The Assignment of the Gene Responsible for Congenital Cataract and Microphthalmia to the Pericentromeric Region of the X Chromosome and Examination of Candidate Genes

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**Background:** X-linked diseases are single gene disorders that are due to the presence of mutations in genes that reside on the X chromosome. X-linked recessive disorders are predicted from the family structure, where only boys are affected and there is no father to son transmission of the mutant allele. Heterozygous females are usually non-symptomatic carriers but can manifest a milder form of the disease. The identification of the genetic defect in X-linked disorders facilitates the diagnosis of affected individuals, aid in providing informative counseling and may help in prenatal diagnosis.

**Objectives:** The study aims at mapping and identification of one gene responsible for congenital cataract and microphthalmia in a three-generation family.

**Methods:** We recruited 12 members of a family with a clear X-linked pattern of inheritance with three affected males, all showing congenital cataracts and microphthalmia. Gene mapping was attempted using a set of microsatellite markers selected to cover the whole X chromosome. Haplotypes were generated for all genotypes and the haplotypes were examined for alleles shared by the affected males and not shared by the unaffected males. Once the region of linkage was identified, we examined a few candidate genes by mutation analysis by resequencing in forward and reverse of one affected individual, one obligate carrier and one unrelated normal control. Candidate genes were chosen from the human genome public databases and were selected based on the possibility that they play a role in eye development or are expressed in fetal eyes.

**Results:** The region of linkage is a 50 Mb in the pericentromeric region of the X chromosome (Xp21.1-q21.2). The candidate genes ARR3, DACH2 and BCOR were resequenced in forward and reverse, but no variations were detected.

**Conclusions:** We were capable of mapping the gene responsible for congenital cataracts and microphthalmia to the pericentromeric region of the X chromosome. We examined 3 candidate genes but no variations were detected. Currently, we are examining other candidate genes. If no mutant alleles are identified by this candidate gene approach, we will proceed by performing whole exome sequencing of the X chromosome (after enrichment) utilizing the next generation sequencing technology.

The Spectrum of MEFV Mutations in an Arabic Cohort

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**Background:** Autoinflammatory diseases are a group of disorders characterized by seemingly unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T cells. Familial Mediterranean Fever (FMF) is an autosomal recessive disorder. It is characterized by recurrent self-limiting episodes of fever and painful polyserositis. FMF is prevalent in specific ethnic groups—namely, non-Ashkenazi Jews, Armenians, Turks, and Arabs. There seems to be a distinctive clinical picture in Arab patients with FMF, and the range and distribution of MEFV mutations is different from that noted in other commonly affected ethnic groups.

**Objectives:** The aim of this study is to delineate the spectrum and distribution of MEFV mutations amongst an Arabic FMF patient cohort and to assist the genotype-phenotype correlation in these patients.

**Methods:** We have collected DNA samples from 188 FMF patients (from Qatar, Jordan and Palestine) who have been clinically diagnosed with FMF, according to international and validated diagnostic criteria. We have designed primers to cover the entire genomic region of MEFV. As a first tier, mutation detection is done by resequencing the entire coding sequence and splice sites; as a second tier the rest of the genomic region including the promoter are resequenced.

**Results:** In the first tier, we have identified 191 out of 376 mutant alleles (50%) by resequencing the entire coding region and splice sites of MEFV. In addition, resequencing of the entire genomic region of 100 patients who had only one identifiable allele was carried resulting in the identification of specific haplotypes and we are currently investigating the phenotypic significance of these haplotypes.

**Conclusions:** The spectrum of MEFV mutations in Arabs seems different from other ethnic groups commonly affected by FMF. The fraction of the identifiable disease causing alleles is the lowest amongst the commonly affected ethnic groups. The results of the genomic resequencing of MEFV may provide some insight into the role of non-coding sequences and may explain the molecular pathology of FMF. Thereby, we are currently working on the development of a low cost and high throughput technique to facilitate the resequencing of the entire genomic sequence of MEFV using Next Generation sequencing technology.