CORRESPONDENCE

Late-onset lattice corneal dystrophy associated *TGFBI* p.H626R mutation in members of a Canadian family

Within the over 70 reported transforming growth factor-beta–induced (*TGFBI*) corneal dystrophy mutations,[1] more than 40 are associated with lattice corneal dystrophy (LCD), subtypes I, III, IIIA, and IIIB according to the Human Gene Mutation Database (QIAGEN, Hilden, Germany). This is a follow-up investigation to a study we published in 2018 in the *Canadian Journal of Ophthalmology* entitled *Trauma-induced exacerbation of epithelial-stromal TGFBI lattice corneal dystrophy*. This study reported 2 cases of post-laser-assisted in situ keratomileusis (LASIK) and postcorneal injury exacerbated late-onset LCD, attributed to a p.H626R mutation in the TGFBI protein.[2] In this follow-up study, we tested 17 additional family members, excluding the deceased female in Generation II (GENII-1), to assess the mutation penetration and identify asymptomatic carriers.

Lattice corneal dystrophy is characterized by the deposition of amyloid, primarily in the stroma, that produces a clinical appearance of thin, branching refractile lattice lines. Histology reveals fusiform deposits scattered throughout the stroma, concentrated predominantly below the Bowman's layer.[6] A number of mutations located predominantly in exon 14 of *TGFBI* are responsible for the many phenotypic variants of LCD.[8] The mutation reported within, located in exon 14 of *TGFBI*, is caused by the single base pair change, c.1877A>G (CAT>CGT), resulting in an arginine (R) for histidine (H) substitution at codon 626. This particular mutation is typically associated with late-onset LCD type IIIB, with first symptoms exhibiting in the fourth to fifth decade of life. This mutation has been reported in China,[4,5] France,[6,8] India,[9] Mexico,[10,11] Poland,[12] Singapore,[11] Switzerland,[7] the United Kingdom,[3] the United States,[12] and Vietnam.[13] This is the first study to report cases in an extended Canadian family of Italian descent.[2]

Materials and methods

Informed consent was obtained from 19 family members spanning 4 generations. Buccal cells were collected on iSwab (Mawi DNA Technologies, Hayward, Calif.) and Copan swabs (Copan Diagnostics, Brescia, Italy). Whole exome sequencing was carried out by Personalis (Menlo Park, Calif.) on the proband and his mother's samples and results confirmed by Sanger sequencing (ELIM Biopharm, Hayward, Calif.). Real-time polymerase chain reaction (PCR) primers and probes were designed using Thermo Fisher TaqMan Custom design tool (Thermo Fisher Scientific, Waltham, Mass.) and was used to test 17 family members. A family tree was constructed illustrating the genotype of each subject.

Results

Proband and proband's mother

The proband, a 27-year-old of Italian descent, residing in Montreal, Canada, presented with symptoms of recurrent corneal erosions in his right eye 4 years after a tree branch injury. His best-corrected visual acuity was 20/25 bilaterally. His right eye (the injured eye) showed 3 epithelial defects within an area of lattice-like changes, and his left eye had a clear cornea with no lattice-like changes.[2]

The proband's 63-year-old mother had bilateral LASIK in 2003. Her right eye showed central lattice-like deposits, and the left eye demonstrated diffuse lattice-like changes.[2] Her optical coherence tomography (OCT) image of the right eye revealed a small deposit at the LASIK flap. The OCT image of the left eye displayed more deposits at the LASIK flap (Fig. 1).

Whole exome sequencing revealed a TGFBI H626R mutation in both the proband and his mother. The results were confirmed by Sanger sequencing, c.1877A>G (CAT>CGT) A to G substitution (Fig. 2).

Family study

A family history of corneal dystrophy was obtained from the proband's mother. Additional family members were ascertained, and a family tree was constructed. Segregation of the H626R mutation in the family, determined by PCR analysis, indicated that 14 of the 19 family members carried a p.H626R heterozygous mutation. Five of the 14 were symptomatic and 9 were asymptomatic (Fig. 3). The age of onset varied from the fourth to the fifth decade, which is later than typically seen with other *TGFBI* mutations. The first and second generations, aged 52 to 92 years, were all symptomatic. Three of the 4 members had corneal transplants due to corneal opacity. The third and fourth generations, aged 6 to 45 years, were asymptomatic. The only symptomatic individual in this age group was the proband who acquired symptoms after corneal trauma. Therefore, early symptoms are usually caused by corneal injuries. One asymptomatic individual in Generation III, #2 (GENIII-2), had bilateral LASIK surgery in 2004; however, the PCR test revealed that she was not a carrier of the mutation. All the children in the fourth generation at the time this data was collected exhibited no corneal abnormalities.

Discussion

In this study, we expand upon the findings of our initial study,[2] which described exacerbation of late-onset LCD after LASIK surgery and corneal injury accompanying a TGFBI p.H626R mutation in an Italian Canadian family. *TGFBI* corneal dystrophy is an autosomal dominant disease with a 50% chance of inheriting the mutation from the parent who is a carrier. This is entirely consistent with the pattern seen in this family, with 14 of the 19 family members inheriting the

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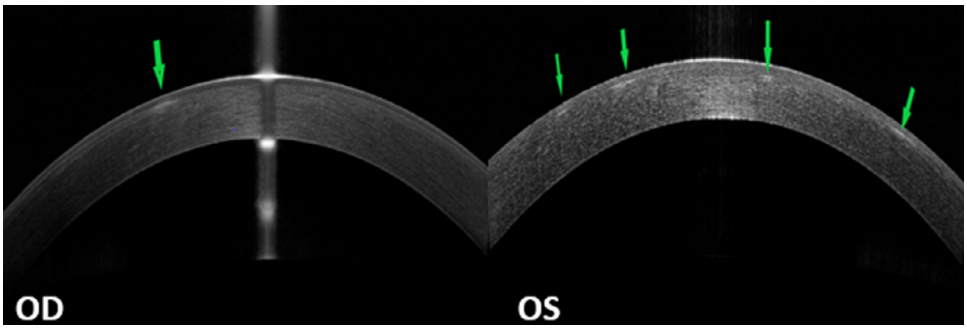

Fig. 1—OCT images of proband's mother. (OD): OCT images of right eye. One deposit was noted on the LASIK flaps where the green arrow points. (DS): OCT images of left eye. At least 4 deposits were noted on the LASIK flaps where the green arrows point.

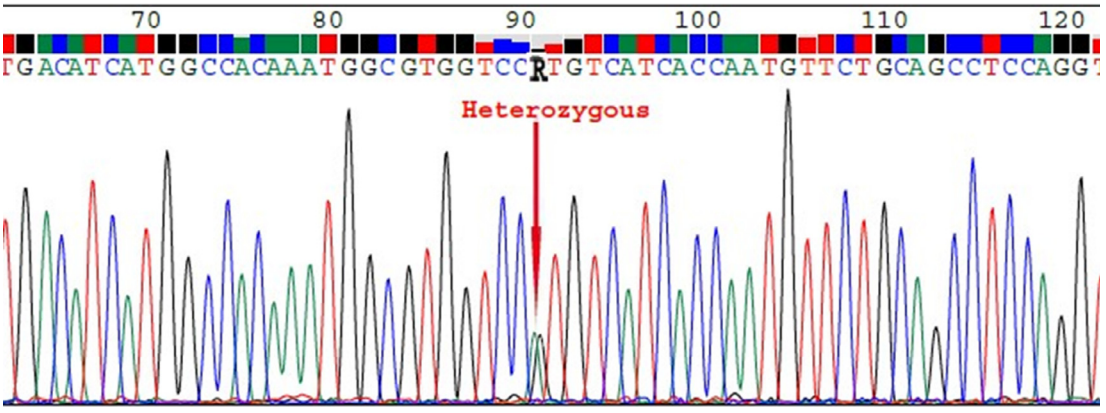

Fig. 2—Sanger sequencing electropherogram. A heterozygous c.1877A>G mutation was confirmed (R), representing by 2 equal peaks of A and G. This nucleotide change resulted in an arginine for histidine amino acid substitution.

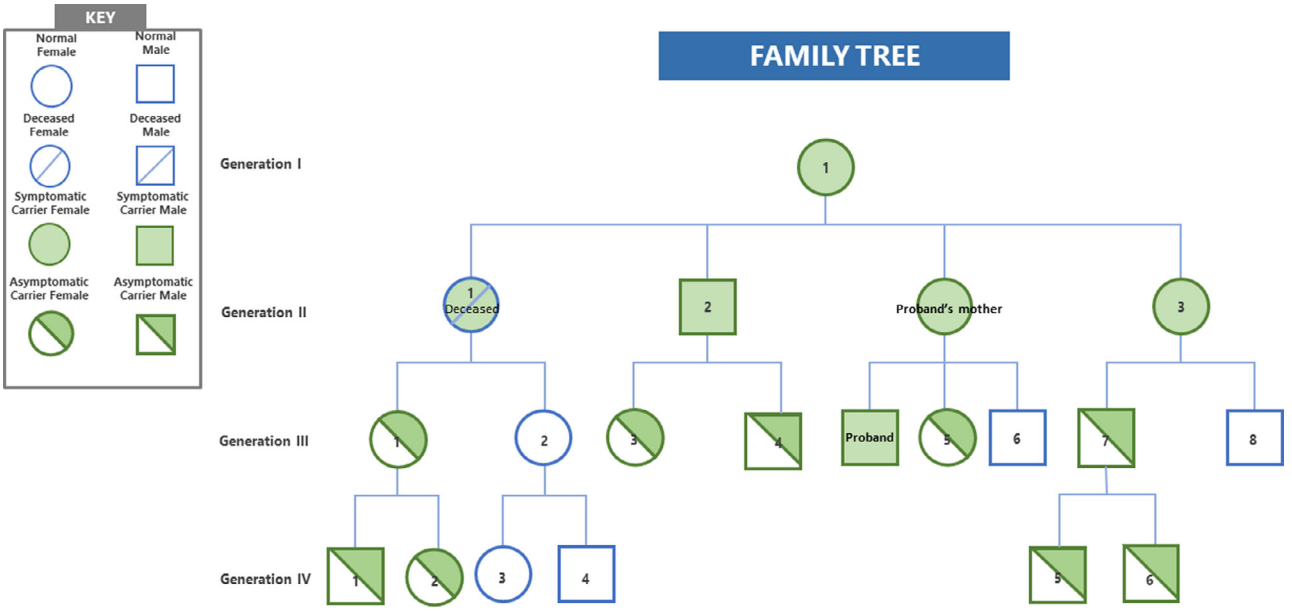

Fig. 3—Family tree. Family tree with test results of symptomatic and asymptomatic heterozygous TGFBI p.H626R mutation carriers and noncarriers. Each individual is numbered in a format as GEN#-#; for example, GENIV-3 means the individual belongs to Generation IV and his/her assigned number is 3. The deceased female, GENII-1, was symptomatic and diagnosed with LCD; however, she was not available for genetic testing.

mutation; fortunately, the GENIII-2 individual who had the LASIK surgery had not inherited the mutation. Therefore, the risk of her developing symptoms is minimal. In addition, all members of the first and second generation exhibited phenotypical symptoms. This indicated that the penetrance of this mutation is 100%. The findings presented here from a Canadian family expand the geographical distribution of this specific form of LCD to Canada. The family study reiterates the importance of performing genetic testing for both screening of LASIK surgery candidates and symptomatic corneal abnormality confirmation. Asymptomatic carriers should not have LASIK surgeries and should be counselled about the risk of corneal trauma to corneal health to avoid developing early onset LCD. A full family history should be carefully taken before LASIK surgeries.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2019.03.007.

Footnotes and Disclosure:

Tara McMullen is a consultant to Avellino Lab USA Inc, Director of the Biomedical Sciences Research Institute, and Professor of Personalised Medicine at University of Ulster, Coleraine, Northern Ireland, United Kingdom. Connie Chao-Shern is a PhD candidate at University of Ulster, Coleraine, Northern Ireland, United Kingdom, and an employee of Avellino Lab USA Inc, Menlo Park, Calif.

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