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Therapeutic Window for Phosphodiesterase 6–Related Retinitis Pigmentosa

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In this issue of JAMA *Ophthalmology*, Khateb et al[1] fill a key knowledge gap by providing a comprehensive retrospective analysis of retinitis pigmentosa (RP) disease progression over time in a large cohort of 54 patients with either *PDE6A* or *PDE6B* mutations. Their findings revealed 29 novel *PDE6A* and *PDE6B* variants among 49 that were identified. Using a wide range of variables as outcome measures—including multimodal retinal imaging, best-corrected visual acuity, full-field electroretinography, and kinetic visual fields—in some cases with more than 15 years of follow-up, Khateb et al[1] found similar rates of disease progression between both genetic groups, although nyctalopia was a more prevalent symptom in patients with *PDE6A*.

Phosphodiesterase-6 (PDE6) is one of the most studied phototransduction enzymes with an overwhelming amount of promising translational and clinical data.[2–5] The *PDE6* genes encode a key phototransduction enzyme, rod-specific cyclic guanosine monophosphate

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(cGMP) phosphodiesterase 6, composed of 1 α (PDE6A; OMIM 180071), 1 β[6,7] (PDE6B; OMIM 180072), and 2 inhibitory γ (PDE6G; OMIM 180073) subunits. Upon light-induced activation, the γ subunits of PDE6 are displaced via G-protein activity, causing a surge in cGMP hydrolysis and subsequent cGMP-mediated rod hyperpolarization. As such, autosomal-recessive mutations in *PDE6A*, *PDE6B*, or *PDE6G* lead to a rise in calcium and sodium ions that triggers photoreceptor cell death.

A wealth of evidence stemming from preclinical *PDE6* RP animal models suggests that *PDE6*-related RP is a directly treatable disease with a wide therapeutic time window. Mowat et al[2] accomplished effective gene augmentation therapy in *Pde6a*-mutant Cardigan Welsh corgi dogs through subretinal injection of capsid-mutant AAV-*Pde6a*—a milestone instance of vision-restoring gene therapy performed in a large animal. Other studies using *Pde6* mouse models—the most commonly studied RP animal model worldwide—have elucidated avenues for metabolomics- and gene-based therapy. By reprogramming rod photoreceptors into perpetual glycolysis in $Pde6b^{H620Q}/Pde6b^{H620Q}$ mice, Zhang et al[4] revealed a novel, non–gene-specific metabolome reprogramming for enhancing photoreceptor survival in RP. Even advanced stages of RP were proven to be treatable in $Pde6b^{H620Q}/Pde6b^{H620Q}$ mice, suggesting that RP possesses a fairly large therapeutic time window after which the disease is considered too advanced for therapy.[5]

The contribution of Khateb et al[1] is timely in the context of emerging human gene therapy clinical trials. *PDE6*, although rare in the absolute sense, is the most common cause of autosomal-recessive RP following *USH2A* and *EYS*; *PDE6A* was found to occur in approximately 2 of 173 cases of autosomal-recessive RP, and *PDE6B* was found to occur in 4 of 92 cases.[8] It is therefore no surprise that the work of Khateb et al[1] is among a growing number of translational and clinical *PDE6* research studies available to date. Their article is impressive in that it summarizes one of the largest longitudinal cohorts of patients with *PDE6A* and *PDE6B* mutations who have RP studied thus far.

Unique to their study is the use of kinetic visual fields as a functional outcome measure of RP progression. The subgroup of patients that underwent Goldmann kinetic visual field testing exhibited sizable degrees of vision (a mean of 13°–14° in both genetic groups) that allowed for a detectable decrease in visual field over time. This finding suggests that the disease progression in a substantial number of patients with *PDE6* mutations may be monitored using kinetic visual field testing as an outcome measure in interventional clinical trials. Khateb et al[1] also quantitatively characterized the rate of decrease of the horizontal and vertical diameters of the hyperautofluorescent ring in RP over time. An analysis of these rates of ring constriction suggested that, as RP progresses, the shape of the ring gradually evolves from an ellipse to a circle—a novel finding that could serve as a prognostic aid or a marker of disease progression in clinical settings and trials. These and other findings in the work of Khateb et al[1] will have considerable implications on the design, duration, and outcome measurements of future *PDE6*-related RP clinical trials yet to come.

Conflict of Interest Disclosures:

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