Novel BMP4 Truncations Resulted in Opposite Ocular Anomalies: Pathologic Myopia Rather Than Microphthalmia

Yi Jiang1, Jiamin Ouyang1, Xueqing Li1, Yingwei Wang1, Lin Zhou1,2, Shiqiang Li1, Xiaoyun Jia1, Xueshan Xiao1, Wenmin Sun1, Panfeng Wang1 and Qingjiong Zhang1*

1 State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China,
2 Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China

BMP4 variants have been reported to be associated with syndromic microphthalmia (MCOPS6, OMIM 607932). This study aims to describe BMP4 truncation mutations contributing to a novel phenotype in eight patients from four Chinese families. In this study, BMP4 variants were collected from a large dataset from in-house exome sequencing. Candidate variants were filtered by multiple in silico tools as well as comparison with data from multiple databases. Potential pathogenic variants were further confirmed by Sanger sequencing and cosegregation analysis. Four novel truncation variants in BMP4 were detected in four out of 7,314 unrelated probands with different eye conditions. These four mutations in the four families solely cosegregated in all eight patients with a specific form of pathologic myopia, characterized by significantly extended axial length, posterior staphyloma, macula patchy, chorioretinal atrophy, myopic optic neuropathy or glaucoma, vitreous opacity, and unique peripheral snow-grain retinopathy. The extreme rarity of the truncations in BMP4 (classified as intolerant in the gnomAD database, pLI = 0.96), the exclusive presence of these variants in the four families with pathologic myopia, variants fully co-segregated with the same specific phenotypes in eight patients from the four families, and the association of the pathogenicity of truncations with syndromic microphthalmia in previous studies, all support a novel association of BMP4 truncations with a specific form of pathologic myopia. The data presented in this study demonstrated that heterozygous BMP4 truncations contributed to a novel phenotype: pathologic myopia rather than microphthalmia. Mutations in the same gene resulting in both high myopia and microphthalmia have been observed for a few other genes like FZD5 and PAX6, suggesting bidirectional roles of these genes in early ocular development. Further studies are expected to elucidate the molecular mechanism of the bidirectional regulation.

Keywords: pathologic myopia, early-onset myopia, BMP4, truncation variants, microphthalmia
INTRODUCTION

Pathologic myopia is characterized by posterior staphyloma, fundus degenerative changes, and abnormal corrected visual acuity. Pathologic myopia usually belongs to a subgroup of high myopia, which is defined as an axial length of 26 mm or more (Ohno-Matsui et al., 2016; Sankaridurg et al., 2021; Spaide et al., 2021). The complications associated with pathologic myopia are among the first to third common causes of legal blindness worldwide (Wong et al., 2014; Sankaridurg et al., 2021). Genetic defects play a major role in the development of pathologic myopia or high myopia, and among these defects, at least 28 loci or genes have been reported to contribute to non-syndromic forms, while variants in a number of genes are known to cause syndromic forms. However, the genetic defects for most cases of high myopia or pathologic myopia are still unknown, and the identification of additional implicating genes may enrich our understanding of the pathogenesis and facilitate the prevention and management of these conditions (Zhang, 2021).

Comparative exome sequencing has been used to detect genetic factors contributing to retinitis pigmentosa and glaucoma in our previous studies (Sun et al., 2019; Yi et al., 2020). Using similar strategy, four truncation variants in BMP4 (OMIM 112262) were detected in four unrelated families with pathologic myopia. These variants were confirmed by Sanger sequencing and cosegregated with pathologic myopia in eight patients from four families but in none of the unaffected individuals or any in-house controls, suggesting that BMP4 may be an important factor for pathologic myopia. BMP4 plays a vital regulatory role in embryonic development (Hogan, 1996) and truncations in this gene are extremely rare and intolerant (gnomAD, probability of being loss-of-function intolerant (pLI) = 0.96; Exp. 14.2 with obs. 1]. Previously, truncations in BMP4 were reported to cause microphthalmia, anophthalmia, and coloboma (MAC) (Reis et al., 2011) and anterior segment dysgenesis (ASGD) (Takenouchi et al., 2013), phenotypes that in contrast to those of pathologic myopia. The identification of a novel and bidirectional ocular abnormality associated with BMP4 truncations may provide new clues for elucidation of the developmental regulation of ocular size and shape.

MATERIALS AND METHODS

Patient Recruitment and Data Collection

The probands with different eye disorders and their related family members were enrolled through the Pediatric and Genetic Clinic, Zhongshan Ophthalmic Center. Clinical data and peripheral blood samples were collected from these individuals. Prior to collection, all the participants or their guardians voluntarily signed informed content according to the tenets of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Zhongshan Ophthalmic Center. Genomic DNA was extracted from the leukocytes within peripheral venous blood samples by following a previously reported method (Wang et al., 2010).

Each participating individual received a routine ophthalmologic examination. Additional specific ocular examinations were performed when required, including anterior segment photography, fundus photography, optic coherence tomography (OCT), electroretinogram (ERG), and scanning laser ophthalmoscopy (SLO).

Variant Detection and Evaluation

Whole-exome sequencing (Li et al., 2015) or target-exome sequencing (Wang et al., 2019) was performed on the genomic DNA from the 7,314 probands including 928 with early onset myopia, and 6,386 with other ocular conditions. After the detection of variants in BMP4 from the exome sequencing data, the variants were filtered by multiple bioinformatic analytic steps. First, variants with low sequencing quality with a coverage of less than 5 were excluded. Second, synonymous and non-coding variants without effects on splicing site alterations, which were predicted by the Berkeley Drosophila Genome Project, were excluded. Third, through the evaluation of the minor allelic frequencies (MAFs) of variants based on the gnomAD database, variants with an MAF ≥ 0.01 were excluded. The remaining variants were evaluated by five in silico tools, including SIFT, Polyphen-2, PROVEAN, CADD, and REVEL. Finally, the variants were classified as potential pathogenic variants (PPVs) after comparison with the distribution of variants in our cohort and the gnomAD database.

The variants were further confirmed by Sanger sequencing. The online design program Primer3.0 was used for primer design and the primer sequences are listed in Supplementary Table 1. Sanger sequencing validation including amplification, sequencing and target sequences analysis was performed following a previously described method (Chen et al., 2013). Then, the cosegregation analysis was conducted based on Sanger sequencing on genomic DNA from family relatives in these families.

Statistical Analysis

IBM SPSS software version 26.0 (Amonk, NY: IBM Corp.) was applied to all statistical analyses in this study. The comparison of the frequency of truncation variants between in-house data related to early onset myopia and data in the gnomAD database was analyzed using the chi-square test or Fisher's exact test. An in-house data comparison between the frequency of these truncation variants in patients with early onset myopia and the frequency of these truncation variants in patients with other eye conditions was also performed using the chi-square test or Fisher's exact test. A P-value less than 0.05 was considered as statistically significant.

Immunohistochemical Staining

To examine the BMP4 protein expression in the retinal tissue, immunohistochemical staining was performed on the human...
RESULTS

Mutation Analysis

Totally, four novel truncation variants in BMP4 were identified in four out of 7,314 unrelated probands with different eye conditions, including c.43delC:p.(Gln15Lysfs*4), c.97A>T:p.(Lys33*), c.419delT:p.(Phe140Serfs*13), and c.766C>T:p.(Arg256*) (Figure 1). These four truncations were novel and potential candidates of disease-causing variants since this type of variants were extremely rare and intolerant based on gnomAD database (pLI = 0.96) (Figure 2B). In the current study, interestingly, all the four probands with these BMP4 truncations had early onset pathologic myopia, accounting for 4 of 928 probands with early onset high myopia, but in none of the 6,386 probands with other eye conditions ($P = 2.58 \times 10^{-4}$, Fisher’s exact test) (Figures 2A,C). Similarly, the frequency of BMP4 truncations in probands with early onset high myopia is significantly higher compared with the frequency in gnomAD ($P = 1.23 \times 10^{-7}$, Fisher’s exact test) (Figures 2A–C). The four truncations in our cohort were

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**FIGURE 1** The pedigrees and sequencing chromatograms of the four families in this cohort with potential pathogenic truncations. The filled pattern represents unaffected individuals. The square pattern indicates males, while the circle pattern indicates female. M represents the mutated allele and + represents the normal allele. The family number is shown above the pedigree and the amino acid effect of the mutation is shown below the pedigree.
confirmed by Sanger sequencing and completely cosegregated with pathologic myopia in all eight patients from the four families (Table 1 and Figure 1): the c.97A>T:p.(Lys33∗) was a de novo variant presented in Family F3; another nonsense variant [c.766C>T:p.(Arg256∗)] and two frameshift variants [c.43delC:p.(Gln15Lysfs*4); c.419delT:p.(Phe140Serfs*13)] were segregated with pathologic myopia in the remaining three families. Here, four novel BMP4 truncation variants exclusively segregated with pathologic myopia in eight patients from four unrelated families suggests a novel bidirectional role of BMP4 in the normal and abnormal development of the eye, since most BMP4 variants were associated with microphthalmia-related disorders based on Human Gene Mutation Database (HGMD) database from previously studies (Bakrania et al., 2008; Hayashi et al., 2008; Reis et al., 2011; Lumaka et al., 2012; Huang X. et al., 2015; Blackburn et al., 2019; Nixon et al., 2019; Thanikachalam et al., 2020; Figure 2D).

Clinical Characteristics

The clinical features of eight patients with novel BMP4 truncation variants were summarized in Table 1. Extra-ocular features were only observed in one of the eight patients, i.e., proband F4-II:3, who had tooth malformation, broad nasal bridge, and hyperextensible joints. Of the eight patients, the four probands were identified to have high myopia due to poor vision before school age. Subsequent systemic ocular examination on the probands and family members revealed pathologic myopia in eight patients from the four families. The best-corrected visual acuity (BCVA) among eight patients ranged from counting fingers (CF) to 1.00 (Snellen equivalent) and the mean BCVA was 0.45. The average axial length of eight patients was 30.62 mm (range, 25.32–37.88 mm). Additionally, the axial length of all patients but one family member (F2-I:2) was more than 26.00 mm. The axial length of F2-I:2 was 25.56 mm in the right eye and 25.32 mm in the left eye, her fundus changes showed a trend toward pathologic myopia. The fundus images of these patients demonstrated typical fundus changes for pathologic myopia, including tessellated fundus, posterior staphyloma, macula atrophy, patchy or diffuse chorioretinal atrophy, and peripheral chorioretinal degeneration (Figure 3). Interestingly, unique fundus changes were clearly observed in peripheral
retinas of three patients from two families (F1-II:1, F1-II:2, and F2-II:1), i.e., numerous small white spots in the peripheral retina displayed a "snow grain" appearance (Figure 4). This characteristic phenotype has not been described previously in pathologic myopia so that it may be considered as a unique sign of pathologic myopia related to BMP4 truncation variants. The fundus autofluorescence and ERG test result were available from both eyes from the proband F1-II:2, demonstrating moderate reduction of rod and cone responses on ERG examination and relatively preserved autofluorescence with non-specific minor changes in the posterior and mid-peripheral retina (Supplementary Figure 1). Additionally, difference in severity of pathologic myopia between the two eyes was observed in all patients (Figures 3, 4), but such difference was relatively mild as compared with pathologic myopia due to mutations in genes responsible for Stickler syndrome or FEVR (unpublished data). The OCT scans of the four probands illustrated optic nerve fiber layer thinning and choroid atrophy (Supplementary Figures 2A–D). The white vitreous strands resembling gossamer anomalies were observed in anterior vitreous cavity in patients from two families (F1, F2) (Supplementary Figure 2E).

DISCUSSION

Previously, mutations in BMP4 were known to cause microphthalmia-related disorders (Bakrania et al., 2008; Reis et al., 2011). On the contrary, in the current study, four novel truncation variants in BMP4 were identified as PPVs in eight patients with pathologic myopia from four families. Our novel findings were supported by the following lines of evidences: (1) As described above, the truncation variants in BMP4 were extremely rare and intolerant in general population (gnomAD database, pLI = 0.96). Although the few BMP4 truncation variants have been reported are related to ocular phenotypes based on HGMD database, the loss of function variant has been identified as a disease-causative mutation related to ocular or systemic disorders. (2) As previously mentioned, the four BMP4 truncation variants considered PPVs, were highly enriched in 928 patients with early onset high myopia in this cohort. In contrast, none of potential pathogenic BMP4 truncation variants were identified in 6,386 patients with other eye conditions. Essentially, the clinical evidence supports that these four truncation variants contribute to phenotype—pathologic myopia. This point reflects that truncation variants in BMP4 are highly related to pathologic myopia. (3) None of these four BMP4 truncation variants were present in databases. These variants segregated with pathologic myopia in all families in this cohort. (4) In the same pedigree, all individuals with same BMP4 truncation variant exhibited a similar ocular phenotype. For example, in the family F1, the fundus images of mother and three children with same variant showed typical pathologic myopia fundus changes based on the Meta-Analysis for Pathologic Myopia (META-PM) classification (Ohno-Matsui et al., 2015). The same snow-grain degeneration in the peripheral retina was observed in the proband's sister (F1-II:1) and the proband (F1-II:2). (5) In our study, the BMP4 protein expression mainly located in the inner nuclear layer and inner plexiform layer of adult human retina (Supplementary Figure 3), indicating that BMP4 might play pivotal role in visual and retinal development. (6) Previous genome-wide association studies on myopia identified that one of new genetic associations in European population was near the location of BMP4 (Kiefer et al., 2013). Based on the above evidences, the BMP4 truncation variants are suggested to cause pathologic myopia.

TABLE 1 | Clinical information of the patients with BMP4 truncation variants in this study.

| Family | Nucleotide acid | Amino acid | Gender | Age (years) | BCVA | Axial length (mm) | Fundus |
|--------|----------------|------------|--------|------------|------|------------------|--------|
| ID     | Change         | Effect     | Onset  | At exam    | OD   | OS               | OD     | OS     | OD     | OS     |
| F1-I-2 | c.766C>T       | p.Arg256*  | F      | EC         | 46   | CF               | 37.88  | 36.31  | MA     | PCA    | TF     |
| F1-II:1| c.766C>T       | p.Arg256*  | F      | EC         | 23   | 0.40             | 29.38  | 31.44  | PWSD   | TF     | DCA    | PWSD   | TF     |
| F1-II:2| c.766C>T       | p.Arg256*  | M      | EC         | 18   | 0.06             | 35.30  | 32.5   | MA     | PCA    | PWSD   | TF     |
| F1-II:3| c.766C>T       | p.Arg256*  | M      | EC         | 17   | 1.00             | 26.05  | 26.25  | DCA    | PWSD   | LD     | PWSD   | TF     |
| F2-I:2 | c.43delC       | p.Gln15Lysfs*4 | NA    | 32        | 1.00 | 1.00             | 25.56  | 25.32  | TF     | TF     |
| F2-II:1| c.43delC       | p.Gln15Lysfs*4 | F     | 3         | 7    | 0.80             | 29.30  | 27.72  | DCA    | PWSD   | LD     | PWSD   | TF     |
| F3-II:1| c.97A>T        | p.Lys33*   | M      | EC         | 31   | CF               | 33.16  | NA     | PS     | DCA    | NA     |
| F4-II:3| c.419delT      | p.Phe140Serfs*13 | M     | 3         | 6    | 0.20             | 32.08  | 31.19  | PS     | DCA    | NA     |

The variant nomenclature is based on the NCBI reference sequence for BMP4 transcript NM_001202.6. All variants are absent in HGMD database and gnomAD database. EC, early childhood; SE, Snellen equivalent; M, male; F, female; NA, not available; SA, affecting splicing acceptor; CF, counting fingers; HM, hand motion; TF, tessellated fundus; DCA, diffuse chorioretinal atrophy; MA, macula atrophy; PCA, patchy chorioretinal atrophy; PWSD, peripheral white spots degeneration; LD, lattice degeneration; BCVA, best corrected visual acuity.

* Translation termination (stop) codon.
† The left eye of proband F3-II:1 has cornea opacity, cataract, and has been performed retinal photocoagulation due to retinal detachment. The fundus photo and axial length of the left eye from this patient is unavailable.
‡ Extra-ocular features were only observed in one of the eight patients (F4-II:3), who had tooth malformation, broad nasal bridge, and hyperextensible joints.
Interestingly, the novel phenotype related to BMP4 truncations observed in our cohort is opposite to previously reported phenotypes. In previous studies, variants in BMP4 have been mainly reported to be associated with microphthalmia, anophthalmia, coloboma (MAC) (Bakrania et al., 2008; Reis et al., 2011) and anterior segment dysgenesis (ASGD) (Takenouchi et al., 2013) in human. As a member of the BMP family and transforming growth factor-β (TGF-β) superfamily, BMP4 is known to play the critical role in the embryonic development (Hogan, 1996). In the eye, the BMP4 gene has been reported to be engaged in normal ocular morphogenesis involving lens induction (Huang J. et al., 2015), ciliary body formation (Rausch et al., 2018), and retinal development (Murali et al., 2005; Maruyama et al., 2006; Thompson et al., 2019). Previous
studies and our current data indicate that BMP4 may play a bidirectional role in developmental regulation of ocular shape and size. Recently, genome-wide association studies based on a large population of individuals of European and Asian ancestry showed that the same set of variants shared contributions to the genetic risk of high myopia, low myopia and hyperopia (Tideman et al., 2021) in multifactorial manner. In fact, contrary phenotype due to a BMP4 truncation mutation was reported in one family, where the proband had unilateral anophthalmia, small cornea, and iris and chorioretinal coloboma, while his three family members with the same mutation had high myopia (Bakrania et al., 2008). Except for BMP4, opposite ocular phenotypes have been associated with mutations in other genes, such as FZD5, in which individuals with the same truncation
variant or different eyes of the same individual exhibited either microphthalmia/uveal coloboma or high myopia (Jiang et al., 2021). Similar situation has been observed for PAX6, a gene known to cause aniridia when mutated, in which several single nucleotide polymorphisms are significantly associated with myopia (Hammond et al., 2004). Besides, similar situation also occurs in extracocular system, for example, variants in M4CR related to a gain of function tended to result in a lower risk of obesity while M4CR variants related to a loss of function contributed to a higher risk of obesity (Lotta et al., 2019). These evidences raise the hypothesis that some genes, such as BMP4, may be involved in bidirectional rather than unidirectional control of early ocular development. The mechanism of bidirectional regulation remains unknown and requires further studies.

In our current study, comparative exome sequencing, mutation-specific phenotypic clustering, cosegregation in multiple families, rarity and intolerant of truncations in general population, all provides strong evidence to support that truncation variants in BMP4 contribute to a novel phenotype of pathologic myopia. The snow-grain degeneration in the peripheral retina may be a characteristic sign specific for BMP4-related pathologic myopia. Further studies are expected to confirm our findings and to elucidate the underlying molecular mechanism of bidirectional regulation of eye development.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found from the following link: https://bigd.big.ac.cn/gsa-human/browse/HRA001597. The accession number is HRA001597.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institute Review Board of the Zhongshan Ophthalmic Center. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XX, SL, QZ, XJ, and LZ contributed to the patient recruitment and diagnosis. XX, QZ, XJ, YJ, JO, XL, YW, and LZ collected the clinical records. XX, SL, PW, and QZ performed the whole-exome analysis and targeted-exome sequencing. QZ contributed to the conception and design of this study and revised thoroughly the manuscript. WS, XX, PW, SL, QZ, and YJ performed the statistical analysis. YJ confirmed the variants by Sanger sequencing and family segregation analysis and wrote the first draft of the manuscript. All authors reviewed the manuscript and approved for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcell.2021.769636/full#supplementary-material

REFERENCES

Bakrania, P., Efthymiou, M., Klein, J. C., Salt, A., Bunyan, D. J., Wyatt, A., et al. (2008). Mutations in BMP4 cause eye, brain, and digit developmental anomalies: overlap between the BMP4 and hedgehog signaling pathways. Am. J. Hum. Genet. 82, 304–319. doi: 10.1016/j.ajhg.2007.09.023

Blackburn, P. R., Zepeda-Mendoza, C. J., Krusselbrink, T. M., Schimmenti, L. A., García-Miñaur, S., Palomares, M., et al. (2019). Variable expressivity of syndromic BMP4-related eye, brain, and digital anomalies: a review of the literature and description of three new cases. Eur. J. Hum. Genet. 27, 1379–1388. doi: 10.1038/s41431-019-0423-424

Chen, Y., Zhang, Q., Shen, T., Xiao, X., Li, S., Gao, X., et al. (2013). Comprehensive mutation analysis by whole-exome sequencing in 41 Chinese families with Leber congenital amaurosis. Invest. Ophthalmol. Vis. Sci. 54, 4351–4357. doi: 10.1167/iovs.13-11606

Hammond, C. J., Andrew, T., Mak, Y. T., and Spector, T. D. (2004). A susceptibility locus for myopia in the normal population is linked to the PAX6 gene region on chromosome 11: a genomewide scan of dizygotic twins. Am. J. Hum. Genet. 75, 294–304. doi: 10.1086/423148

Hayashi, S., Okamoto, N., Makita, Y., Hata, A., Imoto, I., and Inazawa, J. (2008). Heterozygous deletion at 14q22.1-q22.3 including the BMP4 gene in a patient with psychomotor retardation, congenital corneal opacity and feet polydactyly. Am. J. Med. Genet. A 146a, 2905–2910. doi: 10.1002/ajmg.a.32519

Hogan, B. L. (1996). Bone morphogenetic proteins in development. Curr. Opin. Genet. Dev. 6, 432–438. doi: 10.1016/s0959-437x(96)80064-80065

Huang, J., Liu, Y., Oltean, A., and Beebe, D. C. (2015). Bmp4 from the optic vesicle specifies murine retina formation. Dev. Biol. 402, 119–126. doi: 10.1016/j.ydbio.2015.03.006

Huang, X., Xiao, X., Jia, X., Li, S., Li, M., Guo, X., et al. (2015). Mutation analysis of the genes associated with anterior segment dysgenesis, microcornea and microphthalmia in 257 patients with glaucoma. Int. J. Mol. Med. 36, 1111–1117. doi: 10.3892/ijmm.2015.2325

Jiang, Y., Ouyang, J., Li, S., Xiao, X., Sun, W., and Zhang, Q. (2021). Confirming and expanding the phenotypes of FZD5 variants: coloboma, inferior chorioretinal hypoplasia, and high myopia. Mol. Vis. 27, 50–60.

Kiefer, A. K., Tung, J. Y., Do, C. B., Hinds, D. A., Mountain, J. L., Francke, U., et al. (2013). Genome-wide analysis points to roles for extracellular matrix remodeling, the visual cycle, and neuronal development in myopia. PLoS Genet. 9:e1003299. doi: 10.1371/journal.pgen.1003299

Li, J., Jiang, D., Xiao, X., Li, S., Jia, X., Sun, W., et al. (2015). Evaluation of 12 myopia-associated genes in Chinese patients with high myopia.
Invest. Ophthalmol. Vis. Sci. 56, 722–729. doi: 10.1167/iovs.14-14880
Lotta, L. A., Mokrosiński, J., Mendes, de Oliveira, E., Li, C., Sharp, S. J., et al. (2019). Human gain-of-function variants in MC4R variants show signaling bias and protect against obesity. Cell 177, 597–607.e9. doi: 10.1016/j.cell.2019.03.044
Lumaka, A., Van Hole, C., Casteels, I., Ortibus, E., De Wolf, Y., Vermeesch, J. R., et al. (2012). Variability in expression of a familial 2.79 Mb microdeletion in chromosome 14q22.1-22.2. Am. J. Med. Genet. A 158a, 1381–1387. doi: 10.1002/ajmg.a.35353
Maruyama, Y., Mikawa, S., Hotta, Y., and Sato, K. (2006). BMP4 expression in the developing rat retina. Brain Res. 1122, 116–121. doi: 10.1016/j.brainres.2006.08.130
Murrali, D., Yoshikawa, S., Corrigan, R. R., Plas, D. J., Cairn, M. C., Oliver, G., et al. (2005). Distinct developmental programs require different levels of Bmp signaling during mouse retinal development. Development 132, 913–923. doi: 10.1242/dev.01673
Nixon, T. R. W., Richards, A., Towns, L. K., Fuller, G., Abbs, S., Alexander, P., Murali, D., Yoshikawa, S., Corrigan, R. R., Plas, D. J., Crair, M. C., Oliver, G., Maruyama, Y., Mikawa, S., Hotta, Y., and Sato, K. (2006). BMP4 expression in the developing rat retina. Brain Res. 1122, 116–121. doi: 10.1016/j.brainres.2006.08.130
Spaide, R., Ohno-Matsui, and L. A. Annuzzi (Cham: Springer International Publishing), 43ñ58.

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