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An apparently dominant bipolar affective disorder (BPAD) locus on chromosome 20p11.2–q11.2 in a large Turkish pedigree

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Bipolar affective disorder (BPAD), also known as manic-depressive illness, is a common complex, polygenic disorder characterised by recurrent cyclic episodes of mania and depression. Family, twin, and adoption studies strongly suggest a genetic predisposition/susceptibility to BPAD, but no genes have yet been identified. We studied a large Turkish pedigree, with an apparently autosomal dominant BPAD, which contained 13 affected individuals. The age of onset ranged from 15–40 with a mean of 25 years. The phenotypes consisted of recurrent manic and major depressive episodes, including suicidal attempts; there was usually full remission with lithium treatment. A genome-wide linkage analysis using a dominant mode of inheritance showed strong evidence for a BPAD susceptibility locus on chromosome 20p11.2–q11.2. The highest 2-point lod score of 4.34 at $\theta = 0$ was obtained with markers D20S604, D20S470, D20S836 and D20S838 using a dominant model with full penetrance. Haplotype analysis enabled the mapping of the BPAD locus in this family between markers D20S186 and D20S109, to a region of approximately 42 cM. *European Journal of Human Genetics* (2001) **9**, 39–44.

Introduction

Bipolar affective disorder (BPAD), also known as manic-depressive illness, is a common disease characterised by recurrent episodes of mania and major depression. The population lifetime prevalence of BPAD is approximately 0.5–1.5% and, if untreated, is associated with a 20–25% risk of suicide.[1,2] Affective disorder has been known at least since the fourth century BC, when Hippocrates coined the term melancholia,[3] and the second century AD when Aretaeus of Cappadocia provided an excellent description.[4]

Family, twin, and adoption studies strongly implicate a hereditary component in the aetiology of BPAD,[5] but to date no specific genes have been identified with mutations causing or predisposing to BPAD. A series of studies has been performed using linkage analyses in mostly small and medium-size families with BPAD. One chromosomal region with the strongest evidence for a BPAD susceptibility gene was found on 13q32 with a maximum lod score of 3.5;[6] other regions with suggestive evidence for linkage were at 1q31–q32,[6] 4p16,[7,8] 4q35,[9] 5p15.3,[10] 6p24,[11] 7q31,[6] 16p13,[12,13] 18p11.2[6,14] 21q22.3,[15–17] 22q11–q13.[18]

The ascertainment of occasional large families segregating a 'complex' trait such as BPAD is of considerable importance since it may reveal the existence of a single gene that *in these families* contributes considerably to the development of the phenotype. These genes may be minor contributors to the disease in the majority of the patients/families, perhaps via

different, less deleterious mutations. However, their identi-
fication will undoubtedly contribute to the elucidation of the
molecular pathophysiology of the disease. There are four
examples of such families with positive linkage scores on 4p
($\theta = 4.1$; marker D4S394),[19] 21q22 ($\theta = 3.35$, marker
D12S1260),[15,20] 18q22–q23 ($\theta = 4.06$, marker D18S70),[21] and
12q23–q24 ($\theta = 3.37$, marker D12S1639).[22]

We studied a large Turkish BPAD pedigree, with an
apparently autosomal dominant mode of inheritance. A
genome-wide linkage analysis showed strong evidence for a
BPAD susceptibility locus on chromosome 20p11.2–q11.2, in
a region of approximately 42 cM. The identification and

characterisation of this BPAD gene will contribute to the
elucidation of the molecular pathophysiology of this
disease.

Methods

Family ascertainment, diagnosis and sample collection

Family BP-TU1 originally from Konya, Turkey (Figure 1A)
with bipolar affective disorder and an apparent autosomal
dominant mode of inheritance was first ascertained and
diagnosed in 1986 through individual 17 in the psychiatric
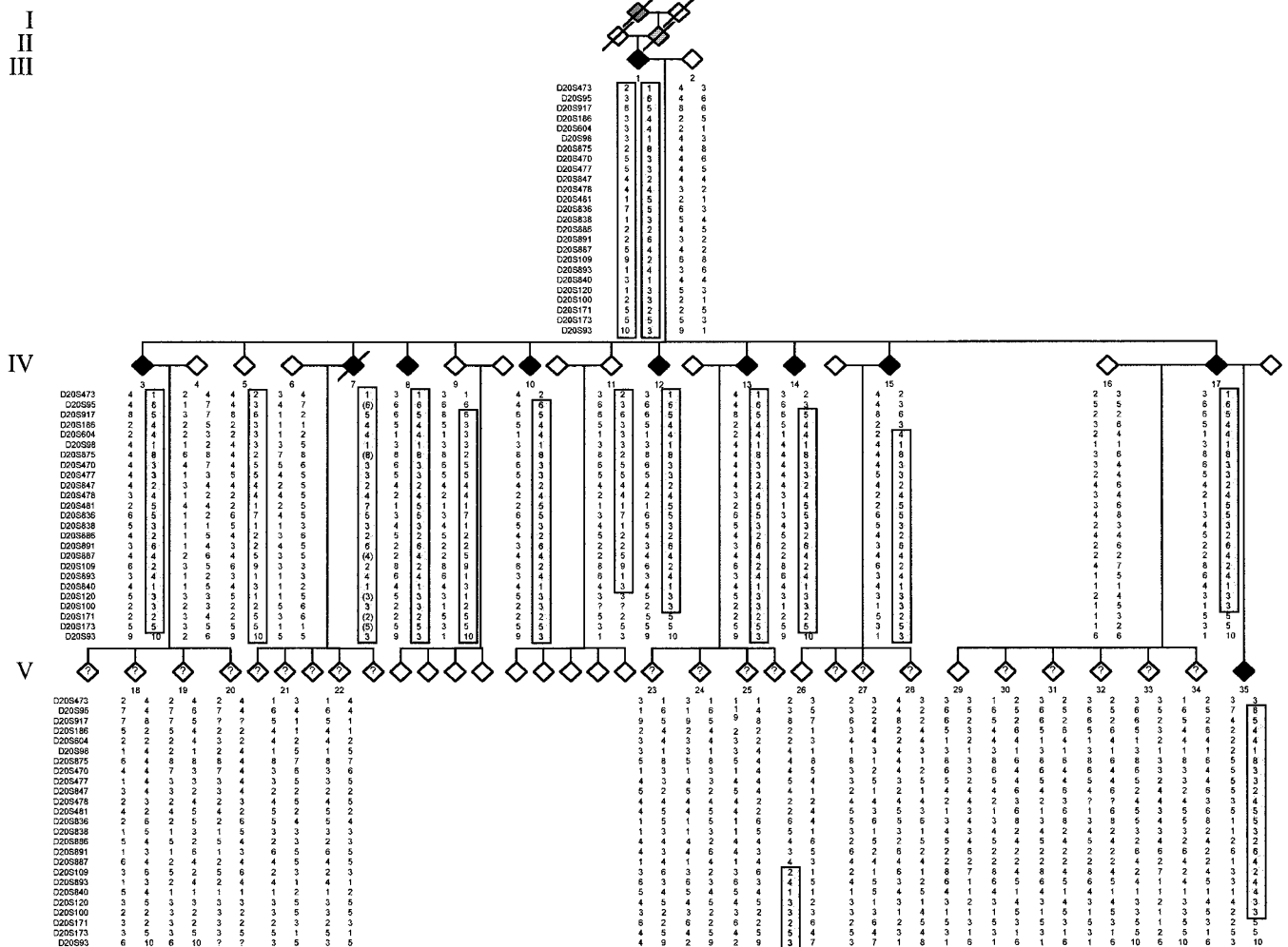clinic of Gazi University, Ankara, Turkey. Further 12 years'

Figure 1 A Partial pedigree of BP-TU1 with bipolar affective disorder. Affecteds are shown will filled symbols and normals with clear
symbols. Symbols in grey (generations I and II) refer to individuals affected according to the family history. Individuals used in the
linkage analysis are numbered 1–35. ? indicates individuals below the cut-off age of 30. To conceal the family identity, information
related to sex, date of birth, and order of birth is not given and the order of individuals in the pedigree is intentionally mixed. This
information could be made available to investigators on approval by the Geneva University Hospital and Gazi University, Turkey
committees on research into human subjects. The genotypes and haplotypes of chromosome 20 markers are given below each
individual. Haplotypes associated with affected status are boxed in grey. The haplotype of the diseased individual 7 was reconstructed
from the data of individuals 1, 2, 6, 21, and 22. The paternal or maternal origin of the alleles in parentheses could not be
determined. Alleles of individual 7 were not used in the linkage analyses.

follow up of different members of the pedigree demonstrated familial aggregation of the phenotype, and recently a field study has been performed to complete the pedigree analysis and to clinically evaluate additional individuals. The phenotypes were extensively characterised using DSM-IV criteria[23] prior to genetic analysis. The clinical evaluation was performed with a Structured Clinical Interview from DSM-IV Clinical Version (SCID-I/CV).[24,25] The diagnoses were determined after direct interviews, examination of medical records, family history, and extensive follow up of the patients by two psychiatrists (HH and SS) and a neurologist (KG). There was no discrepancy in the diagnoses. The age of onset ranged from 15 to 40 years with a mean of 25 years. The phenotypes consisted of recurrent manic and major depressive episodes, including suicidal attempts; there was usually full remission with lithium treatment. Table 1 shows the DSM-IV diagnostic code and the age of onset for each affected member. The complete pedigree consists of 80 people with 11 affected available individuals (in generations III, IV and V) and it is partially shown in Figure 1A. The affected status of the deceased individuals of generations I and II has been provisionally assigned by family history taken from normal relatives. Among the 11 definite affected subjects there were eight females and three males. A total of 34 individuals were available at the time of field investigation. Ten were diagnosed with bipolar disease and one female had one episode of major depression. In generation V, the majority of the descendants from affecteds is below the mean age of onset of the disease and all of these individuals were viewed as unknown diagnosis for the linkage analysis. Individuals at risk that have not developed any symptoms after the age of 30 years (individuals 26 and 29 of Figure 1A) were considered unaffected.

Genotyping and linkage analysis
DNAs were isolated from blood samples of 34 individuals obtained after informed consent. The goals of the study were

explained to each individual of the family, and written agreement was obtained from those who donated blood and had undergone psychiatric evaluation. Lymphoblastoid cell lines were established from selected individuals. For the systematic search of the genome-wide genotyping and linkage analysis we used 230 highly informative polymorphic markers covering the entire genome and selected from the Généthon (http://www.genethon.fr/) and CHLC collections (http://www.chlc.org/).[26,29] The list of markers used is available upon E-mail request. The average heterozygosity of markers used was 0.76. DNA polymorphisms were detected by polymerase chain reaction (PCR) amplification and fragment analysis as described.[30] Family information and marker genotypes were stored in computer program Cyrillic (Cherwell). Analysis was performed using the ILINK, MLINK and LINKMAP programs of LINKAGE v5.2[31] and FASTLINK v.30[32] software packages. Maximum lod scores were calculated for each marker by assuming several models including autosomal dominant mode of inheritance with 100% and 80% penetrance after the age of 30 years; a recessive model was also used.

Results

A genome-wide genotyping of 230 highly informative polymorphic markers evenly distributed throughout the human genome in all available members of the BP-TU1 pedigree was performed. Subsequent linkage analysis using a dominant mode of inheritance was either 100% or 80% penetrance and a threshold for the onset of the disease at 30 years of age, provided strong evidence for linkage of the BPAD susceptibility locus with markers on chromosome 20p11.2–q11.2 (Figure 1B). The maximum lod score, $Z_{max} = 4.34$ at recombination fraction $\theta = 0$ was obtained with markers D20S604, D20S470, D20S836 and D20S838 under 100% penetrance (Table 2). The maximum lod score for these markers using 80% penetrance was 4.05. There was no difference in the maximum lod score when the gene frequency varied from 0.05 to 0.0001. A total of 27 highly polymorphic markers covering the entire chromosome 20 and in particular the area of the positive lod scores, were then used to better define the interval of the BPAD susceptibility locus. Haplotype analysis of polymorphic markers enabled the mapping of BPAD locus in the BP-TU1 family between markers D20S186 and D20S109 (by utilising informative recombinants from individuals 15 and 26) in a region of approximately 42 cM (Figures 1, 2 and Table 2).

Multipoint linkage analysis was performed by using three markers without recombination with the BPAD locus (D20S470, D20S836, and D20S891) and markers D20S186 and D20S109 with recombination. The map intervals used are shown in Table 2. This analysis did not result in a lod score greater than the 2-point analysis.

No other genomic region resulted in a positive lod score including all the chromosomal intervals in which suggestive

Table 1 Phenotypic characteristics (DSM-IV diagnostic codes) of affected members of family BP-TU1. Individual IDs are in capital letters. The order of these letters does not correspond to the numbering of individuals in Figure 1A

ID	Age onset (years)	Present age (years)	Sex	diagnosis	DSM-IV Axis I codes
A	25	69	M	Bipolar I	296.45
B	15	42	M	Bipolar I	296.40
C	20	38	M	Bipolar I	296.04
D	40	53	F	Bipolar I	296.40
E	40	47	F	Bipolar I	296.89
F	25	48	F	Bipolar I	296.54
G	18	36	F	Bipolar I	296.56
H	15	34	F	Bipolar I	296.56
I	21	31	F	Bipolar I	296.46
J	19	28	F	Bipolar I	296.55
K	32	34	F	Major depression	296.25

Table 2 Two-point lod scores between BPAD locus in family BP-TU1 and several chromosome 20p11–q13 polymorphic markers at various recombination fractions and 100% penetrance. The maximum lod score for 80% penetrance is also shown for $\theta=0$

| Markers	0.0	0.0 (80%)	0.01	0.05	0.1	0.2	0.3	0.4	Z_{max}	θ	Marshfield (cM)	CHLC (cM)
D20S473	–∞	–11.84	–7.71	–3.69	–2.12	–0.81	–0.29	–0.09	0.10360	0.647	0.0	
D20S95	–∞	–6.86	–4.49	–1.81	–0.77	0.03	0.25	0.17	0.37312	0.77	7.12	9.0
D20S917	–∞	–5.34	2.03	2.46	2.41	1.96	1.30	0.49	2.46802	0.062	8.05	
D20S186	–∞	–3.76	2.27	2.70	2.65	2.20	1.54	0.72	2.71105	0.062	7.6	
D20S604	4.34	4.05	4.27	3.98	3.60	2.80	1.91	0.89	4.33935	0.0	0.64	26.6
D20S98	3.89	3.58	3.82	3.55	3.20	2.45	1.61	0.67	3.88705	0.0	0.0	4.64
D20S875	3.21	3.08	3.18	3.02	2.79	2.24	1.58	0.79	3.21441	0.0	1.07	
D20S470	4.34	4.05	4.27	3.98	3.60	2.80	1.91	0.89	4.33935	0.0	0.53	6.0
D20S477	3.89	3.51	3.82	3.55	3.20	2.45	1.61	0.67	3.88705	0.0	7.0	
D20S847	4.04	3.65	3.97	3.68	3.30	2.50	1.61	0.60	4.03832	0.0	11.56	
D20S478	1.03	0.83	1.01	0.94	0.84	0.65	0.45	0.24	1.02803	0.0	2.73	7.0
D20S481	4.16	3.81	4.09	3.80	3.43	2.62	1.73	0.72	4.16326	0.0	8.23	9.0
D20S836	4.34	4.05	4.27	3.98	3.60	2.80	1.91	0.89	4.33935	0.0	2.56	
D20S838	4.34	4.05	4.27	3.98	3.60	2.80	1.91	0.89	4.33935	0.0	0.0	
D20S886	1.03	0.83	1.01	0.94	0.84	0.65	0.45	0.24	1.02803	0.0	1.28	
D20S891	3.80	3.58	3.73	3.46	3.11	2.35	1.52	0.58	3.79528	0.0	0.55	
D20S887	3.86	3.59	3.81	3.60	3.31	2.64	1.85	0.93	3.86223	0.0	5.56	
D20S109	–∞	3.35	2.27	2.70	2.65	2.20	1.54	0.72	2.71105	0.062	2.2	10.5
D20S893	–∞	3.35	2.27	2.70	2.65	2.20	1.54	0.72	2.71105	0.062	3.28	
D20S840	–∞	3.05	1.98	2.42	2.39	1.99	1.39	0.64	2.43897	0.066	2.16	
D20S120	–∞	1.32	1.22	1.76	1.84	1.63	1.19	0.60	1.84129	0.092	3.6	
D20S100	–∞	2.88	1.80	2.25	2.22	1.82	1.22	0.47	2.26288	0.066	1.27	
D20S171	–∞	–6.08	–1.49	–0.20	0.25	0.49	0.41	0.17	0.49491	0.214	10.92	
D20S173	–∞	–0.12	–1.24	–0.54	–0.26	–0.03	0.06	0.06	–6.60030	0.352	2.39	21.2
D20S93	–∞	–6.14	–7.71	–3.69	–2.12	–0.79	–0.23	–0.01	–2.04090	0.453	0.0	4.7
										Total	87.93	101.3
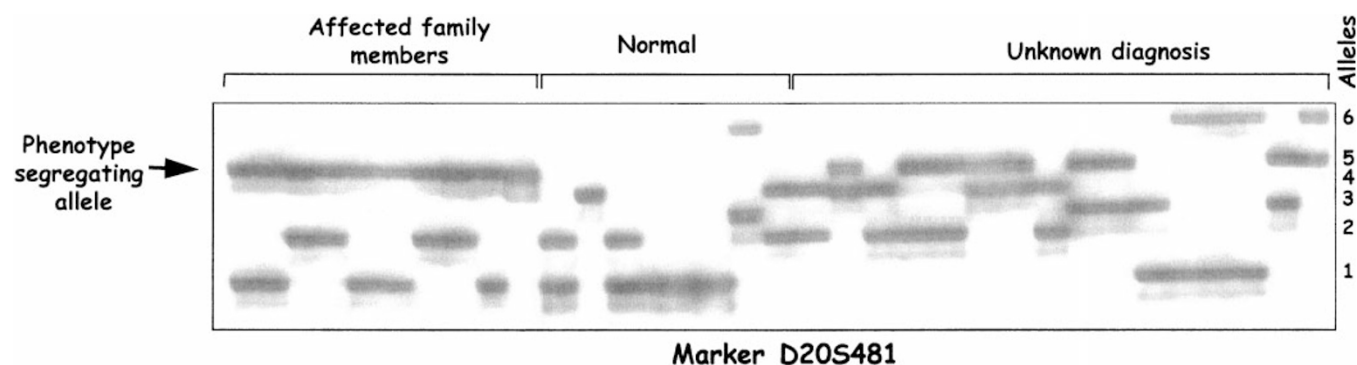
Figure 1 B Representative genotypes for the polymorphic microsatellite marker D20S481 in family BP-TU1. All affected individuals share polymorphic allele 5 of this marker.

evidence for linkage were previously reported. The highest lod scores obtained per chromosome using a dominant model with 100% penetrance are shown in Table 3. The two-point lod scores under recessive models were all negative.

Discussion

Linkage analysis of the BPAD susceptibility locus in the large Turkish pedigree (BP-TU1) with apparently autosomal dominant mode of inheritance showed that the disease locus maps to an approximately 42 cM genomic interval between markers D20S186 and D20S109 on 20p11.2–q11.2. This interval could not be further narrowed down because no additional

members from this family with definitive diagnoses were available for study. The diagnostic status of the majority of the individuals in generation V was unknown since they are below the mean age of onset for BPAD in this family. A follow up in the next 10 years is needed to re-assess the phenotypes and better define the region on chromosome 20 with the potential BPAD susceptibility gene.

Linkage analysis (which we called conservative analysis) was also performed by setting the cut-off age of onset of the disease at age 40 years. In this scenario, individuals 26 and 29 in Figure 1A were changed to unknown diagnostic status instead of unaffected. Furthermore, individual K in Table 1 who is now 34 years old and had only suffered a single
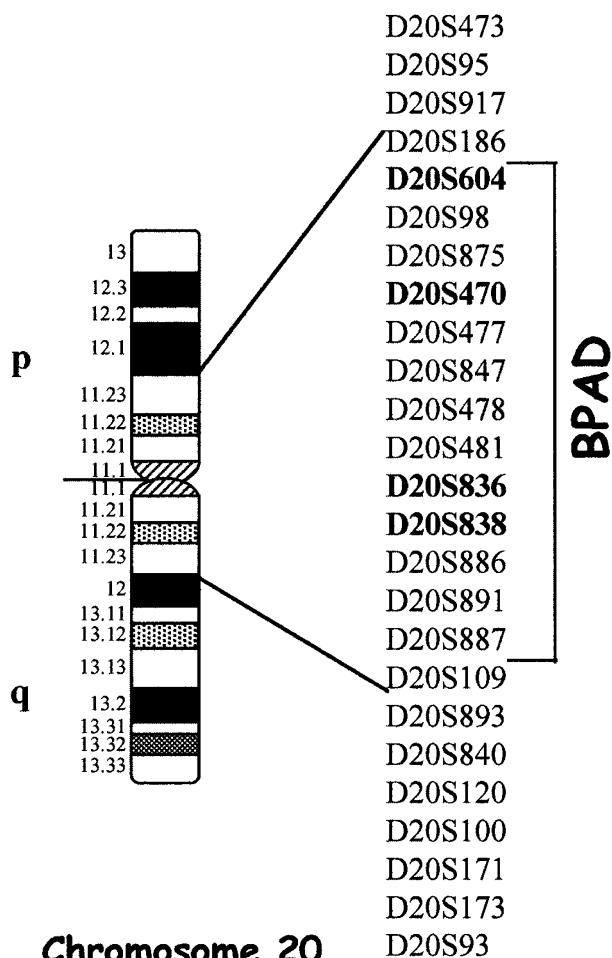
Figure 2 Schematic representation of human chromosome 20. Cytogenetic localisation of the polymorphic microsatellite markers linked to the BPAD is indicated for the region 20pter–qter. The BPAD critical interval is bracketed where no detectable recombination with polymorphic markers is shown. The order of microsatellite markers is determined by using the Marshfield and CHLC linkage maps (http://www.marshmed.org/genetics/ and http://www.chlc.org/).

Table 3 Maximum lod scores and corresponding recombination fraction (θ) per chromosome obtained using a dominant model with 100% penetrance

Chromosome	Marker	2-point lod score	Theta
HC01	D1S1595	1.2	0.091
HC02	D2S434	0.22	0.2
HC03	D3S2406	1.05	0.104
HC04	D4S2366	0.078	0.379
HC05	D5S1471	0.47	0.144
HC06	D6S1610	0.50	0.2
HC07	D7S2846	0.129	0.0
HC08	D8S1132	0.43	0.0
HC08	D8S1132	0.43	0.0
HC09	D9S1824	0.86	0.138
HC10	D10S1426	0.99	0.101
HC11	D11S1985	0.58	0.174
HC12	D12S1042	0.012	0.41
HC13	D13S1493	0.42	0.033
HC14	D14S617	0.23	0.264
HC15	D15S643	0.48	0.0
HC15	D15S653	0.85	0.148
HC16	D16S3253	0.42	0.0
HC17	D17S122	0.69	0.0
HC18	D18S59	−1.62E−07	0.5
HC19	D19S601	0.09	0.093
HC20	several	4.34	0.0
HC21	D21S1435	0.4	0.186
HC22	D22S420	−7.42E−09	0.5

episode of major depression at age 32 was coded as diagnosis unknown. Under this conservative model, the maximum lod scores for markers D20S604, D20S470, D20S836, D20S838, D20S109, D20S893, D20S840 was 3.44 at $\theta = 0$, and the interval of the BPAD susceptibility locus was placed between markers D20S186 and D20S120 (after an informative recombinant in individual 11) in a region of 51 cM.

The large genomic interval between markers D20S186 and D20S109 on 20p11.2–q11.2 contains many putative genes and ESTs (http://www.ncbi.nlm.nih.gov/cgi-bin/SCIENCE96/msrch2). Each of these genes and ESTs could be considered as a candidate for the BPAD susceptibility gene. Mutation analysis for each of these is required to first detect sequence variants and then determine which of these are associated with the affected status in the members of the BP-TU1 family.

Was any chromosome 20 BPAD susceptibility locus detected in the linkage analyses studies using small nuclear families? Detera-Wadleigh *et al*[33] performed a genome-wide scanning by using 540 individuals from 97 families which yielded a weakly increased allele-sharing in affected sibs with markers D20S604 on 20p ($P \leq 0.05$) and D20S173 on 20q ($P \leq 0.019$). No linkage was found in the studies of Pakstis *et al*[34] and Ewald *et al*[35] where chromosome 20 markers were exclusively used. A more recent linkage analysis study of 22 multiplex pedigrees with 396 informative individuals and genotypes of 607 microsatellite markers[6] did not reveal any lod score more than 1.00 for chromosome 20 markers. These data suggest that the chromosome 20 BPAD susceptibility locus detected in family BP-TU1 is unlikely to be a major locus in the common 'polygenic' small pedigrees. This could be explained by the absence of common deleterious mutations of the chromosome 20 BPAD locus in the populations, and/or by the presence of a severe mutation in pedigree BP-TU1, that by itself confers susceptibility to BPAD.

The determination of the complete nucleotide sequence of chromosome 20 in the next 2 years will provide both a large number of SNPs spaced in intervals less than 100 kb[36] (see also http://www.ncbi.nlm.nih.gov/SNP) and a list of all the genes in the BPAD critical region. Linkage disequilibrium, association studies, and mutation analyses may then determine the gene responsible for the phenotype, and the

involvement of its encoded protein in the pathophysiology of this disease.

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