproportionally missing from the cohort available for study. Fortunately, DNA samples from both parents were available in the majority of families. Second, we could still determine parent of origin of the deletion in those families with missing DNA samples from fathers given informative genotypes from the respective proband and mother. The numbers of families for which genotypes for parent of origin were uninformative were too low for drawing conclusions with respect to such a sampling bias.

The incidence of whole-chromosome aneuploidy increases with increasing maternal age in the general population. We were therefore interested to see whether a similar increase in maternal age is linked to the de novo 22q11.2 deletion and could thus explain our findings. We first went to the website of the United Nations Fertility and Family Planning Section of the Department of Economic and Social Affairs (DESA) Population Division (Web Resources) and obtained control data ("Mean Age at Childbearing" section under "Period Fertility Indicators") for 11 countries. The epidemiological data for each country are indicated in Table 1. Data for the 22q11DS cohort are presented in Table 2 and Figure 4A. We evaluated the parental age at time of conception for 1,892 mothers and 1,809 fathers of individuals with the de



	Previous	Current	Combined
Two-Tailed p Value	6.5×10^{-4}	0.0151	2.8×10^{-5}

Figure 3. A Maternal Bias Occurs in the Origin of the 22q11.2 Deletion
The bar graph shows the number of 22q11DS individuals with either maternal or paternal origin of the deletion. Light gray data bars represent the amount of maternal, paternal, and combined deletion origin from previous studies (Table S5). Dark gray data bars represent the amount of maternal, paternal, and combined deletion origin from the current study (Table S2). Black data bars represent the total amount of maternal and paternal deletion origin from the combined previous and current data sets. The two-tailed p value is listed below the figure. Significance is based on a p value < 0.05.

Table 1. Number of 22q11DS-Affected Families Organized by Country

Country	Number of 22q11DS-Affected Families	
	Maternal Origin	Paternal Origin
United States	884	822
Denmark	56	54
France	91	87
Switzerland	113	114
Belgium	103	102
Netherlands	220	213
Spain	25	23
Canada	146	144
United Kingdom	84	81
Italy	95	95
Israel	75	74
Total	1,892	1,809

We obtained data from individual 22q11DS-affected families in which both parents were healthy and the affected child harbored a de novo 22q11.2 deletion. The data are sorted by country.

novo 22q11.2 deletion. On the basis of the data presented in Table 2 and Figure 4A, we found that the mean age is 29.5 years for mothers (n = 1,891) and 32.4 years for fathers (n = 1,809).

We used the one-sample t test to compare the mean childbearing age of the mothers of 22q11DS children with the mean childbearing age of the general population (see Web Resources) and stratified this by country (Table 1 and Figure 4B). To combine data from different countries, we applied both fixed-effects and random-effects models for the meta-analysis. The fixed-effects model assumes that there is no heterogeneity among countries, whereas the random-effects model does not. Under the fixed-effects model, all countries were estimated with the assumption of the same effect size (difference of maternal age), and so weights were assigned to countries on the basis of the number of families for each country. The random-effects model did not assume the same difference for all countries. On the basis of the results from both methods, we found no statistically significant difference between the childbearing age for mothers of 22q11DS offspring and that for the general population (Table 3). Thus, these results do not support a hypothesis of advanced maternal age as an etiologic factor for the finding of enhanced maternal origin of the deletion. General population data were not available for paternal age at the time of conception. Nonetheless, we provide the paternal ages of fathers of 22q11DS offspring for all countries in our study (Table S6). We found comparable paternal and maternal ages (Figure S2).

Next, on the basis of the hypothesis that enhanced maternal origin of the deletion might be a result of increased female recombination rate in the 22q11.2 region, we considered the known female and male recombination rates across chromosome 22 to explain the maternal bias found. According to classic genetic studies, it was shown that the female autosomal genetic-map length is 1.6- to 1.7-fold greater than the male genetic length and that chromosome 22 shows relatively typical results.[16–21] Figure 5 shows a summary of recombination rates for the 22q11.2 region. The recombination rate (cM/Mb) has been previously determined by the genotyping of multigenerational families with the use of microsatellite markers,[16,17,19] and a summary of the data from the UCSC Genome Browser is shown in Figure 5B. Skewing

Table 2. Maternal Age Ranges at Childbirth in the 22q11DS Cohort

Country	Number of Mothers in Specified Age Ranges							
	15–19 Years	20–24 Years	25–29 Years	30–34 Years	35–39 Years	40–44 Years	45–49 Years	Total
United States	24	136	271	286	133	32	2	884
Denmark	2	6	20	18	9	1	0	56
France	3	17	27	34	5	5	0	91
Switzerland	3	12	45	42	9	2	0	113
Belgium	1	18	46	27	11	0	0	103
Netherlands	2	20	68	91	37	1	1	220
Spain	1	3	7	13	1	0	0	25
Canada	3	29	53	44	17	0	0	146
United Kingdom	1	5	23	36	17	2	0	84
Italy	3	13	29	30	14	6	0	95
Israel	3	16	21	27	8	0	0	75
Total	46	275	610	648	261	49	3	1,892

The number of mothers in each age range from each country is shown. The total number of mothers analyzed (1,892) is listed at the bottom of the rightmost column.

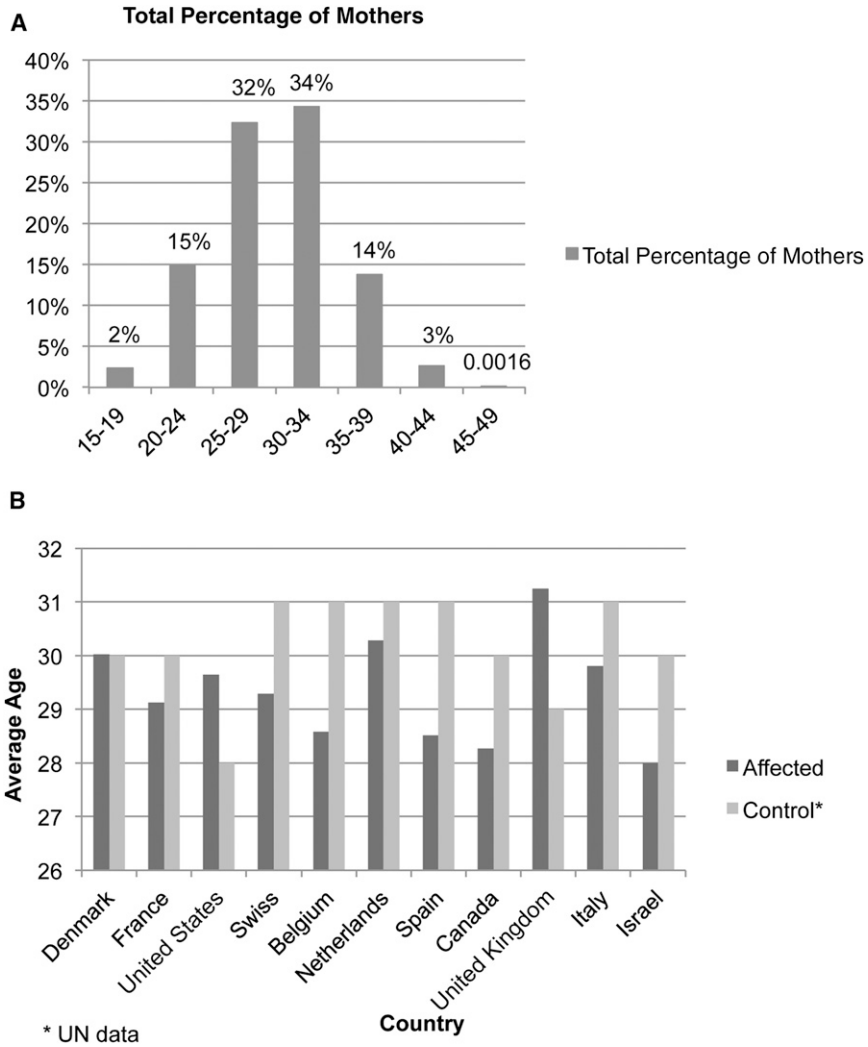


Figure 4. Range of Maternal Age at Childbirth

(A) Range of maternal age at childbirth. For each age range, determined from the values shown in Table 2, light gray bars indicate the percentage of mothers who gave birth to a 22q11DS child.

(B) Average maternal age at childbirth per country for 22q11DS offspring and normal population controls. The average maternal age for 22q11DS offspring was derived from the data shown in Table 2. *Control data were derived from the United Nations DESA Population Division World Fertility Data, 2008 (Web Resources).

of recombination rate is consistent with more recent findings for parent-offspring pairs analyzed with high-density SNP markers, which indicate that the female-to-male map-distance ratio is 2.31 for chromosomal region 22q11.2 and 1.46 for all of chromosome 22 (Figure 5C).[22] These data suggest that there is an increase in the maternal meiotic recombination rate in the 22q11.2 region. If this is true, it might suggest that the 22q11.2 duplication (MIM 608363) might also originate more often from maternal de novo events. There are three complicating features that might make testing this hypothesis difficult: first, the 22q11.2 duplication is frequently inherited; second, the penetrance is reduced; and third, the expressivity is variable. Thus, it might be difficult to obtain the number of subjects needed for an adequately powered statistical study.

To determine whether our finding could be broadly applicable to other types of chromosomal-rearrangement disorders, we examined similar data in the available literature. In one study of 876 cases of any de novo chromosomal-rearrangement disorder (independent of whether it occurred by NAHR mechanisms), 464 (53%) had a maternal origin of the deletion and 412 (47%) had a paternal origin of a deletion, suggesting a marginal maternal bias ($p = 0.04$).[23] In a similar study of 115 individuals with de novo rearrangements found by karyotypic analysis, there was a paternal bias[24] (83/115 [72%]). In addition, there was a significant paternal bias for de novo structural variations by any mechanism in 118 individuals with intellectual disability as identified by array comparative genome hybridization.[25] Notably, these studies included various types of structural variations.

In one recent study of parent of origin of NAHR-mediated rearrangements irrespective of genomic location, it was found that 12 of 30 were of maternal origin and 13 of 71 were of paternal origin.[26] Neurofibromatosis type 1 (NF1 [MIM 162200]) is caused by either deletions or mutations in *NF1* (MIM 613113) in 17q11.2. The NF1 deletion results from NAHR events during meiosis. A strong maternal bias exists for the NF1 deletion, but studies were small in size.[27,28] For Williams Beuren syndrome (WBS [MIM 194050]), which results from NAHR events between flanking LCRs, or SDs, in chromosomal region 7q11.23, we performed a meta-analysis on existing data[29–33] and found no gender bias of origin for the 7q11.23 deletion among 471 probands: 248 (53%) were of maternal origin and 223 (47%) were of paternal origin (two-tailed $p = 0.27$). There is, however, an important confounding feature for WBS in that the presence of an inversion polymorphism[32] greatly increases risk of meiotic NAHR events.[34–36] No such inversion polymorphism exists in 22q11.2.[37] In contrast, in one study of 61 probands with Charcot-Marie-Tooth type 1 (CMT1A [MIM 118220]; 17p11.2–p12), there was a distinct bias for paternal origin of the de novo CMT1A duplication,[23] implying a different mechanism for this rearrangement.

Table 3. Maternal Age Statistics

Countries	Difference of Mean Age [95% CI]
Denmark	−0.2821 [−1.5993, 1.0350]
France	−1.0791 [−2.2300, 0.0717]
United States	1.7425 [1.3810, 2.1041]
Switzerland	−1.4168 [−2.2673, −0.5663]
Belgium	−2.3175 [−3.1176, −1.5173]
Netherlands	−0.7182 [−1.3066, −0.1298]
Spain	−2.3800 [−4.2015, −0.5585]
Canada	−1.3329 [−2.0551, −0.6106]
United Kingdom	2.1500 [1.1920, 3.1080]
Italy	−1.0895 [−2.2444, 0.0654]
Israel	−1.7333 [−2.9001, −0.5666]
All Countries Combined	
Fixed-effects model	0.0858 [−0.1400, 0.3116][a]
Random-effects model	−0.7330 [−1.8078, 0.3418][b]

Data are based on the United Nations World Fertility Data, 2008 (see Web Resources). The difference between the mean childbearing age of mothers of 22q11DS individuals and that of the general population is shown as sorted by country. The following abbreviation is used: CI, confidence interval.
[a] Z score = 0.7447; p value = 0.4565.
[b] Z score = –1.3367; p value = 0.1813.

Another factor for consideration is that the recombination rate is reduced in centromeric regions and increased in the telomeric regions of chromosomes.[38] In previous studies using restriction fragment polymorphic[39] or microsatellite markers[16,17] and newer studies using SNP markers,[18,19] it was determined that the average female recombination rate is 1.6–1.7 for the 22q11.2 region and throughout the genome. This suggests that there is a maternal bias for recombination within the 22q11.2 region, despite its location near the centromere. The same is true for the *NF1* region on 17p11.2, where the maternal bias for origin of the de novo deletion is similar to the enhanced female-to-male recombination-rate ratio. The similar skewing of the female-to-male recombination-rate ratio on 17p11.2 and the absence of gender bias of origin for the 7q11.23 deletion indicate that it is not possible to generalize that NAHR events depend solely on such recombination-rate factors.

This leads to the conclusion that there might be particular features that enhance the vulnerability of the 22q11.2 region in females rather than males, in addition to the known differences in gender-based meiotic machinery. An altered number of crossovers can lead to chromosomal aneuploidies, particularly in female meiosis.[40] In a small haplotype-reconstruction study of 20 families for which DNA samples from three generations of individuals were available, there were an unexpectedly higher number of typical interchromosomal exchanges in the pter–q11.2 region between chromosome 22 homologs than in the rest of the chromosome and other pter–q11 regions on other chromosomes.[41] This suggests that the 22q11.2 region might be particularly susceptible to recombination during meiosis and that there might be gender biases based in part upon differences in meiotic processes. The two LCR22s that flank the typical 3 Mb deletion are over 250 kb in size. Recently, it has been suggested that NAHR events result from ectopic chromosome synapsis and that the likelihood of these events might increase with increased LCR length.[42] Our data suggest that, in addition, there might be gender-specific biases in synapsis formation during meiosis.

Recent studies have compiled catalogs of rare copy-number variations (CNVs) in congenital-anomaly and developmental-delay disorders and have underscored their clinical importance.[43,44] In some cases, there might be a second pathogenic CNV that could help to explain the variable penetrance and expressivity of associated phenotypes.[44] Further studies will be needed for more fully understanding the molecular mechanisms responsible for the etiology of the de novo mutations involved and the molecular basis of their variable phenotypic expression.

Supplemental Data

Supplemental Data include two figures and six tables and can be found with this article online at http://www.cell.com/AJHG.

Acknowledgments

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Web Resources

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://omim.org/
UCSC Human Genome Browser, http://genome.ucsc.edu/cgi-bin/hgGateway
United Nations DESA Population Division Word Fertility Data 2008, http://www.un.org/esa/population/publications/WFD%202008/WP_WFD_2008/Data.html

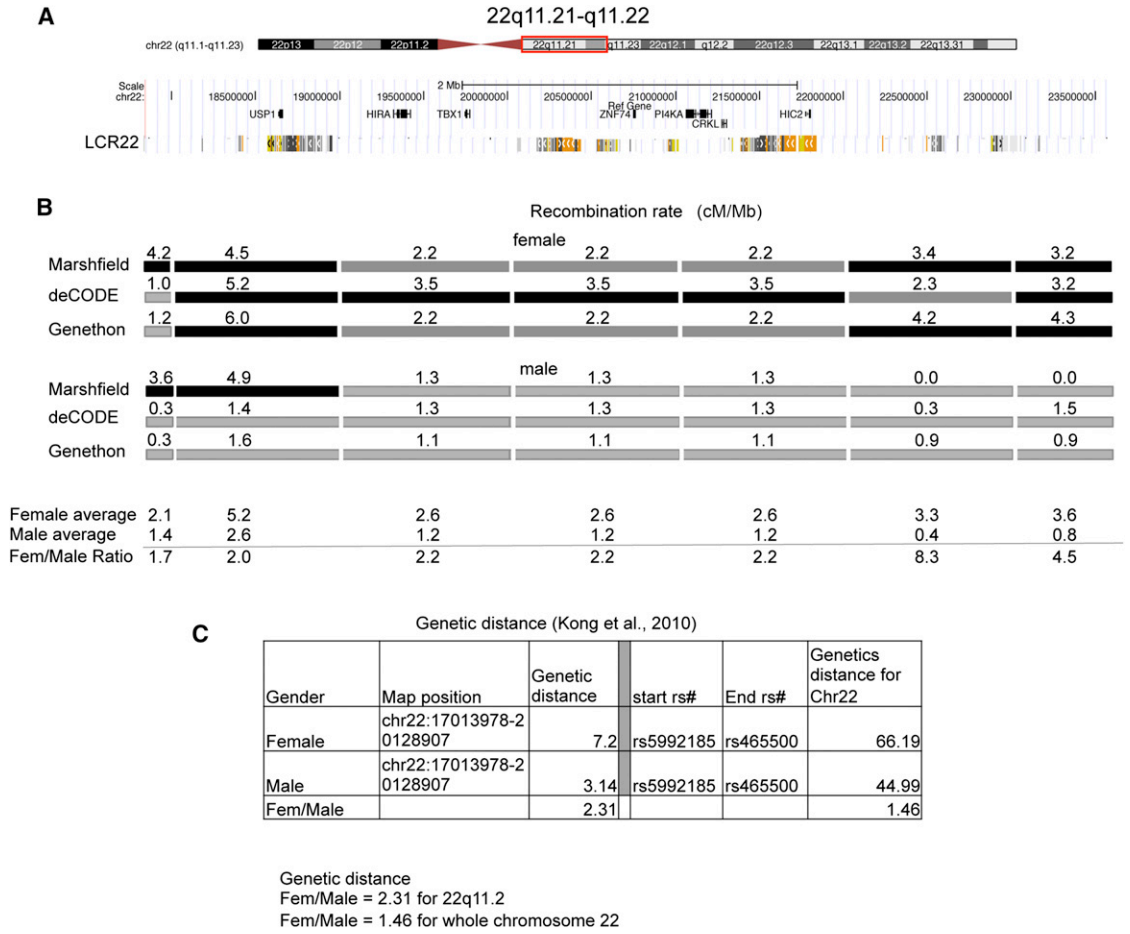

Figure 5. Recombination Rates across the 22q11.2 Region
(A) Position of the LCRs, or SDs, spanning the 22q11.2 region, as well as a snapshot of the representative genes and LCRs, or SDs, from the UCSC Genome Browser (hg19) for the same interval as shown in Figure 5B for the purpose of orientation.
(B) Recombination rates (cM/Mb) across the 22q11.2 region. The recombination rates were taken from UCSC Genome Browser (hg19) tracks (Marshfield, deCODE, and Genethon), which indicate their source of origin. They were derived from the same region shown in Figure 5A. The color coding represents recombination rate: black represents the highest rates, and light gray represents the lowest rates. The female and male averages include data from all three studies. The ratios of the average female-to-male recombination rates (Fem/Male Ratio) are shown across the region.
(C) The genetic distance and recombination rate across the 22q11.2 region (UCSC Genome Browser hg19). Data were obtained from Kong et al., 2010.[22] The female and male genetic distances, as well as the most centromeric and telomeric SNPs, with respect to chromosome 22 are indicated. The female-to-male genetic-distance ratio (Fem/Male) is 2.31 for 22q11.2 and 1.46 for all of chromosome 22.

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