Increasing Evidence for Syndromic Phenotypes Associated with RPGR Mutations

EDITOR:
THIS LETTER IS IN REFERENCE TO THE RECENT ARTICLE BY Koenekoop and associates (Am J Ophthalmol 2003;136:678–687) in which the association between a frameshift mutation (1244 to 1245delGA) in exon 10 of the RPGR gene and an X-linked syndrome inclusive of retinitis pigmentosa and sensorineural hearing loss is reported. We congratulate the authors for this very interesting observation, and would like to draw their attention and that of the readers to additional corroborating evidence for this association that has become available simultaneously with the article by Koenekoop and associates.

We1,2 and others3 have recently documented an association between RPGR mutations and an even broader phenotype, in which the X-linked syndrome of retinitis pigmentosa and sensorineural hearing loss also included recurrent respiratory tract infections. The syndrome was associated with a missense RPGR mutation in exon 6 in a family in the United States,1 leading to the substitution of a highly conserved glycine residue at position 173 (G173R), and with a 2-base pair deletion in exon 8 (845 to 846delTG) in a family in the United Kingdom.3 The latter family had been briefly reported before (Reference 9 in Koenekoop and associates). In our study,1 we corroborated the suspected link between RPGR and these clinical manifestations by presenting immunohistochemical evidence that RPGR is indeed specifically expressed in the epithelial lining of human bronchi and sinuses, and at several locations within the human and monkey cochlea. Particularly, the latter expression pattern was consistent with the possibility that defective RPGR function could lead to hearing loss as a result of a sensorineural mechanism, as in the family reported by Koenekoop and coworkers.

X-linked retinitis pigmentosa with either sensorineural hearing loss or recurrent infections in association with RPGR defects had been noted previously by Rosenberg and associates4 and by van Dorp and associates (Reference 8 in Koenekoop and associates), respectively, but a coincidental association could not be ruled out at that time. Now, in light of the independent reports by Koenekoop and associates, Zito and associates,1,2 and ours,1,2 there appears to be substantial clinical evidence to indicate that the association between X-linked retinitis pigmentosa and sensorineural hearing loss and recurrent infections is anything but coincidental. Although our immunohistochemical findings do not provide direct evidence for a pathogenetic role of any of the aforementioned mutations at either the respiratory or the cochlear level, they do provide a rationale for the observed X-linked retinitis pigmentosa–associated syndromic phenotype.

Since characterization of our reported family we have already identified two additional X-linked families with the same complex phenotype (unpublished observation), the molecular characterization of which is in progress. We hope that the evidence that our groups have independently brought about will heighten the awareness of clinicians and the interest of scientists in this newly recognized X-linked syndromic phenotype, which must be differentiated from Usher syndrome.2 We also hope that this will lead to the identification of additional families, the discovery of RPGR interacting proteins also outside the retina, and the characterization of the pathogenetic mechanism(s) through which impaired RPGR function leads, either directly or indirectly, to both retinal and extraocular manifestations.

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AUTHOR REPLY

WE THANK DR. IANNACCOME AND COAUTHORS FOR THEIR helpful comments and their interest in our retinitis pigmentosa study in the October issue. The addition of their important study to ours and that of Zito and associates confirms that there is an important new association between defects in RPGR and hearing loss, in addition to the now well established relationship with severe X-linked retinitis pigmentosa. Of interest is the fact that in some pedigrees the hearing loss appears to be sensorineural, and in others conductive. Important is the work of Iannaccone and associates, in which they showed that RPGR is indeed expressed in the tissues where our pathology was found (that is, the cells lining the bronchi, sinuses, and cochlea), thereby providing a basis for our collective observations. Of note as well is the observation that one region of the RPGR gene (ORF15) is a hot spot for mutations in retinitis pigmentosa patients. However, all RPGR mutations thus far associated with retinitis pigmentosa, hearing loss, sinusitis, and recurrent infections have been found outside of the ORF15 exon.

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Correcting the Cornea Power Measurements for Intraocular Lens Power Calculations After Myopic Laser In Situ Keratomileusis

EDITOR:
IN REFERENCE TO THE ARTICLE BY SHAMMAS AND ASSOCIATES (Am J Ophthalmol 136:426–432, September 2003), given the same definition as used by Shammas and associates, we present the following alternative equations that relate the preoperative and postoperative K readings (Kpre and Kpost) and the true post-LASIK cornea power (Dpost). The cornea power is given by $D = \frac{377}{r1} - \frac{41}{r2}$, where $r1$ and $r2$ are the cornea radius of curvature for the anterior and posterior surfaces, respectively. It is clear that the posterior surface contributes to approximately 11% of the cornea total power; however, it does not affect the corneal power change in the LASIK procedure, which is only governed by the change of the anterior curvature radius (dr) and its initial value (r1), shown as: $dD = -\frac{377}{(r1)^2}$, in which $r2$ plays no role at all.

$$D_{post} = 1.117 \times K_{post} - 41/r2 \quad (Equation \, 1)$$

$$D_{post} = 1.117 \times K_{pre} + dD - 41/r2 \quad (Equation \, 2)$$

$$K_{pre} = K_{post} + 0.895dD \quad (Equation \, 3)$$

Depending on whether either postoperative or preoperative K readings is known, one may easily calculate the corneal post-LASIK power by Eq. 1 or 2. In addition, Kpre may be calculated by Eq. 3 if one knows the refractive power correction amount after LASIK (the dD term). The standard intraocular lens power calculation using the post-LASIK K reading, therefore, will have errors of about 6.0 to 6.5 diopters for $dD = -1.0$ to $-5.0$ diopters, as shown by the above equations.

The existing commonly used first-order approximation in LASIK does not provide an accurate dD value, which will include the high-order terms as follows: $dD = D_0 \times (1 - C2 + C3)$; and $C2 = 0.19 (W/r1)^2$, where $D_0$ is the commonly used first-order term $D_0 = 3.0 h/W^2$, defined by the central ablation depth of the cornea (h) and optical zone diameter (W) in LASIK procedures, in which $D_0$ and W are the only input in the nomogram without the high-order term that is particularly important for modern LASIK procedures with large optical zones. For example, C2 = (7% to 10%) $D_0$, for W = (5 to 6) mm and $r1 = 7.763$ mm, and C2 increases to 12% for a smaller $r1 = 7.375$ mm.

Wave front technology with customized cornea ablation has become more popular recently. Without an accurate preoperative measurement of corneal anterior surface (the $r1$) and customized input, the initial values of $r1$, W, and $D_0$, supervision correction will not be predictable. Most of the existing LASIK systems are based on a nomogram with a first-order term, in which the high-order errors are “smeared” into another empirical correction factor (CF), which translates the excimer laser ablation rate from a testing PMMA (R1) to clinically averaged cornea surface tissue ablates rate R2. This CF = R2/R1 = (2.5 to 3.5), depending on the manufacturers of the systems used, and based on statistical mean values and cannot be representative for specific subjects when one talks about “customized” ablation. This apparent CF value is also clinically adjusted such that the errors of approximately 7% to 12% on refractive power change (based on the first-order formula) were compensated. The correct method, we