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Genome-wide Linkage Scan of Major Depressive Disorder in Two Dagestan Genetic Isolates

Research Article

Kazima B. Bulayeva[1*], Todd Lencz[2], Stephen Glatt[3], Toru Takumi[4], Farida R. Gurgenova[1], Oleg A. Bulayev[1]

[1] *N.I.Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow, 119991, Russia*

[2] *Division of Psychiatry Research, The Zucker Hillside Hospital, NY 11004, USA*

[3] *Department of Psychiatry and Behavioral Sciences, Medical Genetics Research Center; SUNY Upstate Medical University; NY 13210, USA*

[4] *Hiroshima University, Kasumi 1-2-3, Hiroshima 734-8553, Japan*

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Abstract: We conducted a 10-cM genome-wide linkage scan in two extended pedigrees, ascertained from two diverse Dagestan genetic isolates with high aggregation of major depressive disorder (MDD) and suicides. Using genome wide multipoint parametric linkage analyses with short tandem repeat markers, we found two previously undetected genomic regions with significant linkage in isolate #6007 with LODs=3.1-3.4 at 2p13.2-p11.2 (and some signal in same region for #6008) and in 14q31.12-q32.13. We also obtained suggestive evidence for linkage with MDD at 9q33.3-q34.2 (#6008), 13q31.1-q31.2(#6007), 11p15(#6008), 17q25.3(#6007) and 19q13.31-q13.33 (#6008). Five regions (1p36.1-p35.2, 2p13.2-p11.2, 17q25.3, 18q22 and 22q12.3) demonstrated at least nominal linkage in both isolates' pedigrees, while all other linkage regions demonstrated population-specific genetic heterogeneity.

Keywords: *Major Depressive Disorder • Early onset • Genetic isolates • Multipoint linkage analysis • Cross-isolates mapping • Suicides committed*

1. Introduction

Major depressive disorder (MDD) is a complex psychiatric disorder characterized by persistent sadness, extreme fatigue, feelings of guilt and hopelessness, appetite change, insomnia, poor concentration and suicidal thoughts (DSM-IV). The estimated risk of a diagnosis of major depression in suicide cases is almost 11 times higher than in controls [1].

Although heritability of MDD is lower than other psychiatric diseases, studies of twins demonstrate a significant genetic contribution of approximately 35-45% [2,3]. As with other forms of mental illness, the mode of genetic transmission is complex and poorly understood, and no susceptibility genes have been unequivocally identified to date [4]. Genome wide linkage studies have reported various peaks across multiple chromosomes, including 1q21-42, 4p16, 10q21-26, 11p15, 12q23-24, 13q11-32, 15q25-q26, 18p11, 18q21-22, 22q11-13, Xp11, and Xq24-28 [5-9]; however, most of these results have not been replicated in other studies [10]. Notably, prior linkage and association studies have primarily focused on genetically heterogeneous populations.

Genetic isolates are exceptional resources for detection of susceptibility genes for complex human diseases because they are used to reduce genetic and clinical heterogeneity. This article expands our cross-isolates approach to mapping genes of complex diseases by utilizing genome-wide multipoint linkage

* *E-mail: bulaeva@vigg.ru*

scan [11-13]. To identify genes for such moderately heritable diseases as MDD, it is useful to study a subset of pedigrees with maximal genetic homogeneity, which in turn can enhance the genetic "signal:noise" ratio that is an especially important strategy for complex disorders with many small or weak genetic signals. In this report, we focus on pedigrees drawn from two remote Dagestan highland isolates with aggregation of MDD and suicides.

2. Material and Methods

Description of populations. The Caucasus region between the Black and Caspian Seas is characterized by extreme cultural and linguistic differentiation in a small geographic area that suggests a complex history. Twenty-six indigenous Dagestan (Northern Caucasus, Russia) ethnic groups belong to the four linguistic families: Dagestan-Nakh, South Caucasian, Indo-European, and Altaic. The southern two-thirds of Dagestan with highest ethnic diversity are in the Main Caucasus Mountains, reaching 2,000– 4,000 m above sea level. Our genetic study of Dagestan ethnic populations has demonstrated their possible descent from a common ancestor population that existed several hundred generations ago [14]. In Bulayeva' research group' (VIGG RAS) expeditions of 1999-2005 to the remote highland populations of Dagestan indigenous ethnics were ascertained two genetically isolated villages of ethnic Laks (#6007 and #6008) with aggregation of depression and 11-12 officially documented completed suicides.

Clinical Assessment and Diagnostic Procedure. Most of the affected individuals in the isolates were diagnosed previously in Dagestan mental hospitals with affective or schizoaffective disorders. In our expedition study we re-checked diagnoses of affected pedigrees members DIGS (Diagnostic Interview for Genetic Studies) software translated into Russian and adapted to multi-ethnic study [15,16]. As part of the clinical study in our expeditions, we also interviewed three to four unaffected members of every kindred using the FIGS (Family Interview for Genetic Studies) software, with the goal of obtaining corroborating diagnostic information and to detect MDD symptoms in unavailable or died pedigrees members. DIGS and FIGS were developed in the NIMH Human Genetics Initiative (US) and uses diagnostic criteria proposed in the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV)[17]. Diagnostic assessments were conducted by two Dagestan hospitals psychiatrists trained on the DIGS and experienced with clinical evaluations during their long-term work in regional psychiatric hospitals. We also documented all additional diagnoses and ages at onset and severity for each diagnosis to characterize significant co-morbid condition of patients. The affected subjects who had met the DSM-IV major axis I diagnoses criteria for MDD were included to our genetic analyses, while several probands with schizoaffective disorder symptoms were excluded.

Written informed consent was obtained from each participant prior clinical interviews and blood samples collections. This study was approved by the Dagestan IRB (Dagestan Center of Russian Academy of Sciences).

Pedigrees analysis. Using family history information, we reconstructed pedigrees for every affected and probable-affected MDD subject in both isolates. The final size of pedigree ascertained from genetic isolate #6007 contains 241 members of 12 generations and from isolate #6008 -327 members of 13 generation. In our expedition we observed all available living MDD cases and their healthy relatives who agreed to participate in the study. Also, because genome-scan data were available for only a part of the extended pedigree members, we selected branches from the pedigrees with the highest density of family members with genotypes. The branches contain 119 members of 11 generations in isolate #6007 and 155 of 13 generations in isolate #6007. The selected branches are fully confirmed with extended pedigrees by rate of endogamy and consanguineous marriages, as well as by aggregation of affected family members. Such deep, multi-generation extended pedigrees were available because these ethnic groups have a tradition in which fathers are responsible for transmitting information to younger generations about their direct ancestors extending back seven generations [11]. For drawing of pedigrees and database management, we used Progeny (Desktop Version) software, which combines the power of a pedigree drawing tool and an easy to use powerful backend database.

Genotyping. Blood samples were collected from three or four current generations of affected and healthy pedigree members. Using standard methods, approximately 400 μg of DNA was isolated from each subject's blood sample. This DNA was sent to the high-throughput genotyping facilities at the Mammalian Genotyping Service of the Marshfield Medical Research Foundation of the National Institutes of Health (US). A 10 cM genomic scan using Weber/CHLC 9.0 markers of 64 members (40 affected) of both isolates pedigrees was performed at the Mammalian Genotyping Service of the NIH (US) [18].

Table 1. Description of genetic isolates with aggregation of MDD and other psychiatric diseases.

Isolate ID	Ethnics	F	Nt	AFST*	Total # of affected alive	Total No of observed (affected)	No of pedigree members	No of suicides committed (female/male)†
6007	Laks	0.0138	320	MDD	22	26(15)	241(119)**	11(8/3)
6008	Laks	0.0131	900	MDD	29	38 (25)	327(155)**	12(8/4)

Notes:
Nt= total number of residents in the isolates; F –a total population mean coefficient of inbreeding;
* Affectation status with most prevalence in the isolate;
** - Pedigrees branches with highest density of members whose genomes were scanned for 10 cM STRs (Weber set 9) and selected for multipoint linkage analyses.
† # of suicides committed in the pedigrees reconstructed known during last 3-4 generations.

3. Statistical Methods And Experimental Procedures

Linkage analysis. Extended pedigrees with numerous inbred loops that we ascertained from Dagestan remote highland isolates have enormous power for detection of linkage to disease loci. However, such pedigrees are also very difficult to analyze because require the astronomical number of underlying configurations that are consistent with the available data [19]. The Markov chain Monte Carlo (MCMC) algorithm is able to analyze large pedigrees because it considers the underlying configurations in proportion to their likelihood. For the genome-wide STRs linkage study we used Simwalk 2 based on the Markov chain/Monte Carlo (MCMC) algorithm [19]. Detailed description of Simwalk2 software multipoint analysis algorithms see at www.genetics.ucla.edu/software/.

Multipoint linkage analysis was performed with a statistical genetics application SimWalk2 that uses Markov chain Monte Carlo and simulated annealing algorithms that are suitable for analyzing large complex pedigrees [19]. Here we present multipoint parametric linkage analysis results using method of location scores that are directly comparable to multipoint LOD score (”logarithm of the odds”) and are presented in log10 units [19]. LOD score -a statistical estimate of whether two loci (the sites of genes) are likely to lie near each other on a chromosome and are therefore likely to be inherited together as a package. Location scores indicate the likelihood of several putative positions, among the marker loci, for the trait locus [19].

In multipoint parametric linkage analyses we are testing of both dominant and recessive modes and with a 90% penetrance model of inheritance, the disease allele frequency 0.02, and the assumption of genetic heterogeneity ($\alpha<1.0$) [16,20,21] when we performed a cross-isolates analyzing of two or more pedigrees files simultaneously. Value of α (at #13.2 of Batch file) characterizes the proportion of the pedigrees that contains an affected genotype at this trait locus. Reduced penetrance values we specified for different liability classes. These parameters values were obtained from the disease model provided in the true simulation models and from well known ancient demographic history of ascertained Dagestan ethnic isolates located in stable and extreme highland environment. More details about populations history of Dagestan indigenous ethnics see at [22,23]. We believe that running such multipoint parametric linkage analyses for one clinical phenotype in different genetic isolate pedigrees is a powerful approach toward balancing false-negative and false-positive results.

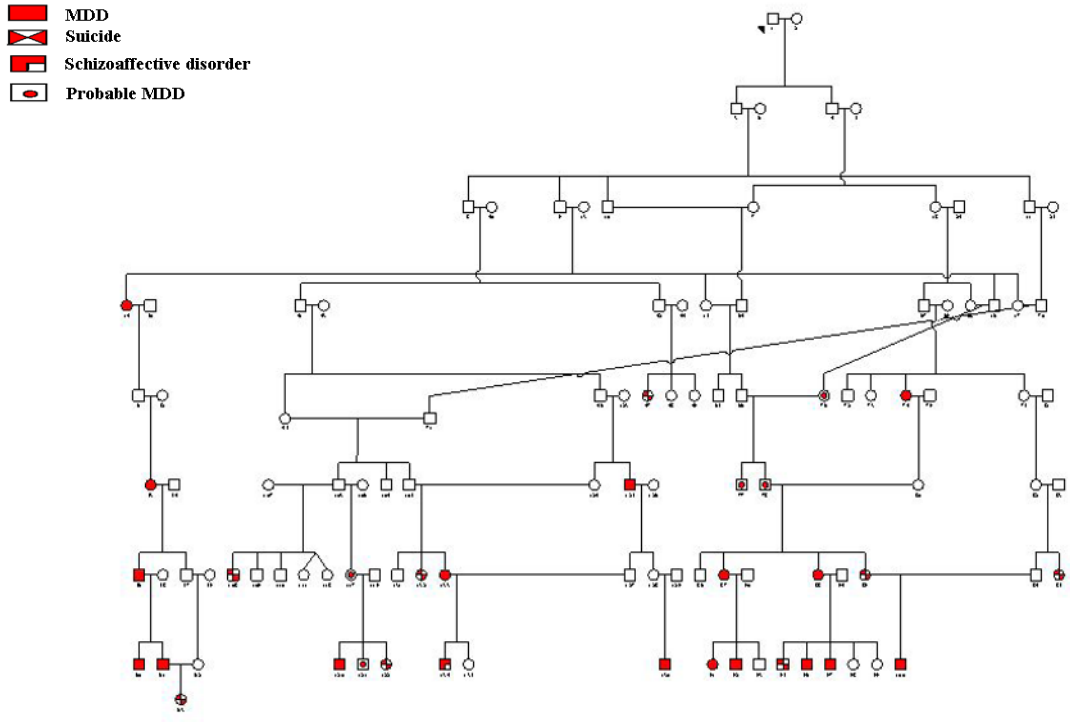
For the linkage analyses we designated pedigree members with MDD as ‘affected,’ and pedigree members who were determined to have no mental illness according to all available information were considered ‘unaffected’. Other individuals, including pedigree members alive with unclear clinical symptoms, were considered ‘unknown’.

4. Results

Our study showed that isolate #6007 has a three times less total number (Nt=320) of residents in comparison with isolate #6008 (Nt=900) (Table 1). Therefore a pedigree reconstructed for affected in isolate #6007 is smaller by size and contain 241 members of 11 generations (15 cases of totally 26 sampled in the pedigree), while in #6008 contains 327 members of 13 generations (25 cases of 38 totally sampled). The number of committed suicides, ascertained during DIGS/FIGS interviews of probands’ family members and collection of family history (and documented in regional administration and hospitals), is high (11-12 committed suicides) (Table 1). Limited number of the pedigrees members is affected by schizophrenia spectrum diseases, mostly-schizoaffective disorders.

Example of the pedigrees branch with aggregation of MDD and suicide are presented in Figure 1. Sex ratio in the pedigrees is similar for both isolates and close to 1:1 (53-54% of male). Both genetic isolates and pedigrees ascertained therein had a high rate of

Figure 1. Pedigree Branch from Dagestan genetic isolate with aggregation of MDD and suicides. Consanguineous marriages between spouses are marked by doubled lines. Lables:



traditional consanguineous marriages. Mean values of inbreeding coefficients calculated in the pedigrees are higher for 2-3 times than mean values of inbreeding coefficients F (Table 1) calculated using a traditional population-genetic method in three generations retrospectively for randomized and representative sample of the isolated population members: for 6007 F_{ped} is 0.0348 (F_{Pop}=0.0138) and for 6008 $F_{ped=}$0.0375 (F_{Pop}=0.0131). We found that MDD affected subjects, as well as all suicides committed, are offspring of close consanguineous marriages. Differences between non-affected and affected MDD cases in inbreeding level are statistically significant: nonparametric Mann-Whitney U-test, Zadj=3.19, p=.0014.

We collected information about age of onset among living MDD cases during DIGS interviews. Results obtained from analyses of data collected demonstrated that the mean age of onset for MDD-affected pedigree members in isolate 6007 was 19.9±1.24 (range: 14-27 years); in isolate 6008, the mean age at onset was 21.1±1.53 (range: 14-35 years). We found that patients who had first-degree relatives with committed suicides tended to have a younger age of MDD onset in comparison with those families without suicides. Age of onset for MDD was significantly earlier (t=2.65, df=78, p=0.009) among offspring of consanguineous marriages (17.4 ± 0.63) than among affected MDD offspring of non-consanguineous marriages, i.e., without known consanguineous marriage within reconstructed 11-13 generations (21.2 ± 0.67) (Figure 2).

Table 2 presents results of the genome-wide multipoint linkage scan. All loci with LOD scores ≥1.2 (nominal p<.05) in either pedigree, under either dominant model (D/M) or recessive model (R/M) are presented along with flanking markers and peak location in cM. Most of the identified linkage peaks are isolate-specific, reflective of genetic heterogeneity. However, six linkage regions (1p36.1-p35.2, 2p13.2-p11.2, 13q31.1-q32.1, 17q25.3, 18q22 and 22q12.3) demonstrated LOD scores =1.3-3.44 that replicated in both pedigrees, although some inter-isolate differences we noted in the genetic model (dominant or recessive) observed at these loci (Table 2). The strongest genetic homogeneity, both in location of the linked genomic region and the mode of transmission, was obtained at 13q31.1-q32.1, 18q22 and 22q12.3 (Table 2). At 22q12.3 we obtained significant linkage (LOD=3.44) in pedigree #6007, and strongly suggestive linkage (LOD=2.80) in #6008 (Table 2). As seen in the table 2, we identified 11 nominally significant linkage signals in #6007 and 13 such signals in #6008; in total, 18 genomic regions in 17 chromosomes were linked to MDD in both genetic isolates. In addition to the region at 22q12.3, we observed two significant (LOD>3) linkage peaks in #6007: one at 14q31.12-q32.13

Figure 2. Variation of MDD age of onset among offspring of non-consanguineous and consanguineous marriages. SD- standard deviation; SE – standard error.

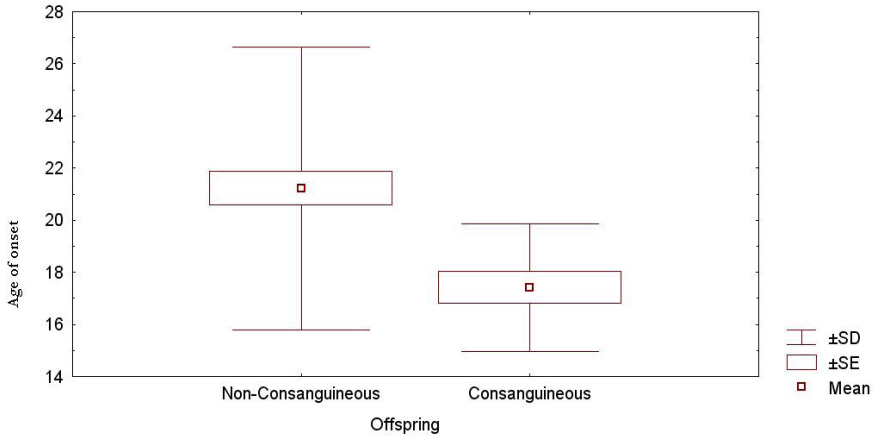


Table 2. Genome –Wide Linkage Scan for MDD in Two Dagestan Genetic Isolates.

#6007			#6008		
MAP	Lod, R/M-D/M	Flanking loci, Peak/cM	MAP	Lod, R/M-D/M	Flanking loci, Peak/cM
1p36.1-p35.2	1.3, D/M	D1S552-D1S1622, 52.4	1p36.21	1.43, R/M	D1S1356-D1S1352, 62.2
2p13.2-p11.2	3.103, D/M	D2S1394-D2S1777, 87	2p12-p11.2	1.4, R/M	D2S1777-D2S1790, 90
4q25-q28.2	1.873, R/M	D4S2623-D4S2394, 114			
			5q14.1-q14.3	1.9, D/M	D5S1501-D5S1725, 94.5
			7p12.3-p14.1	1.64, R/M	D7S2846-D7S1818, 60.2
			8p23.1-p23.3	1.56, R/M	D8S264-D8S277, 3
9q21.33-q22.33	1.24, D/M	D9S257-D9S910, 84.8	9q33.3-q34.2	2.1, R/M	D9S1825-D92157, 129.5
10p13-p12.33	1.7,R/M	D10S1430-D10S1423, 33.5			
			11p15.4-p15.5	2.1, R/M	D11S1984-D11S2362, 3
			12q24.1-q24.3	1.6, D/M	D12S2078-D12S1045, 149.4
13q31.1-q32.1	2.31 ,R/M	D13S317-D13S793, 53	13q31.1-q32.1	1.4, R/M	D13S317-D13S793, 53
14q31.12-q32.13	3.417, R/M	D14S617-D14S1434, 101			
17q25.3	2.48, R/M	D17S784-D17S928, 124	17q25.3	1.3, D/M	D17S784-D17S928, 123
18q22.1	1.3 D/M	D18S1364- ATA82BO2, 97	18q22.1	1.32, D/M	D18S1364- ATA82BO2,90.7
			19q13.31-q13.33	2.7, D/M	D19S178-D19S246, 66.9
20p13	1.95, D/M	D20S103-D20S482, 5			
22q12.3	3.44, D/M	D22S685-D22S683, 30	22q12.3	2.80, D/M	D22S685-D22S683, 28
Total -19	11			13	

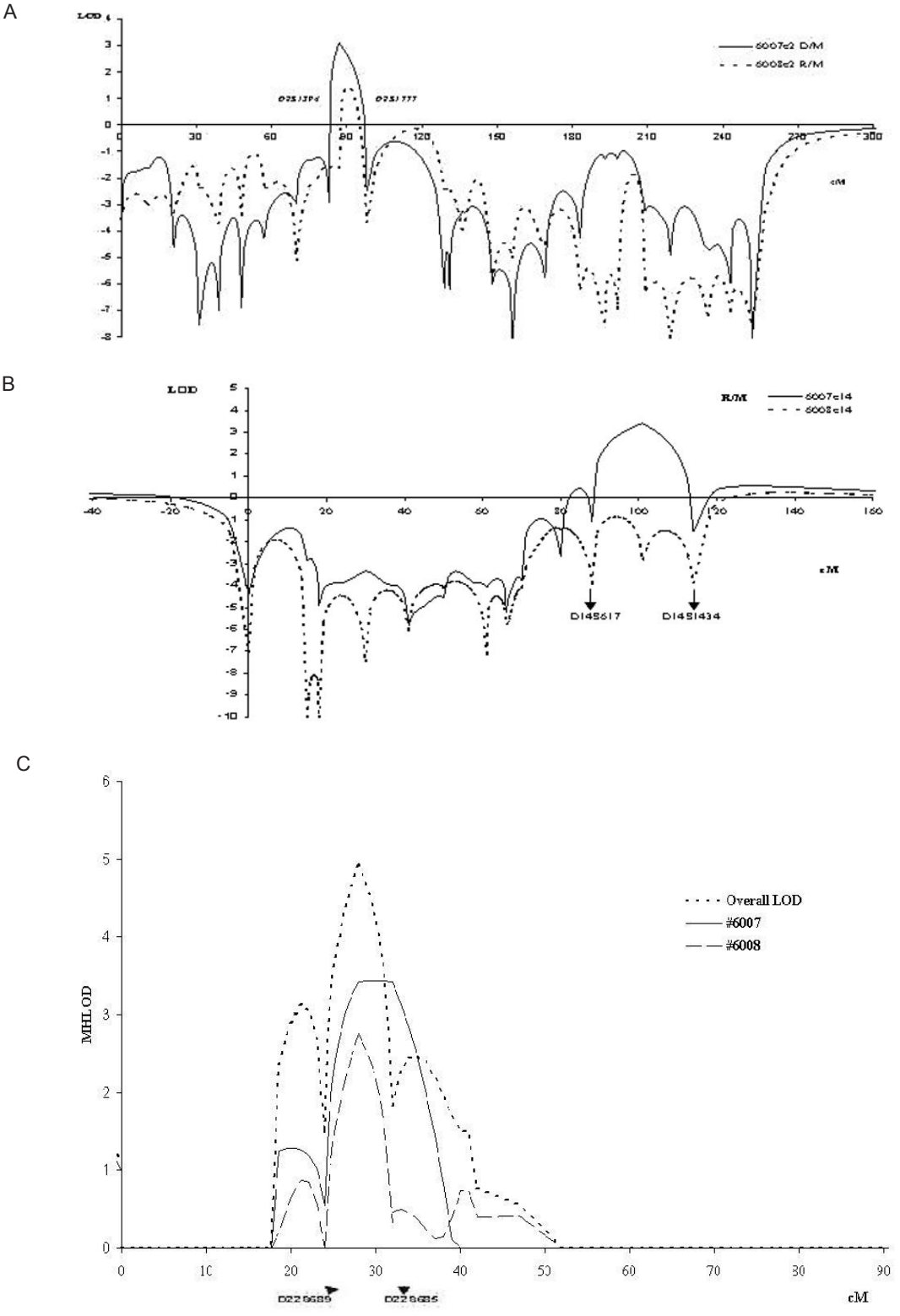
(LOD=3.417, recessive model), and the other at 2p13.2-p11.2 (LOD=3.103, dominant model). Results obtained for linkage analyses on chromosomes 2, 14 and 22 are presented in Figure 3. At 22q12.3 overall LOD are calculated by combining both pedigrees. Overall LOD=4.95 with α=1 we obtained for both pedigrees that implies no locus heterogeneity there.

No genome wide significant LOD scores ≥3 we observed in #6008. Suggestive level (LOD≥2) linkages we found at 9q33.3-q34.2 (#6008, R/M), 13q31.1-q31.2 (#6007, R/M), 11p15 (#6008, R/M), 17q25.3 (#6007, R/M), 19q13.31-q13.33 (#6008, D/M) and 22q12.3 (#6008, D/M) (Table 2).

5. Discussion

Our genetic-epidemiology study showed that prolonged reproductive isolation in severe highland environments during hundreds of generations favored high genetic diversity between these isolated populations and low heterogeneity within them [22]. Two genetic isolates with aggregation of MDD ascertained during our long-term expedition study have a high aggregation of early onset MDD cases and a significant number of committed suicides (Table 1). In contrast to other data

Figure 3. The multipoint LOD scores for MDD across chromosomes 2 (A), 14(B) and 22(C) in two pedigrees ascertained from isolates ## 6007 and 6007.



suggesting that suicidal behavior is a separate domain from psychosis and is connected with gender differences in socio-cultural roles [24], our results support that suicides in these isolates were mostly connected with MDD, insofar as all MDD affected cases are close genetic relatives of suicide completers. In fact, all Dagestan remote highland villages have had the same (insufficient) medical services, same ethno-cultural traditions and socioeconomic circumstances. In both isolates we found that most of affected MDD subjects, as well as committed suicides, were offspring of closest consanguineous marriages (Figure 1). Results obtained support that a smaller isolate (#6007) has a higher rate of affectation and clinical and genetic homogeneity, as well as a higher coefficient of inbreeding (both -F_{Pop} and $F_{Ped)}$, in comparison with larger isolate #6008. MDD affected living cases with suicides completers in their families are mostly offspring of close consanguineous marriages and characterizes by earlier age of onset for MDD (17.4 ± 0.63) than affected MDD offspring of non-consanguineous marriages (21.2 ± 0.67) differences between these groups are statistically significant t=2.65, df=78, p=0.009) (Figure 2).

Previous linkage and association studies have shown some candidate loci for MDD, most of which have been replicated only in two or fewer studies; these regions include 1q21-42, 4p16, 10q21-26, 11p15, 12q23-24, 13q11-32, 18p11, 18q21-22, 22q11-13, Xp11, and Xq24-28 [6-10,25]. Most association studies have focused on neurotransmitter systems for the identification of candidate molecules, including the serotonin transporter, serotonin receptors, dopamine receptors, tyrosine hydroxylase, *MAO-A, COMT*, and tryptophan hydroxylase [4,9,10]. Although the role of a TPH2 mutation (12q21), as well as *HTTLPR* (Xq28) and *BDNF* (11p14.1) promoter polymorphisms, have drawn attention, these associations have been found to be more complex than previously thought [4,10]. Meta-analyses suggest small positive associations between the polymorphism in the serotonin transporter promoter region (*5-HTTLPR*) and bipolar disorder, suicidal behavior, and depression-related personality traits but not yet to MDD itself [10].

Results obtained in our genome-wide linkage scan in two genetic isolates replicated previous findings for MDD at 11p15, 12q23-24, 13q11-32, 18q22 and 22q11-13 (Table 2) while other linkage signals we found were not previously reported as associated or linked with MDD but contain genes which have shown some associations with other psychiatric diseases (e.g., bipolar disorder, anxiety, schizoaffective disease, alcohol abuse, autism etc).

Inter-isolates heterogeneity in 14 linkages with MDD we found can be explained in connection with differences in founders, along with following endogamy and inbreeding within the isolates. Inter-isolates homogeneity with Lod=1.3-3.4 obtained for six genomic regions (1p36.1-p35.2, 2p13.2-p11.2, 13q31-q32, 17q25.3, 18q22 and 22q12.3) can be explained by the existence of a common ancestral meta-population for all Dagestan indigenous ethnic groups that has been supported by our population-genetic study [14].

The highest individual LOD=3.44, occurred in the smaller genetic isolate pedigree #6007 at genomic region 22q12.3 (peak at 28-30 cM); overall for both isolates pedigrees LOD =4.95 with α=1 that implies no locus heterogeneity (Table 2, Figure 3). In this region are located 15 genes, from which LARGE, *TOM1*, *HMG2L1* and *RASD2* genes were previously reported as associated to BP disease and schizophrenia [26,27]. Our results support that a candidate gene(s) of MDD can be located in same region as well.

We found two novel for MDD genomic regions with significant level linkages in #6007 with Lods =3.1-3.4 at 2p13.2-p11.2 (and some signal in same region for #6008) and in 14q31.12-q32.13 (Table 2, Figure 3). In chromosome region 14q31, it was earlier reported that the *ATXN3* gene is associated with schizophrenia, as well as *LGMN* associated with multiple sclerosis, and *GOLGA5* related with thyroid system [28]. Any of these genes may be also involved in the MDD affectation network that underlies our high LOD result (Table 2). In addition to these positive findings we obtained LODs greater than 1.3 and less than 2.0 at 1p36.1-p35.2, 4q25-q28.2, 5q14.1-q14.3, 7p12.3-p14.1, 8p23.1-p23.3, 9q21.33-q22.33, 10p13-p12.33, 17q25.3, 18q22 and at 20p13 (Table 2). The linked region at 1p35-p36, contain genes *HTR6, HTR1D* and other genes related to neurodevelopmental or neurodegenerative diseases. At 2p12-p11 are located genes including *HTRA2, DCTN1*, and *CTNNA2*, which may be related to mental diseases as well. Close to this region are locations of ADH genes connected with alcoholism. At 18q22.1 (rs17077540, p=1.83 x 10(-7) recently were found a strong evidence for association of gene DSEL with BPI and BPII [29].

After a specific chromosomal region has been identified by linkage analysis, we are planning of additional work to refine the location of the susceptibility candidate gene(s) using deeper scanned DNA loci, namely microarray technology in both genetic isolates pedigrees.

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