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Exclusion of Linkage to the *CDL1* Gene Region on Chromosome 3q26.3 in Some Familial Cases of Cornelia de Lange Syndrome

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Abstract

Cornelia de Lange Syndrome (CdLS) is a complex developmental disorder consisting of characteristic facial features, limb abnormalities, hirsutism, ophthalmologic involvement, gastroesophageal dysfunction, hearing loss, as well as growth and neuro-developmental retardation. Most cases of CdLS appear to be sporadic. Familial cases are rare and indicate autosomal dominant inheritance. Several individuals with CdLS have been reported with chromosomal abnormalities, suggesting candidate genomic regions within which the causative gene(s) may lie. A CdLS gene location (*CDL1*) has been assigned to 3q26.3 based on phenotypic overlap with the duplication 3q syndrome (critical region 3q26.2-q27) and the report of a CdLS individual with a balanced de novo t(3;17)(q26.3;q23.1). It has been postulated that a gene within the dup3q critical region results in the CdLS when deleted or mutated. We have performed a linkage analysis to the minimal critical region for the dup3q syndrome (that encompasses the translocation breakpoint) on chromosome 3q in 10 rare familial cases of CdLS. Nineteen markers spanning a region of approximately 40 Mb (37 cM) were used. Results of a multipoint linkage analysis demonstrated total lod-scores that were negative across the chromosome 3q26-q27 region. In 4/10 families, lod-scores were less than -2 in the 2 cM region encompassing the translocation, while in the remaining 6/10 families, lod-scores could not exclude linkage to this region. These studies indicate that in some multicase families, the disease gene does not map to the *CDL1* region at 3q26.3.

Keywords

Cornelia de Lange syndrome; CdLS; chromosome 3q; linkage; mental retardation; limb defect

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INTRODUCTION

Cornelia de Lange syndrome (CdLS), also termed the Brachmann-de Lange syndrome (OMIM #122470), is a complex genetic multisystem developmental disorder. The phenotype consists of characteristic facial features (including synophrys, long eyelashes, depressed nasal bridge with upturned tip and anteverted nares, small widely spaced teeth, small head, and low-set ears), hirsutism, ophthalmologic abnormalities (ptosis, myopia), limb abnormalities (particularly of the upper extremities and ranging from subtle changes in the phalanges and metacarpal bones to oligodactyly and phocomelia), growth retardation, gastroesophageal dysfunction, hearing loss, and neurodevelopmental delay [Jackson et al., 1993; Ireland et al., 1993]. The prevalence of this syndrome has been estimated to range between 2/100,000 and 1 in 10,000 [Opitz, 1985].

Diagnosis and counseling for the Cornelia de Lange syndrome (CdLS) is complicated by the phenotypic variability and lack of a definitive diagnostic marker. Although most cases appear to be sporadic, several families have been reported that demonstrate autosomal dominant inheritance [Bankier et al., 1986; Chodirker and Chudley, 1994; Feingold and Lin, 1993; Robinson et al., 1985]. The clinical phenotype has been shown to be quite variable [Jackson et al., 1993; Ireland et al., 1993]. Establishing a diagnosis in the patient with a classic phenotype is not difficult due to the striking physical findings, although patients with a milder presentation often go undiagnosed. Phenotypic variability has been demonstrated even within families [Feingold and Lin, 1993]. The full phenotypic spectrum will not be appreciated until a gene is identified and the possibility of molecular confirmation of the diagnosis exists.

Several individuals with CdLS have been reported with chromosomal abnormalities [Kousseff et al., 1994]. In some of the earlier described cases, the diagnosis is now considered insecure, and in several cases, the same type of abnormality has been reported in unaffected individuals. In some CdLS individuals, however, the reported chromosomal abnormality may be specific. Two severely affected sporadic children with CdLS have been reported with apparently balanced de novo translocations, one with a t(14;21)(q32;q11) and the other with a t(3;17)(q26.3;q23.1) [Wilson et al., 1983; Ireland et al., 1991]. The 3q26.3 breakpoint has been considered to be particularly worthy of further investigation, and the GDB database records a tentative CdLS gene assignment, *CDL1*, at 3q26.3 because of phenotypic overlap between mildly affected CdLS individuals and individuals with duplication 3q syndrome. In the latter group, the critical region has been reported to be 3q26.3-q27. Individuals who are not trisomic for this region but are trisomic for regions immediately proximal or distal to it do not show a phenotype resembling mild CdLS [Aqua et al., 1995; Ireland et al., 1995; Rizzu et al., 1997].

While some CdLS-associated features, notably pre-natal growth retardation and severe limb abnormalities, are not seen in the dup 3q syndrome, phenotypic divergence between the two syndromes could be explained by differential dosage of active gene copies (given that the overexpression expected in trisomy 3q is unlikely to be consistently paralleled by heterozygous mutations in CdLS). Certainly, differential gene dosage is known to produce

divergent phenotypes in some instances, notably the peripheral myelin protein-22 (*PMP22*) gene [Murakami et al., 1996]. Charcot-Marie-Tooth (CMT) syndrome is caused by duplication of the *PMP22* gene, and tetrasomy for the same region produces an even more severe form of this disorder. Heterozygous loss-of-function mutations in the same gene result in a different disorder, hereditary neuropathy with liability to pressure palsies. Additionally, missense mutations often produce different phenotypes to those resulting from loss of function mutations. *PMP22* again serves as an illustrative example, as missense mutations have been found in patients with Dejerine-Sottas syndrome.

We recently reported the cloning of the 3q26.3 translocation region [Smith et al., 1998]. However, until the present study, the paucity of multicase families precluded verification by linkage analysis and mapping of the CdLS phenotype to 3q26-q27. We now report linkage analysis in 10 such families using markers from the minimal dup 3q critical region on (3q26.31-q27.3) that encompass the breakpoint seen in the translocation patient (Fig. 1). Our results suggest that either CdLS is genetically heterogeneous, or that the causative gene does not map to the proposed *CDL1* region at 3q26.3.

SUBJECTS AND METHODS

Patients

All families were reviewed by one of the authors (LJ) and were ascertained to have CdLS, with the exception of the NCL1 family that has been previously reported [Krajewska-Walasek et al., 1995].

Family I—One male child (CDL-013-98-P) with classical features of CdLS including typical facial appearance, hirsutism, growth failure, developmental delays, and bilateral limb defects (Fig. 2D). Identical bilateral limb defects were identified in a subsequent pregnancy (CDL-013-98-AB) that was terminated. The parents are unaffected and non-consanguineous. There is an unaffected brother.

Family II—Three half-siblings (94-2441, 95-3959, CDL-094-99AB) all through the mother (95-3960), each with a different father (Fig. 2A). The mother has mild facial features suggestive of CdLS but has normal cognitive functioning. All affected children have facial features and moderate mental retardation with normal limbs. One of the affected boys (94-2441) has a full sister who is unaffected.

Family III—Previously reported by Robinson et al. [1985]. The mother (95-3994) demonstrates psycho-motor delays (IQ between 70 and 80), mild facial features, hirsutism, tapering fingers, short fifth fingers with clinodactyly, and short fourth and fifth toes. Her sons (88-1253, 88-1252) both demonstrate classic facial features, growth retardation, micromelia, and severe mental retardation. In addition, one of the brothers (88-1252) has sensorineural hearing loss and a ventricular septal defect. There is also an unaffected daughter.

Family VI—Two siblings born to non-consanguineous parents, a 12-year-old sister (95-0613) and an 11-year-old brother, both with characteristic facial features, elbow

contractures, and cognitive and growth retardation. Neither parent appears to be affected; there are six unaffected siblings.

Family VII—Two siblings born to non-consanguineous parents, both female and both died shortly after birth (92–144, 97–0318). Both with characteristic facial features and upper limb defects. Neither parents appear affected.

Family XII—Two first cousins, a 20-year-old male (95–1817) and an 18-year-old male (95–1682) born to unaffected sisters. Both with typical facial features and severe mental retardation. No limb defects noted (Fig. 2F).

Family XIII—Four affected female siblings born to an affected mother (95–0852). Two of the sisters have donated samples for this study (95–0853, 95–1822). All affected individuals with typical facial features, mild mental retardation, and no limb defects. One sibling (no sample for this study) died at birth due to a congenital diaphragmatic hernia, also with typical facial features of CdLS (Fig. 2C).

Family XVII—Two affected daughters (27571, CDL-012–98-P) (Fig. 2B) born to an unaffected father (27570) through two different partners. Both daughters with typical facial features, hirsutism, micromelia, and developmental delays/mental retardation. There are also three unaffected sons (27572, 27573, 27574) that are full brothers of patient #27571.

Family GE—Two affected siblings, a boy (GE5) and a girl (GE3) born to unaffected, non-consanguineous parents (GE1, GE2). Both siblings with typical facial features, hirsutism, micromelia, developmental delays and severe cognitive retardation. There is also an unaffected female sibling (GE4) (Fig. 2E).

Family NCL1—This family has previously been reported by Krajewska-Walasek et al. [1995]. Two affected siblings, a boy (D25589-AS) and a girl (D25590-AD) were born to non-consanguineous parents (D25592-F, D25591-M). The girl had typical facial features, hirsutism, growth retardation, micromelia. Her early childhood was characterized by mild developmental delay. She was able to speak in short sentences by three years and subsequently able to communicate in complete sentences, although she was unable to count to 10. Her brother has typical facial features, growth retardation, hypospadias, and bilateral cryptorchidism. He has severe mental retardation and was reported to be non-verbal at age 10. An unaffected male child (D25593-S) was born between the two affected siblings.

Samples

Lymphoblastoid cell lines have been established on all families. DNA isolates have also been prepared. High-resolution chromosomal analysis (550 band level and greater) has also been performed on all probands, with all karyotypes being normal.

Genotyping and Linkage Analysis

Genotyping was performed using a panel of 19 polymorphic markers from chromosome 3q spanning the dup 3q critical region (3q26-27) that were fluorescently dye-labeled in three

different colors. The markers used for this study were D3S1607, D3S1614, D3S1282, D3S1574, D3S1548, D3S1565, D3S2427, D3S2421, AFMB331XF5, GATAP19232, D3S2412, D3S3511, AFMA110YE9, AFM190YE3P, AFM072YB7, D3S1262, D3S1580, D3S1314, and D3S1601. Markers were identified through the Whitehead Institute for Biomedical Research/ MIT Center for Genome Research. Fluorescence detection was performed on an ABI 377/373 sequencer. ABI PRISM software was used for gel analysis.

Multipoint parametric lod-score analysis in the CdLS families was performed using the GENEHUNTER program [Kruglyak et al., 1996]. Transmission of the disease was assumed to be autosomal dominant, with a gene frequency of 0.00001, consistent with the lowest reported disease prevalence of 2 per 100,000. All unaffected individuals were coded as unknown for the disease phenotype ("affected-only" analysis). In this way, no assumption about the unknown penetrance of the disease was made.

Marker order and distances (Fig. 1) were established through the use of the on-line databases of the Human Gene Map and the Southampton map. For the markers mapping in the vicinity of the 3q26.3 translocation breakpoint, the genetic map positions were corroborated from the physical mapping distances established from clone contigs [Smith et al., 1998 and unpublished data].

Linkage analysis to the minimal critical region for the dup3q syndrome encompassing the translocation breakpoint on chromosome 3q was performed in 10 informative familial cases of CdLS (Fig. 3A,B). Results of multipoint linkage analysis showed that total lod-scores were negative across this entire region. In particular, negative lod-scores in the range from -4 to -10 were obtained in the region of the translocation breakpoint (data not shown). In contrast, simulation analysis has shown that under the hypothesis of linkage and genetic homogeneity, the total maximum lod-score achievable in these families exceeds 3.5.

Results for each family are shown in Table I. In four of the 10 families (families I, II, XII, and XVII), lod-scores were less than -2 in the 2 cM region encompassing the translocation breakpoint between markers D3S1548 and D3S2427, thus excluding that a gene located in this region may be responsible for the disease in these families.

Family XII appears to be demonstrating an X-linked recessive mode of inheritance. Haplotyping demonstrates that the two affected male cousins do not share a maternal X chromosome, although crossovers within the 10 cM spacing of the markers used cannot be ruled out. If this family were removed from the analysis, multipoint linkage analysis across the chromosome 3q region would still demonstrate negative lod-scores and range from -4 to -10 across the translocation breakpoint.

One additional family (GE) also showed negative lod-scores, although greater than -2, in the same region. Therefore, even if it cannot be formally excluded, it is unlikely that this region contains a gene responsible for CdLS in this family.

In three other families (III, XIII, and NCLI), lod-scores are positive and close to the maximum lod-score attainable in each family as computed by simulation analysis. Finally, one family (VI) gave small positive lod-scores, and one (family VII) gave lod-scores close to

0, due to limited marker information content in this family. It is therefore possible that one or more genes located on chromosome 3q are associated in some, but not all, familial cases of CdLS.

DISCUSSION

Described for the first time over one century ago [see Oostra et al., 1994] and formally classified by Dr. Cornelia de Lange in the 1930s [see de Knecht-van Eekelen and Hennekam, 1994], CdLS is one of the most striking and recognizable syndromic phenotypes in clinical genetics. However, the molecular etiology has remained elusive. Previously, the unavailability of sufficient samples from multicase families precluded any attempts at linkage analysis, and the only clues to subchromosomal localization for disease genes have come from associated chromosomal abnormalities. Of these, a de novo apparently balanced t(3;17) translocation in a severely affected child with a chromosome 3 breakpoint at 3q26.3 appeared to be highly significant [Ireland et al., 1991]. Phenotypic overlap between CdLS and the duplication 3q syndrome had been noted in many reports prior to the identification of this translocation [Yunis et al., 1979; Steinbach et al., 1981].

Subsequent narrowing of the critical region for the duplication 3q phenotype to 3q26.2-q27 [Aqua et al., 1995; Ireland et al., 1995; Rizzu et al., 1997] further supported the possibility of a gene at 3q26.3 that could give rise to different but related phenotypes, depending on whether an extra gene copy was present or whether one of the normal two copies had been mutated. Morbid maps of the Human genome, such as the Genome Database (<http://gdbwww.gdb.org/>) and the UK Human Genome Mapping Project Resource Centre (<http://www.hgmp.mrc.ac.uk/>), have localized CdLS to 3q26-27 based on this evidence. However, in the absence of any other corroborative evidence, the assignment of a CdLS gene location to 3q26.3 has been considered tentative. By collecting samples from rare multicase pedigrees, we have now, for the first time, been able to test this possibility by linkage analyses. Our data demonstrate that in at least three families, and likely a fourth, the disease gene can be excluded from the proposed *CDLI* region at 3q26.3.

Two interpretations are now possible: (1) there is locus heterogeneity in CdLS; (2) the proposed *CDLI* gene assignment at 3q26.3 is incorrect. The CdLS phenotype is certainly quite variable, which could to some extent reflect locus heterogeneity. While the severe “classical” phenotype is easily recognized, there has been increasing recognition of a mild variant of CdLS, and some evidence has been put forward to support a possible phenotypic dichotomy [Allanson et al., 1997]. Different classes of mutation in a single gene could explain phenotypic differences in affected individuals from different families, although severely affected and comparatively mildly affected individuals have been identified in some individual families. In families where classical cases are born to a mildly affected parent [Kozma, 1996], the difference in phenotype could possibly be explained by somatic mosaicism in the parent, but in some families such as the NCL1 family [Krajewska-Walasek et al., 1995], differences in phenotype between sibs may suggest that the same gene mutation can produce variable phenotypes in the absence of mosaicism.

While clinical heterogeneity could be explainable by different mutations in a single gene, or by modifier genes, locus heterogeneity remains a distinct possibility. Locus heterogeneity is known to be a feature in several multiple congenital anomaly disorders. Such disorders include holoprosencephaly [Roessler et al., 1996; Brown et al., 1998; Wallis et al., 1999], Opitz syndrome [Robin et al., 1995], Marshall/Stickler syndrome [Annunen et al., 1999; Williams et al., 1996], Waardenburg syndrome [Baldwin et al., 1992; Tassabehji et al., 1993; Tassabehji et al., 1994], and Pfeiffer syndrome [Schell et al., 1995].

The possibility of locus heterogeneity also raises the question of whether there are alternative modes of inheritance for CdLS. Autosomal dominant inheritance is likely in families showing parent to child transmission and in families where affected children have been born to a common parent through different partners [McKenney et al., 1996; family II and family XVII, present study]. In families where more than one affected child has been born to unaffected parents, there has been an assumption that one parent has gonadal mosaicism. However, if locus heterogeneity is really a feature of CdLS, then the alternative possibility of recessive inheritance needs to be considered in some cases, although the extremely low recurrence risk and lack of any known population predisposition argues against this. In one family in the present study (family XII), the segregation pattern fits most easily with X-linked recessive inheritance (see Results section). Studies have been performed to look at the possibility of an imprinted effect in CdLS [Shaffer et al., 1993; De Marchi et al., 1994], however, uniparental disomy was not demonstrated and the familial cases argue against such an effect.

Many of the associated chromosomal abnormalities reviewed by Kousseff et al. [1994] would appear unlikely to be CdLS-associated for two reasons: the likelihood of mistaken diagnosis for several of the cases that were reported decades ago, and in several cases, the same chromosomal abnormality has been identified in an unaffected parent or in the normal population. Nevertheless, there are still several clear classical cases where there are significant chromosomal abnormalities that could be patient specific. For example, breakpoints at 14q32 and 21q11 have been defined in another published case of a classical sporadic patient with a balanced de novo translocation [Wilson et al., 1983]. Unlike the t(3;17) translocation patient who has severe upper limb reduction deformities [Ireland et al., 1991], severe limb abnormalities were not evident in the t(14;21) case [Wilson et al., 1983]. In addition, another classical patient with a balanced de novo translocation affecting chromosome 2 and either chromosome 10 or 12 was reported by Craig and Luzzati [1965]. Despite the variety of different chromosome abnormalities associated with confirmed classical CdLS patients, there is no evidence that the disease predisposes to an unduly high susceptibility to chromosome breakage. Cytogenetic analyses of large patient series have failed to identify any chromosome abnormalities other than ones reported in unaffected individuals [Merikangas et al., 1977; Beck and Mikkelsen, 1981; IK and LJ, unpublished data; TS, unpublished data].

In order to follow up the issue of locus homogeneity versus locus heterogeneity, we are now conducting extended linkage analyses. Additional individuals from the families described here as well as new families are being recruited into the study, and linkage analyses are being extended in two ways: 1) high-resolution linkage analyses are being conducted at

candidate chromosomal regions suggested from associated chromosome abnormalities, and 2) a genome-wide linkage analysis screen has been initiated because of the possibility that the 3q26.3 *CDL1* assignment is incorrect.

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Fig. 1. Region of chromosome 3q haplotyped in familial CdLS cases for this study. Markers used are indicated below the ideogram, with approximate spacing between markers in centimorgans. The dup3q critical region and t(3;17) breakpoint are indicated above the ideogram.

Fig. 2.
Facial features of individuals with CdLS from family II (A), XVII (B), XIII (C), I (D), GE (E), and XII (F).

Figure 3a

A, B CdLS family pedigrees. Haplotypes with 19 polymorphic markers from across chromosome 3q encompassing the dup3q critical region and the t(3;17) breakpoint are indicated below each individual in the families. A darkened square or circle indicates an affected individual.

TABLE I
Multipoint Linkage Analysis Data for Each Family Across the Chromosome 3q Region *

Marker	cM	Family GE	Family I	Family II	Family III	Family VI	Family VII	Family XII	Family XII	Family XVII	Family NCLI
d3s1607	0	-0.913132	-0.717409	0.602034	-4.221867	0.301022	-0.000001	-3.795941	0.301015	0.301013	-0.000001
	1	-0.907104	-0.776033	0.601013	-0.542275	0.300501	-0.000001	-2.212774	0.298972	0.23378	0.0004
	2	-0.923713	-0.846828	0.600272	-0.242155	0.300153	-0.000001	-1.94794	0.297266	0.154545	0.000793
	3	-0.965795	-0.935285	0.599814	-0.066714	0.29998	-0.000001	-0.805865	0.295899	0.057814	0.001179
	4	-1.041881	-1.051694	0.599636	0.057813	0.29998	-0.000001	-4.715691	0.294873	-0.06671	0.001559
d3s1614	5	-1.173845	-1.219152	0.599740	0.154545	0.300153	-0.000001	-1.655179	0.294187	-0.242146	0.001933
	6	-1.434472	-1.511307	0.600126	0.233781	0.300501	-0.000001	-1.614658	0.293842	-0.542251	0.002301
	7	-4.39795	-4.39795	0.600793	0.301015	0.301022	-0.000001	-1.589288	0.293839	-4.096936	0.002665
	8	-1.116352	-2.515328	0.599956	0.300754	0.300762	-0.001182	-1.596627	0.295128	-2.893178	0.002017
	9	-0.818358	-2.283909	0.599402	0.300668	0.300675	-0.002368	-1.61772	0.296754	-2.77514	0.001357
d3s1282	10	-0.645016	-2.18784	0.599132	0.300754	0.300762	-0.003561	-1.65483	0.298717	-2.893178	0.000685
	11	-0.522593	-2.160036	0.599146	0.301015	0.301022	-0.004763	-1.71259	0.301015	-4.096936	-0.000001
	12	-0.426046	-2.18784	0.599443	0.300754	0.300762	-0.004572	-1.80286	0.300495	-2.893178	0.096759
	13	-0.347636	-2.283909	0.600024	0.300668	0.300675	-0.004388	-1.945422	0.300322	-2.77514	0.175845
	14	-0.281597	-2.515328	0.600887	0.300754	0.300762	-0.004212	-2.211149	0.300495	-2.893178	0.242827
d3s1574	15	-0.224515	-4.39795	0.602034	0.301015	0.301022	-0.004042	-3.795941	0.301016	-4.096936	0.301022
	16	0.130492	-3.094524	0.415539	0.300692	0.252237	-0.003889	-3.056079	0.300647	-2.918339	0.300773
	17	-0.053263	-3.126728	0.091814	0.300543	0.197506	0.003743	-3.097292	0.300626	-2.814065	0.300704
	18	-1.351374	-3.935543	-3.638628	0.300567	0.13499	0.002557	-3.52089	0.300991	-2.943672	0.300782
	19	-0.221739	-3.205048	-2.784035	0.300765	0.061696	0.003409	-2.784787	0.30088	-3.091044	0.300857
d3s2427	20	-0.000001	-3.5051	-2.655343	0.300873	-0.000001	0.004264	-2.660239	0.300999	-3.936173	0.301015
	21	0.000055	-3.042669	-2.713982	0.30048	-0.000075	0.00492	-2.717521	0.300847	-3.529012	0.30089
	22	-0.000239	-2.825372	-3.093720	0.300259	-0.000023	0.003237	-3.072482	0.300892	-3.506156	0.300846
	23	-0.000223	-2.773477	-3.512374	0.300213	-0.000001	0.001552	-3.1045	0.300922	-3.532558	0.300888
	24	-0.018665	-2.848354	-3.858428	0.300339	0.002651	0.001077	-2.910377	0.282325	-3.682194	0.300996
d3s2412	25	-0.36435	-3.020961	-3.386362	0.300639	0.034431	0.014331	-3.053709	-0.063892	-2.862025	0.300765
	26	-3.201141	-3.864379	-2.147757	0.300986	0.063882	-0.029539	-3.434107	-1.454552	-2.759369	0.300645

Marker	cM	Family GE	Family I	Family II	Family III	Family VI	Family VII	Family XII	Family XII	Family XVII	Family NCLI
afma190ye3p	27	-3.478969	-1.583714	-1.395000	0.300931	0.091236	-0.36977	-2.831377	-0.640201	-2.883539	0.300441
afm072yb7	28	-2.762725	-0.771375	-1.197871	0.287728	0.116763	-2.047863	-2.802995	-0.376782	-2.994402	0.293741
	29	-2.457954	-0.504364	-1.116023	0.205666	0.140542	-1.239807	-2.110925	-0.220022	-2.377969	0.254878
	30	-2.357467	-0.34092	-1.098312	0.104729	0.16315	-0.980159	-1.952966	-0.105434	-2.182969	0.212438
	31	-2.351716	-0.222806	-1.136854	-0.026804	0.184733	-0.822906	-1.925713	-0.01501	-2.08949	0.165589
	32	-2.436587	-0.130199	-1.250037	-0.216462	0.205415	-0.710725	-2.000219	0.059772	-2.049706	0.113198
	33	-2.694638	-0.05393	-1.530287	-0.561933	0.225305	-0.624001	-2.251609	0.123627	-2.050355	0.053653
d3s1262	34	-3.497224	-0.000001	-3.380399	-0.974388	0.231127	-0.588222	-0.882492	0.177831	-2.091627	-0.001993
	35	-2.862138	-0.000001	-2.743770	-0.15842	0.171355	-0.74511	-0.227137	0.219618	-2.187402	-0.001199
	36	-2.796261	-0.000001	-2.624139	0.107936	0.102293	-0.998799	-0.219526	0.257988	-2.38777	-0.000563
d3s1580	37	-3.002794	-0.000001	-2.670861	0.271931	0.020309	-1.715061	-0.797771	0.293528	-3.049364	-0.000085
d3s1601	38	-3.574312	-0.000001	-3.250185	0.301004	-0.000001	-2.941777	-3.600813	0.300985	-3.827905	-0.000001

* Lod-scores were calculated at a constant increment of 1 cM along the map. Although all markers were included in the multipoint analysis, only 14 of the 19 markers are indicated in the table, as some markers were spaced less than 1 cM from the previous ones. The shaded area encompasses the t(3;17) breakpoint.