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RISK OF FMF DEVELOPMENT AMONG HETEROZYGOUS PATIENTS IN ARMENIAN POPULATION

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The aim of this study is the investigation of one mutation carriers of MEFV gene among Armenian population. We designed and established the genetic register for proper collection of patients' data including their ethnicity, clinical and laboratory data, as well as family cases. According to the results the frequency of FMF inheritance with only one mutation of MEFV gene among Armenian population is about 17.5% and by autosomal-recessive mode (homozygous or compound-heterozygous) is 82.5%.

Keywords: familial Mediterranean fever, MEFV gene mutations, pseudo-dominant inheritance.

Introduction. Molecular-genetic diagnosis of Familial Mediterranean fever (FMF) is conducted in Center of Medical Genetics and Primary Health Care (CMG). Since 1997 there have been investigated more than 28000 people, which is the largest FMF study group in the world. The results of complex genetic and clinical investigations let us establish the most common mutations of MEFV gene among Armenian population, phenotype-genotype correlations, interpret the results and properly design the further management of the patients.

According to the literature and our data in most cases the inheritance of FMF is autosome-recessive (OMIM 249100). The information on pseudo-dominant inheritance of hereditary fevers in closed population is highlighted still in 1984 by V. Lents. Nowadays due to large material we can see that the typical manifestation of the disease can happen even among heterozygous patients, which probably is the indication of dominant inheritance of MEFV gene mutations [1]. In genome database of OMIM except autosome-recessive type there is already registered autosome-dominant type of FMF inheritance (#134610).

Several authors have already described FMF with autosome-dominant type of inheritance, where the manifestation of the disease happened with only single mutation of MEFV gene [2], yet the data is somehow contradictory. Scientists from Great Britain amyloidosis center linked this kind of inheritance with M694V mutation, but it is highly possible that authors included into the study only FMF patients with amyloidosis [3]. The severe form of FMF with renal amyloidosis and

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resistant to colchicine treatment in Spanish population is associated with H478Y mutation of 5 exon of MEFV gene [4]. If one of the parents is FMF patient (homozygous or compound heterozygous) and the other one is a healthy carrier of one mutation of MEFV gene and their offspring is also FMF patient with only one mutation, then the type of inheritance can be considered as pseudo-dominant [2].

In [1] clinical manifestation of FMF among heterozygous patients is highly associated with high frequency of MEFV gene mutations among Mediterranean basin population. According to the authors, one mutation is predisposed not to the typical FMF, but to FMF-like multi-factorial auto-inflammatory disease.

CMG data also support the idea of typical FMF symptoms manifestation among heterozygous patients with particular mutations of MEFV gene [5, 6].

Materials and Methods. Among 28000 investigated individuals in CMG for FMF the genetic diagnosis has been confirmed in more than 18000 cases.

Clinical examination of patients has been conducted according to Tel-Hashomer criteria [7], including particular clinical and laboratory parameters and with further confirmation of diagnosis with molecular-genetic analysis of MEFV gene. The severity of clinical manifestation of FMF has been also measured by Tel-Hashomer scale, which includes the onset of disease, frequency of attacks, existence of arthropaty, renal amyloidosis and colchincine efficacy.

In cooperation with the Institute of Informatics NAS RA a special NewBuilder program for analysis of clinical-laboratory and genetic data of investigated 28000 individuals in CMG has been designed. The healthy group (CG), as well as asymptomatic carriers of MEFV gene mutations, was also included into NewBuilder program. Analysis were conducted with patients with 0, 1, 2 mutations. The familial cases of FMF with disease manifestation in one or several generations were also analyzed. This allowed examining 357 non-related families, where in 40 families the inheritance type is similar to autosome-dominant one.

For molecular-genetic analysis the material was peripheral blood. For DNA extraction special kits of "MOBIO laboratories" (Ultra Clean Blood DNA Isolation Kit, USA) were used. For MEFV gene mutations detections methods of DNA amplification with multiplex PCR and further electrophoresis in 2% agar gel were used. The next step of mutations analysis located in 2, 3, 5 and 10 exons of MEFV gene was reverse-hybridization of amplicons (Vienna Lab FMF Assay). With the mentioned method the most common twelve mutations of MEFV gene in Armenian population were detected [8], which is according to [9], and is considered to be sufficient for detection of MEFV gene mutations in our population without any need of further gene sequencing.

Results and Discussion. The problem of early diagnosis and treatment of hereditary fevers still remains as a challenge particularly it refers to the heterozygous carriers of MEFV gene mutations [10]. Here we are bringing the results of the current study of families with pseudo-dominant type of inheritance of MEFV gene mutations. Autosome-recessive (OMIM249100) type of inheritance is registered in 79.3% of patients. Out of 17600 patients with FMF in Armenia 3087 were heterozygous (20.7%). During the analysis of 710 probands from 357 non-related families in 146 families the disease was registered in one generation (297 patients) and in 211 families – in two and more generations (413 patients). In the mentioned 211 families the inheritance was similar to autosome-dominant type in 40 families. The results of investigation of familial cases are shown in Fig. 1.

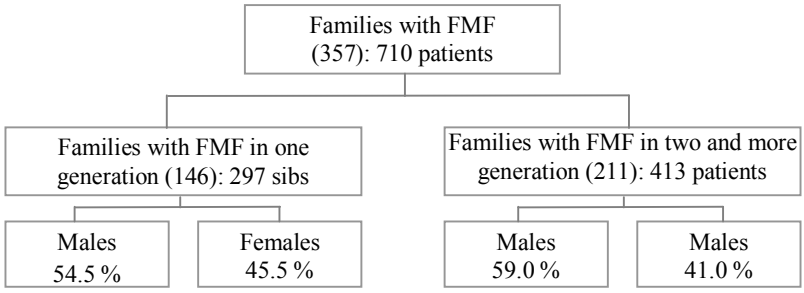

Fig. 1. Analysis of familial cases.

The distribution of mutations of heterozygous patients in the aforementioned families with disease manifestation in two and more generations is shown in Fig. 2, which is according to the graph, which has the following form: M694V (36.0%), V726A (29.5%), M680I (26.2%), R761H (4.9%) and E148Q (3.3%).

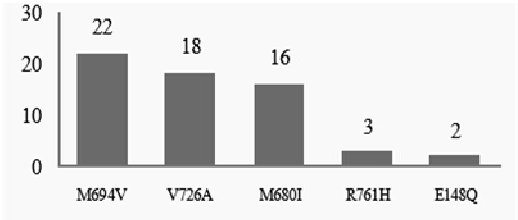

Fig. 2. The most frequent mutations of heterozygous patients detected in 40 non-related families.

It is challenging to clinically differentiate the typical form of FMF from other forms of the disease. Many authors indicate the mild and atypical forms of FMF among heterozygous patients [5, 11]. As an example of FMF manifestations among heterozygous patients and possible dominant type of inheritance below are brought three families with probands in two and three generations (Fig. 3).

Family 1: inheritance of FMF in 3 generations: grandfather had compound heterozygous genotype V726A/F479L; father had also compound heterozygous genotype M694V/F479L, but his two sons had heterozygous genotypes M694V inherited from father. Two boys had similar clinical picture with periodic attacks of fever (t=38–39°C), peritonitis and arthralgia which are typical for FMF (Fig. 3, a).

Family 2: inheritance of FMF in 3 generations: mother and son were carriers of heterozygous genotypes M694V. Mother had clinical picture with peritonitis, pleurisies, arthralgia with periodically repeated attacks less than once in a week. Son mentioned periodic attacks of fever (t=40°C) and arthralgia once in a month. Second son had compound-heterozygous genotype M694V/V726A, where the second mutation was inherited from the father (Fig. 3, b).

Family 3: two brothers with FMF and compound-heterozygous genotypes M694V/M680I: one of the brother's children (son and daughter) inherited the same genotype from the father (the possible rare case of inheritance of complex allele in "cis" position). Since these children's mother was not tested for MEFV gene mutations, the issue of complex alleles inheritance remains questionable. The son of the second brother was heterozygous carrier of M680I mutation with FMF clinical picture (periodically repeated attacks of fever (t=38.2°C) and peritonitis) (Fig. 3, c).

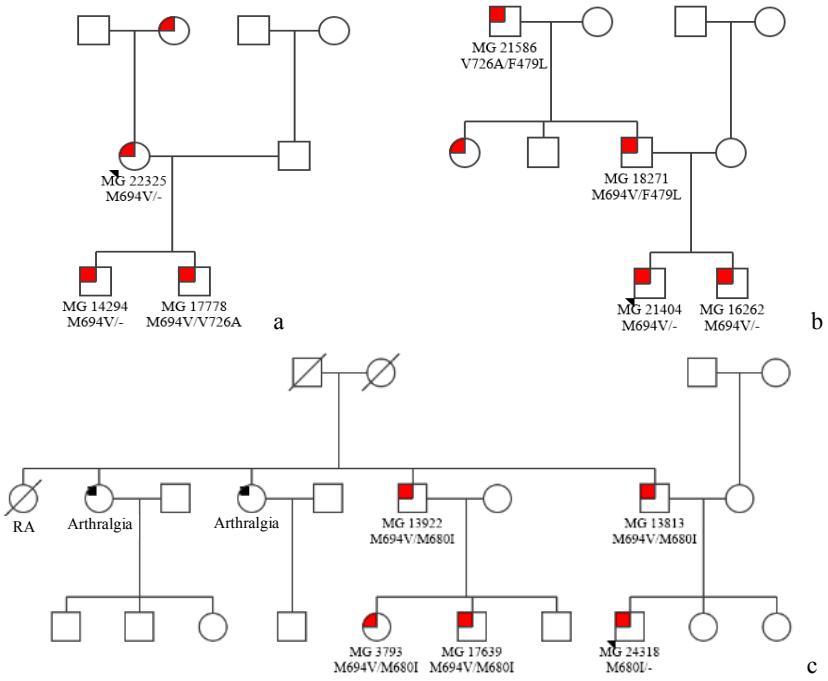

Fig. 3. The examples of pedigrees with possible dominant type of inheritance.

Conclusion. According to our data the frequency of FMF inheritance by pseudo-dominant type in average is 19.8% and by autosome-recessive type is 80.2%. Manifestation of FMF among heterozygous patients is very important information for clinicians during patients management and genetic consultations of families with FMF. Clinicians should take into consideration the high frequency of asymptomatic heterozygous carriers of MEFV gene mutations among Armenian population (35%), 20.7% of whom are individuals with clinical manifestations of FMF. For the confirmation of FMF autosome-dominant type of inheritance the further segregation analysis has to be implemented.

In population with high risk of FMF the frequency of heterozygous carriers is very high (up to 20%), so in many families with FMF the pseudo-dominant type of inheritance are registered [12].

Important indication for clinicians was proposed by Kastner at al. (National Institute of Health Care, US) for prescription of colchicine to the patients with only one mutation of MEFV gene and with clinical manifestation of the disease without need of entire MEFV gene sequencing [13].

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