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Localization of an Ataxia-Telangiectasia Gene to an ~500-kb Interval on Chromosome 11q23.1: Linkage Analysis of 176 Families by an International Consortium

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Summary

We describe a 20-point linkage analysis map of chromosome 11q22-23 that is based on genotyping 249 families (59 CEPH and 190 A-T). Monte Carlo linkage analyses of 176 ataxia-telangiectasia (A-T) families localizes the major A-T locus to the region between S1819(A4) and S1818(A2). When seven nonlinking families were excluded from subsequent analyses, a 2-lod support interval of ~500 kb was identified between S1819(A4) and S1294. No recombinants were observed between A-T and markers S384, B7, S535, or S1294. Only 17 of the international consortium families have been assigned to complementation groups. The available evidence favors either a cluster of A-T genes on chromosome 11 or intragenic defects in a single gene.

Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive disorder characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, cellular and humoral immune deficiency, elevated levels of alpha-fetoprotein, nonrandom chromosomal rearrangements in lymphocytes, cancer susceptibility, and hypersensitivity of fibroblasts and lymphocytes to ionizing radiation (Gatti et al. 1991; Sedgwick and Boder 1991). The last two features are also often observed in carriers, although to a lesser extent (Gatti et al. 1991; Swift et al. 1991). Radiosensitivity has been used to define several complementation groups (Jaspers et al. 1988).

The first successful genetic linkage study mapped the complementation group A gene locus to 11q22-23 (Gatti et al. 1988). Even higher lod scores were observed when data from all families were pooled, regardless of their complementation group assignment (Gatti et al. 1988; Sanal et al. 1990; Foroud et al. 1991). The A-T complementation group C gene locus was shown to link to this same general region (Ziv et al. 1991). In addition, the gene responsible for complementation group D was assigned to chromosome 11 (Komatsu et al. 1990). Thus, the available evidence favors either a cluster of A-T genes on chromosome 11 or intragenic defects in a single gene.

Using 111 families in the A-T International Consortium, the A-T gene(s) was previously localized by linkage analysis to a 5.2-cM (sex-averaged) region of chromosome 11 between the markers STMY and D11S132/NCAM (Foroud et al. 1991). We now extend those studies to include 176 families and 27 additional genetic markers. We also provide a robust 20-point linkage map of the A-T region, on the basis of a combined data set of 59 CEPH families and 190 families in the A-T International Consortium database (a total of ~3,000 meioses). These studies localize the A-T gene(s) to an ~500-kb region that is flanked by the markers D11S1819(A4) and D11S1294.

Material and Methods

Pedigrees in the A-T International Consortium Database

One hundred seventy-six families were studied, 43 of which were consanguineous. The A-T Consortium

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database consisted primarily of families from seven countries: Turkey, Italy, Costa Rica, England, Israel, Norway, and the United States. Partial data from some of these families have been used in previous analyses (Gatti et al. 1988; Sanal et al. 1990, 1992; Foroud et al. 1991; McConville et al. 1993). In all cases, the diagnosis of A-T was established by clinicians with extensive experience, and the DNAs of each family were prescreened for paternity by using Southern blots hybridized with the highly polymorphic D2S44 probe (Nakamura et al. 1987). Selected individuals were sex typed by using a chromosome Y probe. Only 17 families were assigned to complementation groups. Variant families (i.e., A-T_{Fresno}, NBS-V1, and NBS-V2) and families with a questionable diagnosis were excluded from these analyses.

Genetic Markers

Fifty genetic markers from chromosome 11q22-23 were used: CD20, TYR, S84, S36, S876-(CA)n, S35[(CA)n and *Msp*I], STMY, S385, S611[SSCP and *Taq*I], GRIA4-(SSCP), S1816-(CA)n, S1817-(CA)n, S1343-(CA)n, S1819-(CA)n, S384, B7, S535, S1294-(CA)n, S1818-(CA)n, S1897-(SSCP), S1960-(CA)n, S927-(CA)n, S1300-(CA)n, G27.2.1, S424, S897-(CA)n, S132, NCAM[(CA)n and *Bam*HI], DRD2[(CA)n and *Taq*I], S386, S144, S351, APO, S29, CD3G, CD3E, CD3D, PBGD, THY1, S528-(CA)n, S147, S138, S133, ETS1(*Sac*I and *Xba*I), and S83. For brevity, the D11 nomenclature has been omitted when using probes with S numbers. At nine loci, short haplotypes were identified by combining data from closely located markers: S84/S36, STMY/CJ52.75, S611 [SSCP and *Taq*I], GLUR4 (consisting of GRIA4 and S1816), DRD2/CJ52.5 (consisting of DRD2-*Taq*I, DRD2-(CA)n, and CJ52.5), S144/CJ52.208, PBGD/CD3 (combining PBGD with CD3G, CD3E, and CD3D), S133/S138, and ETS1 (*Sac*I and *Xba*I). A single recombinant in a CEPH family localized CJ52.5 distal to DRD2; because of the crossover in this region in this family, the discordant individual's CJ52.5/DRD2 haplotype data were excluded. All recombination fractions between pairs of markers used in short haplotypes were maximized at $\theta = 0$, by linkage analysis. Partial information about these DNA polymorphisms on CEPH and A-T families has been included in previous reports (Charmley et al. 1990; Julier et al. 1990; Litt et al. 1990, 1993; Sanal et al. 1990; Foroud et al. 1991; Hauge et al. 1991; Ziv et al. 1991; Xue et al. 1991; Weissenbach et al. 1992; Lange et al. 1993; McConville et al. 1993; Ambrose et al. 1994; Gatti et al. 1994*a;* Telatar et al. 1994).

Construction of a Framework Linkage Map

Following the methodology of Foroud et al. (1991), a framework linkage map consisting of 20 markers, between S84/S36 and S144/S351, was constructed. A series

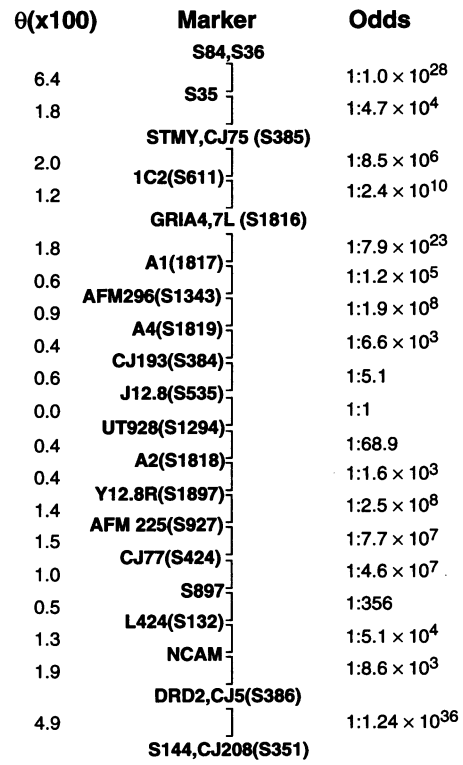

Figure 1 A linkage map of chromosome 11q22-23, showing the linkage distances (θ) and odds for inverting adjacent loci.

of overlapping 9-point location scores were computed on 59 CEPH families and 190 families in the A-T Consortium database (totaling ~3,000 meioses). The latter included 14 families that were excluded from the A-T location analyses because of variant A-T phenotypes. Our analysis resulted in a robust composite map displaying recombination fractions between, and odds for inverting, adjacent loci.

On completely typed pedigrees of simple structure, standard linkage analysis works well in creating maps of common genetic markers. However, many pedigrees in the A-T database included graphical complications such as consanguinity and missing data on deceased individuals. With such pedigrees, linkage calculations (Lathrop et al. 1984) are usually limited to only two or three markers. To overcome this, such problematic A-T pedigrees were broken into nuclear families in constructing the marker map of the chromosome 11q22-23 region (fig. 1).

Physical Mapping

Physical distances between the markers used in the Monte Carlo analyses derive from several sources. S611, GRIA4, S535, and S1897 were mapped by pulsed field gel electrophoresis (PFGE) by Ambrose et al. (1994). S384 and S535 were also mapped by PFGE by Uhrhammer et al. (1994). Further, S384 was later found to be on the 420-kb distal end fragment of a 900-kb YAC but

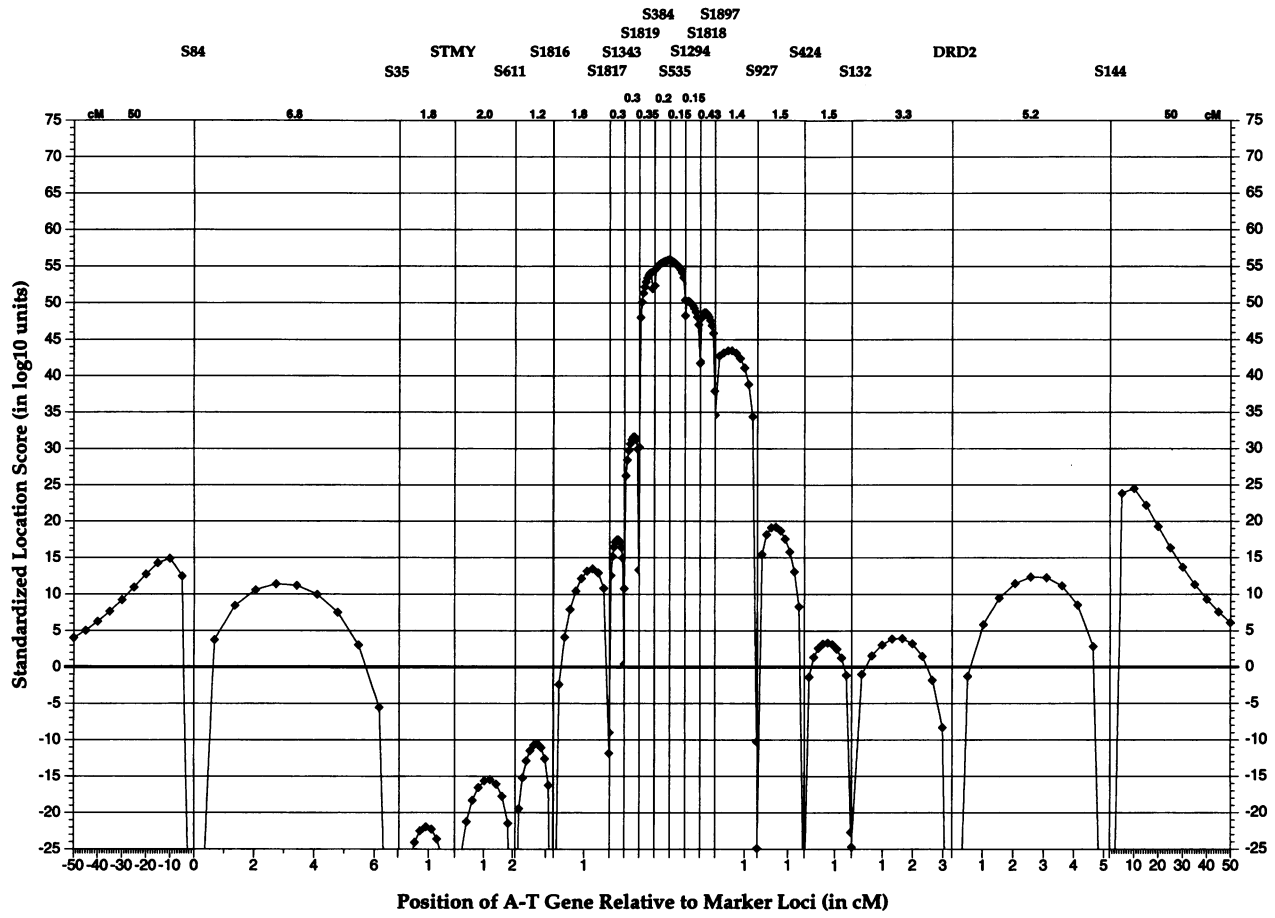

Figure 2 Standardized location scores resulting from the Monte Carlo analysis of 176 families in the consortium

was absent from the 400-kb distal end fragment of the same YAC. S535 was also localized to this YAC on a 220-kb distal end fragment and was absent from the 200-kb distal end fragment (data not shown). S1343, S384, S535, S1294, S1897, S927, S1300, and S1391 were mapped to an 11q22-23 YAC contig by hybridization or PCR by Vanagaite et al. (1994). S1816, S1817, S1343, S1819, and S1818 were mapped by PCR (G. Rotman, unpublished data) to the same YAC contig (Rotman et al. 1994). S384/B7, S535, and S1294 were further localized to a restriction map of a YAC spanning those three markers (N. Uhrhammer, unpublished data). On the basis of these sources, we used the following physical distances (bold) for the Monte Carlo analyses: S1817–**300 kb**–S1343–**300 kb**–S1819–**350 kb**–S384–**200 kb**–S535–**150 kb**–S1294–**150 kb**–S1818–**430 kb**–S1897.

Monte Carlo Technique for Estimating Location Scores

Lange and Sobel (1991) developed a Markov chain Monte Carlo simulation technique for estimating location scores. This technique allows simultaneous analysis of a trait and large numbers of marker loci. Although originally limited to biallelic markers, the method has recently been extended to include multiallelic markers (Sobel and Lange 1993). In brief, this method involves simulating the ordered genotypes for all marker loci, conditioned on the observed marker phenotypes. One then samples several realizations from the simulation. Since marker genotypes and phases are known for each realization, the joint likelihood of A-T phenotypes and genotypes for each candidate position of the trait loci is easily computed. Averaging these joint likelihoods furnishes an estimate of the joint likelihood for the originally observed trait and marker phenotypes. Taking logarithms and appropriately standardizing them gives the location score curve.

The current simulations and analyses were programmed on a Sun SPARCstation 10 and required ~125 h of central processing unit time. Because recombination fraction estimates are subject to considerable error for markers spaced <1 cM apart, physical distance estimates based on PFGE and a conversion factor of 1 Mb:1 cM, were substituted for the values derived by linkage analysis in the pertinent region between S1817(A1) and S1897(Y12.8R). The 1:1 conversion factor was estimated from a comparison of our linkage and physical distance data between S384 and S927, i.e., ~2.5 Mb

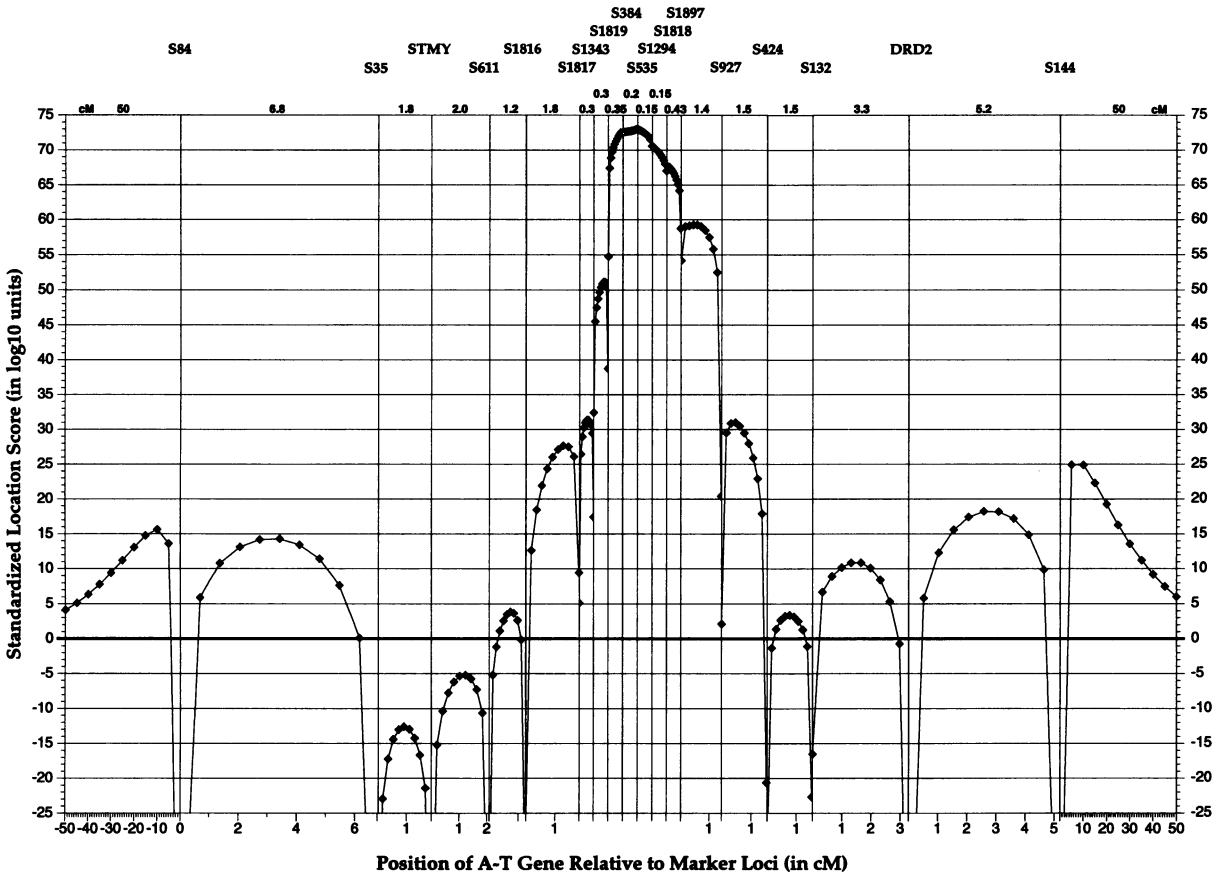

Figure 3 Standardized location scores resulting from the Monte Carlo analysis of 169 families in the consortium that exhibit an A-T locus linked to 11q22-23.

(fig. 1 of Gatti et al. 1994*a*) versus 2.8 cM (fig. 1). Two separate Monte Carlo simulations were performed. The first simulation was run on all 176 families. For the second simulation, the seven families showing strong evidence of nonlinkage to chromosome 11q were omitted. We specifically defined as "nonlinking" those families requiring a double crossover in the ~850-kb region between S1819(A4) and S1818(A2).

Haplotype Analysis

Long haplotypes were analyzed to follow recombinations in individual families. This analysis was performed with the computer program HAPLOTYPE (E. Lange, J. Polakow, and M. Elashoff, unpublished information). Once constructed, these haplotypes determine the flanking markers for the region containing the A-T gene(s) (Gatti et al. 1994*a*).

Results

On the basis of study of 249 families, a 20-point linkage map of the chromosome 11q22-23 region was created by sequentially overlapping several 9-point location scores (fig. 1). Recombination fractions and odds for inverting adjacent loci are included in this map. No recombination events were detected between S535 and S1294. The sex-averaged recombination fraction from markers S1819(A4) to S1294 was 0.01.

Two runs of Monte Carlo linkage analyses were performed; both used physical estimates of distances for markers between S1817(A1) and S1897(Y12.8R) that were based on data described in Material and Methods. In the first run, incorporating all 176 families, the location score curve reached its peak at S535 (fig. 2). A 2-lod support region contained most of the interval between S384 and S1294 and a small segment (~50 kb) between S1819 and S384. The total physical distance within the two noncontiguous support intervals is ~350 kb.

In the second run, the seven apparently nonlinking families were excluded. Again, the location score curve reached its peak at S535 (fig. 3). As expected, the location score curve of the second run was shifted upward (from 56 to 73 lod units); however, it retained the same general shape as the curve of the first run. The 2-lod support region containing the A-T locus for the second run is an interval that begins ~150 kb proximal to S384 and ends just short of S1294 (fig. 4). This interval spans ~500 kb.

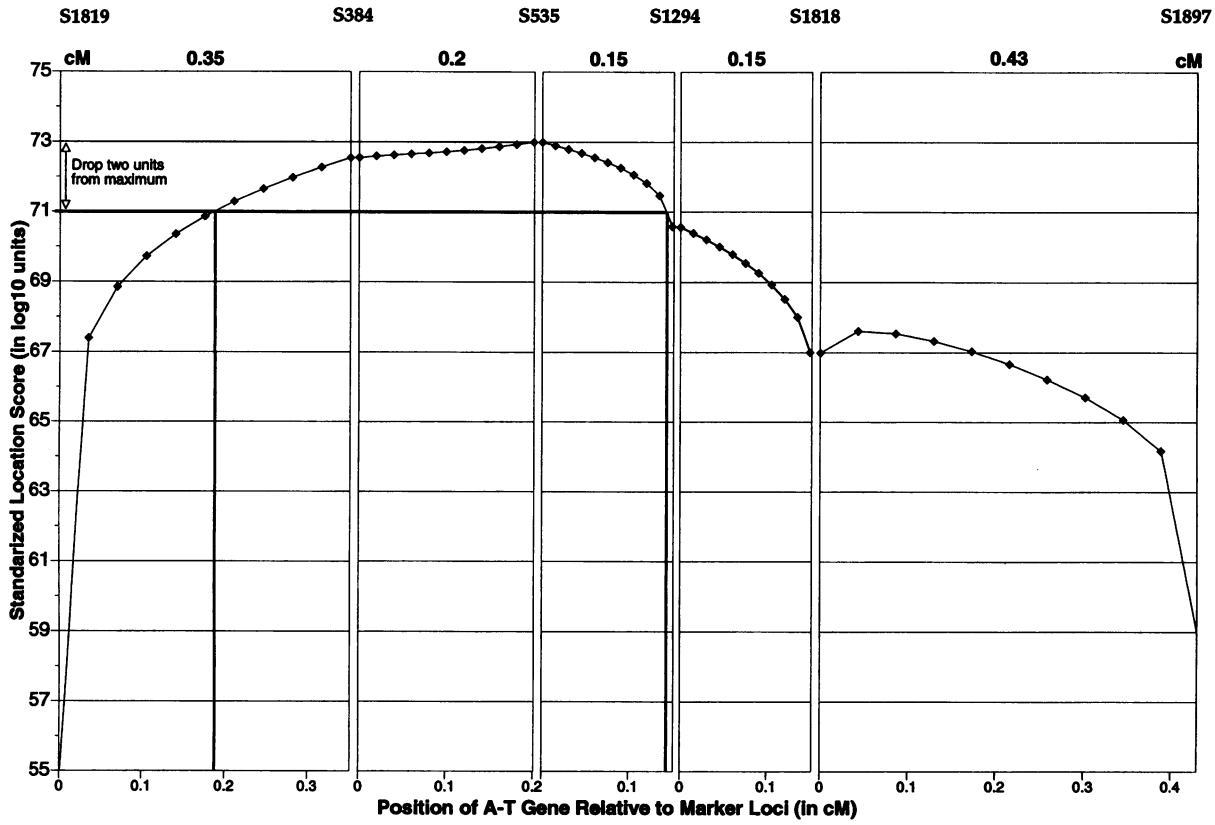

Figure 4 Detailed view of the peak region of the figure 3, containing 169 families, with construction of a 2-lod support interval for localization of the A-T gene.

The vast majority of A-T families support placing the A-T locus inside the interval (shaded in fig. 5) defined by S1819(A4) and S1818(A2). In particular, recombination events in families UCLA06, UCLA31, UCLA40 (shown below), and UCLA67, localize the A-T locus distal to S1819, while UCLA82 (shown below) localizes the A-T locus proximal to S1818. These families are potentially still useful for localizing the A-T gene or genes.

Family UCLA40 (fig. 6) localizes an A-T gene distal to S1819(A4). Affected individual 5 shares the same haplotypes with his affected brother, from DRD2 to S384; however, he gets a different haplotype from his father at S1819 and at all markers proximal to that. Family UCLA82 (fig. 7), a consanguineous family, shows results suggesting S1818(A2) to be the distal boundary for the A-T gene(s). A recombination in affected individual 4, between S424 and S927, localized A-T proximal to S424. However, the loss of homozygosity in the affected individuals at S144, DRD2, S132, S927, S1960, S1897, and S1818 provides evidence for a crossover in an earlier generation that localizes A-T proximal to S1818. S1294 and all proximal markers were homozygous.

No recombination events were detected between A-T and the markers S384, B7, S535, or S1294. In one family, a consanguineous Turkish family, a single affected individual was heterozygous at S1294 (data not shown), suggesting that the gene would be proximal or distal to this marker. However, this individual was homozygous for all other proximal and distal markers studied. (CA)n repeats have been shown to be readily mutable (Kwiatkowski et al. 1992), with most mutations displaying a single CA-unit change; we believe this to be the case in this family, and, therefore, it seems imprudent to further localize the A-T locus on the basis of these data.

Haplotype analyses, thus far, reveal that 7 of the 176 A-T families do not link to the region of chromosome 11q22-23 described above. Six of the families that do not link are nonconsanguineous families with a single affected sibling and, therefore, could be spontaneous mutations. The seventh nonlinking family is described in Uhrhammer et al. (1995), with two affected individuals sharing the same haplotypes as their normal sibling. Further efforts are underway to verify each case of apparent nonlinkage, such as rechecking DNA sample identities and diagnoses.

Discussion

Our findings are compatible with all previous reports (Gatti et al. 1988; Sanal et al. 1990; Foroud et al. 1991; Ziv et al. 1991; Cornelis et al. 1993; McConville et al.

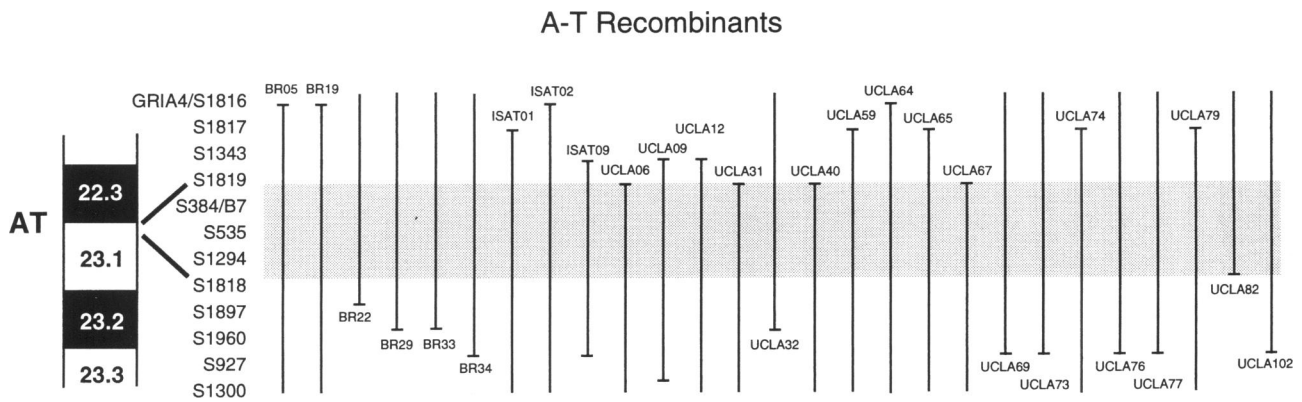

Figure 5 Summary of key recombinants in A-T families within the consortium database. The shaded area localizes the A-T gene to the proximal part of chromosome 11q23.1.

1993) and further localize the major A-T locus to an ~500-kb region flanked by the markers S1819(A4) and S1294. Unfortunately, due to a lack of observed recombinants, our analyses do not resolve the position of A-T relative to S384(CJ53.193) nor to the nearby markers B7 or S535(J12.8). It should be noted that the markers S384, B7, and S535 are all biallelic markers and have been uninformative in key families.

Seven nonconsanguineous families did not appear to link to this region of chromosome 11. However, six of these families contained only a single affected child and could represent new mutations. Other possible explanations included hidden double crossovers, sample identification errors, undetected variant phenotypes, and clinical misdiagnoses. The seventh family is a Costa Rican family with two affected children sharing the same haplotypes as their normal sibling. For reasons discussed in the work of Uhrhammer et al. (1995), this family should in fact map to this region.

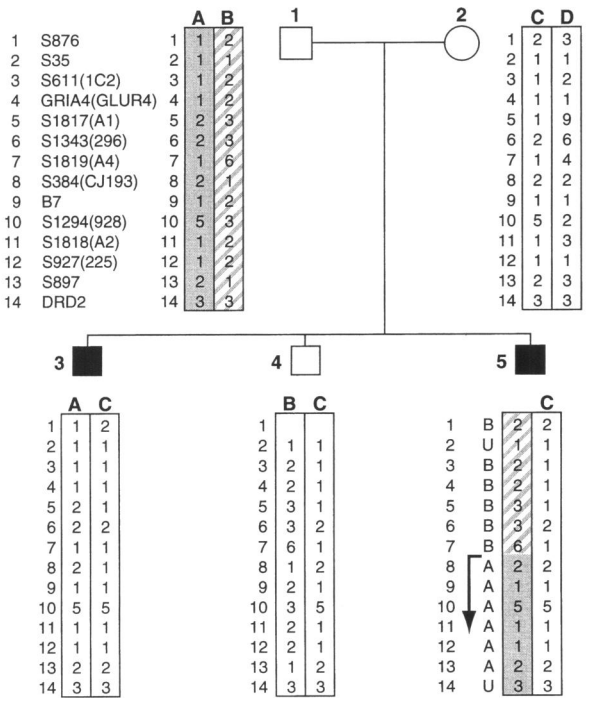

Figure 6 Family UCLA40, with a recombinant in individual 5 that localizes the A-T gene distal to S1819(A4).

Except for rare variants, A-T patients fall into one of the four complementation groups: A, C, D, or E (Jaspers et al. 1988). The existence of these separate complementation groups suggests genetic heterogeneity. However, although all linkage evidence to date identifies a support interval for the A-T locus between S1819(A4) and S1294, most families studied have not been assigned to complementation groups, and, thus, defining the proximal and distal flanking markers for each complementation group becomes more difficult as the interval gets smaller. Gatti et al. (1994*a*) have been able to show, by haplotype analysis in a large Amish pedigree, that the group A gene maps to the region between S1343 and S1300. Similar haplotype analysis of known group C pedigrees in the A-T consortium database localizes the group C gene to the region between S1816(7L) and DRD2. Recently, Oskato et al. (1993) reported a conserved haplotype in Moroccan Jewish A-T patients that places the group C gene between S1819 and S1960 (the map position of S1960 is shown in fig. 5). Results from an English nuclear family, included in the consortium families, are consistent with linkage of the rare group E gene to chromosome 11q (Gatti et al. 1994*b*). Finally, Komatsu et al. (1989) demonstrated restoration of radioresistant DNA synthesis to group D cells by the introduction of a normal chromosome 11. No identified group D pedigrees are included in the A-T consortium database.

Approximately two-thirds of the pedigrees in the A-T consortium database involve multiple affected individuals, consanguinity, or both. It is in these families that one would expect the greatest power to detect genetic

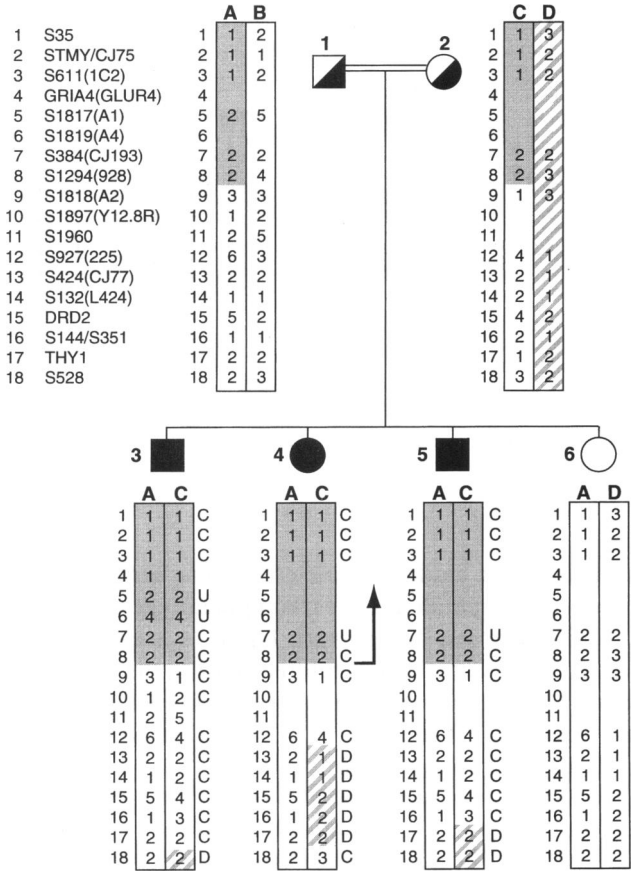

Figure 7 Family UCLA82, with loss of homozygosity that localizes the A-T gene proximal to S1818(A2).

heterogeneity. Elsewhere, Lange et al. (1993) found no statistical evidence for genetic heterogeneity of A-T in a subset of the pedigrees of the current consortium database. Although six new mutations among the 176 families studies seems excessive, the A-T gene may, in fact, have a high mutation rate. This hypothesis is supported by the findings of Uhrhammer et al. (1995), which suggest nine mutations in a fairly small population isolate.

The direct evidence for mapping the D and E genes to the 11q22-23 region is weak. Group D represents ~15% of the consortium families. If the group D gene did not link to this region, then a substantial number of multiplex or consanguineous families should show negative lod scores; we did not observe this. The localization of a group E gene to 11q22-23 presently rests on the one English family mentioned above.

Two Monte Carlo location score curves were calculated, the first containing all 176 families and the second deleting the 7 apparently nonlinking families. The curve representing all 176 families gives a smaller 2-lod support region (~350 kb) than the second curve (~500 kb). Because the Monte Carlo location score technique was designed for mapping a single disease locus (or tightly clustered disease loci), and because the strong possibility exists that 6 of the 7 nonlinking families represent new mutations, it seems prudent to base further positional cloning experiments on the more conservative support region. Despite evidence that an anomalous Costa Rican family probably does link to this region (Uhrhammer et al. 1995), this family was also removed from the second analysis, in order to allow for other genetic explanations besides a double crossover.

Our combined analysis of 249 families provides the most robust linkage map of the 11q22-23 region to date. With these data, it should be relatively easy to localize other new polymorphisms in this immediate region. It is of further interest that, despite an increased rate of mitotic recombination in A-T cells (Meyn 1993) and a possibly increased mutation rate in the A-T gene, recombination fractions across a 30–40-cM region of 11q22-23 did not differ significantly between A-T and CEPH families (Y.-R. Xia, C. H. Warden, E. Lange, T. Fukao, A. J. Lusis, and R. A. Gatti, unpublished data). When all A-T linkage data are considered together, linkage analysis has taken us, in 6 years, from an initial localization at chromosome 11q22-23 to an interval of ~500 kb, an interval small enough to apply the current cloning and complementation strategies for isolating the A-T gene or genes.

Acknowledgments

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