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Is Spatial Distribution of the HIV-1-resistant CCR5Δ32 Allele Formed by Ecological Factors?

Oleg Balanovsky[1)], Elvira Pocheshkhova[2)], Andrey Pshenichnov[1)], Daria Solovieva[1)], Marina Kuznetsova[1)], Olga Voronko[1)], Michail Churnosov[3)], Olga Tegako[4)], Lubov Atramentova[5)], Maria Lavryashina[6)], Irina Evseeva[7)], Svetlana Borinska[8)], Margarita Boldyreva[9)], Nadezhda Dubova[10)] and Elena Balanovska[1)]

1) Research Centre for Medical Genetics, Moscow, Russia
2) Kuban State Medical Academy, Maikop, Russia
3) Belgorod State University, Belgorod, Russia
4) Institute of Fine Art, Ethnography and Folklore, National Academy of Sciencies, Minsk, Belorussia
5) Karazin Kharkov National University, Kharkov, Ukraine
6) Kemerovo State University, Kemerovo, Russia
7) Northern State Medical University, Arkhangelsk, Russia
8) Vavilov Institute for General Genetics, Moscow, Russia
9) Institute of Immunology of Russian ministry of Health, Moscow, Russia
10) Institute of Ethnology and Anthropology, Russian Academy of Sciences, Moscow, Russia

Abstract It has been proposed that the Δ32 mutation in the chemokine receptor gene, inducing resistance to HIV-1 and, probably, to other virus infections, has undergone selection in historical times. The frequency of this mutant allele has changed rapidly both in time (during the last two millennia) and in space (across Eurasia). We compiled a global database on Δ32 allele frequencies in 300 populations. Nearly 10 percent of them are our data on 35 East European populations analyzed here for the first time. A detailed map of Δ32 frequency distribution was constructed and statistically analysed. We found a linearly decreasing trend with a maximum in areas surrounding the Baltic and White seas. Significant correlations with ground surface temperature were revealed. However, compared with our previous results, these correlations diminished, indicating that the influence of climate on Δ32 distribution was, if anything at all, indirect. The proposed scenario includes: i) arise and initial spread of the mutation among Uralic-speaking populations; ii) a frequency increase in northeastern Europe as a result of selection and/or genetic drift; iii) secondary spread (with selection continued) due to gene flow and the migrations of northern Europeans across the globe. *J Physiol Anthropol Appl Human Sci 24(4): 375–382, 2005* http://www.jstage.jst.go.jp/browse/jpa
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Introduction

In the last decade, a mutation in the chemokine receptor gene has attracted special attention and has been studied intensively. The reason is resistance to HIV-1 infection induced by this mutation: mutant allele homozygotes show almost complete immunity against HIV-1 infection. Molecular mechanisms have been well studied (Dragic et al., 1996; Dean et al., 1996; Samson et al., 1996). The HIV-1 virus uses a chemokine receptor to invade the cell. The Δ32 mutation (deletion of 32 bp) results in the lack of a receptor on the cell surface, which alters infection. While homozygotes have a high immunity to HIV-1, in heterozygotes infection still occurs but heterozygotic patients reveal a slowed progression towards AIDS, which is delayed for an additional 2 or 3 years (Zimmerman et al., 1997; Galvani and Novembre, 2005). Besides Δ32, other mutations were also found in the CCR5 gene and in other genes of the chemokine receptor gene family (CCR2, SDF1 and others). Some of these mutations reduce infection rate, but their impact is substantially less than that of CCR5Δ32 (O'Brien and Moore, 2000).

The Δ32 allele is presented mainly in Europeans (10% on average), with frequency decreasing from north to south within Europe. Outside Europe, the mutation can be found at low frequencies in neighboring regions (North Africa, Middle East, Central Asia), but is absent in Sub-Saharan Africa, East and South-East Asia and in indigenous populations of the Americas (Martinson et al., 1997, 2000). Such a plain pattern

is unusual for genes in human populations; and it became really striking when data on mutation age appeared. Based on the diversity of microsatellites linked with the CCR5 gene, Libert and coauthors (Libert et al., 1998) showed that the Δ32 mutation arose about 2000 years before the present. The results of another research group (Stephens et al., 1998) gave an even shorter age (700 years BP). However, 95% confidence intervals in both cases cover a few millennia. Nevertheless, there is no doubt that the mutation has a single and recent origin in Europe. Therefore, the frequency of this mutation in the overall European population has increased from zero to 10% within a relatively short period of time. According to principles of population genetics, this drastic frequency increase within such a large population is not likely to be explained by random genetic drift (see the review of Galvani and Novembre, 2005). Therefore, the presence of positive selection should be considered; this general impression was confirmed by applying a mathematical model (Stephens et al., 1998).

The AIDS pandemic is too recent to change allele frequencies. Factors of historical selection should therefore be pointed out. Based on the fact that, besides HIV-1, chemokine receptors interact with other pathogens, it was supposed that the Δ32 mutation might induce resistance to a set of infectious diseases. The plague hypothesis (Stephens et al., 1998) suggests that the mutation frequency increased due to a plague epidemic. It is based on the fact that an extremely high percentage of the population was killed by the plague in medieval Europe, which means significant selection in favor of any inherited plague-resistance-inducing factor. Though this hypothesis is widely accepted, it has not been directly proved. Moreover, it was recently shown that mutations in the CCR5 gene do not affect the clinical course of plague disease in rats (Mecsas et al., 2004). As suggested by Galvani and Slatkin, it is more likely that smallpox was the disease which influenced ΔCCR5 frequency (Galvani and Slatkin, 2003). Though smallpox did not cause such a dramatic pandemic, it affected Europeans permanently. Also worth mentioning is the fact that most of the victims were children, which is supposed to change allele frequency over generations most effectively. But again, this hypothesis is based not on clinical or molecular genetic data but on statistical analisys of the possible impact of a smallpox epidemic.

Besides disease-related hypotheses, some other efforts have been undertaken to explain the Δ32 spatial pattern. Since some factors, such as climate, provide selective pressure that differs across the globe, the possible impact of climate has been studied and a strong negative correlation between Δ32 mutation and a set of temperature factors has been revealed (Balanovsky et al., 2001; Limborska et al., 2002).

Finally, the Viking hypothesis of Lucotte postulated that mutation arose in Scandinavia and spread over Europe during the "Viking age", when Norse ships reached the distant coasts of Europe (Lucotte, 2001). Generally, the factors which caused the spread of the Δ32 mutation are not fully understood so far (Galvani and Novembre, 2005).

To define the geographic distribution of the Δ32 mutation more precisely we analyzed its frequency in a sample of 35 populations covering East Europe and West Siberia. Having combined our results with data from published sources, we compiled a world-wide database on Δ32 frequencies, which is presented in this paper in the form of a map of mutation spread. Statistical analysis of the mutation distribution aims to evaluate the possible impact of climatic and geographical factors. Considering our previous results, here we present how these correlations change when increasing the dataset.

Materials and Methods

We compiled a global database on Δ32 frequency distribution using data from 51 published sources, with a total of 36,436 samples from 264 populations. In addition, we typed the CCR5Δ32 mutation in 35 populations from Russia, Byelorussia, Ukraine and Moldova (3,784 samples; data are analyzed here for the first time). All DNA samples analyzed were obtained with the informed consent of the indigenous inhabitants originating from the given population with at least three generations of ancestors being local residents. Having built up the global database, we restrict the range of our analysis to data on populations of Eurasia and Africa, since the mutation is virtually absent in populations of other continents. Studied populations with sample sizes lower that 30 were excluded or pooled. Ultimately, data on 31,854 samples from 185 populations is analyzed in this study. Population descriptions and all references are available on our website www.genofond.ru or by request.

Maps of Δ32 frequency distribution were constructed using a GGMAG cartographic package (Koshel and Musin, 1991; Balanovska et al., 1994a, b; Balanovska and Nurbaev, 1995). The digital model of spatial distribution of Δ32 was created by an inverted sixth-degree distance interpolation procedure. The digital model, based on a 125×80 regular grid, contains an interpolated value of the frequency in each of its nodes. The interpolated values were calculated from the initial data points, which correspond to the studied populations. For graphic representation of the digital model the range of trait values was split into regular intervals. Areas being too far from any of the studied populations were visualized by building up a reliability map, which shows the area of reliable interpolation (Nurbaev and Balanovska, 1998). Unreliable areas are presented on the map as "dotted spots" and excluded from the analysis. Statistical analysis of maps (trend modeling, calculating correlation between maps) was carried out with the use of digital models in a MAPSTAT package that we ourselves developed. Geographic distances between studied populations were calculated with the use of geographic coordinates by the *DJ program* built up by Yuri Seryogin (freely available at web http://www.genofond.ru). The correlation coefficient between geographic distances and mutation frequency was calculated with the use of Statistica 6.0 software.

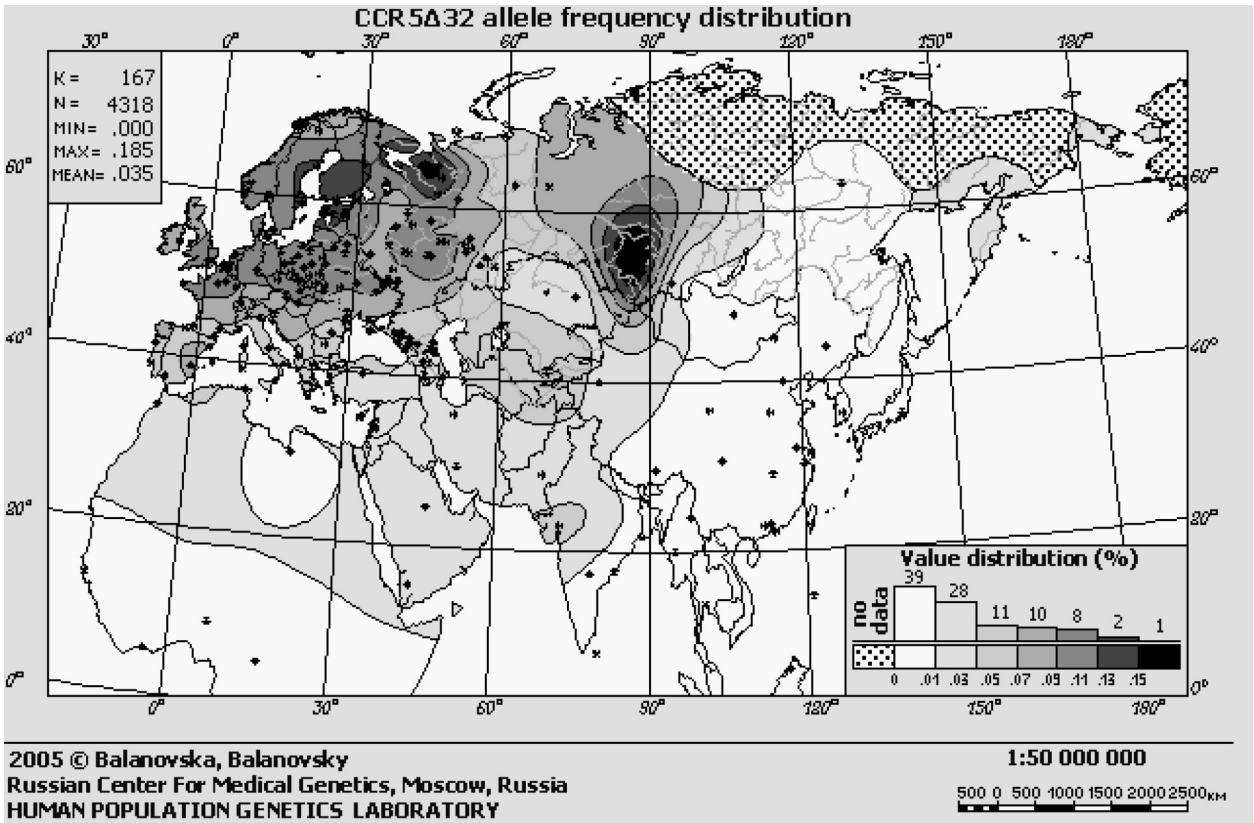

Fig. 1 Map of frequency distribution of the Δ32 allele in Eurasia.

Climatic data on spatial distribution of atmospheric pressure, temperature and precipitation were collected for the first half of the 20th century (before 1930), before global warming took effect. Data on atmospheric pressure is taken from the website of the Climatic Research Unit, University of East Anglia (http://www.cru.uea.ac.uk/cru/data/pressure.htm). Data on January and July ground surface temperature and overall annual precipitation came from the Grand Soviet World Atlas.

Results

The frequency distribution of the CCR5Δ32 mutation in Eurasia is represented on the map (Fig. 1). The areas with unreliable results of interpolation are indicated by dotted white areas. Compared with the maps published before (Martinson et al., 1997; Libert et al., 1998; Limborska et al., 2002; Lucotte and Dieterlen, 2003) more details can now be revealed, as the dataset has increased over the last years. In order to reveal the overall trans-Eurasian pattern, Fig. 1 represents the smoothed map (according to the technique described by Balanovska and Nurbaev, 1995). The frequency of Δ32 is highest in the areas surrounding the Baltic Sea. From this maximum, the frequency decreases gradually in all directions across Europe. This trend continues outside of Europe, since the frequency in North Africa is higher than in Central-South Africa and the frequency in West Asia is higher that that in East Asia.

In order to represent frequency distribution in a clearer and more simplified manner, we use the cartographic method known as modeling by Chebishev's polynoms (Berlandt, 1986; Balanovska and Nurbaev, 1995). This method modifies the observed distribution according to the hypothesis that the geographic variation is clinal (first degree of the polynomial) or variation represents diffusion from one center (second degree polynomial).

Maps on Fig. 2 show modified distribution of Δ32 mutation according to these two hypotheses. Clinal variation can be sometimes attributed to influence of climate or other selection factosr, while diffusion from one center is more likely to be in congruence with the spread of the mutation from the place of its origin. Therefore, maps on Fig. 2 show two possible ways of explaining the geographic distribution of Δ32. The initial map (Fig. 1) has a strong correlation with both maps in Fig. 2: the correlation coefficients are 0.77 with the "clinal" map, and 0.78 with the "diffusion from one center" map.

Figure 3 represents the detailed (non-smoothed) map of mutation spread in Europe. More precisely, the area of highest frequency lies between the Baltic and the White Seas. Frequency above 15% can be observed in populations of central Sweden, West Estonia, Finland and Northern Russia (Fig 3). No data are available on the Karelians but an interpolation map predicts high frequencies of Δ32 mutation in

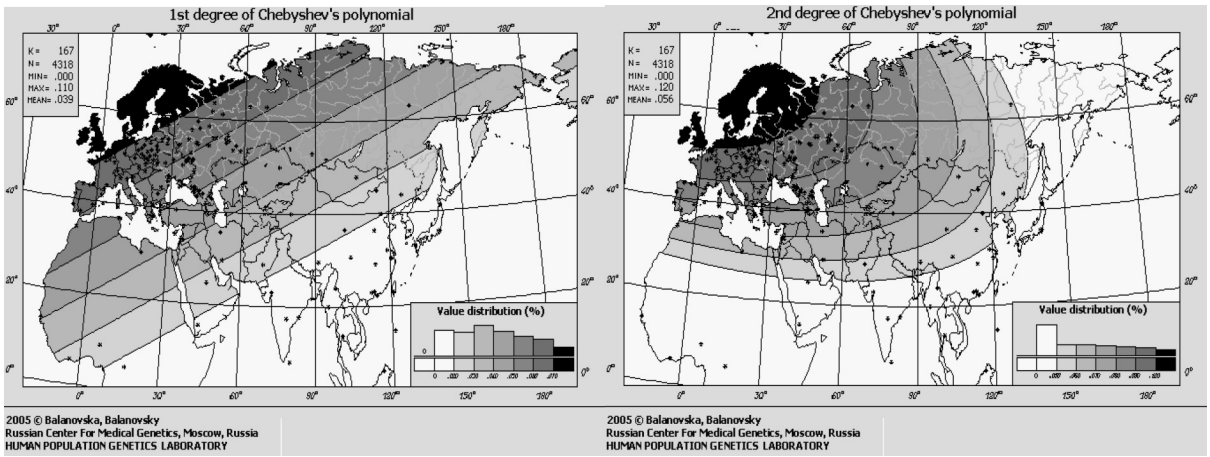

Fig. 2 Modeling the pattern of $\Delta 32$ distribution by 1st (on the left) and 2nd (on the right) degrees of the Chebyshev polynomial.

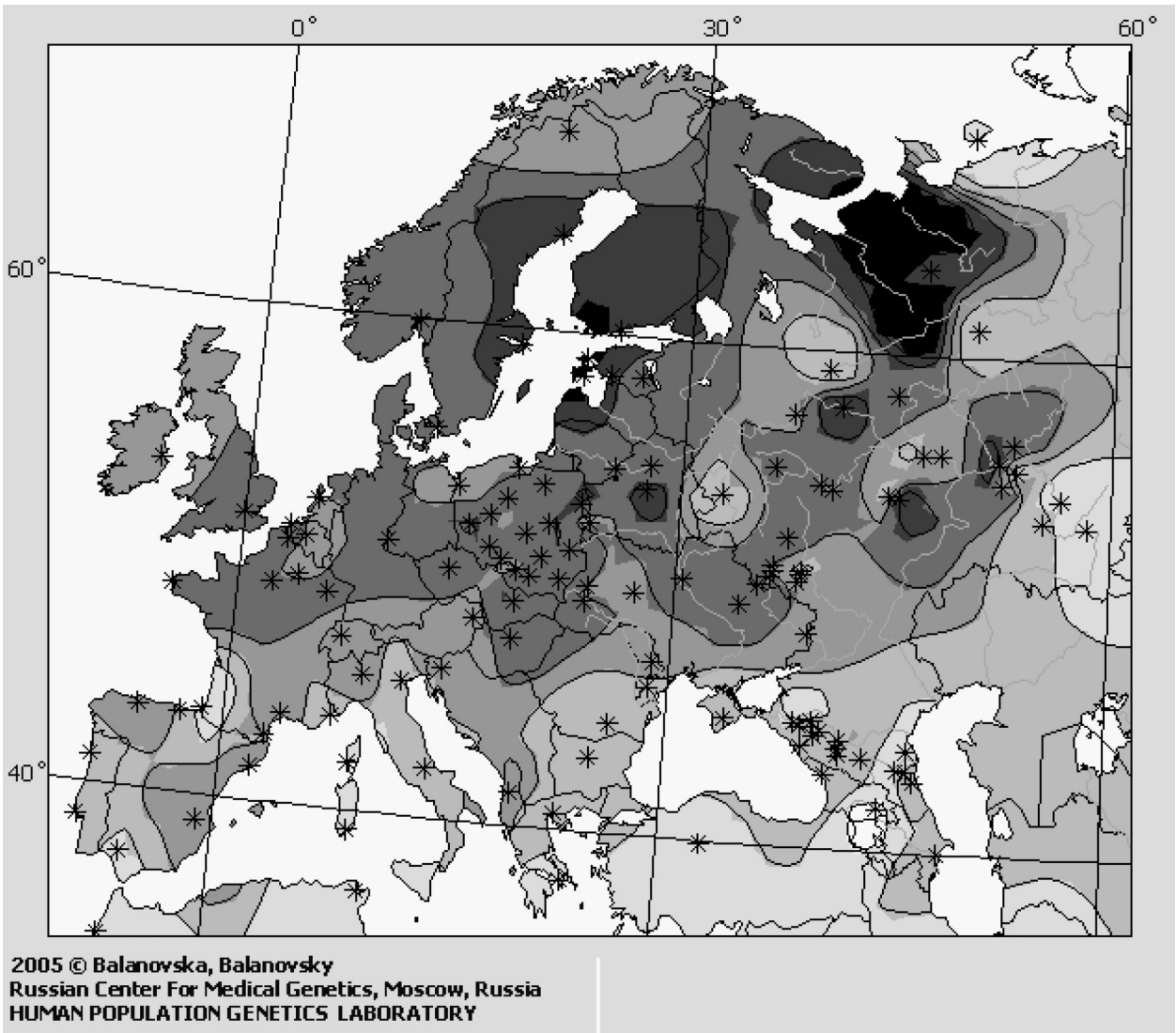

Fig. 3 Detailed map of frequency distribution of the $\Delta 32$ allele in Europe.

this area. In Western Europe, the regular latitudinal trend of mutation distribution can be pointed out, which is interrupted by a lower frequency in the Basque region In Eastern Europe, the pattern is more complicated. Frequency decreases both southward to Ukraine and eastward to the Trans-Ural area. Rapid change in frequencies when entering the Ural region is quite a common picture for many other genes (Rychkov and Balanovska, 1992; Balanovska and Nurbaev, 1995; Balanovska and Rychkov, 1997), which represents significant population genetic differences between Eastern European and Siberian populations; here the Δ32 mutation follows the common pattern of a gene pool. But the regular frequency trend in Eastern Europe and neighboring areas is broken in three points. First, the frequency in west-central Russia (the Smolensk and Vologda regions of Russia) is lower that that in all adjacent populations. Second, the frequency in Tatars (Middle Urals) is much higher than in the vicinity; three Tatar populations show frequencies of 12%, 12% and 16% (Stephens et al., 1998; Limborska et al., 2002). The third is the local maximum in Shorians (south-west Siberia, see Fig. 1). Also there are controversial data on Mordvinians: 16% and 6% in two populations studied by different authors (Libert et al., 1998; Limborska et al., 2002). In similar manner, there are contrasting data on Khants: 12% and 3% (Yudin et al., 1998; Osier et al., 2002). So, the decreasing trend across Europe and Eurasia as a whole is interrupted in these five-to-ten populations, while the rest of the 180 populations follow this trend more or less.

The role of the climate in shaping the geography of human genes is often emphasized (Cavalli-Sforza et al., 1994 and references therein). We performed a formal correlation analysis between the principal climatic factors (temperature, precipitation, pressure) and Δ32 frequency (Table 1).

The correlation with temperature is higher than that with other parameters, in congruence with our previous results (Limborska et al., 2002). However, no remarkable correlation can be pointed out. On the contrary, increased dataset results in lower correlations with temperature. To test the second hypothesis (random diffusion across Europe caused by marriage migrations between neighboring populations) we obtain a correlation between frequencies in studied populations and geographic distance from the probable place of origin. We chose the zone of Baltic frequency maximum as the most probable place of mutation origin. Inside this zone, Saaremaa island has been arbitrarily chosen (as it is located in the middle of this area and the Saaremaa population has an extremely high frequency of Δ32). Figure 4 shows the correlation plot; the correlation coefficient is −0.75.

Table 1 Correlation between frequency of the CCR5Δ32 allele and climatic parameters

Climatic parameters	Coefficients of rank-order Spearman correlation between Δ32 and climatic parameters	
	This study	Limborska, and Balanovsky et al., 2002
Temperature, January	−0.33	−0.50
Temperature, July	−0.29	−0.64
Precipitation	−0.14	−0.07
Pressure, average annual	0.08	
Pressure, January	−0.18	
Pressure, February	−0.07	
Pressure, March	−0.12	
Pressure, April	0.11	
Pressure, May	0.57	
Pressure, June	0.53	
Pressure, July	0.47	
Pressure, August	0.47	
Pressure, September	0.25	
Pressure, October	0.00	
Pressure, November	−0.11	
Pressure, December	−0.18	
Annual radiation balance (kcal/cm^2 per year)		−0.66
Total amount of insolation (kcal/cm^2 per year)		−0.66

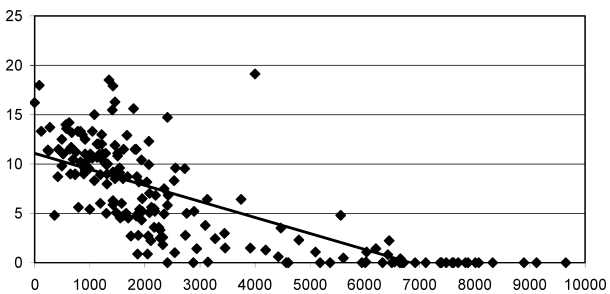

Fig. 4 Correlation plot between frequency of the CCR5Δ32 allele and distance from Saaremaa island. Abscissa: distance, km; ordinate: percentage of frequency; approximation line is presented.

Discussion

Compared with the maps published before (Martinson et al., 1997; Libert et al., 1998; Limborska et al., 2002; Lucotte and Dieterlen, 2003) more details can now be revealed in the geographic distrubution of the Δ32 mutation, according to the increasing dataset over the last years. The general pattern is a decreasing frequency from northeastern Europe in all directions. The pattern is interrupted by a local minimum (in Basque region) and local maxima (in Tatars, in Shorians, and questionable maxima in Mordvinians and Khants). The highest frequencies are observed in two Finno-Ugric populations—Estonians and Finns, and northern Russians, the last populations being supposed to have a strong Finno-Ugric background (Bunak, 1964). Though the Shorian language belongs to the Turkic group, Samodian-speaking populations played a significant role in the ethnogenesis of Shorians. Similarly, in Tatars, which have a complicated population history, there is undoubtedly a Finno-Ugric background. Thus, all populations with a high frequency of Δ32 belong to the

Uralic language family or have had a significant admixture with Uralic-speaking populations (including those which belong to the Finnic, Ugric and Samodian branches of the Uralic family).

Lucotte (Lucotte, 2001) supposed that it was Vikings who disseminated Δ32 across Europe from its place of origin in Scandinavia. Our results allow us to suppose that the Scandinavians themselves took the mutation from their eastern Finnic-speaking neighbors. Indeed, Δ32 is more frequent to the East than to the West of the Baltic Sea. Moreover, we obtain a high negative correlation between Δ32 frequency and distance from the eastern Baltic coast. This correlation is better explained by random diffusion "outward by the ordinary background level of human dispersal in Europe, without requiring a contribution from long-range migrations by Vikings" (Galviani and Novembre, 2005). It is possible that Viking migrations played their role in mutation spread in Western Europe, but for eastern areas other mechanisms should be inferred to explain the more complicated pattern of mutation spread.

In addition to these qualitative speculations, the quantitative results on correlation between Δ32 frequency and a set of parameters of environment can be applied (Table 1). Generally we consider this correlation approach to be useful for rejecting hypotheses rather than for proving them.

Newly attained data on CCR5 distrubution does not increase correlations with climate, compared with our previous results (Limborska et al., 2002). On the contrary, these correlations decrease. This does not support a straight connection of Δ32 distribution with studied climatic parameters. Because correlations with climate are still significant, we suppose that the influence of climate can be mediated by other selective factors (such as more a serious clinical course of plague in a cold climate). In general, we propose the following scenario for forming the modern Δ32 spatial pattern.

1. The mutation occurs in an Uralic population and is spread in neighboring areas due to gene flow. The circle of modern populations having the highest Δ32 frequencies belongs to the area of the Uralic linguistic family and in particular to its Finnic branch. For this reason we consider that the Δ32 mutation occurred in some Uralic population and then spread at low frequencies in quite a large area of Uralic and related populations. No exact localization can be found, to the best of our knowledge.

2. The raising of Δ32 frequency in northeastern Europe (in areas surrounding the Baltic and White Seas) due to selection and/or drift. Independently, frequency increases in Western Siberia but high frequencies there are still to be confirmed by studying the surrounding populations. If the West Siberian maximum is caused by drift, raising in the Baltic region can be better explained by selection, though the selection factor is still unknown.

3. The spread of Δ32 at high frequencies from the Baltic region to neighboring populations due to migrations and gene flow. The map of Chebishev's 2nd degree polynomial (having a high correlation with the observed distribution of Δ32, Fig. 2) illustrates this model. Selection factors such as a pandemic widespread in Eurasia could also support the mutation spread. The modern pattern of Δ32 distrubution was finally shaped at this step.

Based on the proposed scenario, some perspectives for future research can be mentioned. The age of Δ32 indicates that there was a relatively short period of time for the frequency increasing. The nature (drift or selection) of the factor which increased the Δ32 frequency at step 2 is the main question. Drift should have affected other genes, while selection affects few particular genes. Since applying data on other genes we may distinguish these possibilities. Concerning selection, the most promising possible factors are epidemics, which may give a high selective pressure rise of Δ32 frequency in a population that already had this allele due to gene flow. Since the mutation increase did occur in areas surrounding the Baltic and White Seas, the search of the factors can be restricted to this part of Europe. Another important question is whether Δ32 is really widespread in Western Siberia. If so, we are facing two distinct regions having high frequencies of the CCR5Δ32 allele, a fact which still has to be explained.

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References

Balanovska EV, Nurbaev SD, Rychkov YuG (1994a) Computer technology of the genogeographic study of the gene pool. I. Statistical information from the genogeographic map. Genetika 30: 951–965 [*In Russian*]

Balanovska EV, Nurbaev SD, Rychkov YuG (1994b) Computer technology for genetic-geographical study of the gene pool. II. Statistical transformation of maps. Genetika 30: 1538–1555 [*In Russian*]

Balanovska EV, Nurbaev SD (1995) Computer technology of gene geographic analysis of a gene pool: III. Derivation of trend surfaces. Genetika 31: 536–559 [*In Russian*]

Balanovska EV, Rychkov YuG (1997) Human gene pool at the stages of settling the oicumene: adaptive evolution and gene geography. In Man is settling the Earth. Global dispersal of hominids. Moscow, 228–297 [*In Russian*]

Balanovsky OP, Shadrina MI, Limborska SA, Balanovska EV (2001) *Global distribution of the CCR5Δ32 mutation, causing resistance to HIV-1 infection: does it depend on climate, or history, or diseases?* (Materials of the first

international young medics' conference "Young doctors on the threshold of the third millennium", Yerevan, Armenia) [*In Russian*]

Berlandt AM (1986) *The image of space: map and information*. Mysl', Moscow [*In Russian*]

Bunak VV (ed.) (1965) *Origin and ethnic history of Russian people: anthropological data*. Nauka, Moscow, 414 [*In Russian*]

Cavalli-Sforza LL, Menozzi P, Piazza A (1994) History and Geography of Human Genes. Princeton University Press, Princeton, 1069

Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghott E, Gomperts E, Donfield S, Vlahov D, Kaslow R, Saah A, Rinaldo C, Detels R, Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study, O'Brien SJ (1996) Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CCR5 structural gene. Science 273: 1856–1862

Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA (1996) HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature 381: 667–673

Galvani AP, Novembre J (2005) The evolutionary history of the CCR5-D32 HIV-resistance mutation. Microbes and Infection 7: 302–309

Galvani AP, Slatkin MW (2003) Evaluating plague and smallpox as historical selective pressures for the CCR5Δ32HIV-resistance allele. Proc Natl Acad Sci USA 100: 15276–15279

Grand Soviet World Atlas (1937) 1 i 2 kartograficheskie fabriki GUGSK NKVD USSR vol. 1, Moscow [*In Russian*]

Koshel SM, Musin OR (1991) Digital models for studying environmental change. Proc Int Symp on Environmental Change and GIS (INSEG'91). Asashikama Japan 2: 321–327

Libert F, Cochaux P, Beckman G, Samson M, Aksenova M, Cao A, Czeizel A, Claustres M, Rua C, Ferrari M, Ferrec C, Glover G, Grinde B, Guran S, Kucinskas V, Lavinha J, Mercier B, Ogur G, Peltonen L, Rosatelli C, Schwartz M, Spitsyn V, Timar L, Beckman L, Parmentier M, Vassart G (1998) The D ccr5 mutation conferring protection against HIV-1 in Caucasian populations has a single and recent origin in Northeastern Europe. Hum Mol Genet 7: 399–406

Limborska SA, Balanovsky OP, Balanovskaya EV, Slominsky PA, Schadrina MI, Livshits LA, Kravchenko SA, Pampuha VM, Khusnutdinova EK, Spitsyn VA (2002) Analysis of CCR5Δ32 Geographic Distribution and Its Correlation with Some Climatic and Geographic Factors. Hum Hered 53: 49–54

Lucotte G, Dieterlen F (2003) More about the Viking hypothesis of origin of the Δ32 mutation in the CCR5 gene conferring resistance to HIV-1 infection. Infect Genet Evol 3: 293–295

Lucotte G (2001) Distribution of the CCR5 gene 32-bp deletion in West Europe. A hypothesis about the possible dispersion of the mutation by the Vikings in historical times. Hum Immunol 62: 933–936

Martinson JJ, Chapman NH, Rees DC, Liu YT, Clegg JB (1997) Global distribution of the CCR5 gene 32-basepair deletion. Nat Genet 16: 100–103

Martinson JJ, Hong L, Karanicolas R, Moore JP, Kostrikis LG (2000) Global distribution of the CCR2-64I/CCR5-59653T HIV-1 disease-protective haplotype. AIDS 14: 483–489

Mecsas J, Franklin G, Kuziel WA, Brubaker RR, Falkow S, Mosier DE (2004) Evolutionary genetics: CCR5 mutation and plague protection. Nature 12(427-6975): 606

Nurbaev SD, Balanovskaia EV (1998) Computer technology for genogenographic study of the gene pool. V. Evaluation of the reliability of maps. Genetika 34: 825–838 [*In Russian*]

O'Brien SJ, Moore JP (2000) The effect of genetic variation in chemokines and their receptors on HIV transmission and progression to AIDS. Immunol Rev 177: 99–111

Osier MV, Cheung KH, Kidd JR, Pakstis AJ, Miller PL, Kidd KK (2002) ALFRED: an allele frequency database for Anthropology. Am J Phys Anthropol 119: 77–83

Rychkov YuG, Balanovska EV (1992) Gene pool and gene geography of the population of USSR. Genetika 28: 52–75 [*In Russian*]

Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M (1996) Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 382: 722–725

Serbenyk SN, Koshel SM, Musin OR (1990) Methods for modeling the geofields from data in irregular points. Geodesy and Cartography 11: 31–35 [*In Russian*]

Stephens JC, Reich DE, Goldstein DB, Shin HD, Smith MW, Carrington M, Winkler C, Huttley G, Allikmets R, Schriml L, Gerrard B, Malasky M, Ramos MD, Morlot S, Tzetis M, Oddoux C, Giovine FS, Nasioulas G, Chandler D, Aseev M, Hanson M, Kalaydjieva L, Glavac D, Gasparini P, Kanavakis E, Claustres M, Kambouris M, Ostrer H, Duff G, Baranov V, Sibul H, Metspalu A, Goldman D, Martin N, Duffy D, Schmidtke J, Estivill X, O'Brien SJ, Dean M (1998) Dating the origin of the CCR5-D32 AIDS-resistance allele by the coalescence of haplotypes. Am J Hum Genet 62: 1507–1515

Zimmerman PA, Buckler-White A, Alkhatib G, Spalding T, Kubofcik J, Combadiere C, Weissman D, Cohen O, Rubbert A, Lam G, Vaccarezza M, Kennedy PE, Kumaraswami V, Giorgi JV, Detels R, Hunter J, Chopek M, Berger EA, Fauci AS, Nutman TB, Murphy PM (1997) Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. Mol Med J 3: 23–36

Yudin NS, Vinogradov SV, Potapova TA, Naykova TM, Sitnikova VV, Kulikov IV, Khasnulin VI, Konchuk C, Vloschinskii PE, Ivanov SV, Kobzev VF, Romaschenko AG, Voevoda MI (1998) Distribution of CCR5Δ32 gene deletion across the Russian part of Eurasia. Hum Genet 102: 695–698

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Correspondence to: Oleg Balanovsky, Research Centre for Medical Genetics, 115458 Moskvorechie st, 1, Moscow, Russia
Phone: +7–095–111–8280
Fax: +7–095–324–0702
e-mail: balanovsky@inbox.ru