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Analysis of Mutation Associated with Male Infertility in Patients and Healthy Males in the Russian Population

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Abstract : Nowadays there is a growing number of couples with conceiving problems due to male or female infertility. Genetic abnormalities are responsible for about 31% of all cases of male infertility. These abnormalities include both chromosomal aberrations or aneuploidies and mutations in certain genes. Chromosomal abnormalities can be easily identified, thus the development of screening panels able to reveal genetic reasons of male infertility on gene level is of current interest. There are approximately 2,000 genes involved in male fertility that is the reason why it is very important to determine the most clinically relevant in certain population and ethnic conditions. An infertility screening panel containing 48 mutations in genes AMHR2, CFTR, DNAI1, HFE, KAL1, TSSK2 and AZF locus which are the most clinically relevant for the European population according to databases NCBI and ClinVar was designed. The aim of this research was to confirm clinic relevance of these mutations in the Russian population. Genotyping was performed in 220 patients with different types of male infertility and in 57 healthy males with normozoospermia. Mutations were identified by end-point PCR with TaqMan probes in microfluidic plates. The frequency of 5 mutations in healthy males and 13 mutations in patients with infertility was revealed and estimated. The frequency of mutation c.187C>G in HFE gene was significantly lower for healthy males (8.8%) compared with patients (17.7%) and the values for the European population according to ExAc database (13.7%) and dbSNP (17.2%). Analysis of c.3454G>C, and c.1545_1546delTA mutations in the CFTR gene revealed increased frequency (0.9 and 0.2%, respectively) in patients with infertility compared with data for the European population (0.04%, respectively (ExAc, European (Non-Finnish) and for the Aggregated Populations (0.002% (ExAc), because there is no data for European population for c.1545_1546delTA mutation. The frequency of del508 mutation (CFTR) in patients (1.59%) were lower comparing with male infertility Europeans (3.34-6.25% depending on nationality) and at the same level with healthy Europeans (1.06%, ExAc, European (Non-Finnish). Analysis of c.845G>A (HFE) mutation resulted in decreased frequency in patients (1.8%) in contrast with the European population data (5.1%, respectively, ExAc, European (Non-Finnish). Moreover, obtained data revealed no statistically significant frequency difference for c.845G>A mutation (HFE) between healthy males in the Russian and the European populations. Allele frequencies of mutations c.350G>A (CFTR), c.193A>T (HFE), c.774C>T, and c.80A>G (gene TSSK2) showed no significantly difference among patients with infertility, healthy males and Europeans. Analysis of AZF locus revealed increased frequency for AZFc microdeletion in patients with male infertility. Thereby, the new data of the allele frequencies in infertility patients in the Russian population was obtained. As well as the frequency differences of mutations associated with male infertility among patients, healthy males in the Russian population and the European one were estimated. The revealed differences showed that for high effectiveness of screening panel detecting genetically caused male infertility it is very important to consider ethnic and population characteristics of patients which will be screened.

Keywords : allele frequency, azoospermia, male infertility, mutation, population
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