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Genetic Epidemiology of Hereditary Diseases among the Child Population in Eight districts of Tatarstan Republic

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ABSTRACT

The results of the genetic epidemiological study of monogenic hereditary disorders (MHDs) among child population of eight districts of Tatarstan Republic are presented in the report. The total size of the investigated population is 268,894 individuals, from which the proportion of child population makes 21.44% (57648 children). The total population was examined by standard protocol of medical genetic research elaborated in laboratory of genetic epidemiology, Research Centre for Medical Genetics. About 3500 MHDs of OMIM could be identified by this protocol. Clinical investigations were performed by neurologists, ophthalmologists, orthopedic, otolaryngologists, dermatologists, pediatricians and clinical geneticists, focused on diagnostic of MHDs. The spectrum of MHDs detected in the eight districts RT comprises 256 diseases, including 135 autosomal dominant (AD), 97 autosomal recessive (AR), and 24 X-linked diseases. The MHDs diversity in the child population of RT comprised 158 diseases (61.72% the total number of registration disorders), including 84 (62.22%) AD, 54 (55.67%) AR, and 20 (83.33%) X-linked ones. The load of MHDs (AD, AR and X-linked) in rural and urban child population is calculated, the variety of common MHDs is described. The prevalence of MHDs among children from Tatarstan region occurs to be 1:103. Significant differentiation in the values of the MHDs load (AD, AR and X-linked disorders combined) between districts was detected. An attempt to explain the revealed differences is undertaken.

Keywords: the load and variety of hereditary diseases, genetic epidemiology, child population, prevalence rate, Tatarstan Republic.

INTRODUCTION

The Improving of the quality of medical care and the development of molecular genetics have led to relatively increasing of congenital and hereditary diseases proportion in the structure of morbidity, disability and mortality of the child population. According to this line the total

frequency of monogenic, chromosomal and genetic-related diseases is estimated at about 95-139 per 1000 people, of which monogenic hereditary diseases account for 5-17 per 1000 [4,7].

The main load of monogenic hereditary diseases (MHDs) falls on the child population; these hereditary diseases appear during the life of a particular neonate cohort. Up to 25% of MHDs manifests by the birth of a child, up to 70% of MHDs has already diagnosed by the 3rd year, debut and first diagnostic features of the disease has been defined for almost 90% of the MHDs by the end of puberty [4,7].

According to WHO, the approximate incidence of congenital MHDs is 10-15 per 1000 live births, 58% of which early dies, 31 % has cases of chronic conditions and disability, and only 11% is to be medically inpatient and outpatient treated. The precise data on loads of MHDs among children in the populations of the world and in Russia's regions are absent. Summary of the genetic loads is presented by data on chromosomal aberrations and monitoring of congenital malformations in lot of countries, while the MHDs burden remains mainly represented by the WHO data, as well as by the special registers of individual countries [2,7,8].

The purpose of the study. The aim of the study was to genetic epidemiological study of MHDs among the child population of the Republic of Tatarstan.

MATERIALS AND METHODS

In Russia the researches within genetic and epidemiological study of MHDs among children are conducted by the Research Center for Medical Genetics of the Russian Academy of Medical Sciences. Researchers are in progress according with the protocol of genetic-epidemiological studies. This protocol is developed in the laboratory of genetic epidemiology of the Research Center for Medical Genetics. The protocol includes three main research strategies: medical genetic study of populations (providing the capability to identify approximately ½ of currently known hereditary diseases), estimation of the genetic structure using nonbiological population statistical methods, and DNA polymorphisms analysis. The MHD diagnosing was performed by focused specialists in the expedition (they are genetic syndromologist, a pediatrician, a neurologist, an otolaryngologist, a dermatologist, an orthopedician, and an ophthalmologist from research and medical centers of Moscow) [3,5].

The material for analysis was collected in the course of genetic epidemiological study of the whole population of eight Tatarstan districts in 2009–2013 (Arsky, Atninsky, Kukmorsky, Buinsky, Drozhzhanovsky, Aktanishsky, Muslumovsky and Menzelinsky districts). After then, children (0-18 years) were selected the total sample, the load of MHDs was calculated and its variety estimated. The results obtained are compared with the data obtained earlier in some

regions of the European part of Russia (Chuvashia (RC), Udmurtia (RU), Bashkortostan (RB) and the Rostov region (RR) [1,6,9]. The total size of investigated population of Tatarstan comprised 268894 people, including 57648 (24.4%) children. The ethnic structure of the considered sample is presented by more than 80% Tatar population.

RESULTS AND DISCUSSION

While the medical genetic survey of eight districts we found in total 1597 patients from 1077 families with various clinical forms of MHDs. To estimate the hereditary load in the child populations, we considered separately patients with MHDs in the age interval from birth to 18 years inclusive. All in all we found 561 children (35.13% of the total number of patients) from 471 families with various clinical forms of MHDs, including 313 children from 258 families with AD diseases, 191 children from 167 families with AR diseases, and 58 children from 46 families with X-linked diseases.

On average, the total proportion of children with MHDs among all MHD patients was 35.19% (46.85%, 43.53%, 37.25% and 41.65% in RC, RU, RB, RR, respectively) [1,6,9]. The number of diseased children with AR and X-linked diseases prevails in each region and in the total sample. The mean proportions of children with AD, AR, and X-linked diseases in the five regions were 37.94%, 45.24%, and 50.44%, respectively. This situation is explained by the fact that part of the AD diseases manifests in older age. In addition, AR and X-linked pathology clinically is more severe, more often it is lethal either has a reduced fitness of patients for most diseases. Table 1 shows the load (and prevalence rates of MHDs in child populations in the eight districts studied and in some populations of Russia (RC, RU, RB,RR).

Table 1. The load (per 1000 children) and prevalence rates of MHDs child populations of the Republics of Tatarstan (RT), Chuvashia (RC), Udmurtia (RU), Bashkortostan (RB) and Rostov Region (RR).

Population (district)	Population size	Load of HDs (per 1000 children)			Prevalence rate
		AD	AR	X-linked	
Arsky	11029	5.35±0.69	2.36±0.46	1.45±0.51	1:119
Atninsky	2742	12.40±2.11	6.20±1.50	4.38±1.78	1:48
Kukmorsky	11431	4.11±0.60	3.06±0.52	1.92±0.58	1:123
Buinsky	9655	4.76±0.70	2.18±0.47	1.66±0.59	1:129
Drozhzhanovsky	5572	5.56±1.00	3.95±0.84	1.44±0.72	1:98
Aktanishsky	6770	5.76±0.92	2.81±0.64	2.07±0.78	1:104
Muslumovsky	4668	7.93±1.30	5.57±1.09	4.28±1.35	1:64
Menzelinsky	5781	3.46±0.77	4.32±0.86	1.38±0.69	1:118
Mean of RT	**57648**	**5.43±0.31**	**3.31±0.24**	**2.01±0.26**	**1:103**
Mean of RC	**57648**	**5.43±0.31**	**3.31±0.24**	**2,01±0.26**	**1:103**
Mean of RU	**67863**	**2.43±0.19**	**2.18±0.18**	**0.80±0.15**	**1:200**
Mean of RB	**60197**	**3.22±0.23**	**1.81±0.15**	**1.50±0.22**	**1:173**
Mean of RR	**64935**	**3.87±0.24**	**2.51±0.20**	**0.92±0.17**	**1:146**

We found significant differences in the AD genetic load between districts of RT (χ^2=38.26, D.f.=7) and for AR load (χ^2=23.98, D.f.=7). Differentiation between districts with X-linked pathology was not found (χ^2=7.25, D.f.=7). However, the basic medical genetic characteristics of most populations are formed as a result of complex interaction between various population dynamic factors. In addition to genetic drift, which is the main factor in microevolution, modern populations of Russia are also affected by natural selection and migrations [1–6]. With the purpose of definition of communication population structure and factors of microevolution in the formation of differences between districts in the level of MHDs load a correlation between the values of a random inbreeding F_{ST} (F_{ST} in Arsky – 0.00088, Atninsky – 0.00163, Kukmorsky – 0.00072, Buinsky – 0.00058, Drozhzhanovsky – 0.00062, Aktanishsky – 0.00081, Muslumovsky – 0.00075 and Menzelinsky – 0.00042) and load of AD and AR of MHDs in children was calculated. The linear correlation coefficients for AD and AR pathologies were r=0.91±0.17 and r=0.52±0.35. The revealed differences in load values between

districts can to some extent be explained by a lower level of migration, expressed by genetic subdivision and natural selection.

The spectrum of MHDs detected in the eight districts RT comprises 256 diseases, including 135 autosomal dominant (AD), 97 autosomal recessive (AR), and 24 X-linked diseases. The MHDs diversity in the child population of RT comprised 158 diseases (61.72% the total number of registration disorders), including 84 (62.22%) AD, 54 (55.67%) AR, and 20 (83.33%) X-linked ones.

There revealed 24 the most frequent nozological form (with a prevalence rate of 1 : 15000 or higher) among child population. With AD disorders they are the following: Ehlers–Danlos syndrome (prevalence rate 1:721), mental retardation (1:3391), ichthyosis (1:3843), palmoplantar keratoderma (1:4434), neurofibromatosis, type I (1:7206), scoliosis, idiopathic (1:9608), ptosis, hereditary congenital (1:11530), tuberous sclerosis (1:14412), Marfan syndrome (1:14412), Sturge–Weber syndrome (1:14412), curly hair with deafness syndrome (1:14412), polycystic kidney disease (1:14412), cataract hereditary (1:14412), retinoblastoma (1:14412), blepharophimosis with ptosis (1:14412), hypochondroplasia (1:14412).

The most frequent among AR diseases are: nonsyndromic neurosensory deafness (prevalence rate 1:1517), mental retardation (1:2306), oculocutaneous albinism (1:5241), amniotic band sequence (1:7206), congenital hypothyroidism (1:7206), orofaciodigital syndrome II (1:8235), phenylketonuria (1:9608), congenital glaucoma (1:14412).

The most frequent among X-linked disorders (with prevalence rate 1:15000 boys or higher) are: mental retardation (частота 1:1802), congenital nystagmus (1:5765), hemophilia, type A (1:9607), Parkinson disease 12 (1:14412), Duchenne PMD (1:14412), lymphoproliferative syndrome (1:14412).

The comparison of MHDs spectrum in the RT with other regions has shown the existence of pronounced regional features.

CONCLUSIONS

As follows from the present study, the total prevalence of MNDs among the child population of RT accounts for 1:103 children. Given that the methodology used by this research allows to diagnose about half of all known to date hereditary diseases, we may assume that the actual load of hereditary diseases in the child populations of Tatarstan Republic is approaching to 1.5%. Similar results were obtained during the examination of children in Udmurtia (1.2%), in Bashkortostan (1.4%), in Chuvashia (1%), in Rostov Region (1.3%). Most of the identified

diseases in children are significantly affect the duration and quality of their lives, what to consider when developing prevention of child morbidity, disability and mortality.

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