# Author Response: Relationship Between Foveal Cone Specialization and Pit Morphology in Albinism

We read with interest the letter from Alan D. Springer,[1] and would like to thank him for his critique of our recent work.[2] We would like to respond by highlighting valid points, as well as address some clear misunderstandings.

First, regarding the reference to "albinos," a more acceptable term is "patient/subject/individual/person with albinism." This sensitivity in wording places the person ahead of the disease, which is the more favored terminology.

Second, the author says "*Surprisingly they did not perform a t-test to evaluate whether the two groups differed with respect to cone density. Instead, they just emphasized the overlap of the normal and albino density distributions*." We do understand when statistical evaluation is warranted and agree that it is easy to perform a *t*-test given the means, SDs, and *n*/group, which is why we reported those three parameters for all of our data. When reporting the peak cone density in patients with albinism, we state, "*While on average this is below normal, the two distributions clearly overlap*." We find nothing wrong (or inadequate) about this statement or presentation of the comparison between the controls and the patients with albinism, as it correctly reflects the data: patients with albinism indeed have reduced peak cone density.

The author then states that our "*. . .conclusion regarding unusual differences in variability in the data of normal and albinos is unwarranted*." Nowhere in the manuscript did we claim that there were differences in variability between the groups. We would like to reiterate that aspects of foveal anatomy (pit morphology, outer segment elongation, cone packing) are indeed variable, both in patients with albinism as well as healthy controls. In albinism, which, until recently, had universally been associated with foveal hypoplasia, we find it striking that cone specialization can range from nondetectable to falling within normal limits. Another reason to discuss the variation within the group, rather than focus on a group average, is that the data were collected from patients with different subtypes of albinism. It is likely that the degree of foveal specialization differs depending on the underlying genetic defect, thus combining all of the data to draw some general conclusion about how it compares with normal ignores the fact that these patients have different conditions (e.g., ocular albinism versus oculocutaneous albinism).

Next, the author brings up a valid point in discussing limits of in vivo retinal imaging. Our use of adaptive optics (AO) was not through optical coherence tomography (as stated by the author), but rather an AO scanning light ophthalmoscope (AOSLO). The author states, "*many subjects were excluded because their images lacked of clarity.*" With careful reading of our paper, the author would find that what we actually said (after listing the 16 regions of interest where we measured cone density) was that "*not all locations could be assessed for each subject due to poor image quality or incomplete montages*." For all subjects, we measured and reported peak foveal cone density, no foveal images were excluded. Many of the images excluded were from patients with albinism, where the nystagmus sometimes resulted in gaps in the intended large montages. Also, the emergence of rods can complicate identification of cones in the periphery with conventional confocal AOSLO, and this also resulted in some locations not being analyzed. That said, we agree that the normal peak cone densities reported here (and by previous groups using AOSLO) are lower, on average, than those reported by Curcio et al.[3] If it were true that we somehow didn't include people with higher cone density in our normative group, this omission would only increase the mean and expand the normal range. This would not change our finding that some patients with albinism can have peak densities within the normal range.

Finally, we did not claim, nor do we believe, that significant group differences are supported only by nonoverlapping data distributions. That said, a significant group difference does not mean the data distributions don't overlap. This distinction is especially useful in a disease such as albinism, where there is not a single picture that captures foveal morphology; rather there is a continuum of foveal maturity (or immaturity) associated with the condition. As such, a patient who demonstrates some clinical features of albinism (e.g., iris transillumination, no stereopsis, blond fundus) but displays normal-appearing foveal specializations may indeed have albinism and should undergo genetic testing and/or further clinical evaluation (e.g., a visual-evoked potential for retinostriate misrouting). In efforts to understand the retinal versus cortical contributions to vision loss in these patients, we think this is an important observation.

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## *References*

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