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Linkage Analysis in a Large Family from Pakistan with Depression and a High Incidence of Consanguineous Marriages

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Key Words
Genetic linkage · Depression · Consanguinity · Pakistan

Abstract
Objectives: A genome wide scan for linkage was performed in a five generation family with a high incidence of depression and high average coefficient of inbreeding ascertained in a rural area of Pakistan. The effect of inbreeding on linkage analysis in an extended pedigree is discussed. ***Methods:*** 372 microsatellite markers were used in a genome wide linkage study. Inbreeding coefficients were measured by two methods using both genealogical and genotype data. ***Results:*** Of 111 family members with phenotypic information, 82 were diagnosed with recurrent major depression. Linkage analysis using the program Superlink online generated LOD scores of less than one at all loci. A model free analysis with SimWalk did not result in any significant linkage score. The mean inbreeding coefficient was 0.038 estimated from genealogical data and 0.02 estimated from the genotype data. These results did not differ significantly. The effects of inbreeding included a reduction in the polymorphism information content of markers and an overestimate of marker allele frequencies. ***Conclusion:*** The analysis of very large families is computationally demanding. Problems encountered in this analysis, including loss of power due to reduced polymorphism information content and sensitivity of the LOD score method to estimates of allele frequencies, severely limited the chance of detecting linkage.

Introduction

A World Health Organisation study has estimated that depression will rank second only to ischaemic heart disease as a source of disability world wide by 2020 [1] and a community epidemiological survey in US estimated the twelve month prevalence of major depression as 6.7%. One third of these cases were rated as 'serious' causing substantial disability in work and daily living or serious suicide intent [2]. It is well established that genetic factors have an important role in determining the risk of developing depression and relatives of subjects with depression are more likely than controls to develop illness. Siblings have a two to nine fold increase in risk. Heritability estimates in twin studies range from 40 to 70% [3] and for depression with onset in adolescence one estimate of heritability reached 0.8 [4].

Genome wide linkage studies in major depression have been reviewed [5, 6] and are summarised in table 1. These studies differed in ascertainement strategies, clin-

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ical assessment, phenotype definition and analysis methods but several regions, including 1p, 8p and 15q were identified by at least two studies and these results are in keeping with heterogeneity of genetic risk factors.

The difficulties in studying complex disorders such as depression are well known and arise because of uncertainties about phenotypic boundaries and the modelling of the mode of transmission in illnesses that show substantial aetiological and genetic heterogeneity. In keeping with the genetic architecture of other common complex traits the genetic factors contributing to risk of depression are likely to include common sequence variants that contribute a small effect to a large group of individuals (common disease common variant model – CDCV) and some rarer risk variants that have a large influence on the phenotype in a small proportion of individuals and could be the major risk factor in single families (common disease rare variant model – CDRV) [15, 16]. The CDCV model suggests there are low risk common alleles which are frequent in the general population and predispose to illness by additive or interactive effects. However the existence of families densely affected by illness is often consistent with the segregation of a single or small number of risk alleles in one family and studies of single families are complementary to large-scale linkage and association strategies. Isolated inbred populations which are relatively homogeneous with respect to phenotype and genetic risk factors are valuable resources in the search for susceptibility factors and have been particularly useful in mapping recessive genes [17].

We have recruited a five-generation family with a high rate of depression from Punjab, Pakistan. Of the 111 family members interviewed 82 were diagnosed with recurrent major depression. Such a high rate of depression in one community is unusual and was the sole reason for the ascertainment of this family. Rates of depression were not increased in other families living in the same villages and we have shown that depression was not linked to socioeconomic factors, years of education or to factors associated with rural as opposed to urban living. In the family consanguineous marriages are preferred and detailed accurate genealogical information is available making it possible to obtain accurate assessments of inbreeding coefficients from family data obtained by interview and from public records. Inbreeding estimates from family data can then be compared with estimates from genotype data.

The aim of this study was to perform genome wide linkage analysis with this single large pedigree showing considerable homogeneity in clinical presentation and may be relatively homogeneous for genetic risk factors.

Table 1. Summary of published genome wide linkage studies in major depression

Authors	Analysis	Chromosome regions
Zubenko [7]	multipoint non-parametric allele sharing sex specific	1p,1q,2q,4q,5q,8p,10p, 10q,11p,11q, 15q,18q, 19p,19centr,Xq
Abkevich [8]	multipoint parametric sex specific	12q
Holmans [9]	multipoint allele sharing non parametric	15q primary analysis 6q,8p,17p sex-specific analysis
Zubenko [10]	multipoint non-parametric allele sharing	2p,5q,6q,8p,11q,Xq
Camp [11]	multipoint parametric sex specific	3 centr, 7p, 18q (primary analysis) 4q, 15q (sex specific analysis)
McGuffin [12]	multipoint non-parametric allele sharing	1p, 12q,13q and 15q
Holmans [13]	multipoint allele sharing non parametric	15q in total sample, 17p and 8p in women
Levinson [14]	multipoint allele sharing	15q

The size of the family and the extent of consanguinity led to particular difficulties in linkage analyses and these will be discussed.

Methods

Family Recruitment

The family was recruited by M.A. who was familiar with the villages in the western part of the Salt Range when he was posted to a Rural Health Centre and noted the unusual concentration of psychiatric symptoms in one family. Individuals gave informed consent to take part in these studies which were approved by the appropriate Ethics committees in Lahore and Edinburgh. Information on the pedigree was gathered from several sources including multiple interviews with family members, the genealogies kept in the villages and from the records for the lands and their ownerships held in the Revenue Department. Sons and daughters inherit land on the death of a parent and these land records date back to the late nineteenth century. We aimed to interview all living descendants of one couple five generations ago and with permission from the patients we contacted the treating doctor and obtained details of hospital admissions. In addition to direct interview collateral information was obtained from relatives espe-

Table 2. Power to detect linkage in the family under several models

Model	Penetrances	Disease allele frequency	Power % to detect LOD >1	Power % to detect LOD >2	Power % to detect LOD >3
D1	0.0001, 0.5, 0.5	0.01	99	96	88
D2	0.0001, 0.3, 0.3	0.01	98	94	84
D3	0.001, 0.3, 0.3	0.01	98	93	81
D4	0.01, 0.8, 0.8	0.01	99	95	86
R1	0.0001, 0.0001, 0.7	0.1	75	36	9
R2	0.0001, 0.0001, 0.9	0.1	86	53	17
R3	0.01, 0.01, 0.8	0.05	84	49	14
R3*	0.01, 0.01, 0.8	0.05	63	19	2

cially before making a diagnosis in patients who were not currently depressed but gave a history of past depressive episodes. Psychiatric diagnoses were reached according to ICD 10 criteria using the Diagnostic Interview for Genetic Studies [18]. A final diagnosis was reached by consensus between two psychiatrists during regular exchange visits between Edinburgh and Lahore. The most frequent diagnosis in the family was recurrent major depressive disorder. The family live in a close knit community where information about illness is openly shared and subjects rely on one another for support during illness periods. The descriptions of symptoms of depression provided by relatives are likely to be accurate and admission to hospital and impairment in functioning are particularly known to others because these are the periods when practical support is needed by the family. The community has witnessed these episodes of depression frequently and clearly distinguishes major depression from general unhappiness using the name 'bimari', which literally means illness.

Genotyping

Genotyping was performed on 372 polymorphic microsatellite markers. Markers (ABI PRISM linkage set, MD10 version 2) with an average spacing of ~10 cM were labelled with fluorescent dyes (FAM, HEX, NED) and assayed in 28 multiplexed panels. PCR was performed under standard conditions using a Peltier thermal cycler (PTC-225, DNA Engine tetrad) and PCR products were electrophoresed on an ABI 3730 DNA sequencer. Genotypes were called using GeneMapper™ software version 3.0 (ABI-PRISM®) and electropherograms examined visually.

Inbreeding Coefficient

The coefficient of inbreeding is the probability that an individual carries two homologous copies of a gene identical by descent (IBD). The coefficient was calculated by two methods using the genealogical and the genotype data. The relationship information provided in the pedigrees for linkage analysis goes back several generations and to quantify the amount of excess sharing of alleles in the pedigree we calculated a single locus inbreeding coefficient from relationships using the programme KIN (http://www.stat.washington.edu/thompson/Genepi/MORGAN). This method uses all the family data but underestimates inbreeding in older generations because it does not take account of inbreeding in the founders.

The inbreeding coefficient from genotyping data was calculated using the FEstim program for all the individuals for whom we had genotyping information [19]. FEstim estimates an individual's inbreeding without requiring any knowledge of the parental relationships. It uses a hidden Markov model (HMM) for the IBD process of the individual. This method includes only the younger members of the family and should provide an accurate measure of inbreeding because the patterns of consanguinous marriages within this extended family have been unchanged for many generations. The program requires the map of the markers, allele frequencies and genotyping data on individuals. The genotyping data was provided for all the markers across the genome. The allele frequencies were calculated from the family. We also computed the inbreeding coefficient with equifrequent allele frequencies to check the effect of changes in allele frequencies on the coefficient.

Power Calculations

Simulation was used to determine the power of linkage analysis under a range of genetic models as shown in table 2. All individuals were assumed to be typed for a single highly polymorphic marker (heterozygosity 0.8) completely linked to the disease. For each genetic model of interest 200 replicates were simulated using the program SLINK. SLINK simulates marker and disease loci conditional upon a particular pedigree structure and set of individuals with known phenotype [20].

The family was broken into two divisions and loops were broken to allow the simulations to run with reasonable computing resources. For loop breaking various individuals were set as founders. Power was calculated under dominant and recessive models with varying penetrances. Highly informative markers were assumed, equivalent to a moderately dense highly polymorphic microsatellite marker set. We performed the power calculation for one of the recessive model (R3) with less informative markers to mimic the effect of homozygosity. The less informative markers had 4 equally frequent alleles instead of 8 alleles. This model is referred to as model R3* in table 2.

Linkage Analysis

Two point linkage analysis was performed using the online program, Superlink, chosen because of its computing power and exact calculation of the LOD score [21]. However the program cannot analyse the whole family as a single pedigree and we divided the pedigree into two subfamilies. The founder couple had

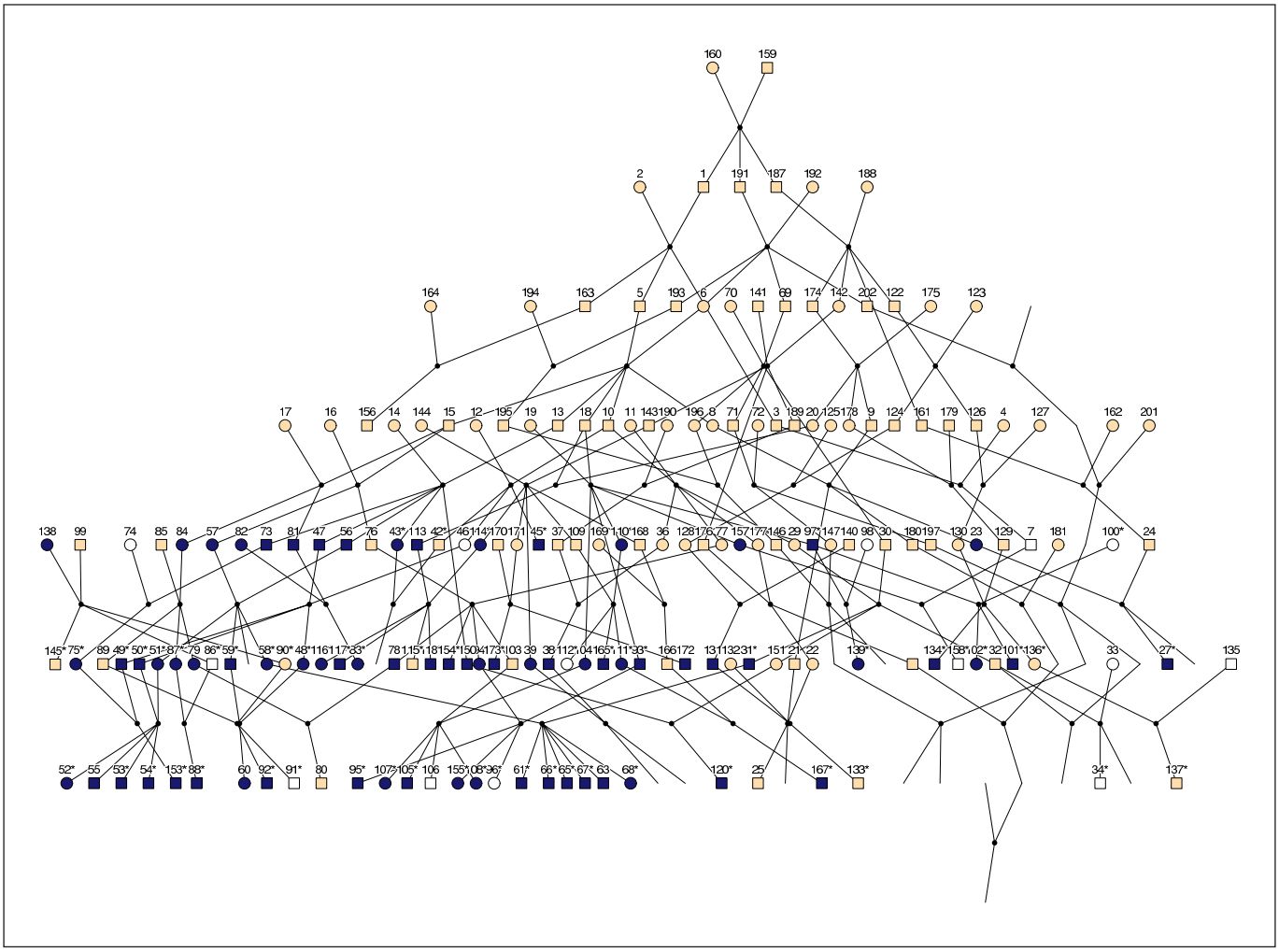

Fig. 1. Illustration of the full pedigree described. Dark symbols are individuals who have been interviewed and diagnosed with recurrent major depression according to ICD 10 criteria.

three sons and the offspring of two of these formed one family and the progeny of the third brother formed the second family. Some individuals were included in both subdivisions to fully describe relationships but no person contributed genotype or phenotype information to both pedigrees. There were 127 individuals in pedigree 1 and 91 individuals in pedigree 2. The whole family is illustrated in figure 1 and the sub-families are shown in figure 2 and figure 3. Figure 3 includes two sons of the founder couple for the purpose of specification of the relationships.

Major depression is almost certainly heterogenous in aetiology, and the mode of inheritance unclear. We tested the family for linkage under both recessive and dominant models.

For a recessive model we assumed a disease allele frequency of 5%. Taken with penetrances of 0.01, 0.01 and 0.8 this gives a disease prevalence of 1.1% (model R3 in the power calculations). For a dominant model an allele frequency of 1% and penetrances of 0.01, 0.8 and 0.8 gave a similar disease prevalence (model D4 in power calculations). A number of authors have shown that for LOD score method if the actual mode of transmission is correctly specified then the power to detect linkage is not significantly affected even if the penetrance is mis-specified [22–24]. For example Clerget-Darpoux and colleagues [22] show that fitting a dominant model to a recessive model adversely affects power and vice-versa. We therefore fitted a recessive and dominant model. To further address this issue for the 10 markers with highest LOD scores we re-ran the parametric linkage for additional models with varying penetrances and disease allele frequencies as presented in table 2. Allele frequencies were calculated from the pedigree itself. The genotyping data was available for 81 individuals to calculate the allele frequencies. To estimate the sensitivity of the LOD score to changes in estimates of population allele frequencies we also selected a group of markers and analyzed them setting all the allele frequencies to 1/n where n is the total number of alleles of that particular marker.

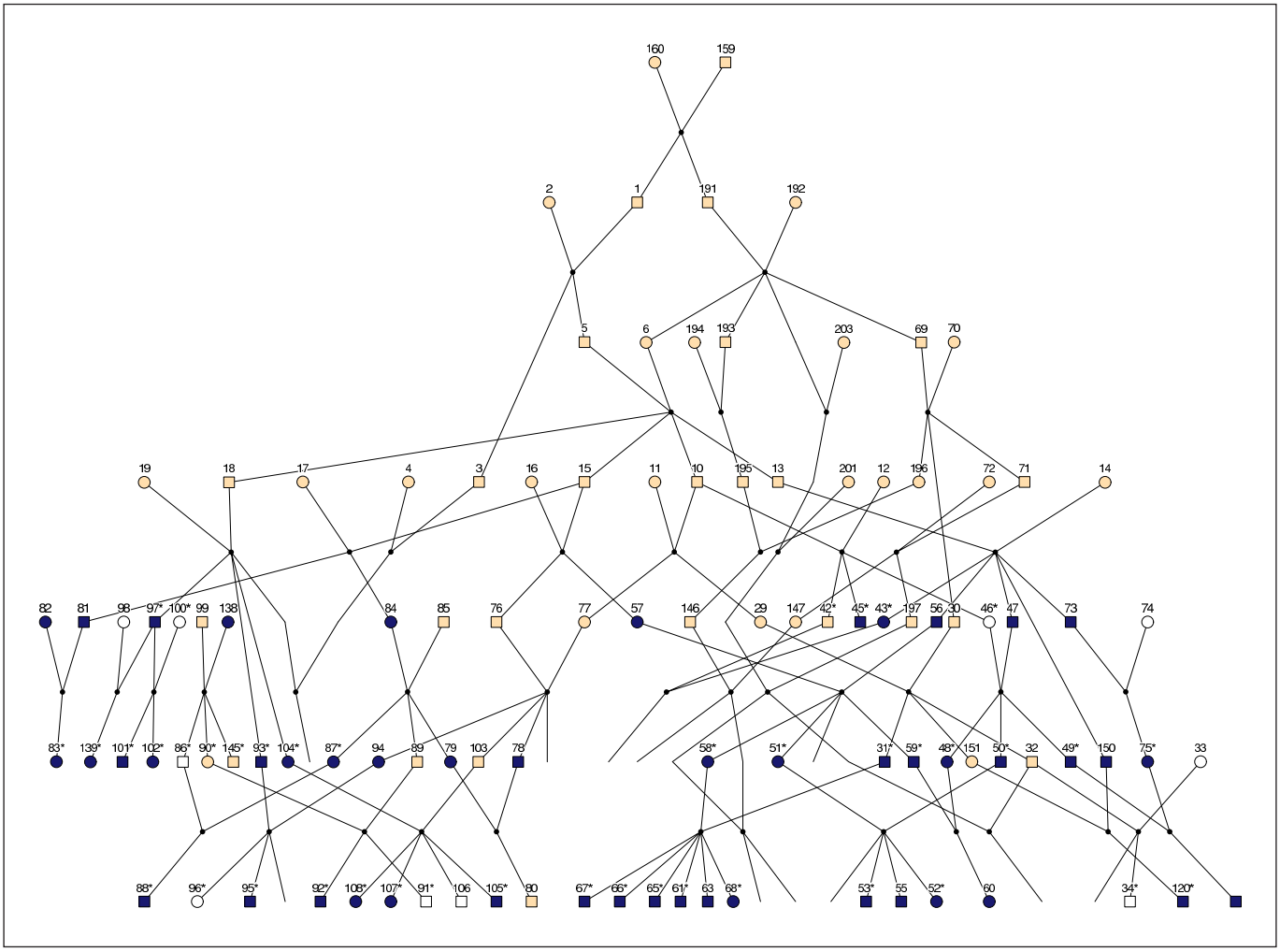

Fig. 2. Illustration of the first sub-pedigree described. Dark symbols are individuals who have been interviewed and diagnosed with recurrent major depression according to ICD 10 criteria.

Results

The family structure is illustrated in figure 1. In total 203 individuals were identified in five generations. 111 subjects were interviewed and 92 could not be fully assessed (deceased, not consenting or moved away from the region). Table 3 lists the diagnoses reached for 111 subjects. Seven subjects with a diagnosis of bipolar disorder or schizoaffective disorder and seven where the diagnosis was uncertain were not included in the linkage analysis where they were coded as 'unknown' phenotype. Genotyping was carried out in 63 individuals with depression (33 men and 30 women), and eleven subjects who were unaffected (6 men and 5 women).

Estimation of Inbreeding Coefficients

The mean inbreeding coefficient computed from genealogical records of the family as illustrated in figure 1 using the program KIN was 0.038 (variance 0.0012) and from genotyping data of 372 microsatellite markers using FEstim was 0.02 (variance 0.00072). The differences did not reach significance. Figure 4 is a scatter plot of inbreeding coefficients computed by the two methods. The regression slope for the two coefficients was 0.68 and both methods yielded similar estimates.

The mean inbreeding coefficient from genomic data with equal allele frequencies was 0.15 (variance 0.003). It was significantly different from the inbreeding coefficient calculated from genealogy (t = 25.5, p = 0.000) and

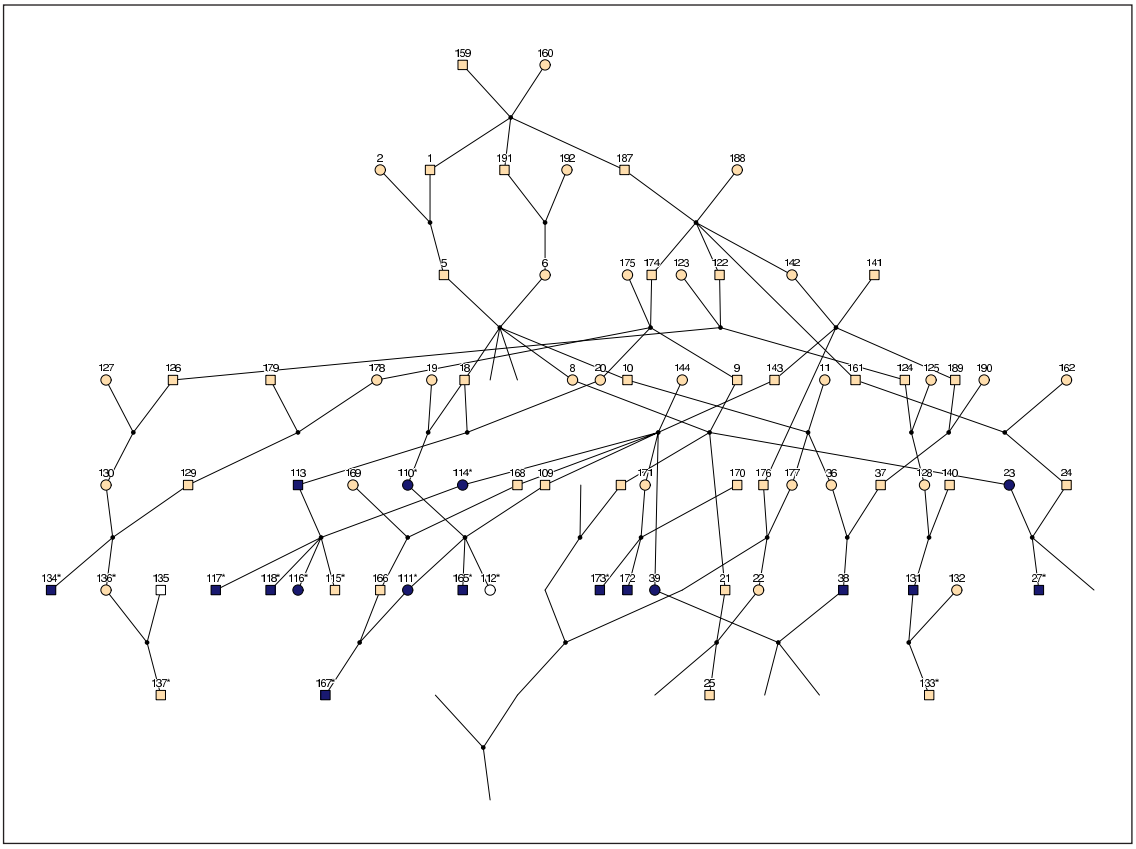

Fig. 3. Illustration of the second sub-pedigree described. Dark symbols are individuals who have been interviewed and diagnosed with recurrent major depression according to ICD 10 criteria.

Table 3. Number of individuals in the family with psychiatric diagnoses and number genotyped

	Total number	Genotyped	Major depression	Bipolar and schizo-affective disorder	Unaffected	Not assessed	Assessed but diagnosis uncertain
Males	107	46	43	5	7	46	6
Females	96	37	39	2	8	46	1
Total	203	83	82	7	15	92	7

Table 4. Effect on LOD scores of two different methods of estimating allele frequencies

Marker	Model	LOD score (allele frequencies from family)	LOD score (allele frequencies 1/n)
D1S2890	recessive	−2.7	1.14
D1S2868	recessive	−2.84	1.52
D10S1693	recessive	0.18	3.7
D10S212	recessive	−2.18	1.24
D6S422	recessive	−1.42	3.66

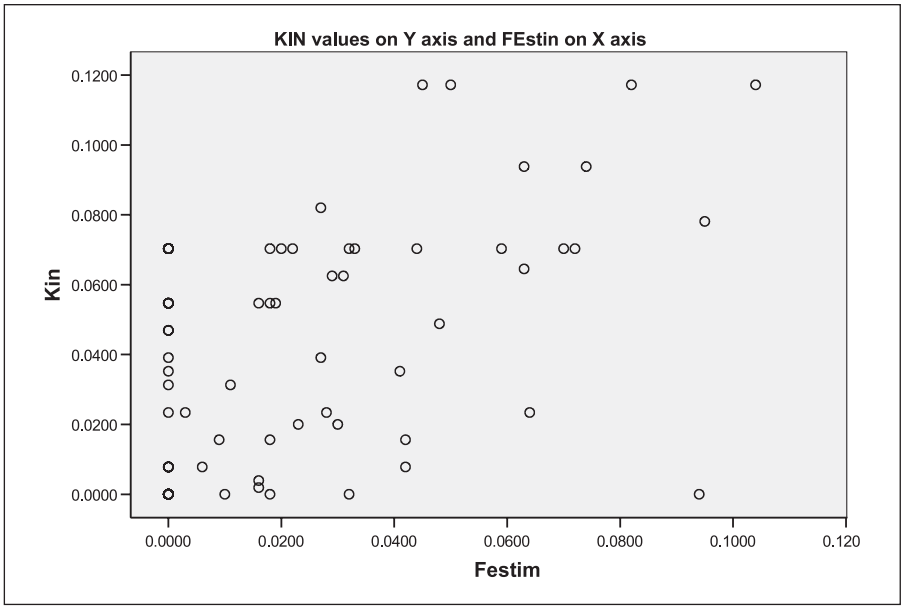

Fig. 4. Scatterplot of inbreeding coefficients estimated from genealogical data using KIN program (X axis) and genotype data using FEstim program (Y axis). The regression slope for the two coefficients was 0.68. There was no significant difference in the mean inbreeding coefficient calculated by these two different methods.

from inbreeding coefficient calculated from genomic data with allele frequencies calculated from the family ($t = 27.7$, $p = 0.000$).

Linkage Analysis

Genotyping errors were checked using the PEDCHECK and GRR programs [25, 26] and genotypes with mendelian inconsistencies were removed from the analysis.

The LOD scores for recessive and dominant models were less than 1 for all markers. Indeed the highest scores were 0.24 for marker D1S450 at zero recombination under a dominant model and 0.12 at D1S484 under a recessive model. The linkage analysis was very sensitive to variation in assessment of population allele frequency. Linkage results based on allele frequencies calculated from the pedigree and under the assumption of equal allele frequencies were compared and at some markers results were dramatic. Table 4 lists five markers where linkage was significantly found (LOD >3) or excluded (LOD <–2) under one or other method.

Table 5 shows the results of linkage under different models for ten markers with the highest LOD scores.

Nonparametric linkage analysis with SimWalk was performed. This program is Markov Chain Monte Carlo based and the whole family was analysed as a single pedigree. SimWalk2 reports the empirical p values for five non-parametric linkage statistics: BLOCKS, MAX-TREE, ENTROPY, NPL_PAIR and NPL_ALL. BLOCKS is designed to be the most powerful for a recessive trait and MAX-TREE for a dominant trait. The remaining statistics are most powerful for additive traits (http://www.genetics.ucla.edu/software/). The p value for Max-Tree (dominant) statistic on one marker was 0.057. All the other p values were higher than that.

Information content of the polymorphic markers within the family was calculated by using the Mega2 program to divide the pedigree into nuclear families [27] then using the Allegro program to compute polymorphism information content (PIC) for the markers [28]. The mean PIC is 0.59 ranging from 0.11 to 1. Ten percent of the total markers have a PIC less than 0.33, 80% less than 0.74 and 90% less than 0.82.

Discussion

There is evidence from clinical studies that recurrent major depression, especially when onset is in adolescence, is a highly heritable disease and inbred families have proved to be a good resource for gene mapping in single gene recessive disorders. We have therefore performed linkage analysis in a highly inbred family with recurrent major depression from a relatively isolated population within the Punjab in Pakistan. The clinical characteristics point to a relatively homogeneous phenotype. However the genome scan using 372 markers spaced at ~10 cM intervals detected no locus showing a LOD score >1 despite the ability of the online program Superlink to provide rapid analysis of the family after splitting into only two

Table 5. The results of linkage under different models for ten markers with the highest LOD scores in the first analysis

Markers		Models						
		D1	D2	D3	D4	R1	R2	R3
D1S450	LODS	0.73	0.61	0.61	0.58	–0.01	0	0.02
	Theta	0	0	0	0.1	0.3	0.4	0.2
D1S199	LODS	0.33	0.3	0.3	0.37	–0.07	–0.08	–0.1
	Theta	0.2	0.2	0.2	0.3	0.4	0.4	0.4
D7S516	LODS	0.46	0.42	0.44	0.78	–0.03	–0.01	–0.06
	Theta	0.2	0.2	0.2	0.2	0.4	0.3	0.4
D7S2465	LODS	0.45	0.4	0.41	0.54	0.22	0.23	0.28
	Theta	0.05	0.05	0.05	0.1	0.2	0.2	0.2
D10S1693	LODS	–0.06	–0.06	–0.07	–0.18	0.45	0.47	0.43
	Theta	0.4	0.4	0.4	0.4	0	0.1	0.1
D10S217	LODS	0.41	0.36	0.36	0.54	–0.11	–0.1	–0.11
	Theta	0.3	0.3	0.3	0.3	0.4	0.4	0.4
D10S1651	LODS	0.23	0.19	0.19	0.42	–0.04	–0.03	–0.04
	Theta	0.3	0.3	0.3	0.3	0.4	0.4	0.4
D11S987	LODS	0.5	0.43	0.43	0.57	–0.05	–0.05	–0.05
	Theta	0.2	0.2	0.2	0.2	0.4	0.4	0.4
D14S985	LODS	0.13	0.1	0.1	0.23	0.23	0.22	0.28
	Theta	0.3	0.3	0.3	0.3	0.2	0.2	0.2
D17S784	LODS	0.22	0.16	0.17	0.41	–0.05	–0.05	–0.02
	Theta	0.3	0.3	0.3	0.3	0.4	0.4	0.4

large subfamilies. Neither did analysis with SimWalk provide any evidence of linkage despite the results in table 2 showing that the power to detect relatively strong effects is high in this family when markers with heterozygosity of 0.8 are assumed. However power was shown to decrease substantially under a recessive model (R3) with the assumption of a less informative marker to mimic the effect of homozygosity. Homozygosity mapping has been used to map recessive diseases in inbred families [29, 30].

Inbreeding in the family means that polymorphic markers are more likely to be homozygous across relatives, reducing the polymorphism information content of the markers and thus the power to detect linkage. We examined the information content of our entire marker set and it ranges between 0.11 and 1.0 across the genome in the pedigree with a significant proportion of loci having low PIC values.

In this family where many founders were not available for genotyping the mis-specification of allele frequencies could result in false positive results. To circumvent that problem we calculated the allele frequencies from the family itself [31–34]. In the presence of inbreeding estimates of population allele frequencies calculated from the pedigree itself are likely to be highly inaccurate because of the reduced genotypic diversity.

Conclusions

We discuss the analysis of a genome-wide scan for linkage in an inbred Pakistani pedigree with recurrent major depression. The program Superlink on line was used to generate LOD scores after dividing the family into two subfamilies. However possible misspecification of the genetic model, low polymorphic information content of the markers and wrongly specified population allele frequencies due to inbreeding are the main reasons for loss of power to detect linkage in this pedigree limiting the value of parametric linkage approaches.

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