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**Research article**
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# Season of birth interacts with measures of inbreeding in multiplex schizophrenia pedigrees: evidence from genetic isolates in Daghestan

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**Abstract:** While the season-of-birth effect is one of the most consistent epidemiological features of schizophrenia, there is a lack of consistency with respect to the interaction between season of birth and family history of schizophrenia. Apart from family history, measures related to consanguinity can be used as proxy markers of genomic heterogeneity. Thus, these measures may provide an alternate, indirect index of genetic susceptibility. We had the opportunity to explore the interaction between season of birth and measure of consanguinity in well-described genetic isolates in Daghestan, some of which are known for their relatively high prevalence of schizophrenia. Our previous population-genetic study showed Daghestan has an extremely high genetic diversity between the ethnic populations and a low genetic diversity within them. The isolates selected for this study include some with more than 200 and some with less than 100 generations of demographical history since their founding. Based on pedigrees of multiply-affected families, we found that among individuals with schizophrenia, the measure of consanguinity was significantly higher in the parents of those born in winter/spring compared to those born in summer/autumn. Furthermore, compared to summer/autumn born, winter/spring born individuals with schizophrenia had an earlier age-of-onset, and more prominent auditory hallucinations. Our results suggest that the offspring of consanguineous marriages, and thus those with reduced allelic heterogeneity, may be more susceptible to the environmental factor(s) underpinning the season-of-the effect in schizophrenia.


*Keywords: Schizophrenia, inbreeding, seasonality, Daghestan genetic isolates*

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## 1 Introduction

Individuals born in winter and spring have a small but significantly increased risk of developing schizophrenia [1]. This has been confirmed in systematic reviews of data from both the Northern and Southern hemispheres [2, 3]. The magnitude of the winter excess of schizophrenia births is also positively associated with latitude [2]. The nature of the seasonally-fluctuating environmental agent (or agents) that drive the season-of-birth effect for schizophrenia remain unclear, however infectious agents [4] and developmental vitamin D deficiency [5] are candidate exposures.

Despite the large literature reporting seasonal fluctuations in schizophrenia birth rates, there is a lack of consistency with respect to how this exposure interacts with genetically-mediated risk factors for schizophrenia [6]. Population-based studies from Denmark and Finland reported no significant interaction between season of birth and family history of schizophrenia [7, 8]. In keeping with these studies, an epidemiological-informed study of schizophrenia in Ireland reported that the risk of schizophrenia in relatives was not significantly associated with season of birth in probands [9]. However, other studies have reported links between season of birth and family history of schizophrenia. A US community-based study reported that first-degree relatives of winter-spring born individuals with schizophrenia were at increased risk of developing schizophrenia, perhaps suggesting that families of winter-spring born individuals with schizophrenia have a more prominent heritable component compared to summer-autumn born individuals with schizophrenia [10]. However another study reported that the season-of-birth excess was more prominent in those without a family history of schizophrenia, suggesting that the seasonally-fluctuated exposure did not require a genetic diathesis [11].

Ideally, gene-by-environment studies exploring season of birth should be based on proven risk haplotypes or alleles. We are not aware of any specific studies exploring the impact of season of birth on the current candidate genes for schizophrenia. However, studies have reported on interactions between season-of-birth and polymorphisms in various candidate genes in a mixed group of affective disorders and schizophrenia [12], and in attention deficit disorder [13].

Apart from examining the interaction between family history and season of birth, measures related to consanguinity may also provide clues into how season of birth interacts with genetic factors. Based on the assumption that genetic heterogeneity provides greater developmental stability both in native and novel environments [14], one could hypothesize that the offspring of consanguineous marriages would be less able to buffer putative winter-spring associated environmental stressors. Thus, we predicted that among individuals with schizophrenia, those born in winter-spring would be from families with higher measures of consanguinity (i.e. marriages that would result in offspring with reduced allelic heterogeneity).

We had the opportunity to explore this hypothesis in several well-characterized genetic isolates [15, 16]. Genetic isolates are exceptional resources for detection of the susceptibility genes for complex human diseases because of the potential reduction in the genetic and clinical heterogeneity. However, the outcome of these mapping efforts is dependent upon the isolates demographic history and related number of meiosis and recombination events over generations.

## 2 Statistical methods and Experimental Procedures

Daghestan, which is located in the Northern Caucasus of Russia, contains numerous demographically ancient isolates comprising 26 indigenous ethnic groups. All these groups are anthropologically and genetically part of the broad European group of populations and have been in existence up to 10,000 years [17, 18]. For a map and demographic information of Daghestan see - http://titus.fkidg1.uni-frankfurt.de/didact/karten/kauk/kaukasn.htm. Apart from the advantage of having so many isolates within the same geographical region, these particular isolates have already been studied for population genetic diversity in collaboration with Drs. Harpending and Jorde (University of Utah, US) using numerous Alus, STRPs and mtDNA HVS1 [19, 20] (see http://harpend.dsl.xmission.com/daghestan_data for available genetic databases). The studies have shown that the indigenous population of Daghestan has extremely high genetic diversity overall, comparable to that of Africa, and that all highland populations exhibit restricted gene flow between neighboring villages resulting a low genetic diversity within them [20]. The rate of endogamy in these isolates is as a rule 87-90% and the average coefficient of inbreeding F in the isolates varies from 0.009 to 0.015, close to the worldwide maximum rate.

Updated regional psychiatric hospitals clinical data using DSM-IV criteria showed inter-isolate differences in types of schizophrenia: one of the isolates had a predominant aggregation of disorganized schizophrenia, while the other three had predominantly paranoid schizophrenia. Of particular importance to this study, the lifetime morbid risk for schizophrenia is particularly high in some of these isolates (up to 4.95%) [15]. Cases were ascertained via state medical records inspected during the 1994-2004 expeditions. All mentally ill patients were diagnosed during hospitalization in two Daghestan psychiatric hospitals. In our own expedition study all clinical diagnoses of affected pedigree members were re-checked using a Russian translation of the structured psychiatric interview, the Diagnostic Interview for Genetic Studies (DIGS) the Family Interview for Genetic Studies (FIGS) [21] based on DSM-IV criteria. Full details of these pedigrees and of diagnostic ascertainment are available elsewhere [15, 16, 22].

Inbreeding occurs when both father and mother are descended from one or more common ancestors. The degree of inbreeding is commonly expressed using Sewall Wright's formula and it is often known as Wrights Coefficient of Inbreeding F. For each individual, an average coefficient of inbreeding F is traditionally based on analysis of marriages over the previous three generations. This method evaluates a minimal rate of the population's F. Because we have ascertained extended pedigrees containing 350-700 subjects of 11-13 generations with limited number of ancestors and with high traditional rate of consanguineous marriages, we were able to estimate a real rate of the F for each pedigree. Our previous studies demonstrated that, on average, F for the general population is about

3-4 times lower compared to our multiplex pedigrees. For example, in a genetic isolate of ethnic Tindals, the population-average F was 0.009, while for the multiplex schizophrenia pedigree (650 members of 13 generations) the average F was 0.0315. Within such pedigrees, we calculated a simple index of consanguinity (CM): 1 = affected subjects are offspring from non-consanguineous marriages in most of generations, retrospectively; 2 = from consanguineous, including cousin, marriages. Because the genetic isolates in Daghestan (a) derive from different historical periods (e.g. highland ethnic groups are more ancient and isolated compared to foothill and lowland ethnic groups) and (b) differ in marriage traditions (e.g. highlanders have a higher rate of consanguineous, preferably a first-cousin marriage than other groups), in this study we included only remote highland genetic isolates with aggregation of schizophrenia.

## 3 Results

Of the 123 schizophrenia cases from the isolates studied, 70.7% are male, similar to the sex ratio found in epidemiology studies of schizophrenia. Average age of onset (mean, standard deviation) was 20.11 (4.5) years. Fifty eight of the 123 affected individuals were born in winter-spring months while 46 were born in summer-autumn. Unfortunately, the months of birth for 19 affected female were not available - ethnic highlanders are less inclined to register birth dates for female babies.

The affected subjects were divided into two groups according to season of birth. In keeping with our prediction, we found that the affected offspring of close consanguineous marriages were more likely to be born in winter/spring than summer/autumn: mean and standard deviation of the index of consanguinity CM = 1.74, 0.44 and 1.44, 0.51, respectively (Mann-Whitney U test: Z=3.31, $p < 0.000$). In addition, we found that winter-spring born schizophrenia patients had (a) earlier age of onset (mean and standard deviation 18.2 and 2.02) in comparison with summer-autumn born patients (21.83 and 4.65; Mann-Whitney U test: Z=3.33, $p = 0.0008$), and (b) were more likely to have prominent auditory hallucinations (94.7% of winter-spring born versus 71.4% of summer-autumn born patients, $\chi^2 = 6.62$, df-1, p=0.01).

In sum, the results obtained showed that offspring of consanguineous marriages have a significant excess of winter births, earlier age of onset and higher rate of auditory hallucination in comparison with group of affected with summer births.

## 4 Discussion

Our findings linking season of birth and inbreeding are in keeping with theories linking schizophrenia to developmental stability [14, 23]. Reduced allelic heterogeneity depletes the repertoire of genes/proteins available to the developing organism to cope with environmental perturbations. Deeply entrenched (canalized) features of development are able to buffer perturbations better than phylogeneticially recent features [24]. Thus, recently evolved features such as the neocortex, may be most vulnerable to developmental disruption ('last in, first to break').

The study has several important limitations. The sample size of the current study is small, and we lack month of birth data on all members of the pedigrees. Despite these caveats, it is interesting to note that a significant effect was detected in this small sample, in contrast to two studies with very large sample sizes [7, 8]. This may reflect the particular high level of traditional inbreeding and the resultant reduced genetic variability in the Daghestan isolates compared to the Scandinavian studies. We should also not assume that the yet-to-be-identified seasonally-fluctuating risk factor operates uniformly across diverse geographical, climatic and cultural gradients. Finally, it is also conceivable that the founders of these isolated populations may have propagated particular susceptibility genes for schizophrenia that resulted in vulnerability to seasonally-fluctuating environmental exposures.

Regardless of the underlying mechanisms, our study suggests that the season-of-birth effect may be more pronounced in individuals with reduced allelic heterogeneity and confirms the power of genetic isolates such as those in Daghestan to help fractionate gene-by-environmental susceptibility factor for schizophrenia.

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