Heterozygous Ala137Pro Mutation in Keratin 12 Gene Found in Japanese with Meesmann’s Corneal Dystrophy

Kozo Takahashi*, Kenzo Takahashi†, Akira Murakami*, Shigekuni Okisaka‡, Tairou Kimura* and Atsushi Kanai*

*Department of Ophthalmology, Juntendo University School of Medicine, Tokyo, Japan; †Department of Dermatology, Gunma University School of Medicine, Gunma, Japan; ‡Department of Ophthalmology, National Defense Medical College, Saitama, Japan

Purpose: To report the molecular genetic analysis of a Japanese pedigree with Meesmann’s corneal dystrophy (MCD).

Methods: Sequencing of the keratin 3 and keratin 12 genes was performed in 2 patients who were siblings and in an unaffected individual in the same family. The patients had the typical corneal microcysts and recurrent erosions with mild photophobia.

Results: A novel mutation resulting in the substitution of alanine to proline in codon 137 of the keratin 12 gene (Ala137Pro) was found in the 2 patients, but not in the unaffected member of the family and the 50 controls.

Conclusion: This novel mutation (Ala137Pro) of the keratin 12 gene found in a Japanese family had caused MCD.

Key Words: Gene, keratin 12, Meesmann’s corneal dystrophy, mutation.

Materials and Methods

Cases

A 60-year-old man (II-5) had had photophobia since childhood. His visual acuity was 1.0 in both eyes without correction. He had a myriad of fine, round epithelial asymptomatic microcysts. It is usually an asymptomatic disorder that is coincidentally detected in ophthalmic examinations. Occasionally there may be symptoms of corneal epithelial erosion. The keratin 3 gene (KRT3) and keratin 12 gene (KRT12) are candidate genes for the mutations that cause MCD because of their expression specificity. Irvine and co-workers identified heterozygous missense mutations in KRT3 or KRT12 in MCD families with European ancestors. Nishida and his co-workers also found four mutations of KRT12 in Japanese pedigrees. Here we present a novel mutation of KRT12 in a Japanese MCD pedigree.

Received: October 25, 2001
Correspondence and reprint requests to: Akira MURAKAMI, MD, Department of Ophthalmology, Juntendo University School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

Introduction

Meesmann’s corneal dystrophy (MCD) is an autosomal dominant disorder characterized by a myriad of fine, round epithelial asymptomatic microcysts. It is usually an asymptomatic disorder that is coincidentally detected in ophthalmic examinations. Occasionally there may be symptoms of corneal epithelial erosion. The keratin 3 gene (KRT3) and keratin 12 gene (KRT12) are candidate genes for the mutations that cause MCD because of their expression specificity. Irvine and co-workers identified heterozygous missense mutations in KRT3 or KRT12 in MCD families with European ancestors. Nishida and his co-workers also found four mutations of KRT12 in Japanese pedigrees. Here we present a novel mutation of KRT12 in a Japanese MCD pedigree.
formed consent, genomic DNA was extracted from leucocytes that were collected from three members of the pedigree. Fifty persons without corneal disease also donated DNA after informed consent and served as controls. All exons of \(KRT3\) and \(KRT12\) were amplified from patient II-5 by using primers described elsewhere, with some modifications.\(^3,4\) Amplified products were purified and sequenced using a cycle sequencing kit. Exon 1 of \(KRT12\) was also amplified from patient II-1, an unaffected member of the family III-4, and the 50 controls, using specific primers that were directly sequenced.

Results

The sequence analysis showed a (G/C) transversion in the first nucleotide of codon 137 of \(KRT12\) in the 2 patients (Figure 2). The change would be expected to result in alanine (Ala) to proline (Pro) amino acid change (Ala\(_{137}\)Pro). This alteration was not detected in the unaffected family member (III-4) and in the 50 unrelated controls. No mutation was detected in \(KRT3\) of the patients.

Discussion

We found a novel heterozygous Ala\(_{137}\)Pro mutation of \(KRT12\) in a Japanese family with MCD. The mutation is located in the \(\alpha\)-helix-initiation motif of the keratin protein. All known keratins have an alanine at the position corresponding to codon 137 of \(KRT12\). Three different mutations at codon 135 in \(KRT12\), which also are within the \(\alpha\)-helix-initiation motif, have been reported.\(^3,5\) Nishida and co-workers suggested that the mutations in the highly conserved keratin helix boundary motifs might cause a relatively severe form of MCD.\(^3\) Ala\(_{137}\)Pro change is also likely to cause symptomatic MCD phenotype with recurrent corneal erosion. Further genetic analysis of MCD patients will reveal additional genotype–phenotype relationships in keratin-related corneal disease.

References