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MULTIGENETIC LANDSCAPE OF THE CENTRAL ASIA

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ABSTRACT

Of a dissertation on the scientific degree competition of the doctor of sciences in medicine

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Dissertation can be reviewed at the information-resource centre of the Institute of Immunology, AS RUz.

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Scientific secretary
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GENERAL CHARACTERISTIC OF WORK

Actuality. Researches of human population genomic variety and scenarios of its genetic pool formation are one of perspective directions of modern genetics. Prompt progress in this field has allowed defining the basic routes of continents settlement. However the information about Central Asian populations (CA) even on «classical» genetic markers has accidental, fragmentary character, and requires additional large-scale investigations. Besides, according to historical, archeological, paleontological and some anthropogenetic studies, given region was playing certain role in ancient moving of modern human ancestors throughout Eurasian continent. Therefore it is extremely important to summarize and perform complex assessment of new and collected data on CA population as practically there are no multivariate analyses studies of given region as a complex population system.

In studies of human population genetic structure are usually used various approaches allowing understanding concept of populations subdivision and character of genetic relationships between them. Among these techniques the prominent place belongs to approaches based on an assessment of genetic distances between populations with their subsequent analysis by multivariate statistics methods. For even more compelling picture of the relationships between the populations on tree diagram we composed «the genetic landscape» of area, where the description of population genetic structure is presented by equally spaced figures consistently consolidating populations according to their genetic distances from each other and thus creating a genetic landscape. This approach is not only a tool for elementary population boundary detection, but also can be effectively used for identification of borders and sizes of population as naturalistic unit.

Study of genomic diversity is important not only to address questions of origin and genetic history of different ethnic groups, but is also the basis for molecular epidemiology of hereditary and multifactor diseases. Each region is characterized by a specific set of common genetically determined diseases. To understand the causes of the prevalence of disease in different regions, and to develop approaches to their early DNA diagnosis and effective prevention, initially it is necessary to conduct population-based studies, which determine the development of the disease.

Relationship of the thesis with the thematic plans of the SRW. CST №FM4-157 «Molecular polymorphism of Y-chromosome and mtDNA at the original Central-Asian population in the territory of Uzbekistan»; GCST №98-00 «Molecular identification of hepatitis B virus in Uzbekistan»; FPR AS RUz №105-02 «New genotype of hepatitis B virus in Uzbekistan»; FA-F11-T111: «Development of algorithms of type II diabetes comprehensive early diagnostics»; the Uzbek-Japanese collaboration «Molecular Epidemiology of Viral Hepatitis in

Uzbekistan» Grant in Aid for Scientific Research and Viral Hepatitis Research Foundation of Japan; French-Uzbek collaboration in the frame of the program «Origin of man, language and languages» of the European Science Foundation (ESF) EUROCORES program; French-Uzbek collaboration under the project "Deciphering the complex evolution of genes involved in human adaptation to diet", ESF; Uzbek-German collaboration «Diversity of *Helicobacter pylori* in human populations of Central Asia» WV Foundation.

Study Purposes.

Implement a comprehensive description of the structure of indigenous CA populations genetic pool, examine demographic, phylogenetic and evolutionary features of CA populations through the analysis of genetic variety of mtDNA, Y-chromosomal, autosomal, X-chromosomal microsatellites and immunogenetic variants of *Helicobacter pylori (H.pylori)* and hepatitis B virus (*HBV*).

Study Objective:

1. Specification of immunogenetic variants of *H.pylori* and *HBV*, allocated at the patients in CA region, with the subsequent comparative phylogenetic analysis of *H.pylori* and *HBV* regional versions with those in other regions of the world.

2. Examination of genetic variety and degree of genetic differentiation of CA populations according to classical population-genetic objects – polymorphisms of mtDNA, Y-chromosomal, autosomal and X- chromosomal STRs.

3. Assessment of the Western and East-Eurasian lines of population inheritance contribution to CA populations' genetic pool at regional, ethnic, sub-ethnic levels and in a level of elementary populations.

4. Reviewing of character of regional populations relationships by genetic variety of mtDNA, autosomal, X-chromosomal, Y-chromosomal STRs markers in view of ethnographic, social and linguistic data.

5. Evaluation of sex-specific genetic structure and the social organization according to polymorphisms of mtDNA, autosomal, X-chromosomal, Y-chromosomal markers in the region.

6. Determination of ancient ways of migrations and scripts of formation of CA populations according to mtDNA, autosomal, X-chromosomal, Y-chromosomal STRs markers and immunogenetic variants of *H.pylori* and *HBV*.

7. Evaluation of ethnogenetic position of studied CA populations in the system of genetic pools of Eurasia and the world in general through comparative analysis of all the studied population-genetic parameters.

Objects of research: 1874 individual from 26 Turkic speaking and Indo-Iranian populations of 6 CA ethnic groups: Uzbeks, Karakalpaks, Tadjiks, Kazakhs, Turkmens, and Kirghiz.

Research approaches: clinical-instrumental, bacteriological, immune –and molecular-genetic and wide range of statistical approaches of the analysis.

Main principals of thesis work.

1. Helicobacter pylori is the high informative system for the analysis of migration history of *Homo sapiens*. *H.pylori* from the territory of Central Asia is similar to Western European isolates. Close relationship between Tajik, Uzbek and Iranian isolates strains from the North of Iran was established. Kyrgyz isolates appeared to be closer to populations from the territory of Siberia.

2. The phylogenetic analysis of the central-Asian *HBV*-genotypes with variants from other parts of the world showed a close relationship of CA-isolates with variants of the virus in Europe, the Middle East and Africa. Prevailing were the 'Western Eurasian' immunogenotypic variants of *HBV*.

3. Ethno-social structure of CA genetic pool. The ethnicity of Turkic groups of Central Asia is the result of structured social system building genetic boundaries with other ethnic groups, and is not a result of the common genetic ancestor - founder. Nomadic Turkic ethnic groups, unlike the settled farmers have shown expressed patrilineal organization. The leading factor shaping the genetic variety in the Central Asia is the language accessory.

4. Sex-specific demography of CA. All the studied genetic systems showed that patrilineal nomads, unlike bilinear farmers have strong sex-specific genetic structure. Demographic history of male part of nomadic populations has structure of linear division of descending groups (the population shares on tribes, tribes on clans, clans on lineage) without the subsequent mixtures between descending groups. The female part of populations in each generation was exposed to massive genetic injections at the level of lineage or clans.

5. Ancient expansion of *Homo sapiens* in Eurasia. Was established a key role of CA in formations of all Eurasian ethnoses in antiquity. Analyses of uniparental systems has established authentic demographic expansion Eurasian *Homo sapiens* from East Eurasia (from the Far East and-or from CA) to the Europe in Paleolith and strong growth of populations in Neolithic age.

6. Multigenetic landscape of CA is characterized by unique high level of genetic diversity. CA occupies intermediate position between genetic pools of the Europe and Asia: two basic components were established – so-called West-Eurasian (dominating) and East-Eurasian, the second component rather recent and first more ancient and occupied CA since old time. *The Uzbek populations* are located between Turkic and Indo-Iranian ethnogroups, have more ancient ancestors than is described in historical sources and was generated as a conglomerate from significant number of the groups including in a greater degree Indo-Iranian populations, as well as nomadic Turkic tribes.

Scientific novelty. For the first time was performed a study of genetic pool structure of 26 CA population from 6 ethnic groups (Uzbeks, Tadjiks, Karakalpaks, Kazakhs, Kirghiz, Turkmens) as complete population systems using a wide range of genetic objects – mtDNA, Y-ch., autosomal and X-ch. STRs, genotypes of *H.pylori* and HBV. For the first time was made an assessment of informativeness of each type of genetic markers. For the first time was received detailed characteristics of genetic pool structure of indigenous CA population on the basis of variability lines of mtDNA, Y-ch., autosomal and X-ch. STRs, immune-genotypic variants of *H.pylori* and HBV. For the first time was defined the ratio of Western-and the East-Eurasian lines of mtDNA, autosomal and X-ch.,Y-ch., *H.pylori* and HBV in a genepool of CA population and were made an assessments of genetic variety level and genetic differentiation degree of regional populations as a whole. Phylogenetic analysis of major haplogroups of mtDNA, Y-ch, X-ch., autosomal markers and immune-genotypic variants of *H.pylori* and HBV was conducted. For the first time the position of CA population in population genetic pool system of surrounding regions and Eurasia in the whole was studied. For the first time the evolutionary-adaptable mechanisms, necessary in the forecast of formations of multigenic pathologies in region were studied at six ethnoses of CA.

Scientific and practical significance. Results of multilocus genetic research of CA native ethnoses can be applied in different areas of science and its practical application: genetics, medicine, microbiology, virology, history, ethnography, medical-genetic consultation. The collected material and the received results will allow creating unique base for the further studying of population-genetic factors in prevalence of hereditary pathology and can serve as a basis for planning of genetic-epidemiological inspection of indigenous population. Results of work are already demanded by a number of scientific and educational collectives-collaborators: RSCS MH RUz n.a. V. Vakhidov, RSSPMC O & G MH RUz , TMA, the National Center of global medicine and healthcare (Japan), SRI of the General pathology and pathophysiology RAMS, SRI of atherosclerosis of Innovative center Skolkovo (Russia), University of Nottingham (Great Britain).

DNA collection created in the process of work can be used for carrying out population, evolutionary, forensic and medical-genetic researches. Research materials can be used in research-educational process as courses of lectures for students of biological, medical, historical specialties.

Results realization. Results of research are introduced to working process of laboratory of Genomic n.a Ruzibakiev R. of Institute of Immunology of AS RUz. Results of research and practical recommendations are implemented and are used in the RSSPMC O & G MH RUz, TCNC MH RUz, TashPMI (Conclusion of Ministry of Health RUz № 83/110).

Work approbation. Conferences of young scientists of Institute of Immunology AS RUz «Relevant questions of immunology and allergology» (Tashkent, 2001, 2006, 2008, 2013); VII Congress of Pediatric infection of Russia «Relevant questions of infectious pathology and vaccine prevention» (Moscow, 2008); Republican scientific-practical conference with the international participation «Clinical immunology, immunogenetic: interdisciplinary problems» (Tashkent, 2010); The 12th Congress of the European Society for Evolutionary Biology (Torino, 2009); Société d'Anthropologie de Paris 1859-2009 (Paris, 2009); 78th Annual Meeting of the American Association of Physical Anthropologists (Chicago, 2009); SMBE 2010-Annual Meeting of the Society for Molecular Biology and Evolution (Lyons, 2010); The 14th International Congress of Immunology (Kobe, 2010); the EECAlink project conference FP7 EU (Bruxelles, 2011); Research and Practice conference of memory prof. R.M.Ruzybakiev (Tashkent, 2011); «International scientific seminar Uzbekistan-U.S. Life Sciences Collaboration: Defining the Opportunities» (Tashkent, 2012); International seminar «CA Anthropogenesis» together with Department «Man, Nature, Society CNRS (Paris, 2012); International scientific seminar «Anthropo- and ethnogenesis of CA from the genetic and linguistic point of view» (Tashkent, 2013); Republican inter-laboratory and inter-university seminars of Institute of Immunology of AS RUz, TMA (2008, 2011, 2012, 2013, 2014).

Published results. Primary results of research are published in 27 scientific publication, including 2 methodical recommendations; 1 international ownership of intellectual property, 17 articles, 14 of them in International English reviewed journals, 3 in the republican scientific editions recommended by HAC RUz for Doctor's degree defense.

Structure and volume of the thesis. Work is stated on 209 pages (including list of referent publications) and consist of an introduction, the review of the literature, the description of materials and investigative techniques, results of research, the conclusion, summary, the list of the literature containing 530 sources, from which 524 - foreign, as well as appendices. Work is illustrated by 23 tables and 25 pictures (including maps).

THE BASIC CONTENT OF THE DISSERTATION

In introduction the urgency of subject matter is proved, objective and problems of dissertation, its scientific novelty, the scientific and practical importance of results are stated, dissertation thesis is formulated, the background of practical implementation of research results is given.

In the first chapter-literature review- questions of the evolutionary approach in learning the basics of the spread of genetically determined disorders are revealed. This approach provides powerful tools for the prediction of the formation of the genome sites potentially related to multifactorial, hereditary-dependent diseases

In the second chapter materials and investigative techniques are described. For research objective, work was being spent in according to following main principles of the analysis:

1. Choice of hierarchical level of analyzed populations. The analysis was led at three levels of population systems: *regional, ethnic and sub-ethnic*. However for the greatest completeness on the ethnic level was held two options of comparative analysis of CA ethnic groups: «*ethnoses among ethnoses*» and «*ethnoses among regions*» of Eurasia.

a) «*Ethnoses among ethnoses*»: comparison was led with populations from regions which have appeared to be genetically close to CA genetic pool. b) «*Ethnoses among regions*»: was led comparison of CA ethnoses with genetically close regions. It has allowed developing the analysis of ethnic variability of CA in a context of distinctions of regional genetic pools.

2. Methods and genetic objects (tabl. 1) used for the genepool analysis: A) Researching of parthenogenetic groups of markers – mitochondrial DNA (mtDNA), HVS-I-region for studying female line of inheritance and Y-cr. (NRY) for studying male line of inheritance; B) Studying of autosomal and X-ch. markers, giving general concept about genealogical set of population based on the total contribution of numerous ancestors of both sexes; C) Complex multilocus population -genetic analysis of regional population for studying multiplane structure of CA-populations in a landscape of Eurasia in general; D) Studying of «housekeeping» genes of *H.pylori* and immunogenetic variants of HBV S-gene for detailed research in history of regional populations migrations. This approach was used as the additional tool to traditional approaches of ethnogenetic analysis on human DNA, in view of high sensitivity and more dynamical character of evolving of viruses and bacteria in comparison with *Homo sapiens*.

Table 1. Analyzed markers and populations.

<table>
<tr><th colspan="3">Markers</th><th>Regions and populations</th></tr>
<tr><td colspan="3">Y-chromosome (105 population)</td><td rowspan="7">26 populations of Central Asia (Uzbeks, Tadjiks, Turkmens, Karakalpaks, Kazakhs, Kirgiz) in comparison with populations from Africa, Middle East, Europe, Volgo-Ural region, Caucasus, Asia</td></tr>
<tr><td>NRY</td><td colspan="2">11 locuses, 89</td></tr>
<tr><td colspan="3">mtDNA (105 populations)</td></tr>
<tr><td>HVS-I</td><td colspan="2">121 polimorph. sites</td></tr>
<tr><td colspan="3">Autosomal markers (105 populations)</td></tr>
<tr><td colspan="3">27 locuses, 437</td></tr>
<tr><td colspan="3">X-chromosome (105 populations)</td></tr>
<tr><td colspan="3">9 locuses, 113</td><td rowspan="3">Strains from Uzbeks, Tadjiks, Kirghiz from territory of Uzbekistan and Kirgizstan in comparison with isolates from Western Europe, Siberia, Middle East.</td></tr>
<tr><td colspan="3">Helicobacter pylori</td></tr>
<tr><td>“Housekeeping” genes</td><td>atpA, efp, mutY, ppa, trpC, ureI yphC</td><td>72 isolates</td></tr>
<tr><td colspan="3">Hepatitis B virus</td><td>Isolates from Uzbeks, Tadjiks, Kirgiz from territory of Uzbekistan and Tajikistan in comparison with virus from Europe, South, Central and North America, Africa, Far East, Central, East, South and South-Western Asia, Atlantic islands and Australia.</td></tr>
</table>

3. Organization of compared ethnoses and regions by a historic-geographical principle. In cases where not all the regions in the literature were presented by full panel of markers, association of regions to macroregions was done.

4. The analysis of genetic pool by different methods of multivariate statistics.

Use of different analysis methods (on the basis of genetic distances - cluster analysis, multidimensional scaling; on the basis of correlation matrixes - the factorial analysis) for the same markers has allowed to lead cross-check and search for the most sustainable patterns that are not dependent on the method of analysis. For the greatest objectivity was led analysis of visualization of genetic distances using two different methods: multidimensional scaling and cluster analysis.

The basic statistical approaches: phylogenetic analysis by Neighbor-joining alignment was led ; paired assessment of genetic distances done by Kimura’s method; for the analysis of multilocus data was used methods of cluster analysis and multidimensional scaling; for analysis of prospective recombinant sequences was used the procedure of bootscaning; bootstrap -value was calculated; probable points of fracture was estimated by maximization of $\chi 2$-square; the factorial analysis was led by analysis of correlation matrixes; was led the assessment of probability of evolutionary inheritance affinity of isolates, etc. Results admitted reliable if they proved by all types of the statistical analysis. Genetic distances maps were estimated according to Nei (1975) and Cavalli-Sforza, Bodmer (1971). Cartography-statistical analysis was led by the original software developed under

the charge of prof. E. Heyer (1997) and with use of simulation program of mutation age calculation (F.Austerlitz, 2003). In the analysis were used following software packages: Microsoft Excel 2010, Microsoft Access 2010, FSTAT, GENETIX, Genepop v.4.0, JMP5.1, CLUMPP, Mega v4, Structure 2.2, Arlequin 3.1, Phylip, Gene Runner v.3, SPSS 14.0, Leadmix41, Batwing, and others.

MULTILOCUS ETHNOGENETIC VARIETY OF *H.PYLORI* ISOLATES IN CA. We have analyzed and compared results of multilocus sequencing of 72 isolates from territories of Kirgizstan and Uzbekistan with 147 isolates from Indo-Iranian populations of Iran, considering data about a geographical/ethnic origin and linguistic belonging. Phylogenetic analysis was carried out in a bigger sample set of 330 strains of *H.pylori* from Europe/North Africa and 147 Iranian and 72 Central Asian isolates. The results of the study show that all strains of *H.pylori* in CA belong to one European (hpEurope) populations, and grouped with isolates from Spain, UK, Finland, Turkey and Italy. Thus we did not manage to identify pure, separate population structure of Iranian isolates at a level of separate strains. All CA-isolates have settled down between different populations in hpEurope group (fig.1). Moreover, distribution in genome of *H.pylori* strains allocated in CA ancestral groups of nucleotides shows an accessory to the European population. Earlier has been shown existence of several ancestral populations of *H.pylori*: ancestral Africal, Africa2, EastAsia, Europel and Europe2. Apparently, *H.pylori* strains, allocated in the modern Europe, are recombinants between bacteria of populations AE1 and AE2. It is supposed, that microorganisms of these populations have got to the Europe from various sources: *H.pylori* populations AE1 mainly from CA, AE2 - from Middle East and North Africa. Therefore at a following stage of work on revealing the basic ways of distribution of *H.pylori* we analyzed strains of *H.pylori*, allocated from various ethnic groups with use of the hierarchical analysis of variants. All isolates have been divided on 3 covariance component: inside-population (IP), between population/inside groups (BP/IG), and between groups (BG). Parameters of variability in components IP, BP/IG and BG were 94.30 %, 1.67 % and 4.04 % accordingly. Consequently significant variability of isolates at a level of population was established. For research of genetic differentiation traces not visible at an individual level, we have counted F_{ST} between pairs of marked populations - CA groups are distributed in five clusters, 3 of them contain not only CA-population. The Iranian-Arabian population is grouped in cluster between Palestinian and Israeli strains. Kurds from Sanadaj in the north of Iran also are grouped near to this group. The second kurdish population from Kermanshah and Lor from Hurramabad (Western-Central Iran) form distinct group with strains from Turkey. The third cluster is generated from the Uzbek and Tajik populations together with the Iranian populations from Northeast border (Sari and Mashhad). I.e., the close relationship of Tajik, Uzbek and Iranian isolates from the north of Iran was shown. Kirghiz strains was more close to populations from Siberia (Russian Federation) that corresponding with

genetic, archeological and historical data where Altai - an ethnic source of modern Kirgiz (fig. 2). Genetic proximity of strains from Uzbekistan with some Iranian isolates possible can be explained by affinity of ethnic roots of Uzbeks, Tadjiks and north-east Iranians.

H.pylori from territory of CA is similar to another isolates from populations of Western Europe and shapes earlier described hpEurope population. HpEurope population has been generated by the contribution of two various ancestral populations, AE1 and AE2 which proportional parities vary depending on the location. CA-isolates is not an exception and also have been generated with the similar contribution of these two ancestral sources.

GENETIC AND GEOGRAPHICAL VARIETY OF *HBV*. One of the features of Uzbek *HBV* population was a high variety of genotypes - 4 genotypes (A, C, D, G) from 7 investigated where dominating were genotypes D and A, 78 % and 19 % accordingly. The analysis of distribution of *HBV* genotypes depending on an ethnic accessory of patients (Uzbeks, Tadjiks, Korean and others) has shown, that genotype A was revealed among individuals of Uzbek and Tajik nationality, genotype D was universal for all ethnic groups, the genotype C was dominating among Korean (60.0%) and also is detected among individuals of Uzbek nationality (40.0 %).

Hypothesis «HBV: Out of Africa» It is known that the distribution of genotypes vary depending on geographical regions of the world, that probably reflects their different origins and pathways of the human migration. P.Simmonds (2000, 2005) has shown phylogenetic likeness of *HBV* variants of human, chimpanzee, gibbon and the orangutan (fig. 4). Virus found in chimpanzees, the most related with human *HBV* variants in comparison with other primates, namely with the genotype E - 'African' variant, which still dominates in Africa (fig.3). Phylogenetic analysis f local *HBV-D*-genotypes with variants from other regions of the world has shown that our strains are in the same cluster with 'African, European, Asian' *HBV-D1*-variants, that shows a close affinity of CA-isolates with variants of the virus from Africa, South/East of Eurasia and Europe.

It is remarkable, that according to results of some independent researches - the least genome distinctions have been revealed at a chimpanzee and human, and an ancestral home of *Homo sapiens* was the African continent, and according to the lead analysis affinity is traced, as Host, and its virus at levels of chimpanzee – Africa, Africa – South/East of Eurasia - CA- Europe. As during transition of *Homo sapiens* to a settled life races and ethnic groups were shaped, so in parallel, possibly, there was evolution of *HBV* - arising mutations/recombination caused occurrence of genotypes.

Probably Africa is «cradle» not only for modern human, but also for *HBV* so there is an affinity of ancient evolutionary processes. Based on the high level of *HBV* infection in Uzbekistan, immunogenotypic diversity of 'Central Asian' virus and comparative analysis of virus *HBV* isolates from other regions of the world, it can be assumed that CA was *HBV*-endemic region since active colonization of the continent and should play a role not only in the settlement of *Homo sapiens*, but in the spread of *HBV* in Eurasia as well.

ETHNOGENETIC LANDSCAPE OF CENTRAL ASIA. ***From lineage to tribe.*** The analysis of 11 STRs loci of Y-ch. at a level of the same lineage in populations of Uzbeks, Kazakhs, Turkmens, Kirghiz, and Karakalpaks shown the maximal percent of genetic relationship: 0.54 ($p<0.001$), 0.34 ($p<0.01$) and 0.77 ($p<0.001$) respectively. However, the genetic proximity at a level of clans was significantly lower for Kazakhs, Turkmens, Karakalpaks from Kungrad, Uzbeks, Karakalpaks from Turtkul: 0.30 ($p<0.01$), 0.21 ($p<0.001$) и 0.40 ($p<0.001$), 0.07 ($p<0.05$) and 0.09 ($p<0.05$), respectively. And already at a level of tribe genetic relationship has not been established: -0.02 ($p<0.05$), -0.04 ($p<0.001$), -0.07 ($p<0.01$), -0.0011 ($p<0.1$) and -0.10 ($p<0.01$), accordingly.

Thus, it is shown that blood relationship as the basis of ethnic structure has the biological basis only at a level of lineage or clan. In fact, in terms of genetic relationship, the tribe is a conglomerate of clans with different genetic origins. Most likely, this 'blood ancestor-founder' was necessary for the social integration of clans "under one banner". In addition, our data show that at the level of the lineage and clan the organization of population is endogamous. Data of genetic diversity of Y-ch. between populations within each ethnic group allow calculating the effective population size, rate of growth of the population and estimating the approximate minimum age of group. The average coefficient of first divergence in almost at all populations was>1000 years ago from the present, with the exception of Karakalpaks, for whom this factor amounted to 880 years. These data demonstrate not the age of population, but minimum time of ethnos origin. Our results go contrary to all known historical records about the dating of all CA-populations. It is fair to say that the state organization of Uzbeks, Kyrgyz and Kazakhs began in 14-17 centuries, but their genetic formation as ethnic groups began more than 1000 years ago.

Thus, our analysis of parthenogenetic markers consistent with hypothesis of F. Barth, that ethnicity, at least for the Turkic population, preferably organized by social principle, creating genetic boundaries with other ethnic groups, and not as a result of the common genetic ancestor.

The comparative analysis of genetic and social structure of CA populations. Polymorphisms of HVS-1 mtDNA inherited on maternal line was analyzed at 12 nomadic and 9 farmer CA populations with the parallel analysis of genetic variety

of six STRs non-recombinant region of Y-ch. (NRY) at 11 nomadic and 7 farmer populations. Both systems were analyzed for the assessment of genetic diversity and demographic growth of nomadic and farmer populations.

In the analysis of mtDNA, heterozygosity (H) and the average number of pairwise differences (*p*), which are the estimates of population diversity, were high in the nomadic (0.99, 5.29) and farmer populations (0.99, 5.32), with minor differences in the two populations for H and *p* (Wilcoxon test $p>0.1$ for both indicators). Low level of differentiation among nomadic and farmer populations (FST=0.01, $p>0$) were established. Moreover, both groups of populations showed significant negative (D) Tajima test for neutrality: 21.90 and 21.76 in the nomadic and farmer populations, respectively ($p>0.1$), which is a sign of demographic growth.

In a counterbalance to mtDNA data, *H* received on Y-ch. was significantly lower in nomadic groups, than among agrarian - 0.86 and 0.99, accordingly ($p<0.01$). Similar data were in the parameters of pairwise analysis (*p*) which were lower at nomadic populations in comparison with agrarian - 2.86 and 3.59, accordingly ($p<0.01$). Besides, nomadic populations show higher level of population differentiation (R_{ST}) in comparison with farmer populations - 0.19 and 0.06, respectively ($p<0.01$). However, such parameters of high level of differentiation in nomadic populations do not grow out of significant gene-geographical distances. Parameters of demographic growth (r), were lower at nomadic populations in comparison with agrarian, but the difference was insignificant - 1.004 and 1.008, accordingly ($p=0.056$).

In general, results on mtDNA have shown that both groups of populations show high level of intra-population variety and low level of inter-population distinctions, both groups of populations are characterized by fast demographic growth. And on the contrary, data on Y-ch. have revealed an essential difference between two groups of populations: nomadic populations showed significantly low level of intra-population distinctions and expressed high level of inter-population distinctions, and the tendency to decrease in a level of demographic growth in comparison with farmer populations.

MDS-analysis of nomadic populations, revealed the existence of individual clusters belonging to one clan and having the same Y-STRs haplotype at Karakalpaks. We called these clusters, genetically identical and belonging to the same descending group (lineage or clan) “identification cores”. Considered identifications cores feature Y-ch. and mostly limited to nomadic populations. In fact, only some of them were considered for Y-ch. in the agrarian populations and for mtDNA in agrarian and nomadic populations. Moreover, the average quantity of individuals who are carriers of the same haplotype (s) was higher on Y-ch. at nomadic populations than in agrarian 2.71 and 1.15, respectively ($p<0.01$). It was

also higher than the average of (C) for mtDNA in both groups of populations-1.19 and 1.21 respectively. For a correctness of parameters in the analysis of Y-ch. identification cores, we carefully prepared sample set at nomadic ethnogroups - samples of the men who are not consisting in close relationship, i.e. all individuals have not been connected in two generations. Therefore these identification cores, possibly, are direct result of internal dynamics of patrilineal descending groups at nomadic populations (the population divides on tribes, tribes on clans, clans on lineages).

In addition we led the analysis of nomadic social organization with use of OBSS-model (One-big-several-small) which allows comparing evolution of genetic variety in populations with panmixia (OB) and populations of the same size, but divided to several isolated local dems (SS). The nomadic population is similar to SS population if to consider men (every descending group -is local deme without migrations between them) which in the long run lose variety of Y-ch. due to complex influence of genetic drift and process of linear decline (H=0.86; C=2.71, P_S=27%). On the other hand, the similar high level of inter-deme migrations at women shows, that the female part of nomadic ethnoses conforms with OB-parameter of population and that in long term conditions the high level of mitochondrial variety is persisting (H=0.99, C=1.19, P_S=74%). Study of genetic diversity among Uzbeks revealed demographic processes, caused by changing lifestyle. Values of genetic diversity on Y-ch. at Uzbeks (P_S*=0.48, C=1.54*) are similar to data from the Indo-Iranian farming ethnic groups (P_S*=0.45, C=1.69*). Probably, apart from the presence of Indo-Iranian groups in the original composition of Uzbeks, such changes are due to changes in the social organization of nomadic lifestyle to a settled the past few centuries. Variety of Y-ch. at Uzbeks and Tadjiks did not contain traces of nomadic social organization. This is well illustrated by comparing the Y-ch. at Uzbeks living in the South and the North of Uzbekistan (P_S*=0.93* и *0.48, C=1.04* и *1.54,* accordingly).

Southern Uzbeks begun sedentary life in 16 century and at northern Uzbeks sedentary life and endogamy are dated by17-18 centuries. This statement also verified by reduction of genetic relationship on Y-ch. at Uzbeks in descending groups in comparison with Kazakhs, Turkmens and Karakalpaks. In such relatively fast transition probably participate 2 demographic processes: 1) Social - transition and loss of nomadic life by Uzbeks in 16 century led to disappearance of descending groups in structure of the social organization and the subsequent reorganization of family traditions in endogamous, characteristic for traditional agricultural populations in the south of Uzbekistan; 2) Intensification of gene stream from traditional agrarian ethnogroups to the Uzbek populations. Genetic distinctions between Uzbeks and agricultural populations reliably lower, than between nomadic and agrarian populations. Parameter of R_{ST} on Y-ch. between northern Uzbeks and agrarian groups has made 0.05, and between northern and

southern Uzbeks 0.03. While the R_{ST} when comparing each of the 8 nomadic groups with farmer populations averaged 0.11.

Genetic distances (ϕst) on mtDNA between traditional farmer populations and 4 Uzbek populations also were low, than at comparison of agrarians with 12 nomadic groups: 0 - 0.014 (0.005) and 0.001-0.047 (0.012), accordingly. This study confirms the theory about urgency of demic processes of distribution at agrarian populations which states that even at such microgeographical scales, there are more likely actual migrations in agrarian ethnoses with subsequent biological injection, than just spread of technologies. Similar processes are described also in one of Indian populations which in a similar way to CA Uzbeks recently passed to agricultural way of life.

Thus, this analysis demonstrates how cultural division (fragmentation) in patrilineal groups was reflected diversity of Y-ch, without affecting the diversity of mtDNA. In fact, the demographic history of man's part of populations has structure of linear division of descending groups without the subsequent mixtures between descending groups that leads to so-called identification cores and to Y-ch. variety decrease. In turn, the female population in each generation is exposed to massive genetic injections between descending groups (lineage or clans) as a result of social rules of exogamy in the given population and by that prevents displaying of mtDNA traces in the social organization of group. The example of genetic variety at Uzbeks evidently shows that such molecular trace of Y-ch. variety can be transient and may disappear within several centuries after disintegration of descending groups.

Sex-specific multilocus genetic structure and the social organization in CA. We genotyped all bilinear populations and 8 patrilineal populations on HVS-1 locus of mtDNA and 11 patrilineal populations on STRs-markers of Y-ch. The level of genetic differentiation in all ethnoses was higher on Y-ch. in comparison with mtDNA. At 10 bilinear populations was not revealed dramatic difference in genetic differentiation - $F_{ST}^{(Y)}$=0.069 and $F_{ST}^{(мтДНК)}$=0.034, whereas among 8 nomadic populations the level of gene-diversity was higher for man's line – $F_{ST}^{(Y)}$=0.177 и $F_{ST}^{(мтДНК)}$=0.010. Using island model of the stochastic analysis of population structure, it was shown, that percent of women migration (m_f) and/or effective women number (N_f) higher, than corresponding parameters at men (m_m and N_m). Yielded results show that at nomadic populations distinction in sex-specific genetic structure is more significant, than at bilinear farmers. Using F_{ST} parameters, we calculated ratio of effective migrant's numbers among man and woman on generation: $N_f m_f / N_m m_m$=2.1 for bilinear populations and $N_f m_f / N_m m_m$=21.6 for patrilineal populations. Results have shown, that ratio of effective numbers in patrilineal populations were significantly higher, than in bilinear populations.

Using 27 untied polymorphic autosomal STRs markers (AR=16.2, H_e=0.803 on the average) and 9 X-linked markers (AR=12.6, H_e=0.752 on the average) we analyzed 10 bilinear farmer populations and 11 nomadic populations of CA. Total heterozygosity slightly differed between X-linked and autosomal markers, and also between the associated samples (p=0.09), in bilinear farmer populations parameter p=0.13, in patrilineal nomadic populations p=0.12. Total gene-diversity of population structures for autosomal markers was significantly higher for the X-linked markers at nomads $F_{ST}^{(A)}$=0.008 (0.006-0.010) and $F_{ST}^{(X)}$=0.003 (0.001-0.006) (H_0: $F_{ST}^{(A)}=F_{ST}^{(X)}$; H_1: $F_{ST}^{(A)}>F_{ST}^{(X)}$; p=0.02). In farmer populations results of distinction of autosomal and X-ch. markers were insignificant: $F_{ST}^{(A)}$=0.014 (0.012-0.016) and $F_{ST}^{(X)}$=0.013 (0.008-0.018 on p=0.36). Proceeding from these results and following the forecast of the used model, it was shown, that at patrilineal nomads where $F_{ST}^{(A)}>F_{ST}^{(X)}$, the effective number of women is higher, than at men. At the analysis of bilinear farmers the same was not observed.

Testing of null- hypothesis spent by comparison of observable and expected value of $F_{ST}^{(X)}$. Following recommendations of Ramachandran et al., we varied values of proportions N_f/N, m_f/m - accordingly to coefficient of effective women number and coefficients of women migration level. Thus, for each complete set of N_f/N, m_f/m values we have received 27 expected values of $F_{ST}^{(X)}$. These expected values of $F_{ST}^{(X)}$ were compared then with 9 observable locus-specific $F_{ST}^{(X)}$ in our sample where p-value were calculated with use of Wilcoxon test for 27 expected values $F_{ST}^{(X)}$ and 9 observable values of $F_{ST}^{(X)}$. The received p-value ($p\leq0.05$) confirmed significant differences in expected and observable values.

In summary, it is shown that the effective women number is higher, than men number in nomadic populations, in farmer populations these parameters differed slightly. Moreover, was established that at exception of all values of complete sets (N_f/N, m_f/m), where $m_f<m_m$ and level of α=0.101, level of migration for women higher among patrilineal populations, than for men, in comparison with bilinear populations. Despite of the fact that both groups patrilocal, such differences in sex-specific migration were expected, as patrilineal nomads are exogamous (marriages between clans) and bilinear farmers are basically endogamous. For example in patrilocal and matrilocal Indian populations where migration is strictly limited inside endogamous groups, sex-specific patterns were not under influence of residing after marriage.

The comparative analysis of mtDNA, Y-ch., X-linked and autosomal markers. It is important to note, that our results on autosomal and to X-linear markers coordinates with results on Y-ch. and mtDNA: values of N_f/N, m_f/m compatible to observable values of $F_{ST}^{(Y)}$ и $F_{ST}^{(мтДНК)}$. These sets of values is identical for bilinear and patrilineal populations as we have revealed $N_f m_f/N_m m_m$=2.1 and $N_f m_f/N_m m_m$=21.6 for two groups accordingly.

All the studied genetic systems – mtDNA, Y-ch., X-linked and autosomal markers demonstrate that patrilineal nomads, unlike bilinear farmers, have strong sex-specific genetic structure. The parameters based on the analysis of X-linked and autosomal markers such presumably because of high level of migration and greater effective number of women, than at men. To find out on what population samples and in what limits we shall apply our approach, we analyzed sex-specific structure of 51 populations presented in HGDP-CEPH where the information on differentiation on 784 autosomal and 36 X-linear STRs is available. The analysis has shown greater differentiation of X-linked markers in comparison with autosomal at the majority of populations, where $F_{ST}^{(X)}>F_{ST}^{(A)}$. Unfortunately, HGDP-CEPH do not contain detailed ethnic information for the investigated groups, therefore it was impossible to differentiate populations depending on life style.

Thus, we showed that the joint analysis of autosomal and X-linked alleles provides rational methods of forecast for sex-specific demography and history in human populations. Multilocus complex approach in the analysis of sex-specific genetic structure at CA populations when the genetic information of mtDNA , Y-ch., X-linked and autosomal markers analyzed collectively, has shown, that contrast distinctions of male and female genetic differentiation can be caused not only by difference in sex-specific level of migration, but also by different effective number of population groups. On example of patrilineal nomads were shown that sex-specific distinction in population structure can be result of high effective number of women and their effective migration. Comparing ethnic groups with different social organization and way of life (patrilineal with bilinear or matrilocal groups), it was shown that the social organization and life style have a huge impact on the distribution of genetic variation in human populations.

Genetic traces of ancient expansion of Homo sapiens in the territory of Eurasia. The analysis of mtDNA has shown, that the age of expansion in territory of Eurasia (τ_w) significantly decreased from the East to the West (Spirman's test between τ_w and longitude: r=0.72, p<0.001). At the rate of female generation is 29 years and frequency of mutations is 10^{-5} on a site and on generation, results of our research have shown, that the age of expansion had the expressed tendency to decrease from 30 thousand years in the territory of China up to 17 thousand years in the Western Europe. The age of expansion in CA-region was 26 thousand years. On the basis that frequency of mutations makes 5×10^{-6} on a site and generation that conforms transient variation of mutation frequency ~1 every 20 thousand years, estimated time of expansion will make: 61 - 63 thousand years in the Far East, 35 thousand years in the Europe and 54 thousand years in CA (fig. 5).

Results on Y-ch. also show decrease in a genetic variety from the East to the West of Eurasia (Spirman's correlation parameter between σ^2 and longitude:

r=0.49, p<0.001). When evaluating men's expansion on the annual calculation, at estimated genealogic mutation frequency 2.1×10^{-3} on a locus and generation (Heyer et al., 1997) and duration of man's generation of 35 years (Tremblay and Vezina, 2000), age of expansion varied from 19 thousand years in China to 11 thousand years in the Europe, and in CA this age made 16 thousand years. When assessing the frequency of mutations based on phylogenesis at 0.69×10^{-3} for 25 years (Zhivotovsky et al., 2004), the age of expansion was 40 thousand years in China, 25 thousand years in the Europe and nearby 36 thousand years in CA (fig. 6).

To understand the evolutionary mechanism underlying the trends reducing the age of expansion from the East to the West of Eurasia, the comparative analysis of the proportions of the LIC were conducted -that is proportional ratio of populations where the age of divergence between populations of different geographical regions is higher than the maximum of two ages of expansion.

According to mtDNA at comparison of populations from various regions of Eurasia (in total 9106 pairwise comparisons), average value of LIC has made 11%. It means that in the majority of cases, parameters of τ_b were less, than age of expansion of one population from the compared pair of populations. At pairwise comparison of population mtDNA from any region of Eurasia, proportion of LIC always was less than 40 %.

For Y-ch. when comparing populations in different regions of Eurasia (in total 1904 pairwise comparisons), average exponent of LIC made 45 %. These rates were highest when comparing Chinese with other Eurasian populations of regions: from 76 % in CA up to 95 % on the Middle East. The lowest parameters were at comparison of regions in territory of the central and western Eurasia: from 15 % up to 39 % between Pakistan, CA, Middle East, Caucasus and Europe.

Accepted age of expansion as 1100 and 900 generations for mtDNA matches to the age of expansion we received when using the frequency of mutations, based on genealogy for China and CA. Significant decrease in proportion of LIC was observed at increase of intensity of genetic drift in 2 populations: proportion of LIC varied between 35 and 99 % without migrations, between 15 and 38 % at m=5 0.005, and within the limits of 5 - 16 % at m=5 0.001. At higher migration rate (m=0.005, 0.01) difference between expected age of expansion of two populations was too small. Using the proportions of LIC were simulated three possible demographic scenario: A) Both populations had independent expansion, i.e. they split before the Chinese expansion and after separation is not exchanged migrants (m=0). In this case of independent expansion in territories of modern China and CA (T_d>1100 generations back and m=0), calculated proportions of LIC were the highest and exceeded 64 %. B) Demographic expansion was diffuse from China to CA through periodic genetic drift (m>0). Accordingly, at diffuse expansion by

periodic genetic drift (m>0) proportions of LIC were lower and have made 5 - 41%. C) Massive and sudden migration of human from China to CA. At this model of population expansion (T_d<1100 generation back), proportions of LIC were from 8 to 63 %. The accepted age of expansion on genealogic mutation frequency for Y-ch. in 530 and 470 generations was coordinated with simulated age of expansion for China and CA (Heyer et al., 1997). The simulation results for Y-ch. showed similar trends as mtDNA: proportions of LIC decreased at increase of migration level - from 30 to 97 % at *m*=0, from 21 to 78 % at *m*=0.0005 and from 11 to 47 % at *m*=0.001. Increase of LIC proportions were observed at increase of divergence time (at $T_{d=}$710 parameters of LIC were twice higher, than at $T_{d=}$470) and at increase of population size before expansion (N_0). Expected proportions of LIC in case of independent expansion in the territories of modern China and CA (T_d>530 generations and *m*=0) also have tendencies to increase (from 47 to 97 %), in comparison with diffuse migrations by periodic genetic drift (from 16 to 78 % at *m*>0) and with the massive and sudden populations movement after Chinese expansion (T_d<530 generations) - from 11 to 58 %.

In general both genetic systems demonstrate the focus of expansion from Eastern Eurasia to the Europe through migrations (either periodic episodes of genetic drift, or massive and sudden populations moving) occurred over the past 60 thousand years. However, the age of expansion received on mtDNA is slightly higher (17-63 thousand years), than on Y-ch. (11-40 thousand years). The differences between these systems might be the result of errors in the analysis of frequencies of mutations and/or socio-cultural differences between men and women, affecting the level of genetic diversity of these two genetic systems.

Consequently, we concluded that the wave of expansion moved from Eastern Eurasia (from the Far East or from CA) to the Europe during early Paleolith.

Multilocus landscape of CA populations. *Genetic variety.* Analysis of allele varieties (*AR*) and expected heterozygosity (H_e) showed amazing distinctions between CA and other populations in allele variety (χ^2=105,29, d.f.=25, *p*<0.0001) and in expected heterozygosity (χ^2=67.98, d.f.=25, *p*<0.0001). Also we detected insignificant differences between Indo-Iranian (*AR*=13.8) and Turkic groups (*AR*=13.7, *Z*=-0.69, *p*=0.49) though expected heterozygosity was significantly higher at Indo-Iranian groups of populations than at Turkic-speaking (H_e=0.818 и H_e=0.787, accordingly; *Z*=-4.55, *p*<0.0001). Particularly dramatic differences were found between populations of CA, Europe, Central and South Asia, Middle East and Eastern Asia in allele variety (K=36.46, d.f.=4, *p*<0.0001) and expected heterozygosity (K=52.94, d.f.=4, p<0.0001). Possibly, such distinctions were formed by low heterozygosity in Eastern Asia and slightly increased *AR* in the Middle East (p<0.0001 for both parameters *AR* and H_e) (fig. 7).

Population differentiation. All 26 CA-populations slightly, but reliably differed (F_{ST}=0.015, $CI_{99\%}$=0.011 - 0.018, p<0.01). At the pairwise analysis, values of F_{ST} varied from -0.004 to 0.056, and at correction by Bonferroni method robust distinctions were in 205 (63.1 %) from 325 pairs of populations. Such picture of robust estimates is formed basically due to pairwise comparisons between one of Turkic and one of Indo-European populations and comparisons between two Indo-Iranian populations. Proportional distribution of genetic variations among ethnic and linguistic groups of populations showed that more than 98 % of all variations were within the population (p<0.0001). The evaluation of the ethnic and linguistic affiliations in the observed variations showed good compliance (F_{ST}=0.007, p<0.0001 and F_{ST}=0.011, p<0.0001, respectively). We didn't find evidence of geographical isolation within the limits of each Turkic and Indo-Iranian groups of populations (p=0.363 and p=0.772, accordingly).

Correspondence analysis (CA) based on the counting of alleles, divided the population of Central Asia into 2 basic groups: Turkic and Indo-Iranian populations. However, 2 Turkic-speaking populations, Uzbeks from Fergana area and Turkmens from Karakalpakstan, were exception and clustered with Indo-Iranian populations. Besides it is remarkable, that according correspondence analysis, some Uzbek populations from Bukhara, Pendjikent and Fergana have shown the mixed picture – have settled down more close to Indo-Iranian groups of populations. The complex correspondence analysis of Eurasian alleles placed CA populations in intermediate position between group of population from Europe, Middle East, Central and South Asia and Eastern Asia. Turkic speaking and Indo-Iranian populations were grouped separately: Turkic speaking CA-populations have settled down more close to populations from Eastern Asia, Indo-Iranian ethnogroups have settled down more close to other populations from Central and South Asia, Europe and Middle East. It should be emphasize, that populations of CA-region are more scattered, than any other groups of populations in Eurasia. It is remarkable, that Hazaras of Pakistan which according to historical annals of this population are direct descendants of Chingiz-khan in the male line situated between Turkic speaking CA-populations.

Cluster analysis. The joint analysis of the populations of Eurasia and Africa showed that the highest rate average posteriori probability (D) after 40 independent simulation researches was- for values K=7 estimated clusters, with Log [P (K=7|D)]-167565.4 (SD=22.8), however at value K=6 average values of posterior probability were only the little below with Log [P (K=6|D)]-167653.8 (SD- 10.6). At post-processing for K with the greatest value of likehood factor, calculated by CLUMPP program, this factor was the highest (0.99) for values K from 2 to 5, and it is more than 0.87 for values K=6, indicating absence of true multimodality of runs. At K=2 we observed a pure cline «East-West». CA-population are an intermediate link between cluster, generated by populations of Europe, Middle

East, Central/South Asia and Africa, on the one hand and cluster of populations from Eastern Asia, on the other hand. Such intermediate position of CA-populations on cluster analysis has coordinated with results of allelic conformity analysis. All individuals from CA belong to these two main clusters at values of K=2.

Thus, there was not a single individual who would belong only to one cluster: among Turkic speaking population Eastern Asian factor was dominated, among Indo-Iranian representatives with greater fraction there was cluster, generated by populations of Europe, Middle East, Central/South Asia and Africa. At values of K=3, six African populations are grouped in unified cluster. At K=4, the European and Near-Eastern populations are grouped together with populations of Central and South Asia, mainly with Indo-Iranian ethnogroups. Besides it has been revealed 2 clusters, exclusive for CA-populations: at K=5, greater component of fifth cluster among Turkic speaking populations and at K=6 dominating component of sixth cluster among representatives of Indo-Iranian CA- populations. It is necessary to note, that the cluster analysis showed a similar contribution with Turkic speaking CA- populations among the Uyghur and Hazaras (fig. 8).

Turkmens of Karakalpakstan and Uzbeks from the Fergana area were the exception, in which the share of East Asian lines amounted to 27.2% and 17.8%, respectively. Indo-Iranian speaking populations had mainly West-Eurasian component (Central/South Asia, Europe and Middle East) within the limits of 72.7–94.5 % from the general contribution, thus individual share of these three regions varied among Indo-Iranian ethnogroups. It is remarkable, that in two populations of Uzbeks of Bukhara area the high proportion of West-Eurasian ancestral participations was established - 81.4 % and 78.5 %, accordingly.

Estimated origin of Indo-Iranian and Turkic speaking CA-populations. Cluster analysis showed that the majority of Indo-Iranian populations have significant factor of participation of two clusters (bright blue and beige on fig. 8), found predominantly in this group of the population. Correspondence analysis and cluster analyses showed that Indo-Iranian population is very close to populations from Central/South Asia. If to consider Indo-Iranian population in a complex we can see that value of pairwise assessments of F_{ST} between almost all pairs of Indo-Iranian populations, high level of variety among these populations and variability of admixture level with assumed ancestry populations confirms the assumption, that Indo-Iranians – are old residents of this region. And this hypothesis is confirmed by archaeological evidence. Conversely, a lower level of genetic differentiation was set among the Turkic populations, despite their broad geographic distribution suggests a younger age compared to Indo-Iranian.

The present study also illuminates an origin of Turkic speaking CA-populations. Cluster analysis has shown that the majority of individuals in Turkic

speaking populations had significant factor of «Central-Asian» cluster participation and the insignificant contribution of «Eastern-Asian» cluster. Possibly, presence of the «Central-Asian» component among Turkic speaking populations is ancestral contribution of the Altay region, and «Eastern-Asian» cluster testifies ancestral injections from the east of Eurasia, which Asian nomads introduced by more recent migrations.

The pro-European sight at continental demographic expansion from the East to the West is usually accompanied by the description of extreme cruelty and violence of Hun armies led by Attila (406-453 B.C.) or the Mongolian empire of Genghis Khan. However, our results have challenged this concept, and rather demonstrate not the complete destruction and replacement of the local population, but only a partial mixing and/or replacement. We do not reveal any evidence of Eastern-Asian contributions among modern representatives of Indo-Iranian ethnogroups (Tadjiks, Turkmens) which means that the ancestors of these populations were not replaced during expansion of nomads from the East. Similar results have been described in researches of Zerjal et al., which indicated absence of «genetic heritage of Genghis Khan» in the studied populations of Tadjiks and Turkmen. The contributions of east nomads detected only in Turkic speaking populations, together with the fact of proximity of cultural traditions and ways of life between these groups, which probably assisted to intergroup marriages, and have generated such genetic similarity.

The Uzbek populations are scattered between Turkic and Indo-Iranian populations (fig 8). Some populations of Uzbeks (the Fergana and Bukhara areas) were genetically closer to Indo-Iranian speaking populations while others (Pendjikent Tajikistan, Kara-Kalpak) are clearly grouped with Turkic speaking populations confirming the historical evidence, which state that the ethnic history of the modern Uzbeks was formed as an alliance of many different groups including both Turkic, and settled Indo-Iranian tribes. Possibly, given union included local Chagatai tribes which, as is known, conducted a nomadic way of life at the moment of association, but were initially shaped from local settled Indo-Iranian groups.

Thus, our results support the hypothesis of Comas et al. (2004) in which CA plays the role of important contact zone between two contrast groups of populations. Our researches show that the so-called «Turkic» group is relatively recent and brought to the region from the East whereas another, presented today by Tadjiks, Turkmens and some Uzbek groups, is more ancient, and occupied this region since earlier times.

RESUME

To date, there are plenty of experimental evidence in favor of different brain activity and structure, behavior, and genetic diversity according to the ethno-cultural conditioning. In general, it is shown that for Western civilization more characteristic of analyticity (rationalism), and for Eastern peoples -holistic (intuitive) thinking. In addition, differences in the prevalence of the type of thinking, depending on the type of activity, for example, for herders is more characteristic rationalism, and for farmers-holism (Henrich, 2010). Furthermore, data of Ebstein et al. (2010) revealed expressed genetic dependence (up to 60%) of social behavior and preferences of different nations-such qualities as sympathy, propensity to risk, leadership abilities and even political views are on 40% of genetic nature.

In the context of these data and the results of present work of traces of social, sexual and language differences in DNA of Central Asian populations, raise complex ethical issues related to differences among people, and raised the 'arguments' for xenophobia -nationalism, racism and sexism. Today we are witnessing a unique combination and interlacing of giant-scale processes in social, economic and cultural spheres. On the one hand there is the convergence of business and consumer culture between the different countries of the world and the growth of international communication, which leads to the promotion of national culture worldwide. On the other hand, despite the obviousness globalization, we are different and divided in many ways.

Commonly known words of Confucius, which were told about the problem of understanding different people-'all the flowers should bloom and smell.' This succinct phrase reflects a moral basis to which modern society yearns-the concept of tolerance to other. Today the attitude toward people with other social, ethno-cultural, political, and other traits and preferences is a measure of the personality with the right spiritual and moral upbringing. But till what extend this concept is viable? As it seen from historical realities that are generated from the misunderstandings and conflicts, it is desirable, but still more theoretical. Perhaps the answers to the ethical foundations of human differences may be a reflection of the great explorers, whose work was far from anthropogenesis, sociology and medicine. Namely, to get away from the concept of tolerance for others, and take these people’s distinctions as an instrument for development through the mutual supplement, penetration, complementarity. The great French mathematician Poincare talked about intuition and rationality: 'pure logic of analitism leads only to tautology, can’t create anything new, cannot in itself give rise to a science, but an accurate tool for proof. To generate absolute new things it is necessary intuitive holism as the tool of the invention '. Perhaps one of the well-known mechanisms of

‘unity and struggle of opposites ' is needed for the biological survival and is the foundation of social and cultural evolution of mankind.

In other words, expanding the saying by Albert Einstein about the nature of his discovery: 'Imagination is more important than knowledge' and 'Dostoevsky gave more than Gauss’, one can say that for a productive symbiosis ‘pro-Western’ rationalism and ‘Eastern’ intuition is needed, and our differences is tutorials for the most fruitful development of human society.

And peoples of Central Asia, which, according to our data from ancient times formed in a close neighborhood, making a color mosaic of genes and traditions have similar symbiosis of the authenticity and transfusion of the genetic-ethnographic characteristics and values, creating total unique semantic field and ethno-cultural dialogue.

It is clear that research of anthropogenetic processes in populations of Central Asia provide unique opportunities and models for multidimensional approaches check existing hypotheses and the launching of new on the evolutionary selection factors that affect the gene pool and its manifestations.

Conclusions

1. H.pylori from CA territory is similar to Western Europe isolates, and shaped by two ancestral populations – genotype Ancestral Europe 1 (dominant) and Ancestral Europe2 at that for AE1-genotype CA-region probably is the source. *H.pylori* from the territory of Central Asia form a separate cluster group: close relationship of Tajik, Uzbek strains and Iranian isolates from the north of Iran is established. Kirghiz isolates were found to be closer to populations from territory of Siberia.

2. High diversity of HBV genotypes in Central Asia was found -4 genotypes (A, C, D, G). Phylogenetic analysis of Central Asian genotype HBV-with options for other regions of the world showed a close relationship between the dominant genotype D (0.78), the D1subtype with variants of the virus in Europe, the Middle East and Africa.

3. The rates of genetic affinity for STRs-NRY in Kazakhs, Turkmens, Karakalpaks Tortkul at the level of the same lineage were high: 0.58 ($p<0.001$), 0.34 ($p<0.01$) and 0.77 ($p<0.001$), respectively. The coefficients of relationship at the level of clan for Kazakhs, Turkmens, Uzbeks and Karakalpaks from Kungrad and Tortkul were lower: 0.30 ($r<0.01$) 0.21 ($p<0.001$) and 0.40 ($r<0.001$) 0.07 ($p<0.05$) and 0.09 ($p<0.05$), respectively. At the level of the tribe, the indicators were negative for all Turkic populations:-0.02 ($r<0.05$),-0.04 ($r<0.001$),-0.07 ($p<0.01$)-0.0011 ($r<0.1$) and-0.10 ($r<0.01$), respectively.

4. The analysis of mtDNA HVS-1 showed that total rate of differentiation level for all populations was low: F_{ST}=0.013; p<0.000. Level of diversity between groups was 0.6% (p<0.001) of the total variability. Parameter of genetic differences between Turkic and Indo-Iranian populations made 0.55% (p<0.0283) of the total genetic variability. The rate of genetic differentiation on a sub-ethnic level was significantly expressed in Indo-Iranian group (F_{ST} 0.0197; r<0.001) than among the Turkic-speaking (0.3%, p=0.10). In all populations, in general, wasn't detected the correlation between genetic and geographic distances at the global level on mtDNA HVS-1: r=0.00682, *p*=0.502.

5. Analysis of STRs-NRY showed that the level of the genetic differentiation between ethnic groups was 5.6% (p<0.02); general differentiation between populations made $R_{ST=}$0.186 (*p*<0.001). Combined analysis, taking into account the language and way of life of Turkic and Indo-Iranian populations, showed the general differences between the two groups - 9.1% Value of genetic differentiation when comparing the ethnos-ethnos was slightly lower than the level within ethnos: 5.6% among ethnic groups, 18.6%, and 13.7%-between populations within the ethnic group.

6. Analysis of heterozygosity (H) and the average number of pairwise differences (*p*) of mtDNA, in nomadic populations were high (av.H=0.99, av.*p*=5.29) and farmer populations (av.H=0.99, av.*p*=5.32). Heterozygosity (H) on Y- chromosome was lower in nomadic groups than in the agrarian - 0.86 and 0.99, respectively (*p*<0.01). Nomadic populations exhibit a higher level of population differentiation (R_{ST}) in comparison with farmers-0.19 and 0.06, respectively (*p*<0.01). Indicators of population growth (r) were lower in nomadic populations compared with farmers-1.004 and 1.008, respectively (*p*=0.056).

7. The level of genetic differentiation in all ethnic groups was higher on the Y chromosome in comparison with mtDNA. The farming populations showed no significant difference in the genetic differentiation $F_{ST}^{(Y)}$=0.069 and $F_{ST}^{(mtDNA)}$=0.034, while among patrilineal nomadic population the level of genetic diversity was higher in the male line of inheritance-$F_{ST}^{(Y)}$=0.177 and $F_{ST}^{(mtDNA)}$=0.010. Genetic diversity of population structure in patrilineal nomads on autosomal and X-linked markers were: $F_{ST}^{(A)}$=0.008 (0.006-0.010) and $F_{ST}^{(X)}$=0.011 (0.001-0.004) (H_0: $F_{ST}^{(A)=}F_{ST}^{(X)}$; H_1: $F_{ST}^{(A)>}F_{ST}^{(X)}$; *p*=0.02). In bilinear farmer populations the differences of autosomal and X-chromosomal markers were insignificant: $F_{ST}^{(A)}$=0.014 (0.012-0.016) and $F_{ST}^{(X)}$=0.013 (0.008-0.018 at *p*=0.36).

8. Analysis of mtDNA indicated that the age of expansion on the territory of Eurasia (τ_w) declined significantly from East to West (*r*=0.72, *p*<0.001). The age of expansion had a pronounced tendency to decrease from 30 thousand years in China to 17 thousand years in Western Europe. Age of expansion in Central Asia amounted to 26 thousand years. Results of expansion analysis on Y-chromosome

also show a decrease in genetic diversity from the East to the West of Eurasia (r=0.49, p<0.001). In Central Asia this age was 16 thousand yrs. According STRs-NRY-Batwing analysis of the minimal age of Uzbek population forming was 1232,71 yrs old (N_e=14088 (6765-23942); α=0.0108 (0.0065-0.0155)).

9. The apportionment of multilocus genetic variations among ethnic and linguistic groups of CA-populations showed that more than 98% of all variations were within the population (p<0.0001). Evaluation of the ethnic and linguistic affiliations in the observed variations showed reliable conformity - F_{ST}=0.007, p<0.0001 and F_{ST}=0.011, p<0.0001, respectively. We didn't find evidence of geographical isolation within each of the Turkic and Indo-Iranian groups of populations (p=0.363 and p=0.772, respectively).

10. Analysis of multilocus allelic diversity (*AR*) and heterozygosity (He) showed differences among the Central Asian and other populations in allelic variety (χ2=105.29, d.f.=25, p<0.0001) and heterozygosity (χ^2=67.98, d.f.=25, p<0.0001). Population differentiation at multilocus analysis at populations of CA is more pronounced than in other regions of Eurasia: in the European and Middle Eastern groups pairwise estimation of F_{ST} ranged from 0.011 to 0.015 and -0.008-0.021, respectively; in East-Asian groups-from -0.011 to 0.046; and finally, in CA these rates ranged from -0.004 to 0.056. Heterozygosity was significantly higher in the group of the Indo-Iranian populations than among Turkic-speaking (H_e=0.818 and H_e=0.787, respectively; Z=-4.55, p<0.0001). According to multilocus analysis all 26 CA populations slightly but significantly differed (F_{ST}=0.015, $CI_{99\%}$=0.011-0.018, p<0.01).

Practical recommendations:

1. Created database of CA population and unique materials of anthropogenetic features, collected in the course of work, is recommended to use for medical-genetic and ecologic-genetic monitoring of CA -region.

2. It is recommended to use the evolutionary approaches estimating a frequency spectrum of mutations, level of population variety in studying bases of distribution of genetically determined pathologies for the forecast of formation of genome sites, potentially connected with the multifactorial hereditary-caused pathologies.

3. Results of research should be included in curriculums of the medical staff at the pre-and postgraduate levels at the departments of medical genetics and at studying section of «genetics» on biology faculties in medical institutes.

4. The received results are recommended to use for further studying the role of population genetic factors in distribution of hereditary pathology and for planning of genetic-epidemiological inspection of indigenous CA populations.

5. As the received results of CA genepool studying play a major part in addressing the history of regional population formation history, it is recommended to use by experts in history and ethnography.

6. Scientific staffs are recommended to use the developed technology of the analysis of complex population systems and assessments of population differentiation at different hierarchical levels with use of panels of the various genetic markers, which cross-checks received results.

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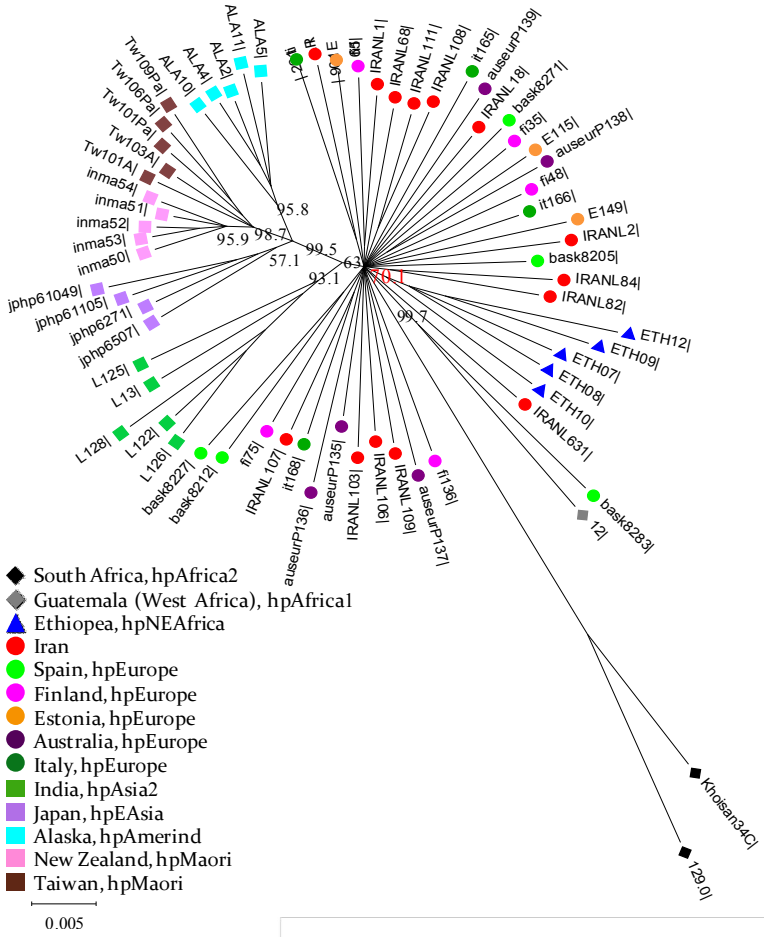

Fig. 1. Phylogenetic analysis of H. pylori strain in Europe and North Africa with 147 Iranian isolates.

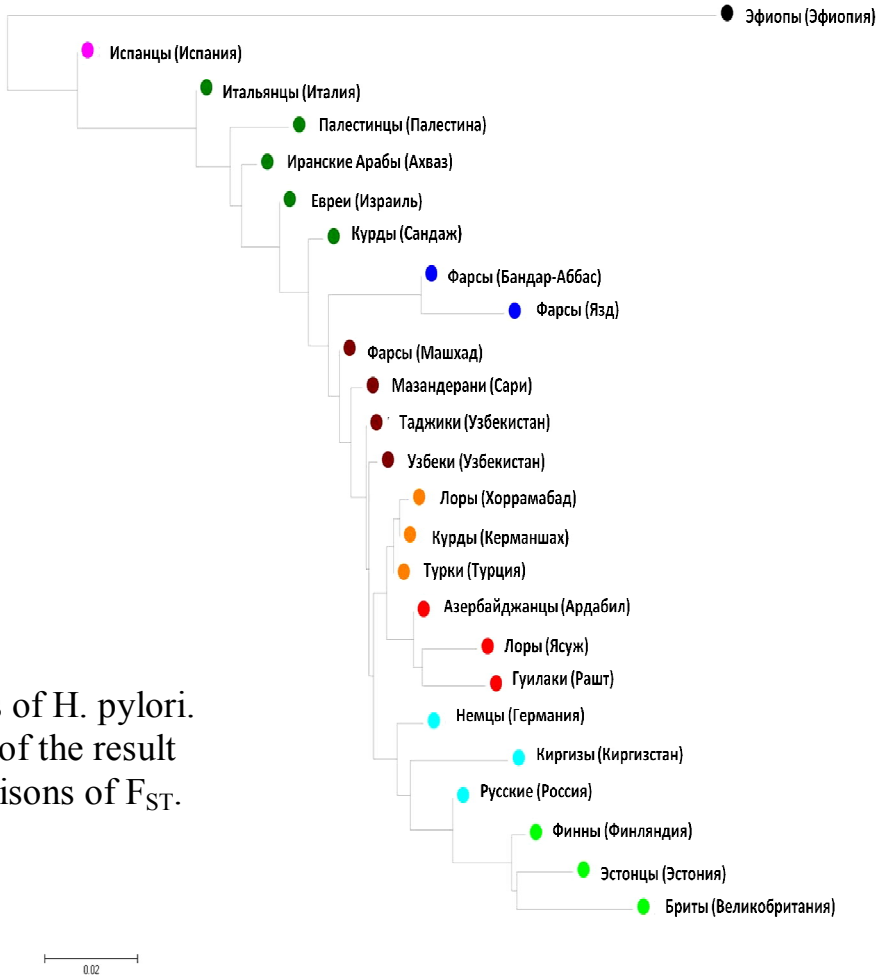

Fig. 2. Phylogenesis of H. pylori. based on the values of the result of pair-wise comparisons of F_{ST}.

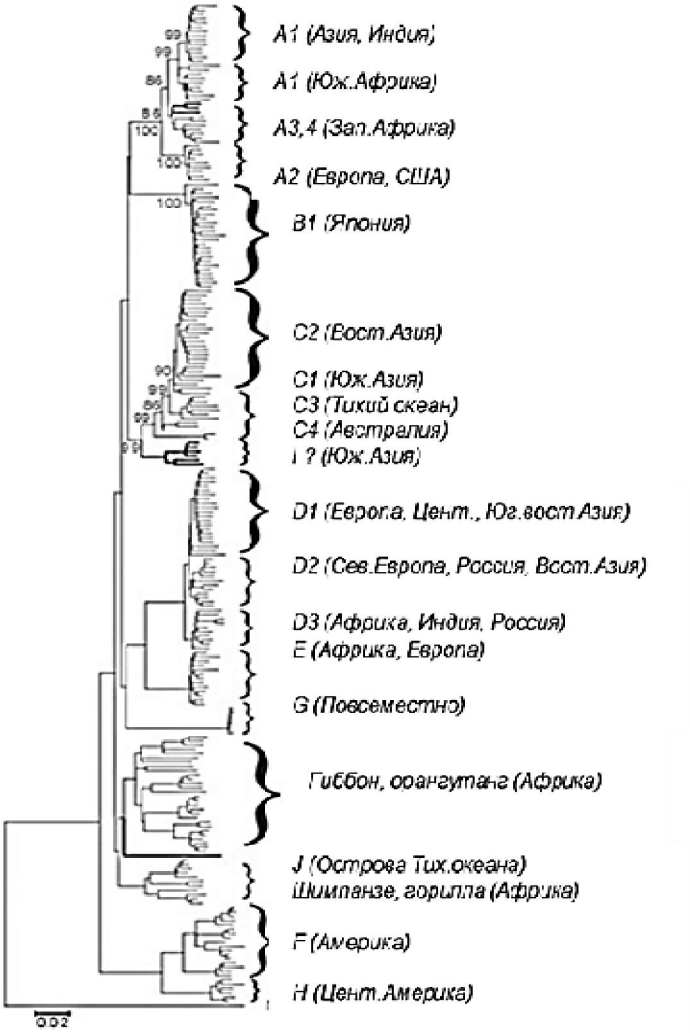

Fig. 3. Phylogenetic tree of HBV strains without traces of recombination

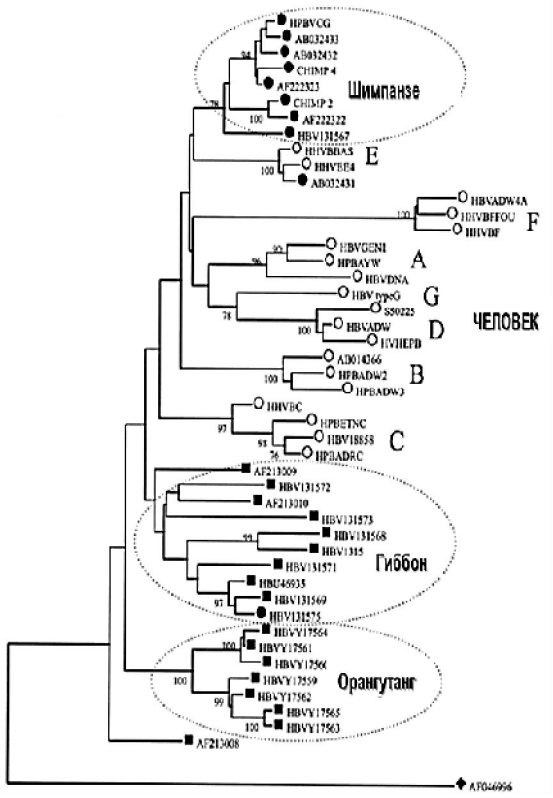

Fig. 4. Phylogenesis of HBV variants S-gene identified in chimpanzees, gibbon, orangutan and human (Simmonds et al).

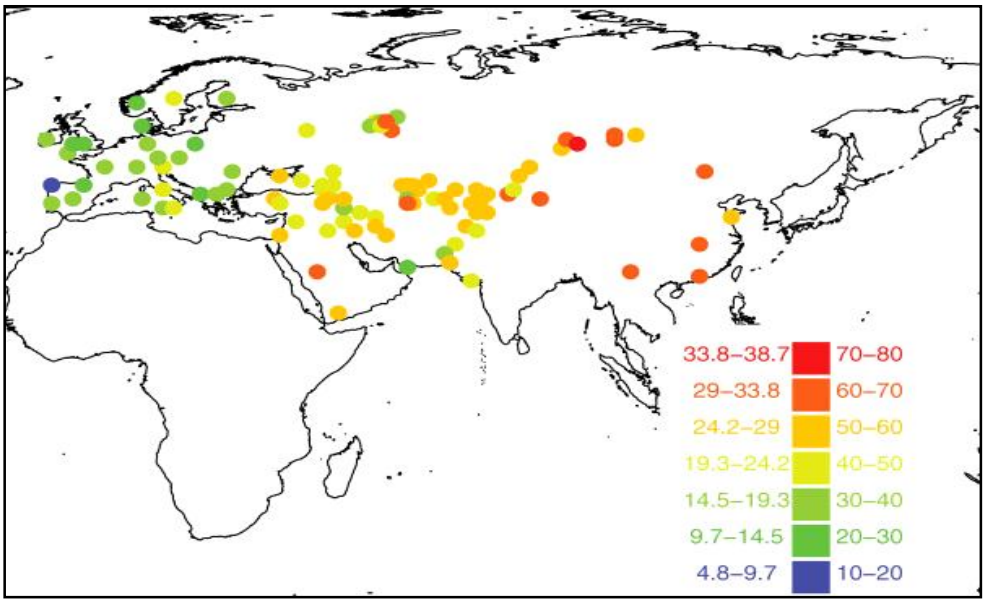

Fig. 5. Distribution of expansion ages in Eurasia inferred from mtDNA data. The color of the points indicate the age of expansion, with on the left of the scale, the ages (in ky) estimated using the pedigree-based mutation rate and on the right of the scale, the ages estimated using the transitional changes rate proposed by Forster et al. (1996).

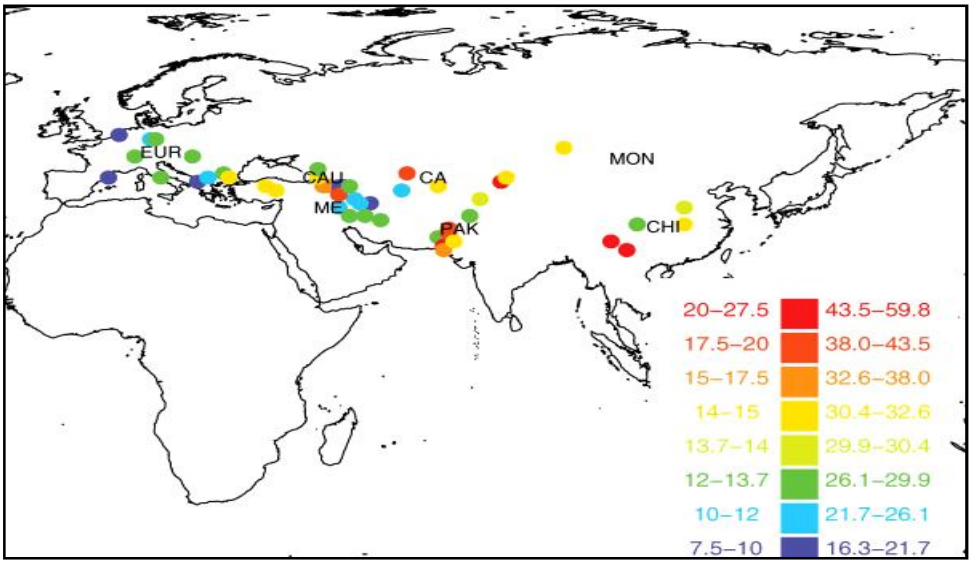

Fig. 6. Distribution of expansion ages in Eurasia inferred from Y chromosome. The colors of the points indicate the age of expansion, with on the left of the scale, the ages (in ky) estimated using the pedigree-based mutation rate and on the right of the scale, the ages estimated using the phylogeny-based mutation rate.

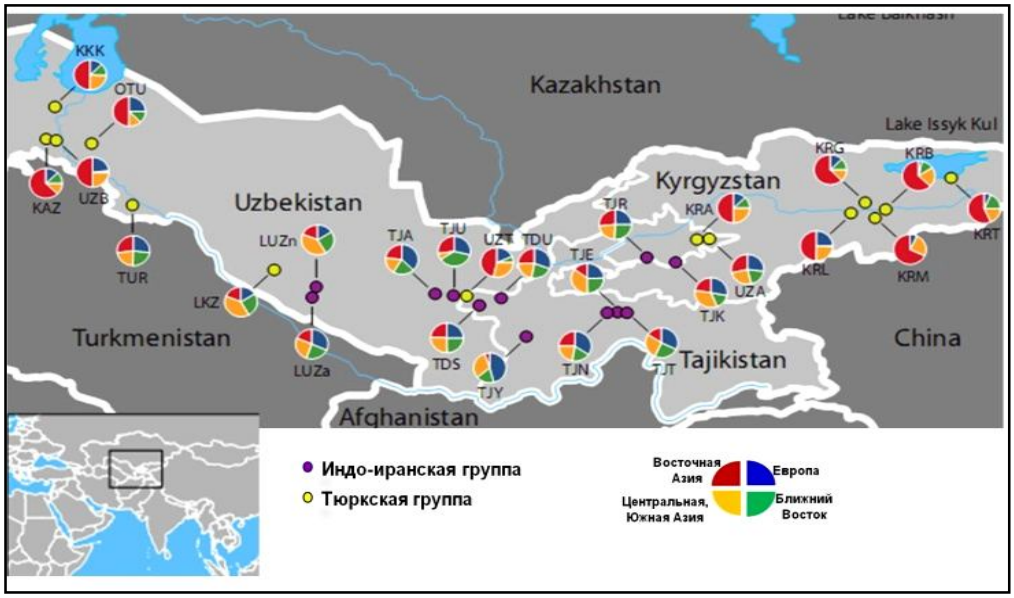

Fig. 7. Geographic location of the 26 Central Asian populations sampled. Linguistic affiliation (violet – Indo-Iranian groups, yellow – Turkic speaking group) and proportion of microsatellites with relative ethnic affiliation are also indicated.

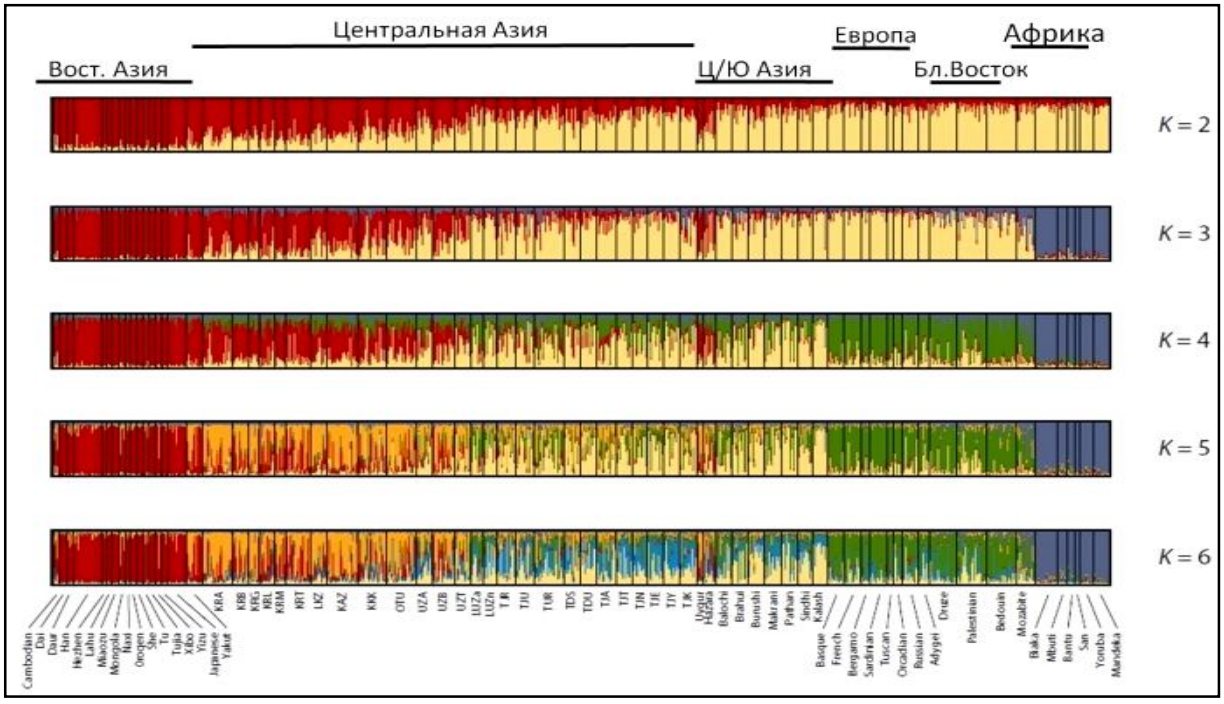

Fig. 8. Population structure inferred from microsatellite data using the software package STRUCTURE. The data consisted in 767 individuals from 26 Central Asian populations genotyped at 27 microsatellite loci, plus 869 individuals from 44 African and Eurasian populations from the HGDP-CEPH Human Genome Diversity Cell Line Panel.

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