Common Mediterranean Fever Gene Mutations in the Azeri Turkish Population of Iran

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Familial Mediterranean fever (FMF) is an autosomal recessive disorder primarily affecting the Mediterranean populations. It is characterized by recurrent attacks of fever and inflammation of serosal membranes and gradual development of nephropathic amyloidosis. More than 70 disease-associated mutations have been identified in the Mediterranean fever gene (MEFV) responsible for FMF. The aim of this study was to determine the mutation carrier rate in the Iranian Azeri Turkish population. A cohort of 200 unrelated healthy individuals was screened for the five most common MEFV mutations (M694V, V726A, M680I, M694I, and E148Q) using the amplification refractory mutation system for the first four and by polymerase chain reaction–restriction-digestion testing for E148Q. Genotyping revealed that the carrier rate in the Azeri Turkish population was 25.5%, with E148Q being the most common mutation (11.5%) followed by V726A (1.75%). The remaining common mutations were not found in this cohort. Our data indicate that the FMF carrier rate and E148Q mutation frequency are high in the Iranian Azeri Turkish population.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder mainly affecting the Mediterranean populations such as Arabs, Armenians, Jews, and Turks, although recently it has been described in many other populations (Touitou, 2001; Onen, 2005). It is characterized by recurrent self-limited attacks of fever with serositis, synovitis, or erysipelas-like skin lesions. A less frequent but very severe complication of FMF is the development of renal amyloidosis, ultimately leading to the end-stage kidney failure (Lidar and Livneh, 2007). The responsible gene, Mediterranean fever gene (MEFV), located on chromosome 16p13.3 encodes for pyrin (marenostrin) (The French FMF Consortium, 1997; The International FMF Consortium, 1997). Pyrin belongs to a class of proteins involved in the regulation of apoptosis and inflammation (Lidar and Livneh, 2007). More than 70 FMF causing mutations have been reported in MEFV (Infevers, 2009). However, five common mutations (namely E148Q, M680I(G/C), M694V, M694I, and V726A) account for more than 70% of the deleterious alleles in the Mediterranean ethnic groups (Papadopoulos et al., 2008). Recently, molecular genetic studies showed that FMF is no longer a rare disease in the northwestern Iran (Esmaeili et al., 2008). There is no available data on the MEFV mutation carrier rate in the Iranian Azeri Turkish population. This study aims to determine the carrier frequency of the five common MEFV mutations in this ethnic group.

Subjects and Methods

A total of 200 unrelated apparently healthy Azeri Turkish DNA samples were obtained from couples undergoing carrier screening for spinal muscular atrophy, Duchenne muscular dystrophy, cystic fibrosis, deafness, and beta-thalassemia. Informed consent was obtained from all the participants. Genomic DNA was extracted from peripheral blood leukocytes using standard protocols (Miller et al., 1988).

The presence of the five most common MEFV mutations was determined using amplification refractory mutation system–polymerase chain reaction (PCR) and PCR–restriction fragment length polymorphism methods as previously described (The French FMF Consortium, 1997; Eisenberg et al., 1998; Livneh et al., 1999; Medlej-Hashim et al., 2002). The appropriate positive and negative controls were employed for each test. The positive results were repeated to ensure reproducibility. PCR products and restriction enzyme-digested fragments were electrophoresed in a 2% agarose gel and observed by ethidium bromide staining. Chi-squared test was used for comparison between discrete parameters.

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Results

Genotyping of 200 Iranian Azeri Turkish control individuals for the five common MEFV mutations showed no carriers for M694V, M694I, and M680I, whereas 11.5% and 1.75% of the tested chromosomes carried the E148Q and V726A mutations, respectively. One 12-year-old female was diagnosed to be homozygous for E148Q mutation. She had no symptoms of FMF attacks or amyloidosis. Carrier frequency has been estimated to reach 1:4 (25.5%) in this ethnic group.

Discussion

This is the first report about the carrier frequency of FMF mutations in Azeri Turks living in northwestern Iran. This ethnic group, constituting 25% of the Iranian population, is ethnically identical to Azeris and closely related to Turks. Our study showed that FMF is no longer a rare disease in this ethnic group (Esmaeili et al., 2008). These data could offer additional incentive to the Iranian health system policy makers to plan for the management of the disease in future.

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References


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