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Ataxia-telangiectasia: linkage analysis in highly inbred Arab and Druze families and differentiation from an ataxia-microcephaly-cataract syndrome

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Summary. Ataxia-telangiectasia (A-T) is a progressive autosomal recessive disease featuring neurodegeneration, immunodeficiency, chromosomal instability, radiation sensitivity and a highly increased proneness to cancer. A-T is ethnically widespread and genetically heterogeneous, as indicated by the existence of four complementation groups in this disease. Several "A-T-like" genetic diseases share various clinical and cellular characteristics with A-T. By using linkage analysis to study North American and Turkish A-T families, the ATA (A-T, complementation group A) gene has been mapped to chromosome 11q23. A number of Israeli Arab A-T patients coming from large, highly inbred families were assigned to group A. In one of these families, an additional autosomal recessive disease was identified, characterized by ataxia, hypotonia, microcephaly and bilateral congenital cataracts. In two patients with this syndrome, normal levels of serum immunoglobulins and alpha-fetoprotein, chromosomal stability in peripheral blood lymphocytes and skin fibroblasts, and normal cellular response to treatments with X-rays and the radiomimetic drug neocarzinostatin indicated that this disease does not share, with A-T, any additional features other than ataxia. These tests also showed that another patient in this family, who is also mentally retarded, is affected with both disorders. This conclusion was further supported by linkage analysis with 11q23 markers. Lod scores between A-T and these markers, cumulated over three large Arab families, were significant and confirmed the localization of the ATA gene to 11q23. However, another Druze family unassigned to a specific complementation group, showed several recombinants between A-T and the same markers, leaving the localization of the A-T gene in this family open.

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Introduction

Ataxia-telangiectasia (A-T) is an autosomal recessive disease expressed as cerebellar degeneration, telangiectasia, immune deficiency, chromosomal instability, increased tendency to lymphoreticular malignancies, and radiosensitivity (Boder 1985; Cohen and Levy 1989; McKinnon 1987). Cultured A-T cells show elevated chromosomal breakage and rearrangements, increased sensitivity to ionizing radiation and radiomimetic chemicals, and a decreased inhibition of DNA synthesis after treatment with these agents (McKinnon 1987; Shiloh et al. 1985; Taylor 1982). To a limited extent, A-T heterozygotes also show a proneness to cancer and cellular hypersensitivity to the same DNA damaging agents (Arlett and Priestley 1985; Morrell et al. 1986; Paterson et al. 1985; Shiloh et al. 1983; Swift 1985).

A-T is ethnically widespread, with an average frequency of 1:40000 live births in Caucasian populations (Spector et al. 1982; Swift et al. 1986). Genetic heterogeneity in A-T is indicated by the existence of 4 complementation groups (A, C, D, and E), defined by in vitro studies (Jaspers et al. 1988a). In addition, a number of genetic syndromes display some of the clinical and cellular characteristics of A-T, usually with additional features (Curry et al. 1989; Fiorilli et al. 1985; Jaspers et al. 1988b; Seemanová 1990; Taalman et al. 1989; Taylor et al. 1987; Ziv et al. 1989). The relationship between A-T und these "A-T like" syndromes is not clear.

Linkage studies recently led to the assignment of two A-T genes, ATA (A-T, group A) and ATC (A-T, group C), to the chromosomal region 11q23 (Gatti et al. 1988; McConville et al. 1990a, b; Sanal et al. 1990; Ziv et al. 1991). These results are expected to help to clarify the genetic and molecular basis of A-T and the "A-T-like" syndromes.

A-T has been found in Israel among Moroccan Jewish, Arab, Bedouin and Druze families. Complementation studies assigned several Moroccan Jewish pedigrees to group C and Arab pedigress to group A (Jaspers et al. 1988 and unpublished results). Bedouin and Druze families have not yet been assigned. The Arab A-T pedigrees are large and characterized by much inbreeding. In view of the ethnic distribution and genetic heterogeneity of A-T, we performed linkage analysis in Arabs and Druze, to confirm the localization of the A-T locus to 11q23 in these ethnic groups. An additional autosomal recessive disease was identified in one of the Arab families with A-T, involving ataxia, microcephaly and congenital cataract. We examine here the possible relationship between the two diseases, using a combination of linkage analysis and comparative studies of the immunologic, cytogenetic and cellular phenotypes of two types of patients in this family.

Subjects and methods

Patients and families

One Druze and three Arab A-T families were studied (Fig. 1). Initial diagnosis of A-T based on clinical examination was confirmed by measurements of serum immunoglobulins and alpha fetoprotein, cytogenetic analysis of peripheral blood lymphocytes and skin fibroblasts, and an assessment of the sensitivity of skin fibroblasts to ionizing radiation and the radiomimetic drug neoncarzinostatin (NCS). Six children in family ISAT9 (Fig. 1) had A-T. Three other children, VI–3, VI–4 and VI–14 (aged 3.7, 1.3 and 2.3 years, respectively, at the time of examination), showed a different disease, apparently inherited in an autosomal recessive manner and characterized by ataxia, hypotonia, microcephaly, bilateral congenital cataracts and searching nystagmus. Patient VI–3 also had bluish irises and moderate psychomotor retardation. Patients VI–4 and VI–14 were of normal intelligence. No telangiectases were observed.

Cell cultures

Primary fibroblast cell lines were established from skin biopsies obtained following informed consent; they were grown in Dulbecco's modified Eagle medium with 10% fetal bovine serum (Beit Ha'Emek, Israel).

Cytogenetic analysis

Lymphocytes. Chromosome spreads were prepared from 0.1 ml peripheral blood as described by Schwarzacher and Wolf (1974). Chromosomal damage was scored according to Cohen et al. (1967) and expressed as the number of chromatid breaks per cell. Structural rearrangements were considered to represent 2 chromatid breaks.

Fibroblasts. Monolayer cultures were split at a ratio of 1:3, and the cells were seeded onto coverslips, 2 days later. Colcemid was added to the cultures for 50 min, the cells were collected and chromosome spreads were prepared. G-banding was performed according to Klinger (1987).

Cellular sensitivity to DNA damaging agents

Fibroblast monolayers at the late logarithmic phase were treated at 37°C for 20 min with various concentrations of NCS (Kayaku Antibiotics, Tokyo) in phosphate-buffered saline. The cultures were then trypsinized and replated at densities of 100–5000 cells per 50 mm dish in order to assay their colony-forming ability.

Inhibition of DNA synthesis by ionizing radiation

Fibroblasts were plated in 30 mm dishes (70000 cells/dish). A day later, their DNA was prelabelled by adding ^{14}C-thymidine (50 mCi/mmole; 0.03 μCi/ml), and incubation was continued for 16 h. Following exposure to various doses of X-rays, ^{3}H-thymidine (25 Ci/

Table 1. DNA probes and polymorphisms used in this study

Locus	Probe	Enzyme	Alleles (kb)	Allele frequency	Source (reference)
D11S84	p2.71D6	*Taq*I	6.4	0.24	M. Litt (Maslem et al. 1987)
			4.2	0.76	
STMY	psp64	*Taq*I	4.6	0.52	N. K. Spurr (Spurr et al. 1988)
			2.1, 1.0	0.48	
D11S132	CRI-L424	*Hin*dIII	2.9	0.60	Collaborative Research, Inc. (Donis-Keller et al. 1987)
			1.9	0.40	
D11S144	pYNB3.12	*Msp*I	2.9	0.53	Y. Nakamura (Carlson et al. 1988)
			2.6	0.47	
D11S351	CJ52.208	*Msp*I	4.0	0.41	M. Lathrop (Julier et al. 1990)
			3.2	0.59	
CD3G	PT3dH	*Msp*I	2.5	0.80	R. A. Gatti (Charmley et al. 1989)
			1.7, 0.8	0.20	
D11S29	L7	*Taq*I	10.9	0.79	E. Dietzch (Warnich et al. 1986)
			13.9	0.21	
D11424	CJ52.77	*Msp*I	7.3	0.25	M. Lathrop (Julier et al. 1990)
			6.8	0.75	

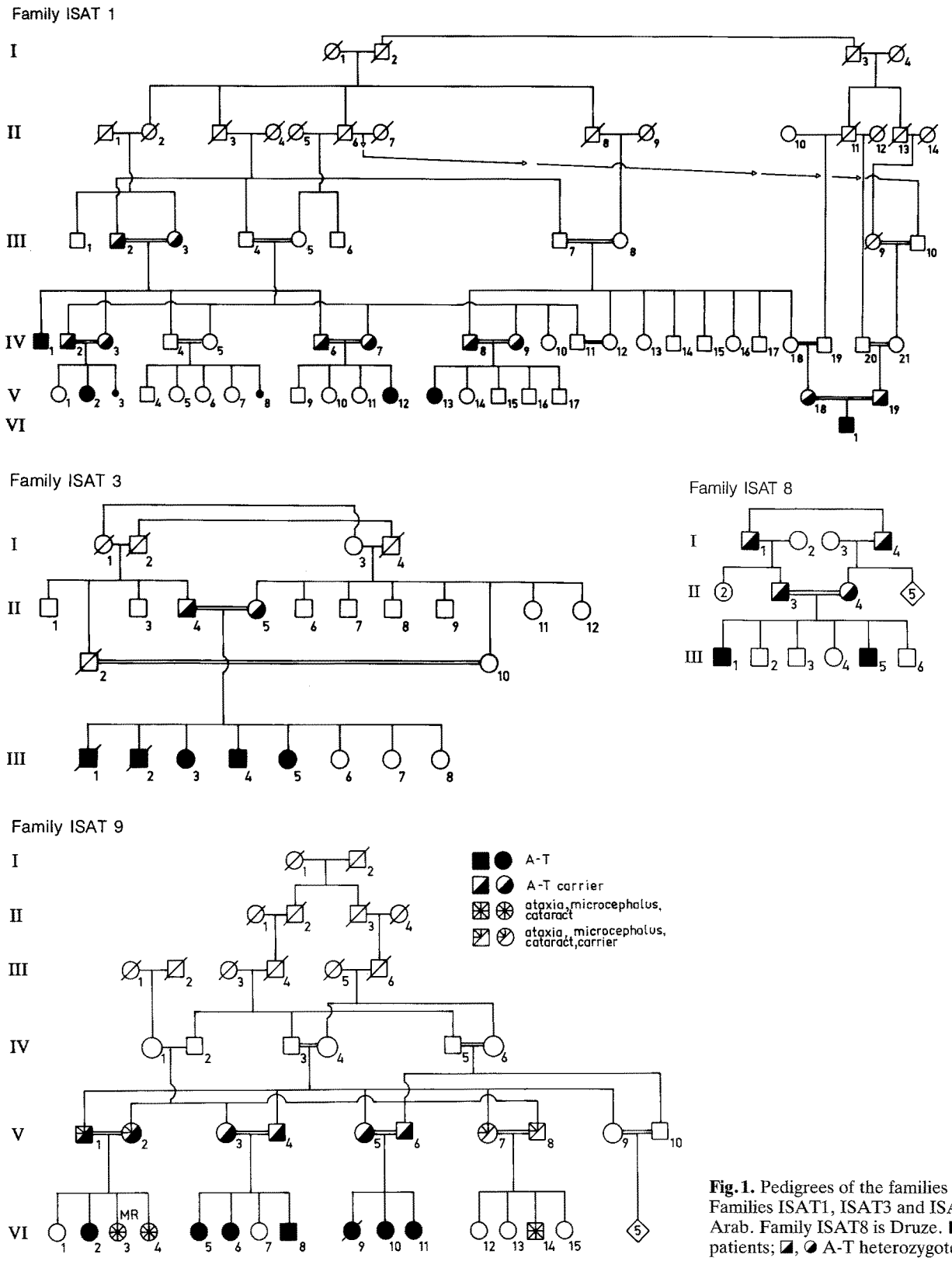

Fig. 1. Pedigrees of the families analyzed. Families ISAT1, ISAT3 and ISAT9 are Arab. Family ISAT8 is Druze. ■, ● A-T patients; ◪, ◒ A-T heterozygotes

mmole; 2.5 μCi/ml) was added and incubation was continued at 37°C for 3 h. The pH of the cultures was maintained at 7.4 throughout the labeling period by the presence of 20 m*M* HEPES. The cells were harvested by scraping, and the ratio of ^{3}H to ^{14}C in trichloroacetic acid precipitates was used to measure the rate of DNA synthesis.

Southern blotting

DNA was isolated from fibroblast cultures according to standard methods (Sambrook et al. 1989), and cleaved with restriction endonuclease under the conditions recommended by the manufacturers. The fragments were separated by electrophoresis in 0.6%–

0.8% agarose gels and transferred to Nytran membranes (Schleicher and Schuell), according to Southern (1975). Probes (Table 1) were labeled by random priming (Feinberg and Vogelstein 1983). Hybridization and autoradiography were performed as described by Sakai et al. (1985).

Linkage analysis

All linkage calculations were performed by the pedigree analysis program MENDEL (Lange et al. 1988). This program is especially appropriate for large inbred pedigrees because of the efficient way in which it handles inbreeding (Lange and Boehnke 1983), and its systematic elimination of superfluous genotypes conducted internally prior to likelihood calculations (Lange and Goradia 1987).

Results

Relationship between the two diseases in family ISAT9

The two genetic diseases that segregate in this family (Fig. 1) apparently share a common feature, ataxia. It was of interest to determine whether they share additional phenotypic features, which would point to the possible identity of the genes that determine them. This was particularly important for linkage analysis in this family since, if both diseases are determined by genes residing at the same locus, a combined lod score should be greater than either of the two separate lod scores.

Table 2 summarizes the immunologic characterization of the A-T patient VI–2, and of those with ataxia-microcephaly-cataract (AMC). The A-T patient showed a significant reduction in IgA and elevation of alpha-fetoprotein levels in her serum, both characteristic of A-T. The three patients with AMC varied: VI–3 resembled her sister with A-T, whereas VI–4 and VI–14 showed normal values of alpha fetoprotein and immunoglobulins. The same was true when chromosomal stability was tested in their lymphocytes and fibroblasts (Table 3): again, both VI–2 and VI–3 showed an A-T phenotype, expressed as high chromosomal breakage, whereas VI–4 and VI–14 showed normal chromosomal stability.

Two additional features of the cellular A-T phenotype are increased sensitivity to the lethal action of ionizing radiation and radiomimetic chemicals, and decreased inhibition of DNA synthesis by these agents. Figure 2 shows the response of fibroblast cell lines from several affected individuals of the family to increasing doses of the radiomimetic drug NCS, as measured by their colony-forming ability. Whereas cells from VI–3 demonstrated an extreme hypersensitivity to NCS, like those of her sister with A-T (VI–2), the other two patients with AMC showed an intermediate response, typical of A-T heterozygotes (Shiloh et al. 1982, 1983). Finally, when the inhibition of DNA synthesis by X-rays was tested, VI–3 again showed a response that was indistinguishable from that of A-T patients, whereas the other two AMC patients demonstrated a normal response (Fig. 3).

These results suggest that: 1) the two diseases do not share additional recognizable features in addition to ataxia; 2) VI–3 is most probably affected by both disorders, whereas VI–4 and VI–14 have only AMC. The latter assumption was further tested by performing linkage analysis in the family, using DNA markers from the re-

Table 2. Immunoglobulin and alpha-fetoprotein levels in the serum of various members of family ISAT9. MR, Mental retardation

Subject	Clinical phenotype	Immunoglobulins (mg/dl)			Alpha-fetoprotein (ng/ml)
		IgA	IgG	IgM	
VI–2	A-T	7	1510	110	87
VI–3	AMC + MR	10	1225	145	40
VI–4	AMC	45	980	90	8
VI–14	AMC	160	1800	90	6.5
Normal range:		25–140	520–1450	40–200	2–20

Table 3. Chromosomal instability in cells from four members of family ISAT9. MR, Mental retardation

Subject	Clinical phenotype	Chromatide breaks/cell	
		Lymphocytes	Fibroblasts
VI–2	A-T	0.26	0.71
VI–3	AMC + MR	0.30	0.63
VI–4	AMC	0	0.03
VI–14	AMC	0.01	0.02

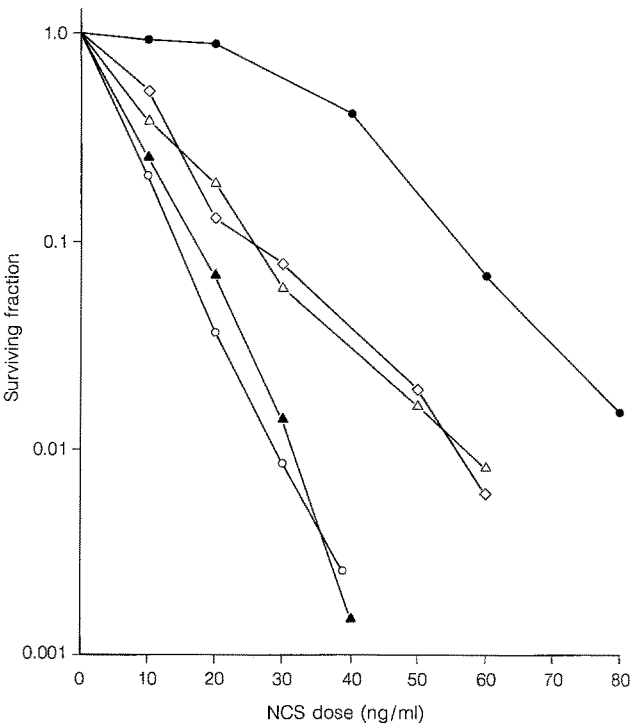

Fig. 2. Survival curves of fibroblast cell lines following treatment with various doses of NCS. ● Normal control; the other symbols denote members of family ISAT9: VI–2 (▲), VI–3 (○), VI–4 (□), and VI–14 (△)

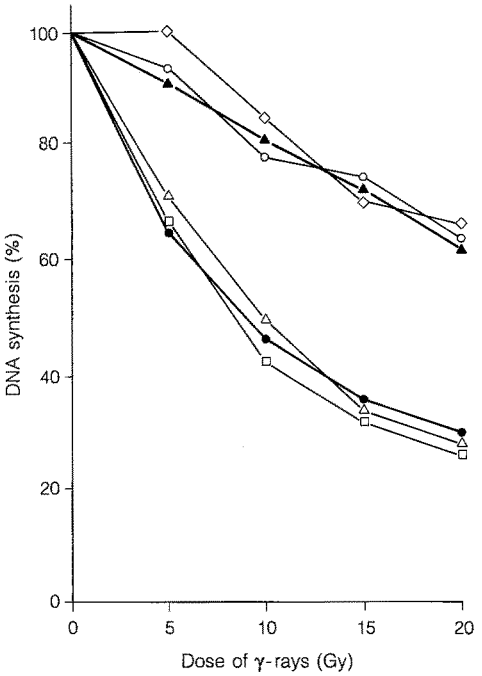

Fig. 3. Inhibition of DNA synthesis by increasing doses of X-irradiation in fibroblast cell lines. ▲ AT5LA, an A-T (group A) cell line; ● CR70, a normal control; other symbols denote members of family ISAT9: VI–2 (○), VI–3 (◇), VI–4 (△) and VI– 14 (□)

Table 4. Lod scores between A-T and 11q23 loci in family ISAT9 obtained for different genotypic assignments

Marker loci	Affected individuals in generation VI					
	2, 5, 6, 8, 10, 11		2, 3, 5, 6, 8, 10, 11		2, 3, 4, 5, 6, 8, 10, 11, 14	
	θ	Z	θ	Z	θ	Z
STMY	0.13	1.942	0.061	3.011	0.27	0.792
D11S84	0.5	0	0.022	0.426	0.5	0
D11S351	10^{-6}	0.595	10^{-6}	1.072	0.5	0
D11S29	0.14	0.824	0.11	1.185	0.24	0.574
CD3G	0.22	0.573	0.18	0.756	0.23	0.543
D11S424	0.116	0.603	10^{-6}	2.140	0.5	0

gion 11q23. Initial analysis was performed with only A-T patients being considered as affected (Table 4, right column). The lod score obtained with the marker STMY was suggestive of linkage. Lod scores were then calculated for two additional genotypic models: 1) A-T patients plus VI–3 are affected; 2) all the patients, with either A-T or AMC, are affected. With 6 markers from the 11q23 region, the highest lod scores for the family were obtained when A-T patients plus VI–3 were considered as being affected (Table 4, middle column). The addition of VI–4 and VI–14, or the elimination of VI–3, reduced the lod scores and increased the genetic distance between the disease locus and each marker (Table 4). The lod scores obtained with the marker STMY for the second model was significant (>3.0). Taken together, these results indicate that, in this family, as in European and American A-T families, the A-T locus is located at 11q23, and AMC is not linked to A-T. Individual VI–3 is apparently affected by both diseases, whereas VI–4 and VI–14 are affected with AMC alone, and are probably also A-T carriers.

Linkage analysis with 11q23 markers

Table 5 presents lod scores between A-T and various 11q23 markers for each family separately, and cumulative values for the 3 Arab families known to be of group A. The results are in agreement with previous data obtained with group A families in Turkey and USA (Gatti et al. 1988; Sanal et al. 1990). Significant cumulative lod scores were obtained with the loci STMY, D11S132, D11S144, D11S351 and D11S424, in the Arab families. No recombination events were noticed between A-T and the latter four markers. D11S132, D11S144 and D11S351 did, however, recombine with the disease in the Druze family ISAT8; this might reflect a recombination event distal to A-T, or a different localization of the disease locus in this family.

Discussion

Three individuals in family ISAT9 had ataxia, hypotonia, microcephaly and congenital cataracts with nystagmus; mental retardation was also observed in one of these individuals. These findings resemble the Marinesco-Sjorgen syndrome (MSS), which is characterized by cerebellar ataxia, congenital cataracts and mental retardation (Sjorgen 1950; Todorov 1965). However, microcephaly is not part of MSS, and mental retardation was present in only one of the three AMC patients in family ISAT9. In view of the young age of these patients and the possibility that the disease is progressive, a longer period of follow up is required before AMC can be defined as a new clinical entity.

The occurrence, in the same family, of two autosomal recessive diseases sharing clinical characteristics raises the possibility of a physiologic or genetic relationship between the two. The variety of genetic syndromes involving different combinations of A-T features has raised some speculation regarding putative genetic loci common to these seemingly related diseases (Ziv et al. 1989). Salient features in these diseases include chromosomal instability, immunodeficiency and radiation sensitivity. However, whereas some of these entities are clearly different from A-T (Byrne et al. 1984; Maraschio et al. 1986; Maserati et al. 1988; Wegner et al. 1988), others are regarded as "variants" of A-T (Taylor et al. 1987; Ziv et al. 1989). Of particular interest are the Nijmegen Breakage syndrome (NBS), which features chromosomal instability, radiosensitivity, immunodeficiency and microcephaly (Seemanová 1990; Taalman et al. 1989), and the AT_{FRESNO} variant, which involves all A-T characteristics together with microcephaly and mental retardation (Curry et al. 1989).

Since microcephaly appears to be a common denominator in many of these syndromes, we were intrigued by

Table 5. Lod scores between A-T and 11q23 loci in various A-T families[a]

Locus/family	θ						θ_{max}	Z_{max}
	10^{-6}	0.05	0.10	0.20	0.30	0.40		
STMY								
ISAT01	−0.760	0.054	0.189	0.276	0.229	0.116	0.207	0.276
ISAT03	0.131	0.104	0.080	0.042	0.017	0.0	10^{-6}	0.131
ISAT09	1.826	3.073	3.019	2.555	1.870	1.013	0.062	3.082
Cumulative (Arab families)	*1.196*	*3.230*	*3.288*	*2.873*	*2.145*	*1.132*	*0.082*	*3.303*
ISAT08	0.793	0.710	0.626	0.456	0.288	0.129	10^{-6}	0.793
D11S132								
ISAT01	2.802	2.268	1.797	0.985	0.358	0.045	10^{-6}	2.802
ISAT03	1.869	1.669	1.465	1.044	0.612	0.205	10^{-6}	1.869
ISAT09	0.159	0.133	0.108	0.064	0.030	0.001	10^{-6}	0.159
Cumulative (Arab families)	*4.830*	*4.070*	*3.370*	*2.093*	*0.999*	*0.257*	*10^{-6}*	*4.830*
ISAT08	−12.434	−1.878	−1.099	−0.438	−0.157	−0.034	0.5	0.0
D11S144								
ISAT01	1.456	1.110	0.797	0.335	0.036	−0.062	10^{-6}	1.456
ISAT03	1.957	1.754	1.547	1.121	0.679	0.241	10^{-6}	1.957
ISAT09			NI[b]					
Cumulative (Arab families)	*3.413*	*2.864*	*2.344*	*1.456*	*0.715*	*0.179*	*10^{-6}*	*3.413*
ISAT08	−5.662	−0.960	−0.657	−0.357	−0.186	−0.074	0.5	0.0
D11S351								
ISAT01	4.136	4.282	3.844	2.681	1.449	0.432	10^{-6}	4.136
ISAT03	0.930	0.811	0.692	0.458	0.239	0.067	10^{-6}	0.930
ISAT09	1.072	0.972	0.869	0.657	0.440	0.221	10^{-6}	1.072
Cumulative (Arab families)	*6.138*	*6.065*	*5.405*	*3.796*	*2.128*	*0.720*	*10^{-6}*	*6.138*
ISAT08	−4.690	−0.983	−0.676	−0.367	−0.191	−0.074	0.5	0.0
CD3-G								
ISAT01	−6.755	−1.118	−0.688	−0.448	−0.325	−0.158	0.5	0.0
ISAT03	0.722	0.645	0.564	0.391	0.213	0.062	10^{-6}	0.725
ISAT09	−8.098	0.193	0.603	0.753	0.602	0.329	0.183	0.757
Cumulative (Arab families)	*−14.131*	*−0.280*	*0.479*	*0.696*	*0.490*	*0.233*	0.175	0.710
ISAT08	1.244	1.113	0.980	0.715	0.461	0.224	10^{-6}	1.244

[a] For family ISAT9 the given values of θ and *Z* were calculated considering VI–2, VI–3, VI–5, VI–6, VI–8, VI–10, and VI–11 as affected
[b] NI, Not informative

its appearance in our AMC patients. However, our search for similarities between AMC and A-T in addition to ataxia revealed no further resemblance between the two diseases at either the clinical or the cellular level. It should also be noted that cataract is not characteristic of any of the above diseases. Further evidence for this differentiation was obtained from linkage analysis, which indicated that the two diseases are clearly not linked genetically. The occurrence of these two autosomal recessive diseases in family ISAT9 is thus fortuitous, and probably reflects the high degree of inbreeding in this pedigree.

The differentiation of AMC from A-T, and the identification of VI–3 as being affected by both, enabled us to extract, from family ISAT9, the maximal amount of linkage information with regard to A-T. The results in the 3 Arab A-T (group A) families corroborate those that were obtained in other ethnic groups, and that localized the ATA gene to a 4 centiMorgan (male-specific) interval at 11q23, flanked on the centromeric side by STMY/D11S35/D11S385, and on the distal side by NCAM/DRD2 (Gatti et al. 1988; McConville et al. 1990a, b; Sanal et al. 1990). Evidence supporting the localization of the A-T gene of family ISAT8 alone to chromosome 11q23 could not be obtained; this awaits new markers more tightly linked to A-T, and the eventual isolation of the A-T genes. Until this question is resolved, our data indicate the need for caution in applying the presently available 11q23 markers for diagnostic purposes in A-T families not assigned to specific complementation groups.

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