SCIENCE
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SCIENTIFIC PRACTICAL JOURNAL

THE WINNERS OF THE ARTICLE CONTEST HELD BY THE JOURNAL «SCIENCE AND INNOVATIONS» IN 2013

Contents

The development of human capital: institutional analysis

The article is published in the journal "Science and Innovations", 2013, #1

Modern economics no longer questions the very real correlation between the level of economic development and the quality of national institutions. However, today the question is not simply about the significance of the latter, but about the specific nature of this causal relationship: are these institutions the prime cause or is their impact a result of other underlying factors.

On one hand, in a strict sense, institutions can be seen as a set of spoken and unspoken rules and it's the quality of which is dependent on the degree of socio-economic development of the country. That is to say, nations which have achieved leading positions also have a highly functional system of institutions.

On the other hand, in a general sense, institutions can be defined as a set of mechanisms and norms that provide redeployment of resources, investment attraction, extended reproduction of human potential and incentives for enhanced efficiency in the economy.

Measurement of the potential of the institutional system, in spite of its complexity and multifunctional quality, is made possible based on several indices which permit a holistic and coherent picture of the economic condition of a country. Using these very indices we can assess the quality of institutions.

Index of Economic Freedom, the integrated index, created by specialists at the World Bank.

Kauffman and Crowe Index, which consists of six governance indicators:

- democracy in elections;
- political stability;
- government effectiveness;
- regulatory quality;
- rule of law;
- absence of corruption.

The higher the indicator value, the better the quality of governance.

Level of financial sector development, which includes two indicators:

- amount of credit, which financial intermediaries extend to private sector (as %of GDP);
- the level of stock market development (total cost of shares on the market, as % of GDP).

The World Bank Report shows that efficient protection of the private property institution and institute of competition can result in GDP growth (annual 2%) [2]. If the quality level of the institutional system reached the worldwide indicator in different countries, then GDP would double in Asian countries and would increase by 1.5 in Eastern Europe.

On average, improvement in quality of the structure of institutions by 1% allows the rate of economic growth to step up by 1.4%.

Thus, market potential of the modern institutes can exert significant influence on the economic growth, realization of human potential, transformation of the socio-economic systems towards enforcement of property rights, market competition, and a high level of economic freedom.

Existing institutes can be classified as follows:

- Judicial;
- Regulatory;
- Institutes of Human Capital Development;
- Institutes of coordination and risk distribution [1].

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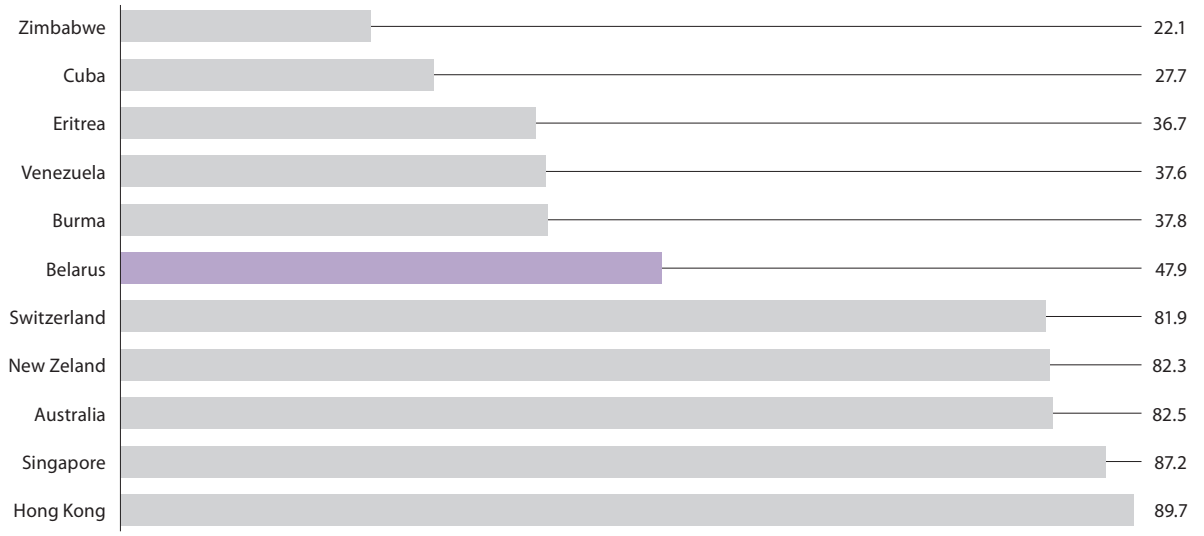
Figure 1: Countries with the highest and the lowest IEF in comparison with the Republic of Belarus



The most common indicator which characterizes the level of development of human capital is the Human Development Index (HDI), calculated be the United Nations Development Programme (UNDP).

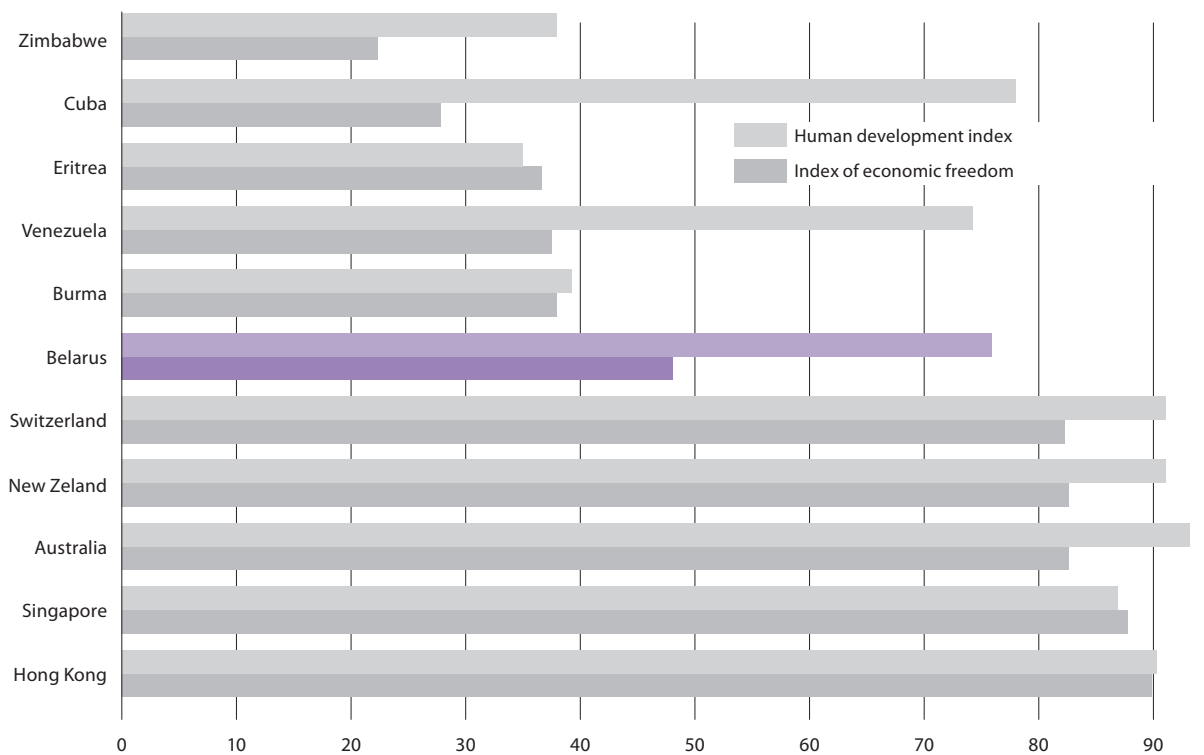
According to the 2011 Human Development Report, there are 47 countries with very high HDI value, 46 with high HDI value, 47 with medium and 46 with low HDI [3]. Norway ranks first. It stayed in first place for six consecutive years (2001-2006). Then Iceland passed Norway to take the top spot, but two years later Norway reclaimed its leading position. The Democratic Republic of the Congo ranks last.

In order to evaluate the quality of Human Capital Development Institutes two indices are used:

Index of Economic Freedom, which characterizes the degree of basic market institutions of economic freedom, competition, private property, etc. and consists of ten institutional factors:

- trade freedom;
- business freedom;
- financial freedom;
- government interference;
- monetary freedom;
- investment freedom;
- fiscal freedom;
- property rights;
- labor freedom;
- freedom from corruption.

Figure 2: Index of economic freedom and Human development index



Each one of the 10 freedoms is graded using a scale from 0 to100. The greater a country's score, the higher its level of economic freedom. All countries in the world are divided in five groups in compliance with its ranking:

- countries with a free economy (80 points);
- countries with a predominantly free economy (70-80 points);
- countries with a moderately free economy (60-70 points);
- countries with a predominantly unfree economy (from 50 to 60 points);
- countries with an unfree economy (under 50 points).

According to the methodology of the Index of Economic Freedom's calculations, as of 2011 there were 6 countries with a free economy and an index over 80: Hong Kong – 89.7; Singapore – 87.2; Australia – 82.5; New Zealand – 82.3; Switzerland – 81.9; Canada – 80.8 (fig. 1) [4].

When performing the analysis of the IEF scale (picture 3) in post-Soviet states, five evident leaders stood out: Estonia – 75.2; Georgia – 70.4; Lithuania – 71.3; Armenia – 69.7; Latvia – 65.8.

Russia is a line higher than Belarus with an index of 50.5. Ukraine occupied the second to last place – 48.8. Turkmenistan rounds out the list – 43.6.

The Knowledge Economy Index (KEI) designates the institutional factors for the formation, accumulation and utilization of human capital. Statistical data of the "Knowledge for Development" programme by the World

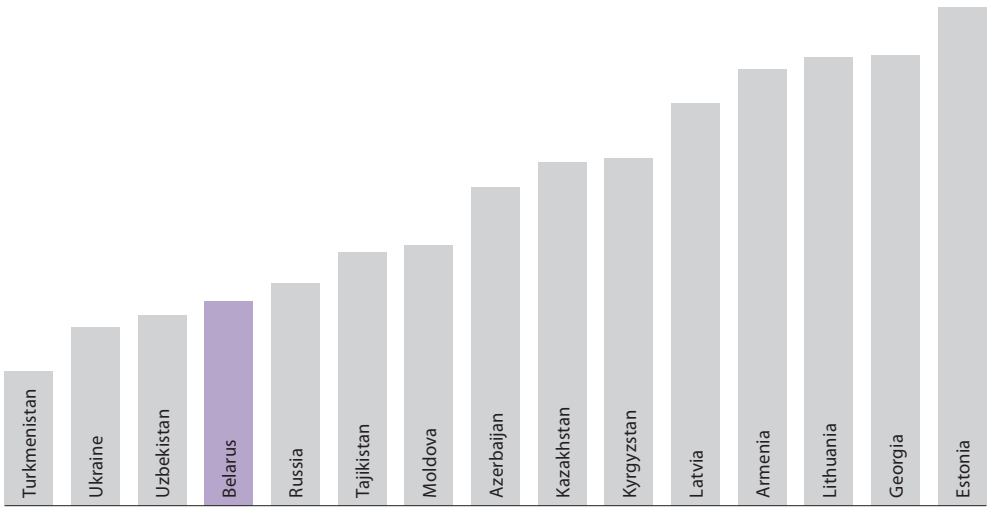


Figure 3: Index of Economic Freedom in post-Soviet states (2011)

Table 1: Knowledge Economy Index and values of aggregate sub-indices of post-communist states of Europe and Central Asia

Rank	States	Knowledge Economy Index	Knowledge Index	Institutional regime	Innovations index	Education	ICT
1	Estonia	8.42	8.31	8.76	7.56	8.32	9.05
2	Slovenia	8.15	8.17	8.10	8.31	8.31	7.88
3	Hungary	8.00	7.88	8.35	8.21	7.73	7.70
4	Czech Republic	7.97	7.90	8.17	7.78	8.23	7.70
5	Lithuania	7.77	7.70	7.98	6.70	8.40	7.99
6	Latvia	7.65	7.52	8.03	6.63	8.35	7.58
7	Slovakia	7.47	7.37	7.78	6.89	7.26	7.95
8	Poland	7.41	7.38	7.48	7.03	8.02	7.09
9	Croatia	7.28	7.28	7.26	7.67	6.56	7.62
10	Bulgaria	6.99	6.94	7.14	6.43	7.65	6.74
11	Rumania	6.43	6.25	6.98	5.74	6.47	6.55
12	Ukraine	6.00	6.58	4.27	5.83	8.15	5.77
13	Serbia	5.74	6.32	4.01	6.15	5.83	6.99
14	Armenia	5.65	5.37	6.48	6.25	6.36	3.52
15	Macedonia	5.58	5.66	5.34	4.67	5.42	6.88
16	Russia	5.55	6.82	1.76	6.88	7.19	6.38
17	Turkey	5.55	5.07	6.98	5.83	4.46	4.92
18	Georgia	5.21	5.15	5.36	5.22	6.46	3.78
19	Moldova	5.07	5.30	4.38	4.79	6.05	5.08
20	Kazakhstan	5.05	5.17	4.70	3.68	7.07	4.76
21	**Belarus**	**4.93**	**6.19**	**1.15**	**5.79**	**8.02**	**4.74**
22	Bosnia and Herzegovina	4.58	4.68	4.26	3.11	5.70	5.24
23	Kyrgyzstan	4.29	4.23	4.49	2.93	6.35	3.40
24	Albania	3.96	3.92	4.09	2.82	4.97	3.96
25	Azerbaijan	3.83	4.05	3.18	3.64	5.01	3.49
26	Uzbekistan	3.25	3.95	1.13	3.35	6.15	2.35
27	Tajikistan	3.22	3.33	2.88	2.01	5.53	2.46
	Europe and Central Asia	6.45	6.69	5.71	6.99	6.62	6.46

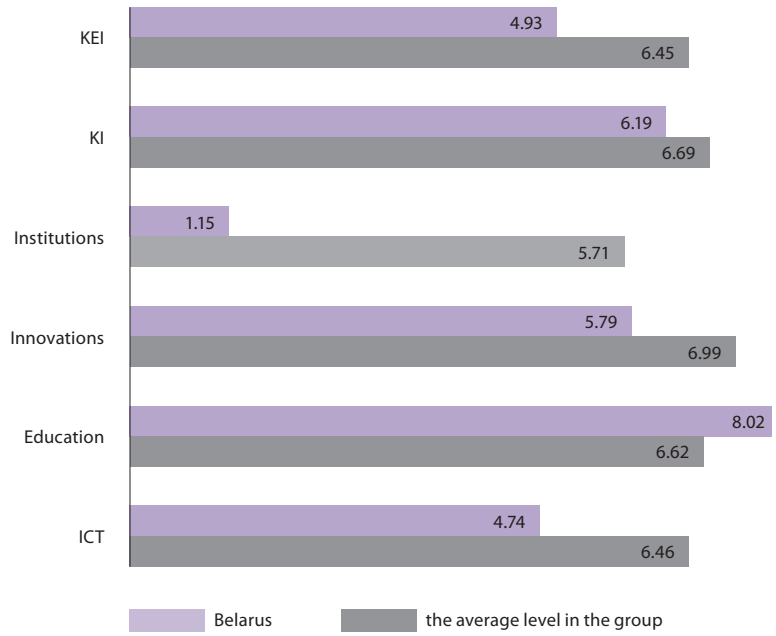


Figure 5:
Value of Knowledge Economy Index and aggregated sub-indices for the Republic of Belarus compared with the average level in the group of countries

Bank became a starting point for the analysis. The programme offers a complex of 83 criteria aggregated into 4 groups:

■ the "institutional regime"- shows to what extent economic and legal systems contribute to the formation, extension and appliance of knowledge, gives an insight into motives of effective utilization of existing and new knowledge, exerts direct influence on the processes of reproducing human capital, characterizes availability of funding for innovative projects, encouragement of education and professional development, and observance of intellectual property rights.

Figure 4:
Value of Knowledge Economy Index and aggregated sub-indices for the Republic of Belarus (2009)

Within this aggregated sub-index, 3 criteria are used:

■ level of tariff and non-tariff barriers;

■ quality of governmental regulation;

■ degree of law enforcement (based on estimation of criminal landscape, predictability of court system, contract law practice);

■ education characterizes the degree education in society, the existence of skills relating to the formation, spreading and application of knowledge (the average with respect to 3 criteria – the level of adult literacy, proportion of persons with secondary and higher education);

■ the national innovation system including firms, development-centres, universities and other organizations that receive and adapt global knowledge for local needs, create new knowledge and criteria based on it (the average with respect to 3 criteria – number of researchers in the field of R&D, amount of patents registered in the USA whose authors may or may not belong to that country, quantity of published articles in scientific and technical journals);

■ information and communication technology (ICT); the median indicator – availability of telephone services, prevalence of computer utilization, share of population using a computer [6].

Therefore, KEI is an average index of four criteria – institutional regime, education, innovation system, information and communication technology.

According to World Bank methodology, Belarus belongs to the post-communist countries of Europe and Central Asia group (table 1).

The low index level and place in the group ratings speaks to the need for carrying-out of an analysis and identifying the

causes of the current situation. The dependency diagram of aggregated sub-indices demonstrates the presence of institutional failure. The meaning of institutional regime index works out 1.15 (fig. 4).

As seen in the diagram, the knowledge index is 6.19, which is guaranteed by the high level of the education sub-index – 8.02. However KEI has shortened to 4.93 due to low institutional regime criterion which is only 1.15. Moreover, whereas the education sub-index in our country surpasses the average value in the group, the criteria of innovations, information and communication technology and institutional regime are considerably below average.

The economic analysis in post-soviet countries under KEI has shown the effectiveness of reforms carried out in the given field after the collapse of the Soviet Union until the present moment (fig. 6).

As with IEF, Estonia, Lithuania and Latvia dominate here. The reason for this is that these countries started to conduct market researches extensively when they gained sovereignty.

The changes in KEI sub-indices shown in the table 2 represent the following trends. In the group of the countries (Belarus, Russia, Uzbekistan) during the period under consideration a consistent trend of the institutional regime decline was observed. Significant positive changes towards formation of the economy of knowledge are happening in Baltic states.

Because KEI differs from the education index by the value of the institutional regime sub-index, the situation when KEI is smaller than the education index is evidence of the dysfunctionality of the institutional regime.

In the group of countries in the study, ranked by institutional security, the following trends have been observed (fig. 7).

Among the leaders in depth of institutional failure three countries stand out. The biggest failure is observed in Uzbekistan – 1.13, then Belarus follows – 1.15 and Russia rounds out the three – 1.76.

The comparison of KEI in Belarus with the worldwide average

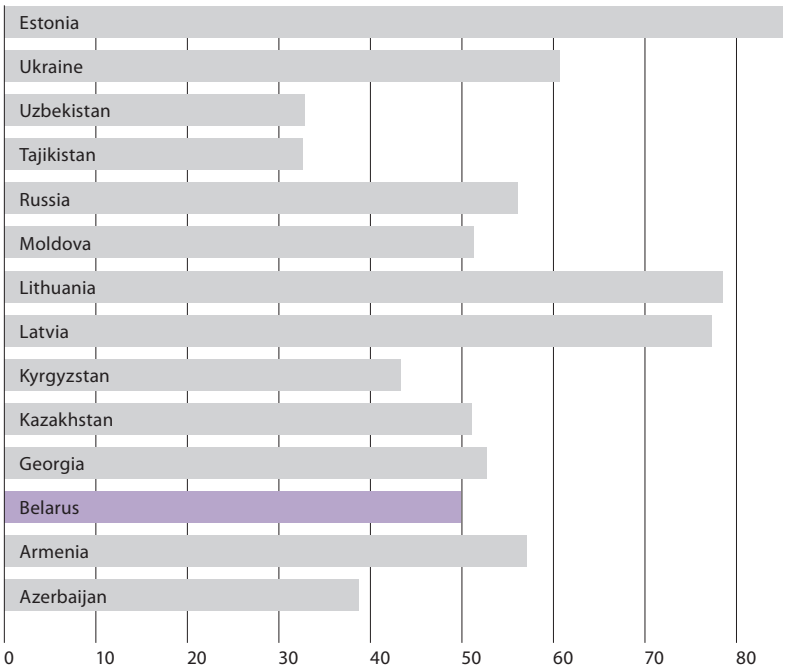


Figure 6:
KEI in post-Soviet countries

State	Institutional regime		Innovations index		Education index		ICT	
	1995	2009	1995	2009	1995	2009	1995	2009
Azerbaijan	0.61	3.18	5.08	3.64	5.62	5.01	2.27	3.49
Armenia	3.19	6.48	5.74	6.25	5.84	6.36	4.55	3.52
Belarus	1.92	1.15	6.75	5.79	7.97	8.02	3.22	4.74
Georgia	2.49	5.36	6.28	5.22	7.04	6.46	4.09	3.78
Kazakhstan	2.81	4.70	3.99	3.68	7.21	7.07	3.94	4.76
Kyrgyzstan	3.25	4.49	3.53	2.13	5.45	6.35	3.03	3.40
Latvia	5.75	8.03	3.98	6.63	7.23	8.35	6.30	7.58
Lithuania	5.11	7.98	6.20	6.70	7.15	8.40	5.74	7.99
Moldova	2.95	4.38	2.95	4.79	6.66	6.05	2.45	5.08
Russia	1.84	1.76	7.87	6.88	7.82	7.19	5.89	6.38
Tajikistan	0.08	2.88	1.68	2.01	6.42	5.53	1.74	2.46
Uzbekistan	1.23	1.13	3.77	3.35	6.63	6.15	2.01	2.35
Ukraine	2.17	4.27	6.68	3.83	7.87	8.15	4.81	5.77
Estonia	8.02	8.76	7.23	7.56	7.97	8.32	8.08	9.05

Table 2:
Value of KEI for post-Soviet states in 1995 and 2009

Figure 7:
Institutional failures in post-Soviet states

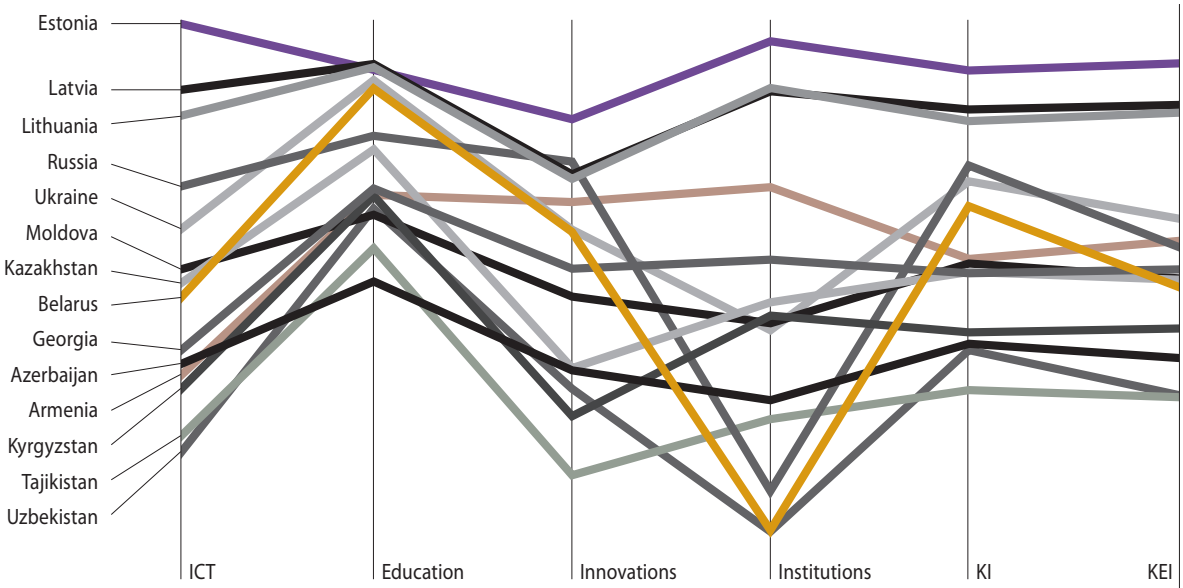
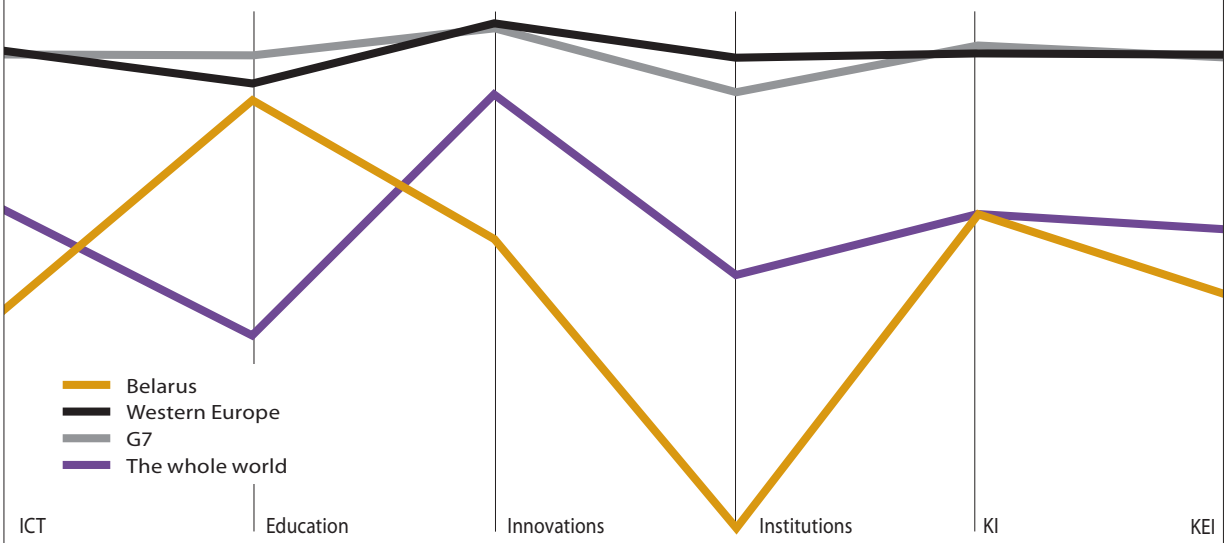


Figure 8:
Value of KEI and aggregated sub-indices of Belarus in regional section drawing



in the Western Europe, G7 (Great Britain, Germany, Italy, the USA, Canada, France, Japan) shows that the knowledge index in Belarus measures up the average level in the world which is 6.19 despite low criteria of the innovation system and ICT development (it's nearly twice higher than the worldwide average, fig. 8).

The considerable lagging behind of Belarus in KEI from Western Europe and the G7 is caused by notable difference in the innovation system and ICT and is exacerbated by the existing institutional failure. In order to avoid this, unsolved problems of the economy of knowledge formation should be mentioned. In particular, it is subject to formation of conditions for extended reprocessing of human capital which is possible under the condition of carrying out a system-based state policy in humanitarian fields and creation of corresponding institutional mechanisms. ■

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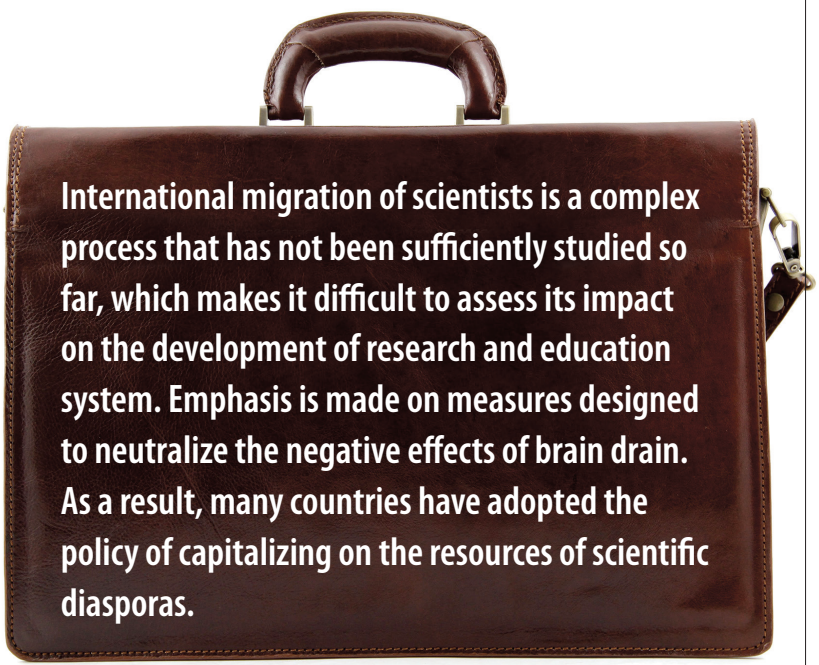
The Belarusian Scientific Diaspora:

Prospects for Cooperation



International migration of scientists is a complex process that has not been sufficiently studied so far, which makes it difficult to assess its impact on the development of research and education system. Emphasis is made on measures designed to neutralize the negative effects of brain drain. As a result, many countries have adopted the policy of capitalizing on the resources of scientific diasporas.

The article is published in the journal "Science and Innovations", 2013, #2

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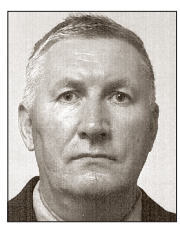

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The scientific diaspora is currently defined as a community of expatriate scientists who came from the same country of origin and continue their research abroad while trying to maintain contact with one another, as well as with their former colleagues in the native country.

Since as far back as the 1990s, the countries most affected by brain drain have been developing strategies aimed at attracting skilled expatriates back to the country. Since the beginning of this century, the number of returnees has increased tenfold. (1). In Brazil, China, India, Poland and other traditional exporters of intellectual capital, the backward flow of migrants has brought about a positive wave effect leading to the creation of returning expatriates networks, which , in turn, facilitates repatriation. These networks reflect new global trends, demonstrating the effectiveness of programs launched by a number of countries to encourage expatriate scientists to return home. Thus, China, which lost 320.000 professionals as a result of migration in the 1980s and 1990s, has special state programs designed to bring expatriate researchers back. Those who are willing to return are offered very attractive terms, including guaranteed positions, personal rates, high salary, housing, and a number of other privileges.(2)

As early as 2001, China had over 100.000 specialists who had returned home after working mostly in Germany and the United States.(3) It should be taken into account that in the 1990s and the first decade of this century, China considerably increased its scientific and technological capacity. Thus, funding for research and development in China was four times that in Russia, securing high growth rates in the number of scientists. Apart from that, China is implementing an active policy in higher education, encouraging young Chinese to study at American, European and Australian universities by financing their studies abroad. There are several million Chinese students studying abroad, with most of them returning to their homeland on completing their studies.

Migration of scientists abroad raises the question of collaborating with them. Over the past decade, Russia, Ukraine, and Belarus have witnessed a new tendency, however weak it may be, for highly skilled professionals to return to their countries of origin. During the 2008 - 2010 economic crisis, this tendency was somewhat enhanced since the familiar notion of developed countries stability was shattered.

	The National Academy of Sciences of Belarus	Higher education institutions	Research sector institutions
1. Scientists' migration rates would go up	33.4	38.6	19.1
2. Scientists' migration rates would go down	3.9	3.5	1.1
3. Scientists' migration rates would not change	32.7	40.4	50.8
4. Cannot answer	30.0	17.5	29.0

Table: Allocation of respondents' answers to the question" Which changes do you think should be expected in scientists' migration to foreign countries?"

In recent years there has been much debate in mass media about preferential measures aimed at enticing distinguished expatriate scientists back home. An important event in this connection was an international scientific conference "International mobility of scientists as a mechanism for integrating Russia into the global scientific community" that was held in Saint-Petersburg in 2009. The main message of the conference was that international migration of students is a significant part of international migration of highly skilled workforce, which facilitates the exchange of ideas, expertise, scientific approaches, and enriches the intellectual potential of a country. It is recognized that academic mobility has become an essential part of integrating Russian scientific community into the common European research and education area. Furthermore, carrying out joint research projects apparently facilitates international recognition of Russian science and helps overcome the limitations of isolated national research. At the same time, practice shows that scientific exchange programs, temporary job contracts, and opportunity for undergraduate and graduate students to earn their degrees abroad may well result in increased migration. The repatriation of scientists itself hardly causes any controversy. There are few, if any, people who object to it. What causes dispute is whether this process is worth the state support and public attention (6).

In 2012, researchers from the Institute of Sociology of the National Academy of Sciences of Belarus surveyed executive officers at research institutions and institutions of higher education about the specifics of human resource development in national science, including collaboration with

More than 409 respondents were polled in a survey based on multistage random sampling. 25% of respondents had a doctor's degree, 54.1% had a candidate's degree, 67. 4 % have been engaged in science for 20 years and more.

As follows from the results, when asked "Do you maintain contacts with expatriate scientists and academics who work in the sphere of science and higher education abroad?" respondents engaged in the sphere of higher education interacted more actively with expatriates (47.4%) than in the science sector (31.8%) and industrial sector (15%).

When asked "Do you consider that cooperation with expatriates is likely to benefit the Belarusian science?" more than half of respondents engaged in science sector agreed (52%). Those who disagreed accounted for 12.2%, and 33.4 % of respondents neither agreed nor disagreed. It's characteristic that respondents from the higher education sector most positively evaluated such cooperation. Thus 68, 4% of them responded that such cooperation could be very profitable for the Belarusian science, while in the industrial sector the corresponding figure was 65.2%. The amount of those who disagreed was negligible.

This research also studied respondents' opinions and assessment of the processes of intellectual migration. When asked "Did any of your colleagues move abroad for permanent residence?", 28.5% of the representatives of the science sector agreed. A still higher percentage of affirmative responses was found in the industrial (29, 2%) and higher education sector (29, 8%). The results obtained show that scientists' migration hasn't entailed any far-reaching consequences for the development of Belarusian research institutions. An outflow of highly qualified researches abroad was considered a problem by 4.9% of respondents in the science sector and 3.5% of respondents in the higher education sector.

Evaluation of the main tendencies of scientists' migration in the near future is presented in the table.

As follows from the data, the number of those who believe migration is likely to decrease is insignificant (not more than 4 %). However, the number of those who believe the opposite is several times greater. The percentage of respondents who expect that scientists' migration is likely to remain the same is still high.

Recent years have witnessed a tendency for return migration. Therefore, respondents were asked the following question" Did any of the expatriate scientists return to their home country and resume their work?" The highest share of positive responses was given in the science (12.5%) and higher education sector (12.3%) while the percentage of positive answers among the representatives of the industrial sector was much lower (5.6%).

To study the problems of collaboration with the scientific diaspora, a survey of research institution executives who had some experience in international

cooperation in the science sphere and maintained contacts with expatriates was conducted in November 2011. 29 executives were polled in the survey, more than half of them holding a doctor's degree (58.6%) and 34.5% had a candidate's degree.

When asked "Do you believe that cooperation with expatriates working in the sphere of science or higher education is likely to benefit your research team and Belarusian science on the whole?", all respondents were unanimous in their choice of a positive response.

While responding to the clarifying question "What are the advantages of such cooperation?", the largest share of respondents (79, 3%) said that "It may lead to new sources of research funding". The second largest share of respondents (74.2%) said about "the possibility of expanding international collaboration through institutions (networks, platforms, societies) we have had no access to before", the third largest share (62%) mentioned "an opportunity to publish papers in prestigious scientific journals which we haven't had didn't before". Highly evaluated was also a possibility to exchange information and get access to it (55, 2%).

Among the directions considered to be less beneficial are facilitating the integration into the global scientific community (27.6%) and an opportunity to work with sophisticated equipment at the institutions expatriate scientists work for (31%).

Worthy of attention are respondents' answers to the question "Do you think that the state science and technology policy aimed at promoting collaboration with expatriate scientists will boost international cooperation, as well as encourage foreign funding?" 65% of respondents preferred the average answer choice, namely "Enhancing collaboration with Belarusian scientific diaspora is worthy of attention, but we should not expect spectacular results from it". 27.6% of respondents chose the answer "Yes, it's a promising direction of state science and technology policy and it should be actively developed. Moreover, it's necessary to launch a special state program designed to develop collaboration with expatriate scientists ". As follows from the data presented, in spite of the fact that joint work with expatriate scientists is an important direction of international cooperation, one can hardly expect any significant results from it.

The survey studied the existing practices of collaboration with expatriate scientists. Respondents were asked: "What types of long-term collaboration with expatriate scientists do you use, if you have ever had such experience?" From the data obtained it follows that they mostly use exchange of information (75%), publish joint articles in Belarus and abroad (66.7 and 58.3% respectively), and carry out joint projects, including multilateral projects (58.3%). Among other forms of cooperation are participation in international scientific conferences (41.7%), participation in international projects contests held by BRFFR (the Belarusian Republican Foundation of Fundamental Researches) (41.7%), joint organization of scientific and technological events abroad (25%) and in Belarus (16.7%), lecturing at foreign universities at the invitation of expatriate scientists (16.7%), participation of expatriate scientists in the examination of Belarusian scientific and innovative projects. (8.3%).

The respondents were asked: "What do you think is the value of joint work with expatriate scientists?"60% of respondents selected the answer "Long experience of working together in the past". Every other respondent mentioned lack of a language barrier as an important factor, 33.3% have chosen "similar mentality", 25% marked "Deep mutual understanding in the process of scientific work". Thus, joint activity in the past is highly evaluated by most Belarusian researchers.

Contacts with expatriate scientists are an important part of international scientific cooperation which should to be taken into account in developing future state policy in this sphere. The Belarusian diaspora is a considerable intellectual resource for our country which needs to be taken advantage at to the full. Since the republic has had no uniform concept of collaboration with the Belarusian scientific diaspora so far, it is necessary to develop an effective mechanism for collaboration and its integration into the development of domestic science and higher education. In the short term, the most realistic option of incorporating the intellectual potential of expatriate scientists into the scientific and innovative sphere is its distance learning, that is, creation of a system and mechanisms using diaspora resource without reverse migration to the country of origin.

To Sum up, at present, brain drain isn't going in one direction only, reverse migration after a long stay abroad is becoming a usual practice for many countries. We are witnessing new tendencies for states to develop and implement new policies and often large scale aimed at creating attracting conditions for highly qualified returnees. Besides, there are other factors stimulating the backward flow of migrants, for example an increase in crisis problems in the country

of residence. A considerable number of expatriate scientists often return to their home country due to personal reasons of personal character. And finally, motives for return can include a combinations of several factors.

Since the rate of international intellectual mobility increase, its influence on the development of personnel potential of domestic science and the international scientific cooperation will also increase. Consequently, the relevance of creating a scientific policy designed to regulate intellectual migration, processes, is going to increase. Development of a system of measures for collaboration with the Belarusian scientific diaspora could significantly increase the efficiency of international scientific cooperation, and become a significant factor promoting neutralization of negative consequences of brain drain. ■

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Belarusians: ethnogenesis and link with other Slavic people in terms of DNA genealogy

The article is published in the journal "Science and Innovations", 2013, #3

> There is tremendous interest in studying the history of Slavic populations. It is considered that the Slavs appeared in the middle of the 1st millennium CE on the territories they occupy nowadays. Where they came from, where their ancestors lived until the middle of the 1st millennium, which languages they spoke – the academic science can not still answer these questions.

Principally important data can be obtained with the use of new science – DNA genealogy. The methodology of the new science allows to translate the dynamic picture of mutations in non-recombining parts of male sex chromosomes to chronological data, timespans to the most recent common ancestors of populations and, actually, common ancestors of the ancient clans and tribes. In the other words, using this methodology one can determine the period of time when ancient clans and tribes lived. At the same time "mapping these timespans" by regions, mainlands and the continents let to understanding the migration routes of our ancestors.

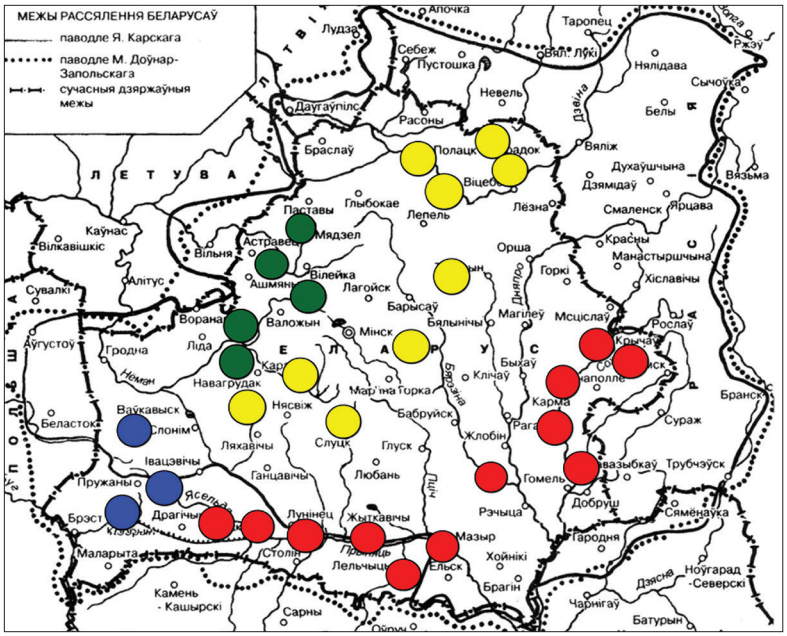
The analysis of the large dataset containing samples of ethnic Belarusians (more than a thousand haplotypes) was done in the study. It allows to make sufficiently deep generalizations regarding the knowledge of not so much the modern structure of the Belarusian people (it is a subject of popula-

tion genetics) as its ethnogenesis and relationships with other Slavic people under the angle of DNA genealogy.

Samples of Belarusian males who during individual questioning assigned their ethnicity and the ethnicity of their ancestors two generations back as "Belarusian" were analyzed in the study. These samples were collected by the scientists of the Institute of Ethnography and Folklore and the Institute of Genetics and Cytology of Belarusian Academy of Sciences, Belarus. The data about sampling points are represented on the map of settlement pattern of Belarusian ethnos (Figure 1).

There is the distribution of Y-DNA samples by the sampling points, the number of samples and the zone on the map (Figure 1), to which sampling points are referred, are indicated in the parentheses: Ponemanie – Volkovysk (A, n=16), Ivye (B, n=27), Molodechno (B, n=19), Novogrudok (B, n=56), Smorgon (B, n=37), Baranovichy (C, n=31); Poozerie – Gorodok (C, n=24), Lugesno and Gorodok (C, n=76), Polotsk (C, n=22), Ulla (C, n=56), Myadel (B, 3 n=9); Centre – Krupki (C, n=21), Mir (C, n=48), Slutzk (C, n=44), Cherven (C, n=29); Podneprovie – Vetka (D, n=15), Klimovichy (D, n=50), Krichev (D, n=34), Slavgorod (D, n=32), Chechersk (D, n=28); eastern Polesie – Gitkovichy (D, n=55), Lelchytsy (D, n=22), Mozyr (D, n=50), Svetlogorsk (D, n=28); Western Polesie – Pinsk (D, n=35), Luninez (D, n=51), Ivanovo (D, n=35), Bereza (A, n=31), Kobrin. (A, n=55).

Haplotypes are listed in the order of markers according to the standard FTDNA nomenclature: DYS393, DYS390, DYS19, DYS391, DYS385a, DYS385b, DYS426, DYS388, DYS439, DYS389I, DYS392, DYS389II,



Fugure 1.
The map of Belarus depicting location of inhabited places where the biological samples were collected. Zones on the map (circles) where the characteristic distribution of genealogical lineages was found are marked with different colors: A - blue, B - green, C – yellow, D – red.

DYS458, DYS337, DYS448, DYS460, GATAH4, DYS456, DYS438, and DYS635. Values for the marker GATAH4 are given according to the convention FTDNA standards. SNPs are known for 312 haplotypes of 1086 in the dataset. For the rest of haplotypes their assignment to haplogroups and subclades was performed by drawing trees, including both classified by SNP haplotypes and those for which such a classification was not done, isolation of the stable branches and assessment of their coalescence to a single common ancestor [1]. Composing haplotype trees was performed using software PHYLIP [2], methods Neighbour Joining and Fitch-Margoliash and graphical processing program MEGA 5 (http://www.megasoftware.net). Time spans to the common ancestor (TSCA) and errors were calculated according to the method described earlier [3, 4].

Mutation counting approach for the series of haplotypes was used. The mutation rate constant for the 17-marker haplotypes (Y-filer format) was equal to 0.034 mutation/haplotype/conditional generation of 25 years [4].

R1a1 haplogroup (SRY10831.2)

R1a1 haplogroup is represented by 551 haplotypes (50.7%) in this dataset, and the percentage generally coincides with the statistics for the neighboring Slavic nations - Russians, Ukrainians and Poles. Calculation using 545 haplotypes in the Y-Filer format, which does not have missing alleles, resulted in total 3143 mutations from the base haplotype:

13 25 16 10 11 14 12 12 10 13 11 30 15 14 20 11 11 15 11 23.

It corresponds to 5100±520 years to the common ancestor, what within the margin of error coincides with a value of 4550±475 years before the present (ybp), obtained with the same method as for the 258 17-marker haplotypes of Russians from the dataset [5], with the base haplotype as follows:

13 25 16 11 11 14 12 12 10 13 11 30 15 14 20 11 11 15 11 23.

The difference in one mutation (DYS390 10 11) for the 17 markers corresponds to 750 years between the base haplotypes. However, more strict consideration with the methods of DNA-genealogy gives the same

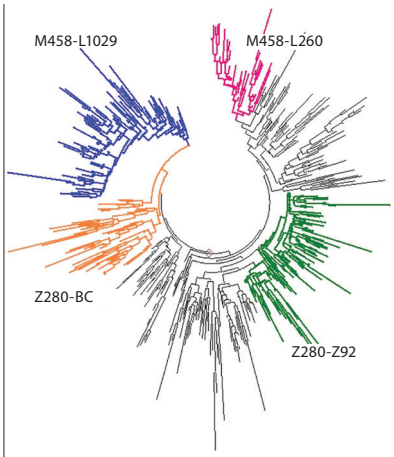


Figure 2.
A haplotype tree of R1a1 haplogroup composed of 551 haplotypes. Branches corresponding to the earlier defined ones of R1a1a1b1 subclade (Z283) are marked with color. Clock-wise, starting top-left: Western Slavic branch (M458, L260, 36 haplotypes), Northern Eurasian branch (Z280, Z92, 128 haplotypes), Balto-Carpathian branch (Z280, 88 гаплотипов, SNP has not yet been defined) and Central European branch (M458, L1029, 131 haplotypes).

ancestor for Russian and Belarusian bearers of R1a1 haplogroup. It is an ancestor of Eurasian R1a1a1b1 subclade (Z283) living about 5500 ybp. The Z283 subclade split into two main branches, found in all Slavs – European M458 subclade and Central Eurasian Z280 subclade [6]. The ratio of these considerably different lineages does not match between Russians and Belarusians (M458 subclade is smaller in the Russians), and the calculation across branches in heterogeneous datasets gives the impression of their different ages.

It would be more correct to analyze the array of Belarusian samples using division by branches, but due to a low resolution of the 20-marker haplotype tree this problem can be solved only partially. On the tree (Figure 2) only four branches of the potential 10-12 branches, found in the eastern Slavs, can be identified in the analysis of extended haplotypes from commercial databases. Central European branch of M458 subclade is significantly

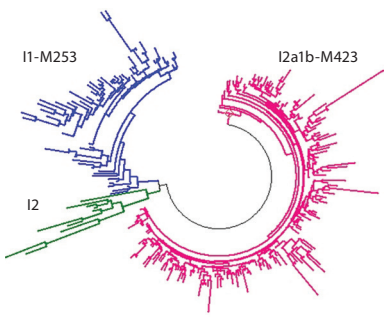


Figure 3.
A haplotype I tree is composed of 262 haplotypes. I1 haplogroup (M253, 61 haplotypes, highlighted in blue), "Dinaric" I2a1b branch (M423, 194 haplotypes, highlighted in magenta), I2 branches which differ from "Dinaric" branch (10 haplotypes, highlighted in green).

distinguished among them, it takes the upper left-hand side and is marked in blue (Figure 2). It consists of 131 haplotypes and converges to the base haplotype:

13 25 16 10 11 14 12 12 11 13 11 29 16 14 20 11 11 17 11 23.

It exactly matches by markers the base haplotype of Central European branch known in its extended format. The timespans to the common ancestor also match within the margin of error and equal to 2625±300 and 2900±400 ybp, respectively.

Western Slavic branch, the second branch of M458 subclade (upper right-hand side, marked in purple) comprises 36 haplotypes and points to their common ancestor of about 2150±320 ybp. The base haplotype matches the base haplotype of Western Slavic branch known in better resolution [6]

13 25 17 10 10 14 12 12 10 13 11 30 16 14 20 11 11 16 11 23.

However, a timespan to the common ancestor calculated for the 67-marker haplotypes is considerably bigger - 2700±300 ybp. The special study showed that the calculation for smaller number of markers in comparison with a calibrated 67-marker standard leads to the underestimation of this value. Bearers of Western Slavic branch in Belarusians does not stand out from the Western Slavic R1a-M458 branch in Europe.

Analysis of about 2000 extended haplotypes of Slavs from the commercial databases shows, that the absolute majority of the rest 384 R1a1 haplotypes (about 35% of the whole dataset) belongs to Eurasian subclade R1a1a1b1a2 (Z280) [7]. Other principal subclades, "South Eastern" R1a1a1b2 (Z93), Scandinavian R1a1a1b1a3 (Z284) and North-Western R1a1a1a (L664), were found at the level below 1% in Slavic people, and highly unlikely that the Belarusians are an exception.

The analysis of extended haplotypes and SNP showed that the subclade Z280 consists of many branches of different "age" and size. However, as a rule, on a tree of 20-marker haplotypes, they overlap, so they can be classified only by circumstantial features. For example, there are statistical data upon results of comparing neighboring nations with respect to extended haplotypes. This approach allowed us to identify two additional branches. First branch takes the sector at the bottom right of the tree (highlighted in green), consists of 128 haplotypes and converges to the following base haplotype:

13 25 16 11 11 15 12 12 10 13 11 30 15 14 20 11 12 15 11 24.

It coincides with the corresponding fragment of the base haplotype of Northern Eurasian branch (Z92), of its younger sub-branch, which is represented in commercial databases mostly by Russians, Belarusians and Ukrainians. Time to the common ancestor for 128 Belarusians from this list also coincides within the margin of error with the time to the common ancestor of the 67-marker haplotype branch - 2675±300 and 2350±250 ybp, respectively. Undoubtedly, both they belong to the same genealogical lineage.

The second branch includes 88 haplotypes and is located near the Central European branch on the tree (highlighted in orange). It has the base haplotype as follows:

13 25 16 10 11 14 12 12 10 13 11 30 15 14 20 11 11 16 11 23.

It coincides with the base haplotype of Balto-Carpathian branch, timespans to their common ancestors, 3750±450 and about 4300 ybp, respectively, point to the identity of these branches. In commercial databases, this branch is typical for

the Baltic countries, as well as for the Polish Pomerania, and its presence among Belarusians is quite natural.

The remaining 168 haplotypes can not be divided into stable branches in the existing 20-marker format. Together, they provide the base haplotype, which is very close to the Balto-Carpathian branch shown above:

13 25 16 11 11 14 12 12 10 13 11 30 15 14 20 11 11 16 11 23.

In this format, it coincides with the base haplotypes of Eastern Carpathian and Western Eurasian branches, as well as with the base haplotype of the whole Z280 subclade, split around 4900 ybp. Timespan to the common ancestor of Belarusians from the list (4200 ± 450 ybp) shows more in favor of the latter option, which is also consistent with the statistical data received upon the results of comparisons of Slavic extended haplotypes. This haplotype differs from the base haplotypes of Central European and Western Slavic branches of M458 subclade by 5 and 4 mutations, respectively. This gives the 4300 and 3325 years between them and taking in the consideration the age of branches themselves (2600 + 4200 + 4300) / 2 = 5550 and (2150 + 4200 + 3325) / 2 = 4800 timespans to the common ancestor of M458 and Z280 subclades. The same date 5500 ± 600 ybp (within the margin of error) was obtained after calculation using the 67-marker haplotypes. Therefore, previously expressed opinion on the same common ancestor of R1a1 subclade bearers in Russians and Belarusian can be considered valid. Naturally, five thousand years ago, he was neither Russian nor a Belarusian. Soon his family and descendants will move to the east and occupy the territories of modern Belarus and Russia, as well as adjacent territories, and his descendants will eventually become modern Belarusians and Russians of R1a1 haplogroup [6].

Haplogroup I (M170)

Haplogroup I takes the second place in Belarusians and encompasses 24% of the whole dataset. The tree has quite a simple structure and splits into the two homogenous branches with relatively recent common ancestors, and also includes small (less than 1% of the dataset) group of haplotypes of other branches (Figure 3).

A common ancestor of the haplogroup I1 in Belarusians lived 3700±450 ybp and had a base haplotype as follows:

13 23 14 10 14 14 11 14 11 12 11 28 15 16 20 10 10 14 10 22.

The same data were obtained after calculations using extended haplotypes. In the 20-marker format branch can not be split into sub-branches. Therefore Belarusian haplogroup I1 can be considered indistinguishable from the others, which are distributed mainly in northern Europe.

I2a1b branch (formerly known as I2a2) is even more homogenous branch represented by 194 haplotypes. The branch has a base haplotype as follows:

13 24 16 11 14 15 11 15 13 13 11 31 17 15 20 10 10 15 10 23.

It coincides with the base haplotype of "Dinaric" branch which was found overwhelmingly in Slavs with its maximum frequencies in Bosnia and Herzegovina. However, the timespan to the common ancestor calculated for the Belarusian dataset was considerably greater than that obtained after calculations using extended haplotypes - 3200±350 and 2200±250 ybp, respectively. To elucidate the reasons of the discrepancy a model calculation for the reference dataset of

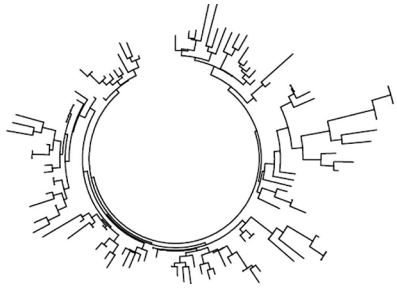


Figure 4.
A haplotype tree of N1c1 haplogroup composed of 109 haplotypes.

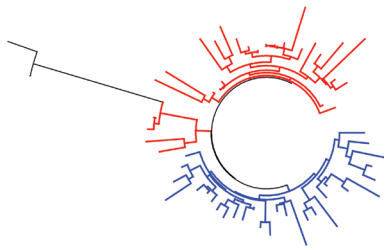


Figure 5.
A haplotype tree of R1b1a2 haplogroup composed of 58 haplotypes. The branch which presumably belongs to the "Eastern" R1b1a2a1 (L150) subclade takes the upper part of the figure and is marked in red. Haplotypes assigned to the Western European R1b1a2a1a (L51) subclade take the lower part of the figure and are marked in blue.

67-marker haplotypes of I2a1b branch was done using the same method as that employed for the Western Slavic branch. As it was expected, calculation for the 17-marker panel gave overestimated values which exactly coincided with data obtained for the Belarusians. Therefore, all I2a1b "Dinaric" branch bearers, independently on the region, have the common ancestor who lived 2200±250 ybp.

Disparate haplotypes of presumably I2a2 subclade (formerly known as I2b1), do not compose separate branches, and can be today regarded as a minor group.

N1c1 haplogroup (Tat)

Similar to the branches of haplogroup I, N1c1 haplogroup composed from the Belarusian 109 haplotypes is pretty homogenous. It is difficult to divide it into sub-branches (Figure 4). This haplogroup has the base haplotype as follows:

It is the Southern Baltic branch (N1c1a1a1-L550 according to the ISOGG) having the base haplotype in the full 67-marker format as follows (matching alleles are labeled):

14 23 14 11 11 13 11 12 10 14 14 30 – 17 9 9 11 12 25 14 19 28 14

14 15 15 – 11 11 18 20 14 15 17 19 36 36 13 10 – 11 8 15 17 8 8 10 8 11 10 12 21 22 14 10 12 12 17 7 13 20 21 16 12 11 10 11 11 12 11 (Southern Baltic base haplotype)

The timespan to the common ancestor of Belarusians is 3825±400 ybp. This value is on 1000 years higher than that obtained after calculation using 67-marker haplotypes. Model calculation with usage of the dataset of Southern Baltic branch gave the same value of the timespan to the common ancestor as for the 67-marker haplotypes – around 2700 ybp. Numerically N1c1 haplogroup embraces 10% of Belarusians what is considerably less than in ethnic Russians (14%) [5, 8], however, it is more compared with 6-7% in the ethnic Russians with respect to the Southrn Baltic branch only.

R1b1a2 Haplogroup (M269)

R1b1a2 haplogroup is the most common haplogroup in Western Europe. 58 haplotypes of Belarusian dataset (5.3%) belong to this haplogroup what practically coincides with the statistics in Russians (4.8%) [5, 8]. The tree splits into two branches, each branch includes 29 haplotypes. The first branch is descended from the common ancestor who lived 3725±520 ybp. Its base haplotype is as follows:

12 24 14 11 11 14 12 12 12 13 13 29 16 15 19 11 11 15 12 23.

The second branch has almost the same "age" – 3825±520 ybp, but its base haplotype differs from the base haplotype of the first branch by 5 mutations:

13 23 14 10 11 14 12 12 12 13 13 29 17 15 19 11 11 16 12 23.

The first base haplotype coincides with the corresponding fragment of the 67-marker haplotype of R1b1a2a1 (L150 +, L51-) branch with a common ancestor of 6000 ybp. R1b1a2a1 is very rare in Western Europe, but it is typical for a number of ethnic groups of the North Caucasus and Transcaucasus (Armenians, Georgians, Assyrians, Ossetians, Dagestans), Eastern Europe (Bashkirs, Tatars, Czechs, Greeks) and Central Asia (Turkmens, Kazakhs, Uighurs), and Ashkenazi Jews. The second base haplotype is one of the variants of European branches of R1b1a2a1a (L51 +) subclade. According to the current classification ISOGG there are 155 branches in R1b1a2a1a (L51 +) subclade. The difference in 5 mutations between "Western" and "Eastern" base haplotypes corresponds to 4300 years between them and results in (3725 + 3825 + 4300) / 2 ≈ 5900 years to their common ancestor what within the margin of error coincides with the timespan to the common ancestor of R1b1a2a1 (L150) subclade. Relatively recent lifetime of the ancestor of "Eastern" branch in Belarusians, perhaps, says that representatives of some sub-branches of R1b1a2a1 (L150) subclade dominated among Belarusians. R1b1a2a1 subclade is still insufficiently studied in comparison with other Western European branches.

E1b1b1 haplogroup (M35.1)

The percentage of E1b1b1 haplogroup bearers in Belarusians is relatively small (4%), at about the same level as that of other European nations, inhabitants of non-Mediterranean countries. The base haplotype of E1b1b1 haplogroup is as follows:

13 24 13 10 16 18 11 12 12 13 11 30 15 14 20 9 11 16 10 21

It coincides with the base haplotype of E1b1b1a1b (V13) branch, which is the most represented in Europe. But the timespan to the common ancestor calculated for the extended European haplotypes V13 differs from that obtained for the Belarusian dataset - 3600 and 5750±700 ybp, respectively. Calculation using 17-marker fragments of the reference dataset V13 gave 4250±450 ybp to the common ancestor. The obvious reason of this discrepancy is the same like it was discussed above for the N1c1 haplogroup: overlap of several widely separated branches. Insufficient resolution does not allow a reliable separation along the branches, which leads to "overestimation" of timespan to the common ancestor at the expense of haplotypes which are not assigned to E1b1b1a1b subclade.

Haplogroup J (P209)

33 haplotypes (3% from the whole dataset) are assigned to the haplogroup J. The branch composed of 13 haplotypes with an ancestor of 3100±600 ybp has the base haplotype as follows:

12 24 15 10 13 17 11 15 12 12 11 28 16 16 19 11 10 13 9 21

It differs by only one mutation (highlighted in red) from the base haplotype of J2b2a branch (L283), having "age" of 4000 ± 450 ybp and scattered at a low frequency throughout Europe, but almost never occurred in the Middle East. Obviously, 13 Belarusians belong to the same quite rare European branch of the haplogroup J2. Traces of another rare genealogical lineage are found among haplogroup J1 bearers that form a fairly compact branch with the base haplotype as follows:

13 24 14 10 13 19 11 13 12 13 11 29 19.2 14 21 11 11 15 10 21

This small branch with the common ancestor of 3000±650 ybp differs by 5 mutations (highlighted in red) from the base haplotype of J1* branch (DYS388=13) with an age of around 5000 years and typical for countries of North Caucasus.

For the latter branch SNP Z1842 has been found, which is still not indexed in ISOGG. The 5-mutation difference in this format corresponds to the 4300 years between haplotypes and results in (3000 + 5000 + 4300)/2 = 6150 years to the common ancestor of both Belarusian and North-Caucasian datasets. Therefore, haplogroup J1 bearers from Belarus compose the branch, which can be a sub-branch of a Caucasian subclade. Contrary to common definition that haplogroup J1 is a Semitic haplogroup, early splinted Z1842 branch does not contain haplotypes of neither Arabs, no Jews. Therefore it is extremely unlikely that considered 8 haplotypes is a trace of Ashkenazi Jews that embraced up to 20% of the population before the First World War.

Haplogroups C3, G1, G2a, N, Q, R1b1a1, R2, T

32 haplotypes (3% of the whole dataset) are distributed among the rest of haplogroups. 15 of them belong to G2a haplogroup. Their base haplotype is as follows:

14 22 15 10 14 15 11 12 11 12 11 29 17 16 21 11 11 15 10 21.

It coincides with the base haplotype of the parent branch of G2a1c2a subclade (P303, formerly known as G2a3b), typical for the North Caucasus, but occurred at a low frequency throughout Europe and, according to the findings of fossil DNA, representing one of the main genealogical lineage of Neolithic Europe [9]. Timespan to the common ancestor of Belarusian haplotypes (7200±1100 ybp) coincides within the margin of error with evaluation for P303 subclade (around 6300 ybp). Obviously, if not all, but a significant part of this haplotype bearers in Belarus belongs to G2a1c2a subclade.

Single haplotypes from other branches are collected on the right side of the tree. Their assignment was done by search for close haplotypes in commercial databases and with the program by Whit Athey (http://www.hprg.com/hapest5/). At least nine haplotypes of them can be attributed to the lineages of the Central and East Asian origin. These haplogroups are C3 haplogroup (M217), G1 haplogroup (M342), N1b haplogroup (P43, N1c2b in the current annotation), Q1a2 haplogroup (M25) and R1b1a1 haplogroup (M73). They are very few in number, at the level of one percent, as in the Russians. And those that are, perhaps, partially inherited from the Lithuanian Tatars, whose relocation from Crimea to the Grand Duchy of Lithuania in the XV century is well documented. Tatars lost their language early and started to speak the old Belarusian language, and some of them were baptized, thus merging with Belarusians.

The analysis showed that the same Y-chromosome lineages with the same common ancient ancestors are found in both Russians and Belarusians. Therefore, these two East Slavic people close in their origin since they are descended from the same groups of ancient populations. The differences mainly concern the percentage of these lineages, as well as geographical distribution for some of them. It should be understood that, although haplotypes, identified in the genetic structure of ethnic Belarusians and Russians, share ancient common ancestors (with the base haplotypes described above), this does not mean that these ancestors lived (whether they lived) on the territories occupied by modern ethnic groups. The question of who specifically from the descendants of ancient genealogical lineages eventually

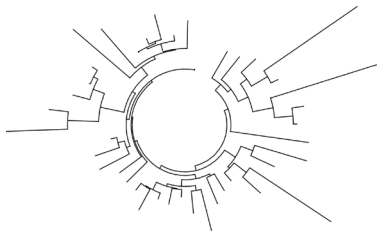


Figure 6.
A haplotype tree of E1b1b1 haplogroup composed of 41 haplotypes.

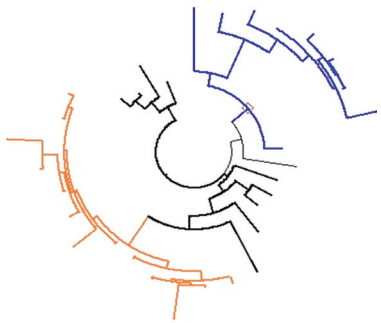


Figure 7.
A haplotype tree of haplogroup J composed of 33 haplotypes. The J1 haplogroup (Z1842) takes the upper right-hand side (8 haplotypes, highlighted in blue). The branch J2b2a (L283) is on the lower left-hand side (13 haplotypes, highlighted in orange).

settled in a given territory is more complicated. Analysis of the geographical distribution of Y-chromosome lineages illustrates the problem more clearly.

Statistically significant results of such analysis can be obtained from Table 1 containing data for Slavic people, as well as for Balto-Slavic (Lithuanians), the nearest neighbors of Belarusians.

An important feature of the analyzed dataset of ethnic Belarusians is that DNA samples were collected mostly in rural areas. District centers usually tend to accumulate the local population that, despite many wars, remained stable and in historical times was not influenced

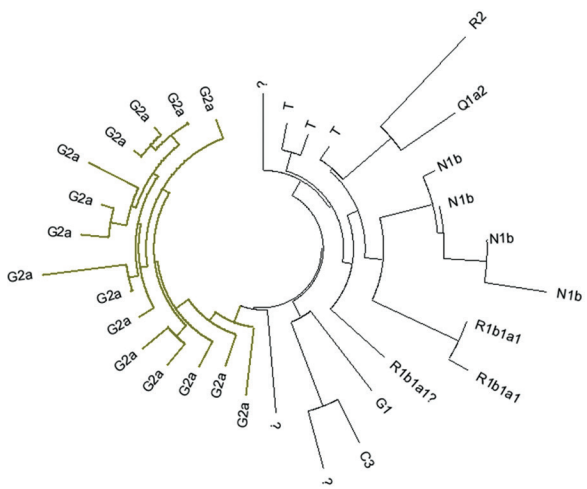


Figure 8.
A haplotype tree of minor haplogroups composed of 32 haplotypes

Ethnos	Belarusians					Russians	Poles	Croatians	Lithuanians
Zone	A	B	C	D	Total				
N	122	178	351	435	1086	545	825	1100	256
R1a-Z280	18.9	20.2	14.2	13.6	15.5	21.5	21.1	22.0	13.6
R1a-CE	13.1	9.6	12.3	12.6	12.1	6.0	9.4	…	5.0
R1a-NEA2	9.8	11.8	13.4	11.0	11.8	10.8	1.7	…	7.2
R1a-BC	3.3	6.7	8.5	9.7	8.1	6.4	5.7	…	7.9
R1a-WS	1.6	4.5	4.0	2.8	3.3	3.2	17.2	…	1.4
I2a1b	17.2	7.9	16.5	23.2	17.9	11.7	6.4	37.8	3.5
N1c1	7.4	14.6	11.7	7.8	10.1	14.3	5.8	0.4	46.5
I1	9.8	6.7	3.7	5.5	5.6	9.5	7.5	5.5	5.5
R1b1a2	8.2	8.4	4.8	3.7	5.3	4.8	12.6	7.9	3.9
E1b1b1	2.5	2.8	4.3	4.1	3.8	2.9	2.7	10.7	0.8
J2	4.1	1.1	2.6	2.1	2.3	2.9	3.6	6.2	1.6
G2a	0.8	1.7	0.6	2.1	1.4	1.8	1.3	2.7	1.2
J1	0.8	0.6	0.9	0.7	0.7	0.9	0.2	1.1	0.0
I2a2	0.0	0.6	1.4	0.2	0.6	0.2	2.2	1.5	1.2
Others	2.5	2.8	1.1	0.9	1.5	2.9	2.4	4.2	0.8

R1a branches are designated as CE – Central European, WS – Western Slavic, NEA2 – Northern Eurasian sub-branch (Z280+, Z92+) with the ancestor of 2350±250 ybp, BC – Balto-Carpathian, Z280 – the other branches of R1a, indistinguishable in the 20-marker format. Haplogroup distribution data for Russians, Croatians and Lithuanians were taken from the references [5, 10, 11], respectively. Statistical data for Poles were obtained from Polish FamilyTree DNA (FTDNA) project. R1a1 haplotypes distribution along branches was received from the IRAKAZ database [7], currently containing 3126 R1a1 haplotypes with a length of 67 and 111 markers. Because of the lack of statistically significant data for Croatians, only the cumulative percentage of R1a1 bearers is shown in the table.

by external migrations. With a relatively uniform representation of historical and ethnographic regions (Figure 1), this gives reason to believe that the geographical distribution of genealogical lineages of Belarusians may provide additional information about their ethnogenesis.

Since the distribution of some genealogical lineages in Belarus has a clear gradient (I2a1b, R1a-Z280, Table 1), the use of average values for the analysis will be obviously incorrect. For this reason and taking into account the peculiarities of the pool of haplotypes, data on sampling points were distributed between 3 zones: B – northwestern territory immediately adjacent to Lithuania; C- center of Belarus and part of Poozerie; D - Polesie and southern part of Podneprovie. In addition to these three westernmost sampling points, Volkovysk, Kobrin and Bereza (part of the Western Polesie and southern part of Ponemanie) were assigned to the zone A, because there is no factual basis to refer them to the zones B, C or D.

The special position of the zone B, bordering with Lithuania, can be clearly seen from the distribution of branches in the zones. In the zone B the percentage of I2a1b branch bearers is considerably reduced (8% versus 18% on average in Belarus) while the percentage of N1c1 branch bearers are increased (15% versus 10% on average in Belarus). With increasing the distance from Lithuania (zones C and D) percentage of N1c1 bearers naturally decreases and percentage of I2a1b bearers grows. If we compare these data with the statistics for Lithuanians (4 % of I2a1b branch and 47% of N1c1 branch), it is obvious that this trend can be explained by the contribution of the Baltic ancient ethnic groups to the ethnogenesis of Belarusians. An additional argument in favor of such a classification is that N1c1 haplogroups bearers are represented solely by Southern Baltic branch (L550 +) as in Lithuanians and as in Belarusians in the commercial databases. In Russians, that include descendants of assimilated Finno-Ugric people, this branch encompasses not more than 40-50% of all N1c1 bearers. These data also suggest that the contribution of Finno-Ugric people of the Russian Plain to the ethnogenesis of Belarusians was minimal, or was absent at all.

Branches of R1a1 haplogroup do not show statistically significant correlations with geography: they are distributed quite evenly in Belarus. Northern Eurasian branch (Z92), one of the main genealogical lineages of Belarusians, Russians and Lithuanians, but rarely occurred in the western and southern Slavs, has a special position. In the zone A, bordering with Poland, we can also note a higher proportion of bearers of I1 and R1b1a2 haplogroups - 10% and 8% vs. 6% and 5% on average in Belarus, respectively. The rest of the genealogical lineages which together embrace 10% of Belarusians are too small to make such estimations.

Belarusians occupy "strategically" important region between Balts in the north and Ukrainians in the south, between Poles in the west and Russians in the east, to the north of the Carpathians, where there were multiple migration routes of ancient Slavic tribes. From the point of view of interaction and interference of ethnic groups it might be interesting to analyze the distribution of genealogical lineages in the territories adjacent to neighboring ethnic groups (Table 1).

Such analysis shows that between Belarusians from the zone A and Poles significant differences within the Northern Eurasian and Western Slavic branches of R1a haplogroup are revealed, as well as between R1b1a2 and I2a1b haplogroups. The same tendency was observed at the

comparison with the zone B. There is a significant difference between Belarusians from the zone B and neighboring Lithuanians (R1a-Z280, R1a-CE, R1a-NEA2, R1a-WS). When comparing the territories adjacent to Russia (zones C and D), attention is drawn to the difference within R1a haplogroup (R1a-Z280, R1a-CE, R1a-BC) and between I2a1b and I1 haplogroups.

Thus, differences identified with neighboring ethnic groups may indicate that, despite the origin from the common ancestors (the existence of common ancient genealogical lineages), the historical development of the modern Belarusian nation had its own characteristics that are unique to this area.

Joint analysis of dates and distribution of genealogical lineages in Belarusians and the neighboring nations makes it possible to outline several waves of settlement, which contributed to the ethnogenesis of modern Belarusians. The earliest dates are traced back to the period of the 4300 years ago when the growth of Balto-Carpathian R1a1 branch, as well as parent branches of Western and Central Eurasian branches of the same Z280 subclade started. The majority of bearers of haplogroup I1 in Belarusians and Russians are, most probably, related to the same wave. This wave can be called autochthonous as genealogical lineages of those who have previously lived in this area, could have been vanished, and their Y- chromosome haplogroups are unknown to us.

The next wave is associated with the spread of the Southern Baltic N1c1 branch which started 2700 ± 300 years ago. Currently, the peak prevalence of this branch is observed in Lithuania and Latvia, but it does not necessarily mean that its ancestor lived there. Haplogroup N1c1 is of Asian origin, and therefore no less likely that its Southern Baltic branch formed somewhere east and its bearers came to the shores of the Baltic Sea later. Since the time and routes of migration of respective ethnic groups are not yet known, this wave is difficult to correlate with any of its contemporary archaeological cultures.

Finally, the third key date is the middle - end of the 1st millennium BCE. It corresponds to the rapid growth of the "Dinaric" I2a1b branch (2200 ± 250 years ago), Northern Eurasian R1a1 branch (2350 ± 250 years ago), as well as several sub-branches of Z280 subclade, which are not allocated on a 20-marker haplotype tree (Fig. 2), but were characterized by extended haplotypes [6]. Based on the geographical distribution of these lineages it is obvious that they spread from different centers. Rather, there were counter-migrations from the south or south-west (I2a1b and some branches of Z280) and from the Baltic Sea (Northern Eurasian R1a1 branch). It is very possible that the latter branch is originated from Belarus. The picture with M458 subclade is not entirely clear. It splits into branches 3000-2700 years ago. But based on the data that its peak prevalence was in the Czech Republic and Poland and then the decrease in the number was observed in the eastern direction one can conclude, that, bearers of M458 subclade, which is quite distinct from Z280, could appear on the territory of Belarus later, perhaps, with the same migration waves described above. Representatives of these genealogical lineages now constitute the basis of all Slavic people without exception - modern people as well as assimilated Germans, Hungarians, Romanians, Greeks, and Turks. There is every reason to associate this chain of demographic events with migrations of Slavs and distribution of Slavic languages. As can be seen from the analysis of dates and geography, it is doubtful that all these events are related, but yet those different people fall under the same archaeological culture. This apparently explains the unsuccessful attempts to link the original homeland of the Slavs to any particular place and date. Considering

all facts one can conclude that their formation was extended in time and space. Details of this process remain to be seen, but no doubt that the territory of Belarus played a key role in it.

Thus, the studies have shown that the main Belarusian haplogroups are R1a1 (51% of all considered haplotypes, with a common ancestor of 5500 ybp), I2 (18%, with a common ancestor of 2200 ± 250 ybp), I1 (6%, with a common ancestor of 3700 ± 450 ybp), N1c1 (10% , with a common ancestor of 2700 ± 400 ybp). Those haplogroups are unevenly distributed across Belarus.

The same Y-chromosome lineages with the same ancient common ancestors are represented in ethnic Belarusians and Russians. Therefore, both the East Slavic people are close in their origin and are descended from the same ethnic groups.

However the contribution of ancient Baltic ethnic groups to the ethnogenesis of Belarusians clearly stands out: bearers of N1c1 haplogroup in Belarusia are represented by exclusively Southern Baltic branch (L550 +).

The contribution of the Finno-Ugric people of the Russian Plain to the ethnogenesis of Belarusians was minimal, or absent at all. It distinguishes Belarusian and Russian ethnic groups: in Russians, that include descendants of assimilated Finno-Ugric people, the Southern Baltic branch embraces not more than 40-50% of all N1c1 bearers.

The presence of minor haplogroups of Central and East Asian origin indicates some degree of assimilation of the gene pool of "Lithuanian" (Crimean) Tatars in the gene pool of Belarusians. At the same time the analysis did not reveal in the gene pool of Belarusians lineages found in Ashkenazi Jews. Thus, from the genetic point of view Belarusian and Jewish ethnic groups, despite the long-term coexistence, did not interact.

Differences identified with neighboring ethnic groups may indicate that, despite the common ancestors (the existence of common ancient genealogical lineages), the historical development of the modern Belarusian nation had its own characteristics that are unique to this area.

In general, according to DNA genealogy Belarus is a common Slavic zone with the Slavs of Eastern Europe in terms of their common migration history and common timespans to the common ancestors of DNA genealogical lineages. ■

Acknowledgements

The authors are sincerely indebted to Dr. Alexander S. Zolotarev for assistance in preparing the manuscript and fruitful discussions.

The article was accepted on December 3, 2012.

The article was translated from Russian into English by Dr.rer.nat. Alena Shyla.

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Summary

A series of 1086 Y-chromosomal 20-marker haplotypes from Belarus was analyzed in terms of DNA genealogy. It was found that these haplotypes belong to Eastern Slavic (R1a1), North-Western Slavic (I1), Southern Slavic (I2), and Southern Baltic (N1c1) tribes, and detailed analysis of history of the tribes was presented.

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MOBILE ENTERPRISE: HOT WORD OR REALITY?

The article is published in the journal "Science and Innovations", 2013, #11

Mobile technologies have not just provided new tools of communication for us, but have changed the way of our everyday lives.

Total mobilization

Nowadays it's so convenient and usual to stay connected even on the beach or at a summerhouse in the country. We take for granted the opportunity of watching sport shows on the internet or reading news as fast as they emerge in the online media. Most of us can't imagine life without mobile banking, interactive maps and navigators, virtual personal managers and assistants, online translators etc.

As expected in the near future we'll also change our understanding of work. If today our presence at the office is almost unavoidable, tomorrow this maxima can become looser. Availability of smartphones, tablet computers and other mobile devices together with the extremely rapid development of mobile application market will make it possible for an employee to work from any point of the world at any time of day and night.

As a consequence several analytical agencies forecast the coming of business environment total mobilization and the age of the so called mobile enterprises. Is such a forecast reasonable and value added? What are the main distinctive features of these mobile enterprises and are these differentiative features real? Can we foresee a "mobile revolution" in Belarus?

Let's define the terminology

Wikipedia uses "mobile enterprise" as a term to "describe a corporation or large organization that supports critical business functions and use of business applications via wireless mobile devices" [1]. It means that project and document management, customer relationships, access to the corporate web site, calendar, address directory, email and other information resources are being handled by tablet PCs or smartphones via special mobile business applications [1].

Leonid Chernyak, the editor of "Open systems. DBMS" has another opinion. He notes that the implementation of mobile devices doesn't mean an enterprise becomes truly mobile. For this to happen it must be seen an increase in speed and quality of the business processes and the overall efficiency of a company based on mobilization.

The authors do not deny the importance of efficiency as an indicator of useful implementation of mobile technologies, but consider such an approach for mobile enterprise definition too vague. For example, if a company uses mobile phones just as a tool

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for corporate communications and this is being done efficiently, allowing pretty fast communications with low costs, we could call this company a mobile enterprise. But this kind of "mobility" obviously do not have any sense in the context of our topic.

The definition offered by Tennenbaum Institute deals not with efficiency, but with the ability of an enterprise to adapt to environmental changes. Such adaptivity is based on "processes and technologies which offer tools and allow access to all resources of a company enabling by this collaboration of employees, customers, partners and suppliers whatever location they have" [2].

So, even such a short review shows different methods of defining of a mobile enterprise.

Perhaps the difference in definitions is rooted from the difference in meanings of the very word "mobility". We should clearly understand at least two cases here: (1) mobile as flexible, versatile, agile, and (2) mobile as based on mobile technologies.

The authors think the main classification criterion for tagging a company as a "mobile enterprise" label should be the second one – the depth of "penetration" of mobile technologies into the business processes. If this penetration leads to the breakthrough and game-changing new business processes we can easily talk about a truly mobile enterprise.

Just two examples.

The usage of POS-terminals takes retail companies to the new orbit: no need of a physical point of sale, no territory restriction, no "schedule of work". It's enough to have agents with mobile POS-terminals, who deliver products at time and place convenient for a customer (for example, on Sunday at his/her summerhouse). A customer can make a payment via his/her banking card or money deposited on his/her phone account and get a receipt after this. And the transaction will be automatically fixed in the corporate information system.

We know that the so called 24x7 service in reality means the service only within working hours for many IT companies. Top-management just asks employees to check their emails accounts during weekends or even nighttime if possible and respond the most critical calls. Of course if an employee needs a desktop version to handle a problem of company clients he/she is naturally not eager to spoil their free time. Implementing mobile version of service desk systems or remote software support tools can make it truly "wherever whenever" kind of servicing.

Thus a company gets a bunch of competitive advantages by investing in mobile technologies. What are they? Let's look closer.

Faster. Cheaper. More productive

Of course, we cannot fully rely on advantages of mobile business solutions found in advertisements of its supplier, but having this in mind we can use them as a starting point.

Let's look at, for example, excerpts from the list made by InterraIT [3]:

- [Mobile technologies] connect employees from anywhere and hence increase productivity.
- These solutions allow employees to work according to their convenience and ensure that they can perform their job smartly and even faster.
- Using mobile apps reduces the cost as it cuts down the cost of other equipment needed to work like marketing and sales.
- It ensures the optimum utilization of resources such as inventory data, customer information and sales and marketing data etc.
- These apps provide a centralized way to perform business operations.
- Such solutions provide CRM apps to offer superior customer service and apps that can easily handle customer queries and problems.
- Confidential and important information like customer data, mails can easily be accessible when required. The exchange of reports and information and data from anywhere allow to make quick decisions and saves lots of time.
- Create awareness among employees about what is going on in their project team and allow them to make quick and right decisions.
- Ensures the availability of centralized communications both outside and inside an organization including clients, customers, stakeholders and vendors etc.

Mark Jordan, Senior Product Manager of Sybase Company adds the possibility to hire more experienced and high-qualified specialists to this list, including specialists living in other countries. He also notices that decreasing documents circulation helps to lower office expenses of a company and in case if employees use their own mobile devices – hardware expenses as well [4].

The analysts of the Yankee Group Company based upon the results of the conducted by this marketing agency research of American mobile enterprises market, gives a number of quantitative measures. According to them, enterprises

using the special mobile business applications can "increase the field selling time by 28%, the win rates by 26% and the forecast accuracy by 25%. They also can eliminate the redundant activities (by 27%) and reduced the sales calls costs (by 25%)" [5]. Eventually such enterprises get a lot of advantages which help them to increase the productivity by 45% [6].

According to the words of Stefan Stieglitz and Tobias Brockmann – German researchers of the processes, connected with the transformation of traditional enterprises into their mobile form – the full-scale implementation of mobile devices not only increases the efficiency of business processes execution but also causes the revision and changes of the corporate strategy [7].

On the other side

Not denying attractive perspectives and opportunities which an enterprise gets after the total mobilization of all its business activities, we should notice that the implementation of mobile business technologies supposes a number of technological, financial and organizational problems. Such business transformation imposes specific requirements not only on the IT-infrastructure of the company, but also on the mobile business applications market.

Technological infrastructure. A mobile enterprise must have an adequate network and telecommunications equipment as well as the necessary amount of wireless mobile devices. Certainly, it is not a big problem to buy the needed hardware, but we should remember about the equipment that is already being used by companies. In practice each enterprise has its own park of high-performance desktop computers and notebooks and the expenditures related to the purchase of new equipment are too considerable in order to immediately insist on global hardware modernization.

As a possible solution of this problem the BYOD-concept could be taken into account. This concept supposes that employees can bring their own mobile devices and use them for work. The company provides them with access to business applications and corporate information resources. Such approach allows to lower the capital costs on retooling and modernization considerably upon condition that the market offers the sufficient amount of cross-platform mobile applications.

Though we can't speak about the worldwide expansion of the BYOD-concept yet, there is a number of impressive examples. The share of employees using their own devices at work reached the value of 75% in 2012 in Brazil and Russia [8].

Mobile applications market. Besides hardware a mobile enterprise requires a special software – mobile applications which allow to execute all business processes in the company by using wireless mobile devices. In spite of the fact that the mobile applications market is actively growing and according to the experts forecasts reaches the value of 174$ Bln in 2017 [9], there is no reason to speak about complete business customers satisfaction.

First of all, the market runs short of full-featured cross-platform mobile applications. Most of the available corporate applications are aimed at the usage of specific devices or platforms and thereby can be useless for the enterprises using an other kinds of devices.

Secondly, developers have to simplify the functionality of mobile applications with a view to mobile traffic economy and it can put in question the creation of such kind of business applications which the enterprises really need.

And finally, the main problem according to Andrey Tikhonov – the head of corporate sales department of Samsung Electronic Company in Russian region – is the absence of the formed ecosystems market in the countries of the former USSR. Meanwhile there is no other way to develop a good business application, consistent the requirements of a mobile enterprise except the cooperation between vendors, system integrators, mobile operators and business customers [10].

Disadvantages of the mobile enterprise. Generally speaking a mobile enterprise has only one main disadvantage, which is closely related to the list of its advantages. Transfer of all business communications and working processes into the Internet makes such an enterprise dependent on the stability and safety of the communications channel. Too high network traffic or negative external conditions (natural disasters or technological cataclysms) can break off a connection and disrupt the regular activities of the company.

Mobile stakeholders for new type of economics?

What is the position of mobile enterprises among the other business entities in Republic of Belarus? Are they

able to play main roles on the economic scene? And if no, when could it happen?

The authors can't afford to make the detailed forecast with the specific dates and description of national economics transformations, related to the consequences of the modern mobile technologies implementation. It should be mentioned that the process of evolutionary transformation of traditional economics to its informative electronic form not only has a place but gradually gathers speed. In such circumstances the further progressive growth in this direction seems as more presumable scenario than the revolutionary breakthrough. It is evident that the mobile technologies will play very important role in this process.

The owner of the biggest Belarusian media portal Yuri Zisser in one of his articles determined the number of basic attributes indicative for new type of economy.

First of all, the increasing number of companies, providing different services via Internet (online payments systems, e-banking, e-insurance, etc.).

Secondly, some business processes of traditional enterprises are being transformed and realized in the electronic form (sales via web-stores, online booking and reservation systems).

Thirdly, the increasing share of Belarusian mass media, distributed and available exclusively via Internet (in form of information and news portals, distributed via RSS-subscription or by direct email distribution).

Fourthly, increasing popularity of the Internet television (IPTV), providing to the subscribers an access to the hundreds TV-channels at the convenient time.

Fifthly, spread of different web-services, content of which being created and updated by efforts of their direct users (different forums, blogs, photo- and video hosting services, social networks).

Sixthly, more availability of the high-speed mobile Internet access. As a consequence people will be able to use wide range of digital services in any time and in any place.

Seventhly, the information technologies and mobile technologies in particular are being actively used for internal and external forms of business communications (videoconferences, online presentations, webinars, etc.).

And finally, the information technologies are becoming an integral part of the state management (electronic government, electronic passports, electronic voting) [11].

It's not so easy to appreciate, if the implementation of wireless technologies into the productive and managerial processes is an objective and obligate consequence of the scientific and technological progress or it's only the result of aggressive marketing efforts of different mobile applications developers highly motivated to expand beyond the B2C-market limits and get access to the enormous business software market. Anyhow, the fact of the "mobilization" of our working processes becomes too evident in order to deny it, while the advantages of numerous mobile services become too visible in order to ignore them. ■

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INNOVATIVE TECHNOLOGY FOR POTASH INDUSTRY WASTE PROCESSING

The article is published in the journal "Science and Innovations", 2013, #6

JSC "Belaruskali" is one of the world's largest producers and suppliers of potash fertilizers holding about 20% of the global potash market. Large-scale mining and processing of silvinite ores have a serious negative impact on the ecosystem in the area, which comes out primarily in the earth's surface subsidence above the worked out underground workings and in the use of large areas of native lands for storage of mining wastes.

Ore mined at the Starobin deposit is composed of clay, sodium and potassium chlorides, among which only the latter is of industrial interest. Other two components are wastes. Sodium chloride is stored on a surface in the form of piles, and the clay suspension in a saturated saline solution - in special sludge storage (lagoons), which are also costly structures. They cover vast areas of arable land; require the creation salt protection screens to prevent soil salinization and penetration of brines into groundwater. In addition, in order to save space they need depth of 20-40 m and are surrounded by high banks. However, despite the efforts, the long-term existence of salt ("dead") lakes causes great harm to the region's ecology.

For more than fifty years of operating Starobin mines deposits accumulated more than 800 million tons of wastes on a total area of over 1.500 hectares. With current methods of ore dressing as well as plans to expand production their number will only grow as the most eco-friendly way of storage (in depleted aquifers) is not applicable in the hydrogeological conditions Soligorsk mining region.

Besides the environment, it is necessary to take into account the economic aspect of the problem. In addition to the cost of waste storing much more substantial financial losses appear due to the fact that the liquid phase of saline suspension contains potassium chloride, and its annual losses reach the amount to about 3% of total production. In fact, it is not waste sludge stored, but secondary raw materials, however, its use is practically impossible, since it is necessary to separate the liquid salt phase.

This problem for decades attracted the attention of chemists and miners , but so far attempts to develop clay sludge dewatering technology were not successful. For example , drying with heat treatment is highly power-consuming option, as the clay in suspension is very fine and retains moisture very well. The use of modern filtration equipment (centrifuge-decanter, filter press, Figure 2) based on a mechanical spinning in case of clay-salt dispersions are also not effective. Absence of large particles or agglomerates of small solid particles of clay in the sludge makes it technically impossible to separate the dispersions using different kinds of filter partitions and, on the other hand fine composition of the suspension significantly reduces the efficiency of separation in the centrifugal force field. Moreover offered methods are not enough focused on resource savings and do not allow to get useful components (primarily potassium) from clay-salt sludge.

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Scientists of the Institute of General and Inorganic Chemistry of NAS of Belarus developed new technology for dewatering of clay-saline suspensions based on phase separation using polyacrylamide flocculants. Targeted use of polymers provides structuring of clay sediment and allows to mechanically separate liquid phase (brine) from the solid on a standard filter equipment.

Fig. 1 shows photographs of the clay-salt suspension without polymer, with polymeric flocculant and clay product after separation of brine. It is characterized by a low concentration of soluble salts contains about 70% clay and 30% moisture. This product is well compatible with the mineral substances and organic nature, it can be used in agricultural chemistry, construction, forest management, etc. It should be mentioned that for the application of dewatered materials they need to be processed into a marketable product (for example, to a granular form).

Granulation technology of dewatered clay-salt sludge into granules developed by scientists of the Institute of General and Inorganic Chemistry provides a high strength, low dusting and

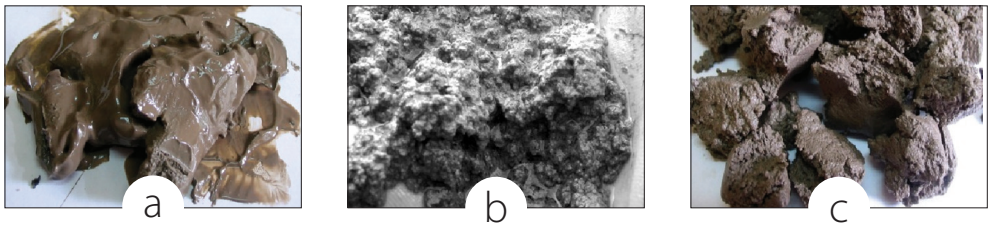

Figure 1.
Photos of saline suspension of clay without treatment with flocculant (a), treated with flocculants prior to dewatering (b) and dewatered on a belt filter press (c)

caking granules, that are optimal for the transportation, storage and use. Additionally, there are options for their enrichment during the granulation of mineral fertilizers and other additives that increase the agrochemical value of the product. Granulated product passes extensive testing as a long-acting fertilizer and an ameliorator. It was found that for agrochemical effects on yield and quality of crops (sugar beet, corn, winter grain crops, perennial grasses, potatoes) new potash fertilizer is not less effective to the standard one and gives a positive effect on agro soil properties. Its high efficiency appears due to the fact that new formultaion besides potassium chloride comprise mineralized components (clay minerals, sodium), which are not synthetic, which are natural compounds in complex form and are better absorbed by plants. At the same time the mineralized part does not dissolve in soil moisture and swells slowly and gradually breaks down to release water and nutrients whereas the resulting clay-mineral aggregates give better structure to the soil particles.

Fertilizers derived from clay-containing raw component potash ores, like any new product, are of particular interest. There are concerns related to the possibility of soil oversalination, although, as noted above, the salt solutions in the liquid phase dewatering technology are removed from the product. In our climate the amount of salt that accumulates in soil using standard potash, is 1-2 % of the permissible level. New fertilizer applied to the soil at the same level as potassium increases the rate to 2.3%. Thus, it does not make sense to speak of soil salinization in this case. Of course, processing technology and use of new products as granular fertilizers require many tests, however, because of their composition properties, natural origin and the absence of harmful components, we can talk about the environmental safety and the possibility of using them agricultural chemistry.

Other interesting and promising areas of application of structured clay materials may also include the area of forest management in the field of forest roads construction and protective coatings for the road slopes, as well as waterproofing and as shielding materials for the treatment of burial sites of household and municipal waste. It is planned to create a new production of granular products for various industries, primarily agriculture and forestry.

Thus, the introduction of the new integrated technology for processing can help to fully utilize large-tonnage waste of potash production, which is currently the source of environmental pollution, at the same time providing a gradual transition from the liquid waste to a granular product (Fig. 3). Suspension of clay in brine is flocculated by polymers and liquid phase is separated on filtration equipment and then is returned to the process, thus providing significant economic benefits by increasing the extraction of potassium. The solid phase is granulated, if necessary – with various additives for the use in a particular area. ■

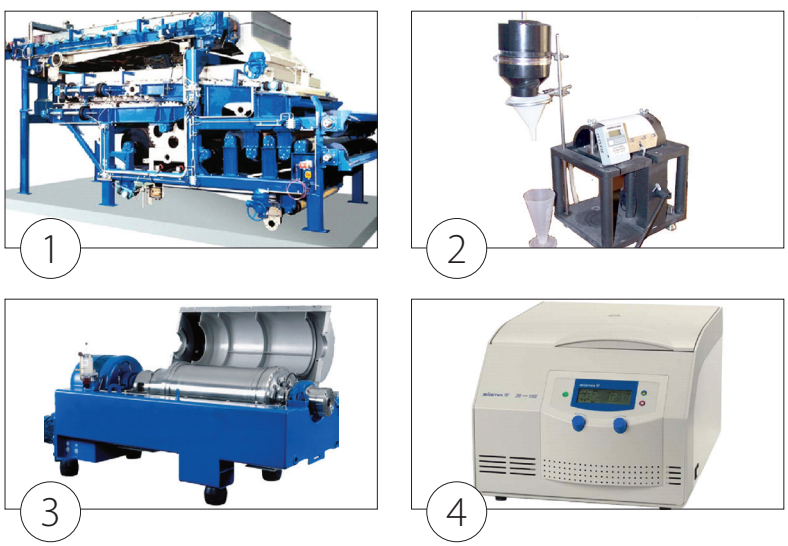

Figure 2.
Modern industrial and model equipment for dewatering of various suspensions . Industrial equipment: belt filter press - 1; decanter centrifuge-- 3; chamber filter press - 5. Model laboratory equipment: belt filter press - 2; decanter centrifuge-- 4; chamber filter press

Figure 3. Stages of complex technology for processing of liquid potash production waste: Liquid potash production waste in sludge ponds (a); after separation of the solid phase from the salt solution (b); granular solids - a product ready to use (c)

Laser spectroscopy of processes with molecular oxygen participation

The article is published in the journal "Science and Innovations", 2013, #3

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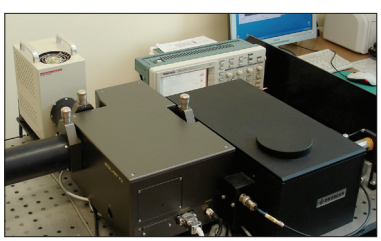
Molecular oxygen (O_2) is one of the most important molecules in the world. The vast majority of living aerobic organisms use O_2 to produce energy in cellular respiration. This is the following reaction $O_2 + 4H^+ + 4e^-$ $2H_2O$. The standard oxidation potential of this reaction is +1.23 eV. Therefore, O_2 reduction to H_2O requires four protons and four electrons. In natural systems, this reaction is catalyzed by special hemeproteins. Successive reduction of an isolated O_2 molecule is accompanied by the release of reactive oxygen species – O_2^-, O_2^{2-}, and some others. These intermediates are very toxic to the body, but they are not released during respiration, if cells are functioning normally.

It is well known that O_2 reactions with the majority of compounds occur very slowly under a low temperature and an ordinary pressure. Thus, from a chemical point of view, molecular oxygen is relatively inert, although in the ground state it has two unpaired electrons being a biradical. Of course, there is an explanation of this extraordinary chemical property of O_2. Realization of the abovementioned respiration reaction with a simultaneous collision of all reagents is very unlikely. Under normal conditions, reduction occurs sequentially. It is known that the addition of the first electron to O_2 is thermodynamically unfavorable because of the negative redox potential for the pair O_2/O_2^- (–0.33 eV). This ensures the kinetic stability of substrate molecules. In the case of two-electron reduction of O_2, it is prohibited by the Wigner's low of spin conservation during physical processes and chemical reactions.

There is another active form of molecular oxygen, the so-called singlet oxygen, $^1O_2$ ($^1\Delta_g$). Being in $^1\Delta_g$-state, molecular oxygen overcomes spin forbidenness on reaction with other molecules that are in the singlet ground state. $^1O_2$ molecule is capable of very effectively destroy organic materials. This property is found to be useful for technology and medicine. First of all, photodynamic therapy (PDT) of cancer should be mentioned, where singlet oxygen is the main chemical agent effecting on cancer cells and destroying them.

In the laboratory of molecular photonics of B.I. Stepanov Institute of Physics, using the methods of laser kinetic spectroscopy, we study processes and reactions involving molecular oxygen both in the ground state and in the lowest excited singlet state. The main attention is paid to O_2 reactions with hemoglobin and myoglobin. Joint efforts of these two hemeproteins ensure delivery of molecular oxygen from the external environment to tissues, where the abovementioned multi-step reaction of the O_2 reduction to water takes place. It should be noted that hemoglobin is an interesting physical object. It possesses unusual nonlinear cooperative and magnetic properties, which ensure self-regulation during saturation with oxygen, as well as fast response to changes in physiological and biochemical conditions of the surrounding medium.

Hemoglobin is capable to bind sequentially four molecules of oxygen with increasing affinity. It is quite difficult for hemoglobin to bind the first



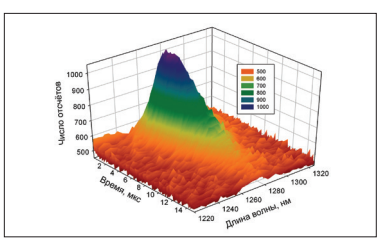


Fig.1 and 2. Laser fluorometer and three-dimensional time-resolved spectra of singlet oxygen luminescence obtained using the fluorometer

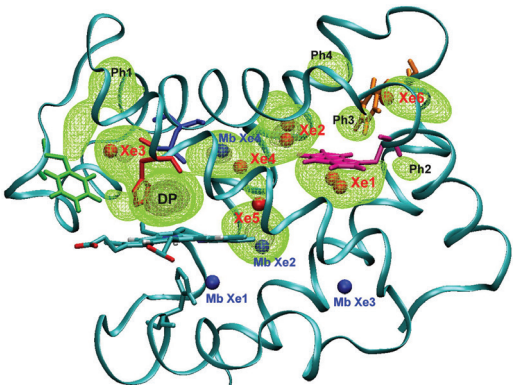


Fig. 3. Density maps of O_2 migration within the isolated α chains of human hemoglobin.

The O_2 probability density is depicted by colored isosurfaces. Xe atoms bound in human hemoglobin α subunits and sperm whale myoglobin are shown for comparison. Xenon sites for the α subunits and myoglobin are represented by red and blue spheres, respectively. The location of the distal pocket is labeled as DP. Polypeptide backbone is represented by cyan ribbons. Fig. also shows the following amino acid residues in color: Trp14 (magenta), Leu29 (blue), Phe46 (green), His58 (red), His87 (cyan), and Phe117 (orange).

molecule of oxygen, but the next three molecules are associated much easier, especially the fourth one. Accordingly, hemoglobin returns the fourth molecule with difficulty and much easier the other three molecules. It should be noted that the hemoglobin's binding sites are formed by the ions of heme iron.

Myoglobin is similar to hemoglobin but it is simpler protein. Myoglobin accepts molecular oxygen from hemoglobin and delivers it to cytochrome c-oxidase, which is a protein that reduces molecular oxygen to water.

Under normal conditions of the body functioning, molecular oxygen binding to hemoglobin or myoglobin is the dark reaction. This makes it difficult to study kinetics and dynamics of molecular oxygen binding in detail. However, it was found that oxyhemoglobin (hemoglobin with bound oxygen) is sensitive to light. Irradiation of oxyhemoglobin leads to dissociation, i.e. to iron–oxygen bond rupture, and an appearance of free molecular oxygen, which begins to migrate within the protein matrix. However, only about 10% of molecular oxygen escapes from the protein, where organism is waiting for them. The remaining 90% move in complex inner paths, come back and bind with iron. Why is this happening? Addressing this issue is crucial for biophysics, biochemistry, and medicine. In particular, knowing the answer, it will be possible to design intelligently blood substitutes instead of the complicated procedure of accumulation, storage and usage of donor blood.

The abovementioned dissociation of molecular oxygen, its subsequent migration inside and outside of the protein, and molecular oxygen rebinding occur in the time range from 10^{-13} to 10^{-1} s. Thus, to study these processes we should apply spectroscopic techniques with appropriate temporal resolution. Necessary measurements cannot be performed using only one experimental setup or device. In the laboratory of molecular photonics, laser facility has been created. A set of several experimental setups, each of them operating in a specific time range, has been made. Using these techniques, we obtained a complete kinetic description of molecular oxygen rebinding from within the protein matrix of hemoglobin. Moreover, using molecular dynamics simulations we got the full kinematic description of molecular oxygen migration inside the protein.

It is known that carbon monoxide is close in a size to molecular oxygen. Last year, a group of American and French physicists at the European Synchrotron Radiation Facility (Grenoble, France) investigated the migration of carbon monoxide within hemoglobin. To study this process, the scientists used an X-ray crystallographic technique with a time-resolution of $1.5 \cdot 10^{-10}$ s. We are pleased to note that, to analyze the data of these sophisticated measurements, the foreign colleagues used the results of our research performed in 2004-2010.

To observe singlet oxygen directly, say, during PDT, the most convenient way is to control its luminescence. However, for a number of reasons, its luminescence is very weak. For example, in water, only one from every 10 million molecules emits light in the near infrared region.

The laboratory of molecular photonics has great experience in the study of physical and chemical properties of singlet oxygen. So, in 1978, an original method to detect and record the luminescence of singlet oxygen has been proposed and implemented. This method has been generally accepted through the world. Usage of modern ultra-sensitive photomultipliers resulted in further development of this method. In 2008 in the laboratory, highly sensitive laser fluorometer has been developed for detection of luminescence in the range of 950-1400 nm and, subsequently, for construction of a complete spectral and temporal picture of this radiation. Then, in 2010, a new unique device called a laser spectrometer of singlet oxygen has been designed and constructed. The aim of this setup is to study the dynamics of photosensitized singlet oxygen luminescence in solutions, cell cultures or biological tissues with nanosecond time resolution. Monitoring of spectral and kinetic properties of singlet oxygen luminescence will make it possible to trace the appearance and disappearance of singlet oxygen in the medium, in particular during PDT. It will provide an opportunity to optimize the light regime of tumors destruction methods for purpose of experimental and practical photomedicine. ■

Genetic risk factors of obesity and overweight

The article is published in the journal "Science and Innovations", 2013, #10

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According to the World Health Organization (WHO) obesity is increasingly spreading and becoming a serious problem of the 21st century. "Obesogenic" environments developed due to overconsumption of food and sedentary life is observed in economically developed countries with redundant food resources. From 30–80% of adults have overweight in the countries of the WHO European Region [1]. Obesity in children is very dangerous since it will result in developing serious chronic diseases [2].

Human obesity indices are comprised of several anthropometric criteria. A case of obesity is diagnosed in adults, when body mass index (BMI) is equal or exceeds 30 kg/m2. For children and adolescents, age, sex and BMI are considered in total. However BMI doesn't take into account the ratio of muscle and fat muss therefore additional anthropometric indices are applied such as waist circumferences (to assess the quantity of abdominal fat), hip circumferences (to provide information about gluteal-femoral muscle mass and bone structure) and waist/hip ratio (WHR) [3].

The adipose tissue is very important body organ for maintenance of energy balance and valuable metabolism. The main pathways of energy balance regulation consist of interactions between hypothalamic neurons and hormonal signals secreted from peripheral organs (distal gastrointestinal tract, adipose tissue, stomach and pancreas) (fig.1). Two neuron pools in the arcuate nucleus play an essential role in this system: the first produces agouti-related protein (AGRP) and neuropeptide Y (NPY) and the second secrets pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART). NPY/AGRP neuron activation reveals orexigenic effect, promoting food intake while POMC/CART neuron complex produces an opposite anorexigenic effect reducing energy expenditure and appetite [4]. Several peripheral organs send information to neurons through endocrine hormones. Adipose tissue secretes leptin, which through the leptin receptor (LEPR) inhibits the NPY/AGRP neurons and stimulates the POMC/CART complex. Pancreas secretes insulin sending orexigenic signal to the hypothalamus arcuate nucleus. The stomach and duodenum secrete ghrelin stimulating the orexigenic NPY/AGRP neurons which through the growth hormone secretagogue receptors (GHSRs) inhibit the POMC/CART neurons through the release of -aminobutyric acid (GABA). The peptide YY3–36 (PYY3–36) is secreted from L-cells of the distal gastrointestinal tract and through Y2 receptors (Y2Rs) signals produce an inhibitory effect on the orexigenic NPY/AGRP neurons. The orexigenic and anorexigenic signals are transmitted by the NPY/AGRP and POMC/CART neurons to second-order downstream effector neurons where are expressed the Y1 (Y1R) and the melanocortin 4 receptors (MC4R) as well as dopamine, serotonin and endocannabinoid inputs are transformed [4].

There are monogenic forms of obesity caused by mutations in any of the genes coding leptin–melanocortin axis (leptin

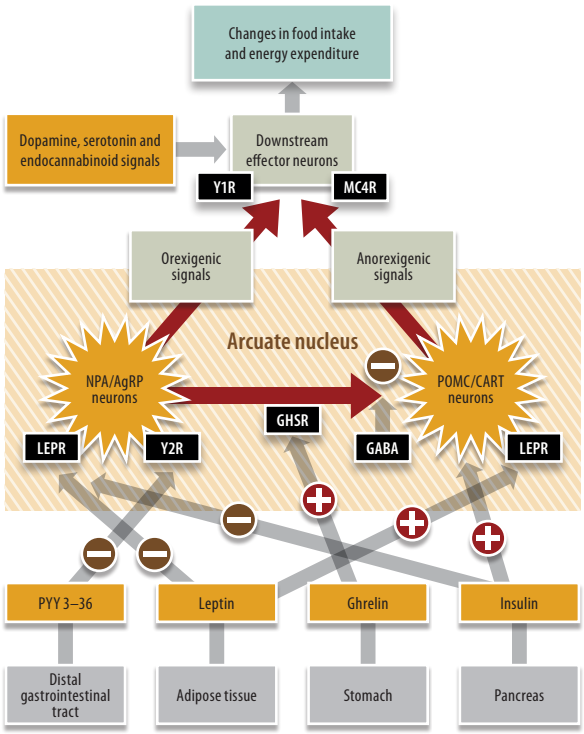

Figure 1. Physiological regulation of energy balance [4]

(LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), melanocortin 4 receptor (MC4R)), that has resulted in severe hyperphagia early onset [5]. Obesity is also revealed as accompanying manifestation of a serious organism pathology caused by Mendelian chromosome syndromes such as Prader–Willi syndrome; Wilson-Turner and others. Eleven monogenic forms of obesity have been reported, and 50 loci related to Mendelian syndromes relevant to human obesity have been mapped in a genomic region [6], but the cases are quite rare [5].

In most cases obesity is of multifactor nature. Heritability of overweight and obesity range from 25 to 40% in families with native and adopted children and reaches 70% in monozygous twins [7]. Obesity in parents is a factor of children obesity not only due to genetics, but also because of family habits in food and life style [8].

In 1994 a genetic obesity map «Human Obesity Gene Map» was firstly published, which was updated for the last time in 2005. There was reviewed evidence from transgenic and knockout murine models relevant to obesity studies, quantitative trait loci (QTL) from animal cross-breeding experiments, association studies with candidate genes, and linkages from genome scans. In total 253 QTLs and 127 candidate genes for obesity-related phenotypes were reported [6]. Since many genes are involved in the regulation of adipogenesis, lipid metabolism, energy balance and appetite, the complex investigations of obesity risk genotypes are required [9].

Table 1. The list of genetic association related to obesity [10]

Relation with obesity	Candidate gene
Low metabolic activity (thriftiness)	β-adrenergic receptor (ADRB2; ADRB3), uncoupling proteins 1, 2, 3 (UCP1, UCP2, UCP3)
Hyperphagia	dopamine D2 receptor (DRD2), 5-hydroxytryptamine (serotonin) receptor 2C (HTR2C), leptin receptor (LEPR), melanocortin 4 receptor (MC4R); leptin (LEP); nuclear receptor subfamily 3, group C, member 1 (NR3C1)
Low lipid oxidation	angiotensin-converting enzyme (ACE), adiponectin (ADIPOQ), guanine nucleotide binding protein, beta-3 subunit (GNB3), hormone sensitive lipase (LIPE), low density lipoprotein receptor (LDLR)
Adipogenesis	peroxisome proliferator-activated receptor gamma (PPARG), vitamin D receptor (VDR), resistin (RETN), interleukin-6 (IL6), tumor necrosis factor alpha (TNF)
Low physical activity	dopamine D2 receptor (DRD2), melanocortin 4 receptor (MC4R)

Researches consider more than 30 candidate gene involved in the regulation of energy intake and expenditure, in feeding behavior, in different responses to gain or loss weight. (Table. 1).

In addition evidence for the presence of linkage with obesity-related phenotypes for following genes was shown: monoamine methabolic enzymes (MAOA и COMT), estrogen receptors (ESR1, ESR2), Cytochrome P450 family (CYP11B2), hepatic lipase (LIPC), melanin-concentrating hormone receptor 1 (MCHR1) and growth-hormone-releasing hormone receptor (GHRHR) [6, 10].

The significant influence of the particular genes is still illusive. Not long ago FTO (fat mass and obesity associated protein also known as alpha-ketoglutarate-dependent dioxygenase) gene was described. The A allele in rs9939609 locus FTO gene increased the obesity chances among the type 2 diabetes patients by a factor of 1.39. But the BMI variability varied around 1% [11]. Physical activity significantly affects BMI reduction in the presence of the risk A-allele FTO gene [12].

In our investigations jointly carried out with colleagues from the 1-st Department childhood diseases Medical University the significant differences were shown between obese and normal-weight children in Belarus populations in occurrence frequency of -23HphITT genotype insulin (INS) gene (higher frequency for girl with morbid obesity), -308AG tumor necrosis factor alfa (TNF-) gene (for boys with early obesity twice frequently than for boys with morbid obesity) and -11377G allele adiponectin (ADIPOQ) gene (more frequently in girls with early obesity than in children with normal weight) and -11391AA genotype adi-

ponectin (ADIPOQ) gene (we didn't find in boys with obesity).

The most productive studies are those which take into account environmental factors, genetic, biochemical, physiological and psychological in total. Also when studying the allelic diversity of the gene associated with activity change or functionality of the encoded protein, it is necessary to take into account the diet, physical activity, medication and predisposition to other diseases. ■

Summary

Obesity arises from perturbations of the balance between food intake and energy expenditure regulated by peripheral signals coming into the brain. Many genes are involved in the regulation of energy balance, appetite, lipid metabolism, and adipogenesis. This small review describes the contribution of genetic factors to the development of obesity.

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HRM technology– to determine the SNP

The article is published in the journal "Science and Innovations", 2013, #2

The last two decades are marked by the widespread introduction in the biological, medical and agricultural sciences molecular genetic methods. Modern technology has made it possible in many cases at a deeper level to begin the study of fine structural and functional organization of nuclear and extra-nuclear genomes of various organisms. It had special significance for the development of new methods of diagnosis and treatment of various diseases. [1]. In recent years have become more common methods, which are based on polymerase chain reaction (PCR). American scientist Kary Mullis has won the Nobel Prize for the discovery PCR in 1983. Using the principles of analysis of the human genome, which was based on various modifications and variations of PCR, was the beginning of a huge number of molecular genetic studies as the molecular structure of DNA and RNA, and the study of their expression in different conditions and with different pathologies. [1].Among the various options PCR gained great popularity as technology real-time PCR [4]. Another most important event in molecular biology and medicine there was the implementation in 2000 of an international project to decipher the human genome, which has allowed to establish the functional significance of the large number of genes, and to identify their numerous allelic variants, including single nucleotide polymorphisms (single nucleotide polymorphisms, SNPs) [2]. As a result, role for many of the identified polymorphic variants of genes was determined in the developmental characteristics, including the development of various pathologic states. [3]. Effective use of genotyping SNPs depends on the development of cheap and easy-to-performance detection methods, one of which is a melting curve analysis based on the identification of the thermodynamic characteristics of dissociation of double-stranded molecules of DNA samples, reflecting features of the primary structure of nucleic acid. Application analysis of melting curves can detect significant differences within Tm (melting temperature), equal to d 0.10 C. Improvement of this technology has made it possible to increase the diagnostic resolution of the method to 0.01 0 C, which

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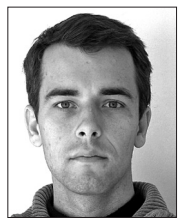

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Gene	Structure primer	Source
CYP2D6*4	GCCTTCGCCAACCACTCCG AAATCCTGCTCTTCCGAGGC	[7]
ADD1	CGACGAAGCTTCCAAGGA ACAGTAAGGTAGGCACAGA	The original design
ADRB1	CGCTCTGCTGGCTGCCCTTCTTCC TGGGCTTCGAGTTCACCTGCTATC GCCTCTTCGTCTTCTTCAA GCGCAGCAGAGCAGT	The original design
ACE	GCCCTGCAGGTGTCTGCAGCATGT GGATGGCTCTCCCCGCCTTGTCTC	[8]

Table 1. Structure of the primers for the genes studied HRM-analysis.

in turn allowed to identify single nucleotide differences compared samples of DNA molecules. This kind of method is called High Resolution Melt analysis (HRM). Prerequisite of precision HRM analysis is the use of: special fluorescent intercalating dye (Eva Green, SYTO9, LC Green, Chromofy, BEBO), equipment, characterized by high-resolution

Gene	Genotype frequencies, n (%)			Classification SNP on NCBI genebank
CYP2D6*4	GG	GA	AA	rs 3892097
	30 (60)	18 (36)	2 (4)	
ADD1	GG	GT	TT	rs 4961
	35 (70)	11 (22)	4 (8)	
ADRB1	CC	CG	GG	rs 1801253
	28 (56)	21 (42)	1 (2)	
ACE	II	ID	DD	rs 4646994
		27 (54)	16 (32)	

Table 2. Frequencies of genotypes studied polymorphisms in the control groups and the main groups.

temperature scale, and appropriate software. Thus, the applications of DNA analysis are major innovative ways to gain new knowledge about the pathogenetic mechanisms of socially significant chronic noncommunicable diseases, including cardiovascular diseases as the most prevalent. Among them are the genes system drug metabolism CYP2D6, ADD1, ADRB1 and ACE.

Functionally defective allelic variants of the gene CYP2D6 show themselves inactive protein synthesis, protein synthesis, or the lack of synthesis of defective protein with reduced activity. Carriage functionally defective allelic variants of the CYP2D6 gene is associated with higher values of the maximum concentration of metoprolol in plasma and lower values of its clearance by slowing drug biotransformation. Polymorphism of the gene encoding the 1-adrenergic receptors (ADRB1) capable of directly affect the pharmacodynamics of -blockers In hypertension, along with -blockers are used drugs from the diuretic groups. Mutations in the gene for -adducin (ADD1) lead to changes in protein structure, which in turn causes changes in reabsorption in the renal tubules. Patients with a mutant allele, taking hydrochlorothiazide drugs have more significant decrease in mean arterial pressure compared with the normal genotype. Heterozygotes also noted more significant reduction in blood pressure after salt sensitivity test that confirms the importance of determining the presence of the mutant allele to identify patients who need to limit their intake of salt. Angiotensin converting enzyme (ACE) — protease, which controls the formation of angiotensin II from angiotensin I. Significant impact on antihypertensive therapy observed in the study of the combination of I / D polymorphism of the ACE gene and adducin. Homozygotes for the D allele of ACE gene and gene adducin Gly460 were virtually immune to diuretic therapy.

The aim of this study was to analyze the allelic variants of genes (CYP2D6, ADD1, ADRB1 and ACE) system drug metabolism using technology HRM.

During the work we examined 50 patients (25 men and 25 women) aged 34 to 78 years (mean age 63,74 ± 8,49 years) with arterial hypertension (AH) II degree, treated at "Republican Scientific Center for Radiation Medicine and Human Ecology" in the period from February to May 2011 and "Gomel City Clinical Hospital № 2 " in the period from March to September 2012 in the target group consisted of patients with Stage II degree, outpatient treatment at which has not been effective, requiring hospitalization. The disease was complicated by hypertensive crises or associated clinical conditions: myocardial infarction, angina, heart failure, and paroxysmal atrial fibrillation, which indicate the complexity of the selection of effective therapy in this group of patients.

Material for the study served as DNA extracted from blood leukocytes of patients using reagent kit for DNA extraction from clinical material "DNA-Cytolysin" "AmpliSens" (RF). The concentration and purity of DNA preparation are important factors influencing the course of further analysis, it is necessary to set these parameters using a spectrophotometer.

This study reveals the loss of nucleic acid isolation process and determination the impurities present in the formulation. Qualitative and quantitative assessment obtained DNA preparations were carried out using spectrophotometer ND-1000 (NanoDrop Technologies Inc., USA), allowing to carry out qualitative and quantitative assessment of nucleic acids in a sample 1 mkl. [5].

HRM — analysis was performed with a thermal cycler Rotor Gene Q (Qiagen, Germany) Based on the use of oligonucleotide primers (Table 1) as they Following programs: 1 step (1 cycle) 4 0–3'; Stage 2 (35 cycles) CYP2D6 92 °C –20'', 66 °C –20'', 72 °C –20'', ADD1 92 °C –20'', 96 °C –20'', 72 °C — 15'' ACE 91 °C –20'', 68 °C –15'', 72 °C –20''; Stage 3 (1 cycle) HRM 72–94 °C T = 0,050 C).

For the analysis of gene ADRB 1 we used the software, consisting of two rounds: Round 1: Stage 1 (1 cycle) 95 0 C –10 ';

Stage 2 (40 cycles) 95 0 C — May 1'', 63 °C –15'', 72 °C –30''; Round 2: Stage 1 (1 cycle) 95 °C –5 ', Stage 2 (40 cycles) 95 0 C — 10'', 55 °C –30'', 72 °C –10''; Stage 3 (1 cycle) HRM 72–94 °C T = =0,05 °C).

The work used a set of «Type — it HRM PCR Kit » (Qiagen, Germany). Structure nucleotide primers original design was chosen based on the following criteria: length of 18–24 nucleotides, four or more 3'-terminal nucleotide should not be very complementary to the primer in a primer pair, sample or other synthetic oligonucleotides being added to the reaction, the temperature as a annealing — in the range of 60–70 0 C; melting temperature (T m) of primers employed in a pair, for most applications should be similar, and T m 5'-terminal portion of the primer is greater than T m 3'-end portion [4].The primers used in were synthesized by "Primetech" (Belarus).

HRM results were evaluated with help of appropriate software «Rotor — Gene Screen-Clust HRM Software». In the course of studies for each of the studied genes were identified polymorphic variants shown in Table 2. Examples typing alleles using HRM — Analysis and an algorithm for identifying SNP G460W gene -adducin (ADD1), the determining efficacy of diuretics in the treatment of patients with cardiovascular disease. Preliminary analysis of the samples was carried out by restriction analysis of the amplicons [6]. ADD1 locus melting curves of the investigated samples are shown in Figure 1.

On the basis of differences in the thermodynamic parameters dissociation amplicons samples were combined into 3 groups. In the first — sample having a one melting point (Tm = 83,43 °C) — GG type homozygote; in the second — samples having two melting peaks (Tm = 82.70 °C and 83.40 °C) — heterozygotes GA; in the third — with a single peak (Tm = 83.39 °C) — homozygotes AA. Evaluation results HRM analysis confirmed the separation of samples on 3 cluster thermodynamic characteristics which is presented in Figure 2.

A restriction analysis completely coincided with the results of HRM, obtained manually and with the help of the program «Screen Clust».

Thus, studies have shown that the use of technologies for analysis of HRM-curves allows the analysis of single nucleotide polymorphisms in the molecular genetic assessment of family history of patients to form groups at higher risk of various diseases, including cancer and cardiovascular diseases, that will serve to focus their prevention. Moreover, this technology is characterized by relatively cheap and fast execution compared with alternative technologies (sequencing, restriction analysis, electrophoretic analysis, etc.).

Obtained genetic data to assess the level of strategies allow you to personalize risk prevention and are a powerful motivating factor for each patient to comply with healthy lifestyle, nutrition and physical exercise regimes. Furthermore, this analysis opens up new possibilities in the implementation of individualized treatment selection by creating a "molecular profile" for each patient's disease. This method is also applicable for screening of congenital and acquired mutations in predictive studies (studies penetrance/entanglement-tracking the disease within the family), species identification, HLA-compatibility assessment of epigenetic methylation.

Work was performed on the base of Central Research Laboratory in Education Institution "Gomel State Medical University"

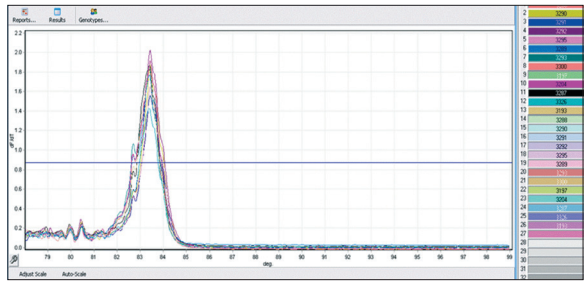

Fig. 1. Melting curves of amplicons ADD1.

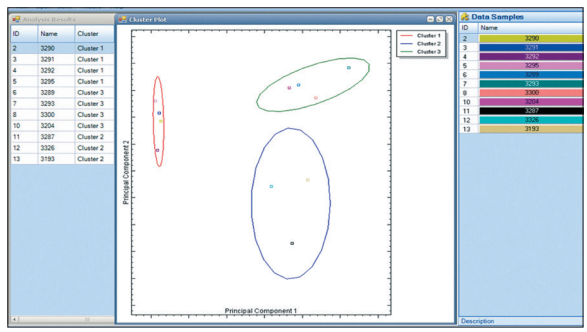

Fig. 2. Division into clusters samples program Rotor-Gene ScreenClust HRM Software

in the framework of project № 1.2.22 "Molecular mechanisms of genetic predisposition and peculiarities of diseases of the gastrointestinal tract, reproductive, cardiovascular and hematopoietic systems» № 20112832 State registration from 24.08.2011, State research program "Medicine and pharmacy." ■

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PROSPECTS FOR ANTIFIBROTIC THERAPY OF CHRONIC LIVER DISEASES

The article is published in the journal "Science and Innovations", 2013, #12

The progress made in research into cellular and molecular mechanisms of liver fibrogenesis over the last 25 years opens up fresh opportunities for treatment of liver cirrhosis and fibrosis. Understanding fine chemical and molecular-biologic mechanisms of fibrosis development and degradation made it possible to apply a targeted pharmacological effect on individual units in the pathogenetic chain of this disease.

Liver fibrosis and its consequences (cirrhosis, portal hypertension and impaired parenchymal function) are caused by from chronic liver diseases, in particular chronic viral hepatitis, alcoholic and nonalcoholic steatohepatitis, hemochromatosis and immune liver injuries. Progress in liver fibrosis leads to cirrhosis, the final stage of this process. In its turn, liver cirrhosis is assessed as a precancerous state which can be transformed to hepatocarcinoma. Liver fibrosis and cirrhosis are one of the key problems in public health on the world scale. According to the WHO reports, since the year 2000, the mortality rate of liver cirrhosis in Europe amounted to 1.8% of all death cases in Europe and made up 170 thousands deaths per year in absolute values [1]. Over the last ten years, the southeast regions of Europe (Hungary, Moldavia, Slovakia, Slovenia and Romania) as well as the northeast regions of Europe (Baltic States, Poland, Czech Republic) have been faced with an unprecedented burst of mortality caused by liver cirrhosis, reaching the level of 102 cases per 100 000 population in Hungary. Simultaneously a considerable elevation in the rate of liver cirrhosis-caused deaths has been also observed in West European countries (Great Britain, Ireland). According to the data of the Ministry of Health of Belarus, by 2012, the rate of deaths caused by diseases of alimentary organs had increased and amounted to 28.2 per 100 000 population, approximately 17 persons per 100 000 population dying of liver diseases, predominantly of liver cirrhosis.

Fibrosis develops due to excess liver accumulation of extracellular matrix, with the main component being collagen forming a mechanical basis for the extracellular matrix and subjected to proteolytic destruction by specific matrix metalloproteinases during fibrolysis. In liver cirrhosis, the relative collagen content can increase by tens of times [2].

The key effectors in the pathogenesis of liver fibrosis are hepatic stellate cells (HSC) locating in the subendothelial Disse's space (Fig.1). In the normal state, these cells are at rest, but some pathogenic factors convert them into an active form, microfibroblasts. The mechanism of HSC activation is complex and involves various changes in cellular metabolism. For example, liver parenchymal cells and Kupfer cells contribute to activation of HSC, inducing oxidative stress and enhancing production of various cytokines, including the tumor growth factor- (TGF-β), the platelet-derived growth factor (PDGF) and endotheline-1 [3]. Being regulators of intracellular signal transmission, these cytokines play an important role in activation of HSC. It should be noted that there are also antifybrogenic cytokines, for example, interleukin-10 that is an antagonist of the key anti-inflammatory cytokine, TNFα, and inhibits liver inflammatory process.

Activated HSC proliferate, producing components of extracellular matrix, mainly interstitial type I and II collagens, basal membrane type IV collagen as well as fibronectin, laminin and proteoglycans. The active form of HSC, myofibroblasts, as well as macrophages and Kupfer cells secrete enzymes degrading the extracellular matrix and matrix

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matalloproteinases (MMP). In acute viral injuries of viral and toxic nature, fibrogenesis is balanced by fibrolysis, i.e. removal of excess matrix by MMP. Under repeated pathogenic exposures, fibrosis prevails due to inhibition of MMP secretion and activity by tissue MMP inhibitors (TIMP).

Angiogenesis, i. e. formation of new liver blood vessels, has recently been determined as one of the most significant factors of fibrogenesis. It was known earlier that angiogenesis precedes progression of tumor and occurrence of metastases, i.e. the development of a vascular network providing for vascularization of the tumor locus precedes the development of the locus itself.

Data on enhanced angiogenesis preceding the development of liver cirrhotic nodes were published later [4].

Lately a relationship between angiogenesis and fibrogenesis has been proved and an antifibrotic effect of compounds with antiangiogenic properties demonstrated. During angiogenesis, a key role is played by the vascular endothelial growth factor (VEGF) that stimulates vascular growth and is produced by activated HSC. Since collagen, MMP, TIMP and VEGF are mainly secreted by activated HSC, myofibroblasts and portal fibroblasts, these cells are the most preferential target for antifibrotic therapy.

Recent research, carried out at our laboratory, enabled us to detect a new regulatory factor for liver fibrosis, a pituitary tumor transforming gene (PTTG) [5]. The experiment was carried out on knockout mice with the absence of PTTG (PTTG -/-) and control mice (PTTG +/+). Liver fibrosis was induced in mice by injections of the hepatotoxin thioacetamide (TAA). After 3 months following the TAA administration, livers of the

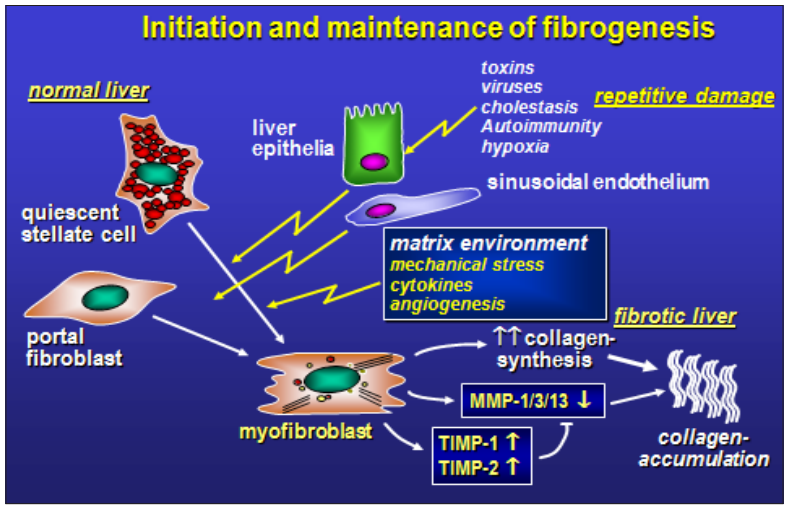


Fig. 1. Schematic representation of the present concepts of fibrogenesis and fibrolysis in the liver.

PTTG +/+ animals, in contrast to the PTTG -/- mice, showed a tuberous surface with formation of small nodes (Fig.2). The histological examination demonstrated the presence of connective tissue cords of varying thickness and length going from portal tracts deep into the parenchyma and nodal transformation in both the TAA-treated groups of mice. However, the signs of this pathology were much more pronounced in PTTG +/+ animals (Fig.2). The morphometric evaluation of extracellular matrix deposition in the liver parenchyma shows a considerable increase of the connective tissue area in liver sections of TAA-treated mice: 3.4-fold for PTTG +/+ and 2.6-fold for PTTG -/- (Fig.3). The liver hydroxyproline content used as the so-called "gold standard" for assessment of fibrosis was significantly increased in PTTG +/+ TAA -treated rats, whereas in a similar PTTG -/- mice group this index was not significantly different compared to the control group (Fig.3). Thus in the presence of PTTG in mice, development of liver fibrosis was considerably slowed. These results indicate an important role of PTTG in development

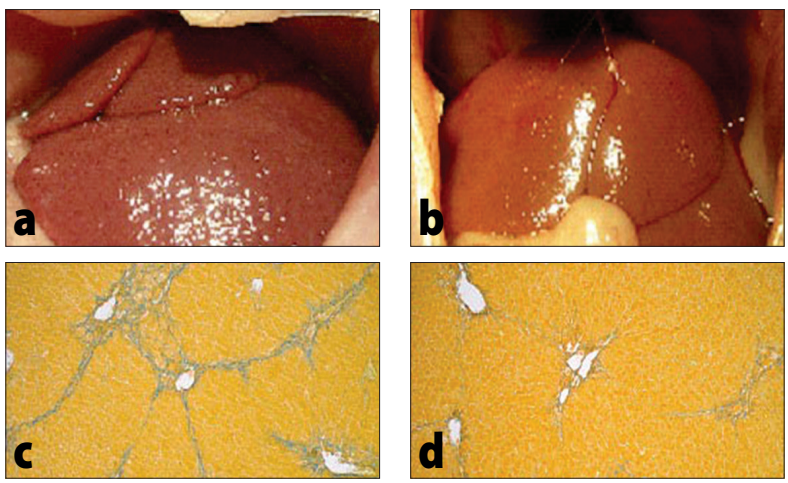
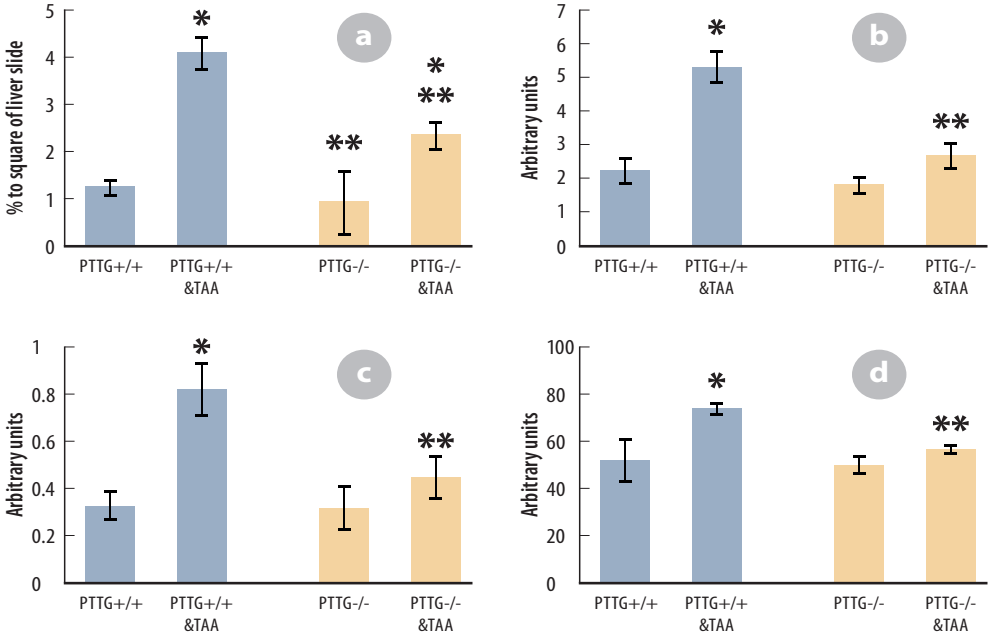


Fig.2 . The liver photograph shows tuberous surface and smoothed edges of the liver in PTTG+/+ mice (A) and single fibrotic nodes on the liver surface in PTTG-/- animals (B). Staining of the connective tissue according to Azan-Mallory is much more pronounced in liver sections of PTTG +/+ mice (C) compared to PTTG -/- animals (D).



A. Connective tissue area; B. Expression of TNFα mRNA; C. Expression of TGFβ mRNA; D. Expression of VEGF mRNA.
*p<0.05 compared to the corresponding TAA-untreated group;
**p< 0.05 compared to PTTG+/+ TAA-treated group.

Fig.3. Parameters of computerized morphometric measurement of connective tissue area (% to the total section area) and mRNA factors expression (in conventional units) governing the development of fibrosis in the liver of PTTG+/+ and PTTG -/- mice treated with thioacetamide (TAA).

of liver fibrosis/cirrhosis by its regulatory effect on the processes of fibrogenesis, angiogenesis and inflammation. This gene is sure to be an important target for antifibrotic therapy, and search for PTTG inhibitors will be a promising direction for design of new generation antifibrotic agents.

Before description of potential therapeutic approaches to liver fibrosis, we should dwell on the problem of reversibility of this process. Fibrosis and cirrhosis were long thought to be irreversible processes. However, over the last ten years different research centers, including our laboratory, obtained decisive evidence for reversibility of liver cirrhosis and fibrosis [6]. The reversibility of liver fibrosis was demonstrated in some experimental models, as well as in paired biopsies in patients with liver injuries. The research analyzing the results of randomized control experiments with chronic hepatitis C provides an undoubtable proof for reversibility of liver fibrosis under the influence of antiviral therapy by interferon and ribavirin [7]. The mechanism of extracellular matrix degradation under liver fibrosis is related to both the levels of matrix metalloproteinases and their inhibitors, mainly with TIMP-1, and to HSC apoptosis.

Based on the present-day ideas of fribrogenesis, fibrolysis and angiogenesis, we can formulate the main trends in the modern therapy of liver fibrosis. It should be noted that preference is given to a combination therapy where 2 or 3 agents are used which affect different targets in the pathogenetic chain that stipulate development and degradation of fibrosis. Most promising drugs can combine abilities to affect simultaneously several different targets governing fibrogenesis/fibrolysis. Table 1 summarizes the main principles of antifibrotic therapy.

We carried out some studies on preclinical evaluation of antifibrotic activities of some most promising drugs listed in Table 2, in particular of nor-ursodeoxycholic acid, mycophenolic acid, pentoxifylline and galofuginone as well as some statines (simvastatine and fluvastatine).

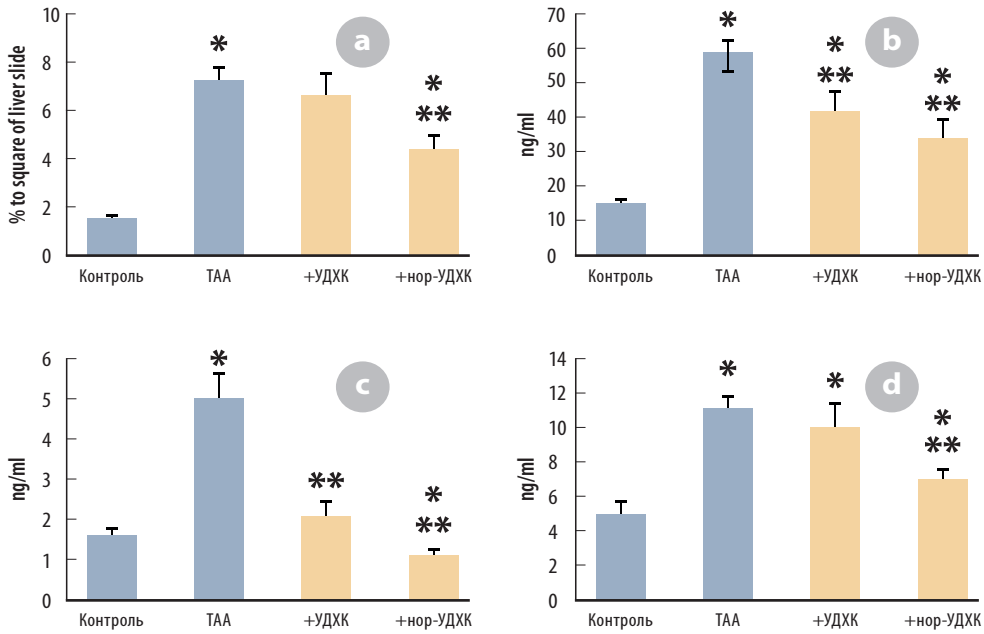
Mycophenolic acid inhibited transcription level of αl(I) procollagen in CFSC-2G stellate liver cells and primary culture of activated stellate liver cells/microfibroblasts. Expression of TGFβ1, the main profibrogenic cytokine, was inhibited 2-fold by mycophenolic acid in both types of cells.

Galofuginone inhibited the level of profibrinogenic procollagen αl(I) and metalloproteinase MMP-2. Expression of procollagen αl(III) mRNA was inhibited similar to procollagen αl(I). In moderately activated CFSC-2G cells, $2 \cdot 10^{-7}$ M galofuginone drammatically activated MMP-13 (the main intestinal collagenase), the extent of activation varying between 10-and 200-fold. Gallofuginone severely inhibited DNA synthesis in both cell lines and primary HSC/MF culture dose dependently, with maximum inhibition being at a concentration of $2 \cdot 10^{-7}$. M In addition, at submicromolar concentrations (10^{-7} M) gallofuginone completely blocked HSC/MF migration, induced by calf fetal serum in a confluent monolayer.

We also investigated the antifibrotic effect of an ursodeoxychlic acid (UDCA) derivative, nor-UDCA. UDCA is a widely-distributed hepatoprotector with moderate antifibrotic properties [8]. In an experiment on rats when liver fibrosis was induced by thioacetamide (TAA) during 3 months, the administration of nor-UDCA exerted both a preventive effect, by slowing down the development of liver fibrosis, and a therapeutic action, by diminishing the signs of fibrosis after withdrawal of the hepatotoxin. In this situation, the nor-UDCA administration decreased the morphometric values for deposition of the extracel-

lular matrix in the liver, as well as reduced the content of liver hydroxyproline and the levels of serum liver fibrosis markers (Fig.4). It should be noted that according to the majority of parameters the antifibrotic effect of nor-UDCA was much better than that of UDCA.

It has been found during the last decade that pentoxifylline, a known drug for treatment of vascular disturbances, is an efficient anti-inflammatory agent decreasing production of the key proinflammatory cytokine TNFα. In studying the application of pentoxifylline in rats fed on a choline- and methionine-deficient diet we found a pronounced antifibrotic effect of this drug. Pentoxifylline effectively decreased the area of connective tissue and oxyproline content in the liver in TAA-treated rats. Pentoxifylline decreased mRNA expression of procollagen α1 and MMP-3. The data obtained formed the basis for design of a novel hepatoprotective and antifibrotic combined drug containing pentoxifylline. Now this drug is being designed by our laboratory and the GP "Academpharm".



A. Connective tissue area; B. Content of collagen I; C. Content of collagen III; D. Content of procollagen III-NT

Fig. 4. Parameters of computerized morphometric measurement of connective tissue area (% to the total section area) and content of serum markers of liver fibrosis (ng/ml) in rats with TAA-induced liver fibrosis treated with UDCA or nor-UDCA.

Antiinflammatory measures

- Removal of damaging agent
- Activation of interleukin 10 production
- Inhibition of TNFα production
- Antioxidant measures

Effect on production of extracellular matrix

- Inhibition or decrease of HSC activation
- Decreased matrix synthesis and secretion
- Inhibition of HSC migration and proliferation
- Inhibition of angiogenesis

Effect on fibrosis resolution

- Initiation of HSC apoptosis
- Activation of MMP secretion and activity
- Inhibition of TIMP production.

Effect on regulatory systems

- Inhibition of PTTG expression
- Modulation of signal transduction from cellular receptors

Table 1. Main approaches to treatment of liver fibrosis

Thus, mycophenolic acid, galofuginone, pentoxifylline and nor-UDCA manifested potential antifibrotic properties both in the culture of stellar liver cells and in experiments in vivo and are promising components for combination therapy of liver fibrosis.

We did not find pronounced antifibrotic properties of the statins in a model of TAA-induced liver fibrosis in rats. Simvastatin (10 mg/kg body weight) moderately decreased the area of connective tissue in liver sections and increased mRNA expression of some metalloproteinases, whereas fluvastatin at the same dose diminished the level of procollagen α1 transcript and elevated this parameter for MMP-3.

In an experiment in vivo, we investigated the effect of the nitrogen oxide (NO) donor, $NaNO_2$ on transformation of chronic hepatitis and fibrosis in rats treated with dimethylnitrosamine (DMNA). Histological examinations made it possible to conclude that $NaNO_2$ slows down or even prevents development of DMNA-induced

Ursodeoxycholic acid derivatives

Nor-ursodeoxycholic acid is a homologue of ursodeoxycholic acid with a side chain shortened by one carbon atom. It decreases deposition of extracellular matrix, manifesting antifibrogenic and anti-inflammatory effects.

Bis-nor-ursodeoxycholic acid is a homologue of ursodeoxycholic acid with a side chain shortened by two atoms. The mechanism of action is likely to be similar to nor-ursodeoxycholic acid.

Vegetable components

Silimarin, a flavonoid from Saint-Mary thistle, is an antioxidant which decreases activation of HSC and inhibits expresson of protocollagen 1 and TIMP-1

Galofuginon, an alkaloid with antimalarial properties, inhibits procollagen α1.

Baikalein is an alkaloid applied in Chinese traditional medicine, antioxidant, prevents HSC activation.

Modularors of signal transduction

Rolipram and Losartan are specific phosphodiesterase 3 and 4 inhibitors, induce STAT-1 signal molecule. Inhibit procollagen α1 and TGFβ1.

LU135252, an ETA P antagonist, decreases collagen accumulation by 60%.

Pioglitazone and Rosiglitazone, ligands of peroxisomal proliferator-activated gamma receptor (PPAR) and antidiabetic thiazolidinediones, inhibit HSC activation and collagen synthesis.

Mycophenolate mophetil (mycophenolic acid) is an immonodepressive agent, used in transplantogy, inhibitor of guanosine nucleotide synthesis. Its inhibitory effect on development of kidney fibrosis has been described.

Antagonists of profibrogenic cytokines

Peptide TGFβ1 analog

Soluble TGFβ1 type 2 receptor

Statines (lovastatin, simvastatin), hypocholesteremic drugs, inhibit oxymethylglutaryl-CoA reductase, depress CTGF expression and induce MF apoptosis.

Donors of nitrogen oxide (pyrro-NO etc.) inhibit TNFα anti-inflammatory and profibrogenic effects.

Antiangiogenic drugs

Captopril, enalapril, aniotensin-converting enzyme inhibitors, antioxidants, inhibit HSC angiogenesis and activation

Interferon-α, antiviral drug, inhibits angiogenesis, HSC activation/proliferation and collagen synthesis. Induces STAT-1 signal molecule

TNP-470 is a VEGF receptor blocker

Table 2. Promising antifibrotic agents

hepatitis. The results of biochemical research also confirmed that $NaNO_2$ partially prevented development of chro-nic hepatitis and its transformation to fibrosis. We suggest this to be due to modulation of free radical processes in the liver [6].

Attention should be paid to the fact that most of the drugs listed in Table 2 with the known degree of clinical safety have already been used in clinical practice according to other indications. After the necessary preclinical trials these drugs can be easily used in clinical practice for treatment of liver fibrosis and cirrhosis.

The present publication is a part of our work on Fundamental Approaches to Pharmacological Correction of Liver Pathology which was awarded the Khwarizmi International Award, Teheran, 2013. ■

Summary

The modern view on mechanisms of liver fibrosis including fibrogenesis, angiogenesis and fibrolysis is presented. Authors formulated main trends of actual pathogenetic therapy of liver fibrosis and presented the list of mostly prospective antifibrotic compounds. The role of pituitary tumor transforming factor in liver fibrosis, newly discovered in author`s laboratory, is presented in this review. The own data on high antifibrotic activity of nor-ursodeoxycholicacid and some other compounds are also presented.

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