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Patients within the Broad Holoprosencephaly Spectrum have Distinct and Subtle Ophthalmologic Anomalies: Response to Khan

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To the Editor:

We appreciate the points raised by Dr. Khan in response to our recent article, as well as the opportunity to clarify our findings in an effort to provide a thorough phenotypic characterization of patients within the holoprosencephaly (HPE) spectrum [Pineda-Alvarez et al., 2011; Solomon et al., 2010b]. One question raised by Dr. Khan pertained to the methods of corneal measurements. The horizontal corneal diameters of the patients in our study were measured using digital scaled-photography technique. Despite arguments of lack of precision and overestimation of the horizontal corneal diameters, there is extensive evidence that this technique correlates with gold-standard techniques, for example, via calipers under general anesthesia [Lagreze and Zobor, 2007; Puvanachandra and Lyons, 2009; Robinson et al., 1989]. In response to Dr. Khan's questions about specific ocular phenotypes we described in our article, Patient 1 was a 34-year-old woman at the time of the exam and presented with horizontal corneal diameters of 10.5 mm OU, which are in the lower end of "relative" microcornea. Patient 2 was a 12-year-old boy who presented with smaller than average ocular axial lengths (below the 5th centile in the right eye measuring 21.69 mm, and approximately at the 5th centile in the left eye measuring 22.48 mm). These latter measurements can be classified as "simple microphthalmos" since the use of the term nanophthalmos has acquired a different connotation [Khan and Zafar, 2009; Khan, 2008]. In addition, Patient 2 has a small peripapillary crescent in OS and a blood vessel running very close to the fovea centralis in OD, with a vision of 20/30 that was not improvable with manifest refraction. These findings suggest mild foveal hypoplasia in the right eye [Pineda-Alvarez et al., 2011].

While we agree with Dr. Khan that the ocular anomalies in these two patients are not typical for the general population, we also believe that the presentation of phenotypic features in patients with HPE are unusual and that most of these features have not been meticulously characterized. Furthermore, there is evidence that Sonic Hedgehog (SHH), an important morphogen implicated in the pathogenesis of HPE, also plays key role in the causality of several ophthalmologic anomalies. As we described, SHH regulates several aspects of the

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development of the eye, including ventral-dorsal patterning, eye field separation, and optic fissure closure, among other processes [Carlson, 2009; England et al., 2006; Hallonet et al., 1999; Kobayashi et al., 2010; Zhao et al., 2010]. Consequently, insults that affect directly or indirectly the generation of a proper SHH morphogenic gradient may alter the normal development of the eye and result in unusual ophthalmologic features, such as seen in the patients we described. These anomalies have been mentioned in the literature with varying degrees of detail, but they have not been consistently evaluated in the rest of the patients of our large cohort (over 1,000 individuals with HPE) [Bakrania et al., 2010; Horn et al., 2004; Lacbawan et al., 2009; Schimmenti et al., 2003; Solomon et al., 2010a]. We also concur that further research should be conducted in order to improve our understanding of the broad phenotypic variability among patients with mutations in HPE-associated genes. However, we feel strongly that relegating the unraveling of our patients' ocular phenotypes to the marvels of newly available genomic sequencing technologies violates Occam's razor, and is a potentially overly simplistic reaction to any incomplete etiologic explanation. Among the limitations of this approach are the immense genetic heterogeneity and the broad phenotypic variability of HPE, as well as perhaps-related ocular conditions.

Lastly, and most importantly, we would like to emphasize that ocular anomalies are prevalent among patients with HPE; therefore, we encourage clinicians to refer these patients to an ophthalmologist familiar with this disorder in order to promptly characterize any anomalies, initiate an adequate treatment and avoid possible complications.

REFERENCES

- Bakrania P, Ugur Iseri SA, Wyatt AW, Bunyan DJ, Lam WW, Salt A, Ramsay J, Robinson DO, Ragge NK. Sonic hedgehog mutations are an uncommon cause of developmental eye anomalies. *Am J Med Genet A*. 2010; 152A:1310–1313. [PubMed: 20425842]
- Carlson, BM. Human embryology and developmental biology. Philadelphia, PA: Mosby/Elsevier; 2009. p. 541xvi
- England SJ, Blanchard GB, Mahadevan L, Adams RJ. A dynamic fate map of the forebrain shows how vertebrate eyes form and explains two causes of cyclopia. *Development*. 2006; 133:4613–4617. [PubMed: 17079266]
- Hallonet M, Hollemann T, Pieler T, Gruss P. Vax1, a novel homeobox-containing gene, directs development of the basal forebrain and visual system. *Genes & development*. 1999; 13:3106–3114. [PubMed: 10601036]
- Horn D, Tonniés H, Neitzel H, Wahl D, Hinkel GK, von Moers A, Bartsch O. Minimal clinical expression of the holoprosencephaly spectrum and of Currarino syndrome due to different cytogenetic rearrangements deleting the Sonic Hedgehog gene and the HLXB9 gene at 7q36.3. *American journal of medical genetics Part A*. 2004; 128:85–92.
- Khan A, Zafar SN. Variable retinal presentations in nanophthalmos. *JPMMA The Journal of the Pakistan Medical Association*. 2009; 59:791–793. [PubMed: 20361684]
- Khan AO. Posterior microphthalmos versus nanophthalmos. *Ophthalmic genetics*. 2008; 29:189. [PubMed: 19005993]
- Kobayashi T, Yasuda K, Araki M. Coordinated regulation of dorsal bone morphogenetic protein 4 and ventral Sonic hedgehog signaling specifies the dorso-ventral polarity in the optic vesicle and governs ocular morphogenesis through fibroblast growth factor 8 upregulation. *Dev Growth Differ*. 2010; 52:351–363. [PubMed: 20298259]
- Lacbawan F, Solomon BD, Roessler E, El-Jaick K, Domene S, Velez JI, Zhou N, Hadley D, Balog JZ, Long R, Fryer A, Smith W, Omar S, McLean SD, Clarkson K, Lichty A, Clegg NJ, Delgado MR, Levey E, Stashinko E, Potocki L, Vanallen MI, Clayton-Smith J, Donnai D, Bianchi DW, Juliusson PB, Njolstad PR, Brunner HG, Carey JC, Hehr U, Musebeck J, Wieacker PF, Postra A, Hennekam RC, van den Boogaard MJ, van Haeringen A, Paulussen A, Herbergs J, Schrandt-Stumpel CT, Jancke AR, Chitayat D, Hahn J, McDonald-McGinn DM, Zackai EH, Dobyns WB, Muenke M.

- Clinical spectrum of SIX3-associated mutations in holoprosencephaly: correlation between genotype, phenotype and function. *J Med Genet.* 2009; 46:389–398. [PubMed: 19346217]
- Lagreze WA, Zobor G. A method for noncontact measurement of corneal diameter in children. *American journal of ophthalmology.* 2007; 144:141–142. [PubMed: 17601441]
- Pineda-Alvarez DE, Solomon BD, Roessler E, Balog JZ, Hadley DW, Zein WM, Hadsall CK, Brooks BP, Muenke M. A broad range of ophthalmologic anomalies is part of the holoprosencephaly spectrum. *American journal of medical genetics Part A.* 2011; 155:2713–2720. [PubMed: 21976454]
- Puvanachandra N, Lyons CJ. Rapid measurement of corneal diameter in children: validation of a clinic-based digital photographic technique. *Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus / American Association for Pediatric Ophthalmology and Strabismus.* 2009; 13:287–288. [PubMed: 19541269]
- Robinson J, Gilmore KJ, Fielder AR. Validation of a photographic method of measuring corneal diameter. *The British journal of ophthalmology.* 1989; 73:570–573. [PubMed: 2757999]
- Schimmenti LA, de la Cruz J, Lewis RA, Karkera JD, Manligas GS, Roessler E, Muenke M. Novel mutation in sonic hedgehog in non-syndromic colobomatous microphthalmia. *Am J Med Genet A.* 2003; 116:215–221. [PubMed: 12503095]
- Solomon BD, Lacbawan F, Mercier S, Clegg NJ, Delgado MR, Rosenbaum K, Dubourg C, David V, Olney AH, Wehner LE, Hehr U, Bale S, Paulussen A, Smeets HJ, Hardisty E, Tylki-Szymanska A, Pronicka E, Clemens M, McPherson E, Hennekam RC, Hahn J, Stashinko E, Levey E, Wiczorek D, Roeder E, Schell-Apacik CC, Booth CW, Thomas RL, Kenwick S, Cummings DA, Bous SM, Keaton A, Balog JZ, Hadley D, Zhou N, Long R, Velez JI, Pineda-Alvarez DE, Odent S, Roessler E, Muenke M. Mutations in ZIC2 in human holoprosencephaly: description of a Novel ZIC2 specific phenotype and comprehensive analysis of 157 individuals. *J Med Genet.* 2010a; 47:513–524. [PubMed: 19955556]
- Solomon BD, Mercier S, Velez JI, Pineda-Alvarez DE, Wyllie A, Zhou N, Dubourg C, David V, Odent S, Roessler E, Muenke M. Analysis of genotype-phenotype correlations in human holoprosencephaly. *Am J Med Genet C Semin Med Genet.* 2010b; 154C:133–141. [PubMed: 20104608]
- Zhao L, Saitsu H, Sun X, Shiota K, Ishibashi M. Sonic hedgehog is involved in formation of the ventral optic cup by limiting Bmp4 expression to the dorsal domain. *Mechanisms of development.* 2010; 127:62–72. [PubMed: 19854269]