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The ascertainment of multiplex schizophrenia pedigrees from Daghestan genetic isolates (Northern Caucasus, Russia)

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Abstract

This article describes the preliminary ascertainment of multiplex schizophrenia pedigrees from the isolated mountain region of Daghestan (Northern Caucasus, Russia). Daghestan has a population of two million people and contains 26 aboriginal ethnic groups. Many of the ethnic groups reside in remote mountain villages that can be classified as 'primary isolates'. Prolonged reproductive isolation and severe environmental conditions in the highlands have created diverse, genetically isolated ethnic populations in Daghestan. A number of the isolates in this region contain large extended multiplex schizophrenia pedigrees that are ideal for genetic analyses. During summer expeditions of 1996 and 1997, 14 separate large multiplex schizophrenia pedigrees were ascertained from 14 different mountain villages. Of the 14 kindreds, one had 50 schizophrenic cases available for ascertainment, one had 32, and another had 24. Seven of the remaining pedigrees had between 11 and 23 living cases. Within the kindreds, the number of males with chronic schizophrenia was at least twice that of females. The average age of onset of schizophrenia is 21.2 years for offspring of consanguineous marriages and 17.4 years for offspring of nonconsanguineous marriages ($P = 0.033$). Although the pedigrees ascertained from the remote mountain villages may not be representative of the general population, they are unique kindreds for mapping schizophrenia susceptibility genes.

Keywords

Daghestan; genetic isolates; ethnic groups; epidemiology; schizophrenia; inbreeding; age of onset; age of menarche

INTRODUCTION

Mapping susceptibility genes for complex human diseases is difficult due to the likelihood of genetic heterogeneity, oligogenic inheritance, reduced penetrance and phenocopies. A potentially powerful approach to detect genes for complex traits is through the study of isolated human populations characterized by a limited number of founders followed by prolonged isolation. In such a population, it is likely that most disease alleles are derived from common ancestors, a phenomenon that increases the power of detecting susceptibility alleles (Terwilliger and Ott, 1994; Jorde, 1995; Kruglyak, 1997).

Among the most interesting isolated populations for genetic study are those located in Daghestan (Northern Caucasus, Russia). This region contains approximately two million people and 26 aboriginal ethnic groups. Many of the Daghestan highland villages are like individual countries as they have unique languages, traditions, arts, and customs. A number of the highland villages have unique specialties; the village of Kubachi is noted for its goldsmiths, Gotsatl for its silversmiths, Untsukul for its wood-carvers, Balhar for its potters and Kurah its carpet makers.

The extraordinarily high ethnic diversity of Daghestan suggests a complex history. Archeological data indicate that some ethnic groups of the highland region have been in existence for up to 10 000 years (Gadjiev *et al.*, 1996). Other ethnic groups are younger, ranging between 800 and 5000 years. All the Daghestan aboriginal ethnic groups are anthropologically part of the broad European group of populations (Alexeev, 1964; Gadjiev, 1971).

Previous genetic studies show that the basic population unit for many Daghestan ethnic groups is a remote mountain village (Dubinin and Bulayeva, 1982; Bulayeva, 1991). These villages can be classified as 'primary isolates' according to Neel (1992). These isolates probably grew from a small number of founders, with subsequent growth characterized by restricted gene flow among neighboring villages. The results of our long-term genetic study in this region showed that prolonged reproductive isolation and the severe highland environment favored genetic diversity of the Daghestan ethnic populations (Dubinin and Bulayeva, 1982; Bulayeva, 1991; Bulayeva and Pavlova, 1993; Bulayeva *et al.*, 1993, 1997). During summer expeditions of 1996 and 1997, 14 separate large multiplex schizophrenia pedigrees were ascertained from 14 different mountain villages.

MATERIALS AND METHODS

The natural landscape of Daghestan is very diverse, ranging from high mountains in the western region to very flat plains in the east where Daghestan borders the western shores of the Caspian Sea (Figure 1). The Caucasus Mountains comprise two-thirds of Daghestan, reaching 10000–12000 feet above sea level, and the remaining third is a flat plain in the east (70 feet below sea level).

The highland and mountain villages are still relatively inaccessible because of difficult terrain and poor communication. This region comprises 26 aboriginal ethnic groups and exhibits considerable diversity of environmental habitats. Based on the 1996 census data, the

population of the larger aboriginal ethnic groups is as follows: Avars, 380768; Dargins, 321564; Koumiks, 259302; and Laks, 97673. The populations of the smaller ethnic groups fluctuate between 9000 (ethnic Ahvabs) and 1000 (ethnic Gunzebs). These smaller ethnic groups, as a rule, are limited to one village. Most of the ethnic groups are located in the highland region of Daghestan. Only one of them, the historically youngest group of ethnic Koumiks, resides in the lowlands.

Ascertainment of the schizophrenia families was initiated by Department of Ethnic Population Genetics of Daghestan Center of the Russian Academy of Sciences in 1996, and was continued in 1997 together with US collaborators at the Department of Psychiatry, University of Utah. Information from several sources was used for ascertainment of the schizophrenia families during the expeditions.

1. Regional statistical information from the Daghestan State Statistic Office.
2. The official regional (by village and cities) register of the Daghestan psychiatric hospitals. The register is based on the annual regional reports to the Minister of Health detailing the numbers of the different types of psychiatric illness in the different villages and cities. The register includes only patients hospitalized at the psychiatric hospitals.
3. Clinical observation of subjects using a semi-structured psychiatric interview — the Schedule of Affective Disorders and Schizophrenia (SADS-L), which was translated into Russian. All interviews were carried out in Russian, which is the ‘common language’ used by the different ethnic populations since the early 1900s. For the few subjects who did not speak Russian (older individuals), local medical doctors or nurses were used to carry out the interviews in the subjects’ native languages. Subjects gave informed consent before participation.
4. Information obtained from multiple family informants.

In Daghestan, a patient with a psychiatric illness is only clinically diagnosed during hospitalization in one of two central psychiatric hospitals located in cities far (1800–3000 miles) from the highland isolates. The highland regional hospitals, as a rule, have no professional psychiatrists. From the official register of thousands of schizophrenics recorded in the Daghestan central psychiatric hospital from 50 regions, we randomly selected several highland regions with different ethnic backgrounds. These villages vary from 100 to 1200 km in their distance to a central psychiatric hospital. A review of the records indicated that some villages contain relatively large numbers of schizophrenics, while some villages did not contain any known cases of schizophrenia.

Table 1 displays the official statistical data since 1897 on the total population size and the number of childbearing (reproductive) individuals in the general population of Daghestan. The reproductive period in Daghestan populations is 16–57 old years for females and 17–70 old years for males. Table 1 shows that these demographic parameters decreased from 1897 to 1996 (Daghestan State Department of Statistics, 1997).

Table 2 characterizes the main parameters of human viability — the rate of fertility and mortality in the general Daghestan population from 1940 (per 1000). After the Second

World War, decreased mortality and fertility were common among all the ethnic groups in Russia. Differences between rates of mortality and fertility (called 'Natural Growth') demonstrate that the rate of mortality decreased by 297% and the rate of fertility decreased by 185% in 1996 when compared with 1940.

Official statistical data in 1995 show that the rate of all psychiatric diseases in the Daghestan population was 105.4 per 100000, of which 40.03 per 100000 were schizophrenics (The Daghestan General Indexes of Medical Care, 1996, p. 97).

RESULTS

To date, 14 multiplex pedigrees from 14 different mountain villages have been identified, primarily from the highland region of Daghestan. For most of the families, pedigrees were constructed that included seven to nine generations with 200–450 members. Of the 301 subjects studied so far in the 14 families, 87 individuals were diagnosed with chronic schizophrenia. Forty-one additional individuals with symptoms of schizophrenia were also found in the villages using the SADS-L interview. These probable schizophrenia cases were found in almost every village studied. Most of these individuals are either siblings or parents of the 87 schizophrenia subjects. None of the probable cases of schizophrenia have had previous psychiatric evaluation. These subjects will be re-interviewed in a future study by local Daghestan psychiatrists.

Table 3 displays the population size of the isolates, ethnic background and time of isolation, while Table 4 displays the number of officially diagnosed schizophrenia cases ascertained, the number of schizophrenia cases to be ascertained, and the total numbers of schizophrenia cases in the villages. Every village also has additional cases of probable schizophrenic individuals.

The presentation and course of schizophrenia in Daghestan are similar to those found in the USA and elsewhere. For instance, of the 87 chronic schizophrenics interviewed to date, 91% had relatively chronic auditory hallucinations, 67% had experienced visual hallucinations, 25% admitted to olfactory hallucinations, 92% had relatively persistent paranoid delusions, 21% had ideas of reference, and ~ 50% had a variety of other types of delusions (e.g. Scheiderian's delusions).

Among the officially diagnosed schizophrenia subjects, 65 (78.3%) are male and 22 (21.7%) female [$\chi^2 = 11.6$, $df = 1$, $P = 0.00066$]. Among 'probable schizophrenia' subjects, 18 (48.9%) are male and 23 (51.1%) female.

Significant differences were found in the number of offspring with schizophrenia from consanguineous and nonconsanguineous marriages in the pedigrees (Levene Test for Homogeneity of Variance, $F = 4.56$, $P = 0.034$). There were also significant differences in the age of onset between offspring from consanguineous and nonconsanguineous marriages. Age of onset for offspring from consanguineous marriages is significantly older ($\mu = 21.21$, $sd = 5.4$), than for offspring from nonconsanguineous marriages ($\mu = 17.4$, $sd = 2.44$) (Kruskal–Wallis test: $H = 4.52$, $df = 1$, $N = 80$, $P = 0.033$).

As a rule, most of the affected subjects within an isolate are found in one large extended pedigree, which typically includes a number of marry-in branches with complicated lines of descent and relationships. Figure 2 displays the section of Daghestan pedigree 3511. All 197 members of the family are descendents of two known ancestors. Nineteen members of the family are affected with schizophrenia (15 living), and 13 have a diagnosis of 'probable schizophrenia' (seven living). Of the marriages within the family, 38.3% are consanguineous. About 60% of the individuals with schizophrenia are offspring from consanguineous marriages (Figure 2).

DISCUSSION

During the 1996 and 1997 expeditions, 14 separate multiplex schizophrenia pedigrees from 14 mountain villages with different ethnic backgrounds and different degrees of isolation were ascertained (Tables 3 and 4). Of interest, some of the neighboring villages of same ethnic backgrounds and same population size from the same regions do not have any officially diagnosed cases of schizophrenia. It is possible that mild cases were not detected in these villages, but severe cases of schizophrenia were unlikely to be missed because, as a rule, the village members and psychiatric personnel typically know them. Some of the isolates without known cases of schizophrenia show an above average aggregation of other diseases such as cancer, psoriasis, cardiovascular diseases, neuromuscular dystrophy, kidney disorders and other diseases (Bulayeva, 1991; Guseinov *et al.*, 1996; Illarioshkin *et al.*, 1996). Molecular-genetic analysis may improve our understanding of the processes leading to the population variation in schizophrenia.

The average age of onset of schizophrenia is 21.2 years for offspring of consanguineous marriages and 17.4 years for offspring of nonconsanguineous marriages ($P = 0.033$). The significant differences in the age of onset between offspring from consanguineous and nonconsanguineous marriages may be related to puberty, which marks a period of high risk for the onset of schizophrenia. A later age of menarche among inbred females may explain this variation, with the average age of menarche of these females being 14.05 years compared with 13.4 years for female offspring of nonconsanguineous marriages ($t = 2.23$, $df = 194$, $P = 0.026$) (Bulayeva, 1991).

Of the 87 schizophrenia cases from the isolates studied, 78.3% are male. This sex ratio is similar to those found in recent epidemiology studies of schizophrenia (Gottesman and Shields, 1982; Kendler *et al.*, 1993; Cannon *et al.*, 1998; Myles-Worsley *et al.*, 1999). Only 15 (17%) of the 87 cases demonstrated alcohol or drug abuse. For almost all schizophrenics, drug use occurred after the onset of psychotic symptoms, with many using alcohol or marijuana in an attempt to self-medicate. The majority of cases have had persistent social and occupational dysfunction. Almost all of the schizophrenics are unemployed.

For almost all of the pedigrees studied, there are additional schizophrenic cases that will be ascertained. For example, kindred 4034 has 44 total affected and 'probable' affected cases, kindred 3511 has 73 total cases, kindred 4055 contains 36 total cases, while the large extended kindred 3516 has 14 affected and 'probable' affected cases.

In our previous genetic studies, we found that all highland ethnic groups of Daghestan have higher degrees of inbreeding ($F = 0.0134\text{--}0.0110$) than the historically younger ethnic Koumiks group ($F = 0.0017\text{--}0.0031$) (Bulayeva, 1991; Bulayeva *et al.*, 1993). Some Daghestan kindreds studied are from very isolated and inbred highland isolates, others are from moderately isolated communities, and still others are pedigrees derived from comparatively less inbred populations. Most pedigrees are characterized by high frequency of consanguineous marriages (Figure 2). The frequencies of consanguineous marriages are higher in the pedigrees from isolates 1 and 2 (ethnic Laks), isolate 5 (ethnic Tindals), isolate 12 (ethnic Avars), and isolates 7 and 9 (ethnic Dargins) than in others. The lowest degree of inbreeding is demonstrated from isolate 6 (ethnic Koumiks) (Tables 3 and 4). The results of study showed that the number of affected cases was significantly higher for consanguineous marriages compared with non-consanguineous marriages.

In summary, the presentation and course of schizophrenia in Daghestan are similar to that found elsewhere (Hambrecht *et al.*, 1993; Walker and Lewine, 1993; Byerley *et al.*, 1995; Cannon *et al.*, 1998). Although the pedigrees ascertained in the remote mountain villages may not be representative of the general population, they are ideal for mapping schizophrenia susceptibility genes. Molecular and statistical analyses of the pedigrees are under way.

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FIGURE 1.

Map of Daghestan showing the isolated populations (black points) studied in the expeditions of 1996 and 1997.

FIGURE 2.

The section of Daghestan pedigree 3511 with a high aggregation of schizophrenia cases (■, affected subjects; □, probably affected subjects).

TABLE 1.

Dynamics of total population size (N_t) and reproductive part of general population (N_r) in Daghestan (1897–1996)

Year	N_t	N_r	N_r/N_t
1897	571 154	287 942	0.504
1926	744 200	387 331	0.520
1939	1 023 300	443 610	0.434
1959	1 062 500	544 685	0.513
1970	1 428 500	603 500	0.422
1979	1 627 800	798 000	0.490
1989	1 802 600	893 600	0.496
1996	2 181 100	1 068 739	0.490

TABLE 2.

Dynamics of mortality and fertility rates in Daghestan (per 1000) from 1940 to 1996

Year	Fertility	Mortality	Natural growth ^a
1940	37.0	22.0	15.0
1950	29.8	10.1	19.7
1960	40.0	7.2	32.8
1970	28.7	6.6	22.1
1979	26.0	7.0	19.0
1989	27.4	6.4	21.0
1996	20.0	7.4	12.8

^aDifference between rates of fertility and mortality.

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TABLE 3.

Description of the Daghestan highland isolates

Isolate	Ethnic background	Population size	Time isolated (years)
1	Laks	931	5000
2	Lake	335	2000
3	Laks	340	1500
4	Laks	248	1000
5	Tindals	1800	7000
6	Koumiks	2000	600
7	Dargins	1340	800
8	Dargins	1450	700
9	Dargins	3000	700
10	Dargins	4500	800
11	Avars	2153	1000
12	Avars	1302	1000
13	Dargins	140	700
14	Dargins	183	700

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TABLE 4.

Schizophrenia (Scz) subjects ascertained and to be ascertained

Pedigree	Number of Scz subjects ascertained to date	Number of Scz subjects to be ascertained	Total number of Scz subjects in pedigree
4055	9	15	24
3504	5	8	12
3513	1	6	7
3516	2	2	4
4034	10	24	32
3515	16	7	23
3505	14	5	19
3506	11	5	16
3511	30	20	50
3509	3	8	11
3510	6	16	22
3512	3	12	15
3507	2	5	7
3508	1	3	4
Total	113	136	249