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Extremely High Carrier Frequency of the GJB2 Splice Site IVS1+1G>A Mutation in Eastern Siberia is Comparable to the Carrier Frequency of the Sickle Cell Anemia in Africa

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Abstract

This study presents data on the carrier frequencies of IVS1+1 G>A mutation in *GJB2* gene, causing by autosomal recessive form of deafness among various ethno-geographical groups of Yakut population and in a random sample of the Yakuts. 350 DNA samples of hearing individuals from various ethno-geographical groups of Yakut population: Central (n=60), Vilyui (n=60), Northern (n=60) and random samples of Yakuts (n=170) were obtained from the DNA Bank of the Department of Molecular Genetics of Yakut Research Center of Complex Medical Problems of RAMS (Yakutsk, Russian Federation). The average carrier frequency of IVS1+1G>A mutation in Yakut population (n=350) detected was - 10.3%. Extremely high carrier frequency of the splice site IVS1+1G>A mutation in *GJB2* gene in the Yakut population is comparable to the carrier frequency of the sickle-cell anemia in Africa, which may indicate a possible selective advantage of carriers of this IVS1+1G>A mutation in subarctic climate

Keywords

Autosomal recessive deafness 1A, Eastern Siberia, Sickle-cell anemia, Africa

Introduction

Recently, it was found that Eastern Siberia, subarctic part of Russia, is the region with the most extensive accumulation of the IVS1+1G>A mutation in the world. As a result of founder effect in the unique Yakut population isolate (Asian background population) [1].

The extremely high carrier frequency of IVS1+1G>A mutation (11,7%) from six investigated populations (Yakuts, Dolgans, Evenks, Evens and Yukaghirs), has been found in Yakut population. The age of mutation was estimated to be approximately 800 years. These findings characterize Eastern Siberia as the region with the most extensive accumulation of IVS1+1G>A mutation in the world as a result of founder effect [1].

However, this extreme rate of carrier frequency could be due to the effect of the sample, as to calculate the carrier frequency was used by two ethno-geographical (Central and Vilyui) groups of Yakuts.

The aim of this study is to analyze of the carrier frequency of the IVS1+1G>A splice site mutation in the extended community sample of the Yakuts, involving northern ethno-geographical groups and random sample of the Yakuts.

Material and Methods

Sample

350 DNA samples of hearing individuals from various ethno-geographical groups of Yakut population: Central (n=60), Vilyui (n=60), Northern (n=60) and random samples of Yakuts (n=170) were obtained from the DNA Bank of the Department of Molecular Genetics of Yakut Research Center of Complex Medical Problems of RAMS (Yakutsk, Russian Federation).

The genomic DNA was extracted from lymphocytes of peripheral blood. Amplification of the coding exon 2 and flanking intronic regions was performed using the following primers: Cx26A-U/Cx26U-L (F 5^1-TCT-TTT-CCA-GAG-CAA-ACC-GC-3, R 5^1-GAC-ACG-AAG-ATC-AGC-TGC-AG-3^1) (285 bp) [2], Cx342U/Cx739-L (F 5^1-AGG-CCG-ACT-TTG-TCT-GCA-ACA-3^1, R 5^1-GTG-GGC-CGG-GAC-ACA-AAG-3^1) (415 bp), [11] 5^1-TAT-GTC-ATG-TAC-GAC-GGC-T-3^1, 5^1-TCT-AAC-AAC-TGG-GCA-ATG-C-3^1 (239 bp) [3]. Amplification of the noncoding exon 1 and flanking intronic regions was performed using primers Ex1-F/Ex1-R (F 5^1- CCG-GGA-AGC-TCT-GAG-GAC-3^1, R GCA-ACC-GCT-CTG-GGT-CTC-3^1) with the addition of 10% Betaine (Sigma, USA) [4]. The products of PCR were subject to direct sequencing using the same primers on ABI PRISM 3130XL (Applied Biosystems, USA).

Ethics approval

All testing procedures were conducted with a written informed consent signed by parents. This work was approved by the local bioethics committee at the Yakut Research Center of Complex Medical Problems of Siberian Branch of the Russian Academy of Medical Sciences (Yakutsk, Protocol 16, on April 16, 2009).

Table 1: Carrier frequency of the IVS1+1G>A mutation in *GJB2* gene in Yakut population (Eastern Siberia).

Population	Number of heterozygotes/ examined samples	Carrier frequency	95% CI	References
Yakuts (Central)	8/60	0,133	0,070-0,242	[1]
Yakuts (Vilyuy)	6/60	0,100	0,047-0,202	[1]
Yakuts (Northern)	5/60	0,083	0,037-0,181	This study
Yakuts (random sample)	17/170	0,100	0,064-0,154	This study
Yakuts (total)	36/350	0,103	0,075-0,139	This study

Results and Discussion

This study presents data on the carrier frequencies of IVS1+1G>A mutation in *GJB2* gene, causing by autosomal recessive form of deafness among various ethno-geographical groups of Yakut population and in a random sample of the Yakuts. In a sample of northern ethno-geographical groups of Yakuts were found 5/60 heterozygotes for the IVS1+1G>A splice site mutation in *GJB2* gene, carrier frequency - 8,3% (Table 1). The average carrier frequency of IVS1+1G>A mutation for all population samples Yakuts – 10,3%. In a random Yakut sample was found 17/170 heterozygotes, carrier frequency – 10,0% (Table 1).

The carrier frequency of IVS1+1G>A in the northern ethno-geographical group and in a random sample of the Yakuts are consistent with previously registered (11,7%) extremely high values of carrier frequency of IVS1+1G>A mutation in Yakut population [1]. The lower rate of mutation carriers in the northern group of the Yakuts (8,3%) compared with Vilyuy (10,0%) and Central (13,3%) groups is consistent with the results of haplotype analysis in which the most highest diversity of IVS1+1G>A haplotypes was found in the Central and Vilyuy subpopulations of Yakuts (excluding of the Yakutsk city), indicating that the expansion of mutant chromosomes on the territory of the Sakha Republic had started from the Lena-Amga interfluves area (Central district) [1]. Extremely high carrier frequency of the splice site mutation IVS1+1G>A in Yakuts (8,3-13,3%) living in Eastern Siberia in conditions of extreme continental climate can be explained not only by stochastic factors in the population dynamics and founder effect, shown earlier using different systems, such as STR-[1], and SNP-markers [4]. The selective advantage of heterozygous carriers of pathological alleles inherited autosomal-recessive disease known from classic example of sickle- cell anemia [5], common in Africa, South and South-East Asia (not uncommon in the Middle East and southern Europe) [6,7], as well as in the America [8]. Geographic stratification of the sickle-cell indicating an extremely high frequency of this disease near the equator [9], and evidence of the genetic adaptation of human populations to other common diseases in these regions - malaria [10]. The findings of the extremely high prevalence of mutations in the *GJB2* gene splice site in Eastern Siberia (in some sub-populations of the Yakuts to 13,3%) is comparable with the frequency of heterozygous carriers of sickle cell anemia in Africa (HbS allele), where the carrier frequency of HbS allele was higher than 10% registered only in certain areas, sub-Saharan Africa (Figure 1) [11]. Extreme values of the frequency of heterozygous carriers of a mutation IVS1+1G>A *GJB2* in the gene in Yakut population may indicate a possible selective advantage of carriers of this mutation in a subarctic climate [12-14].

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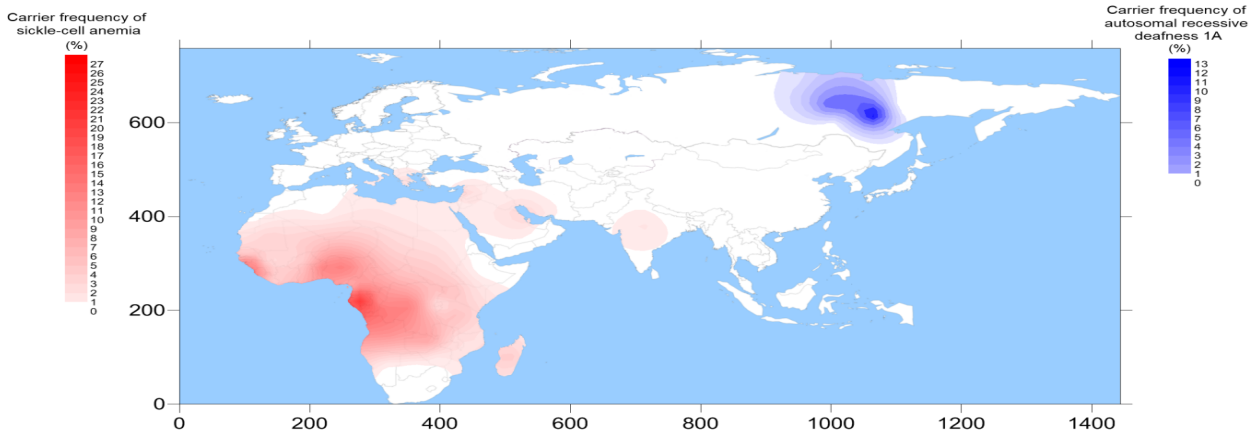

Figure 1: The spatial distribution of the carriers frequency of Autosomal recessive deafness 1A in Eastern Siberia [1], comparison with the carriers frequency of sickle-cell anemia in the equatorial region [11] (using with the program SURFER 8.0 Golden Software Ink).

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