Int. J. Dev. Biol. 51: 235-240 (2007)
doi: 10.1387/ijdb.062236rm

Developmental Expression Pattern

The *Xenopus* ortholog of the nuclear hormone receptor *Nr2e3* is primarily expressed in developing photoreceptors

REYNA I. MARTINEZ-DE LUNA and HEITHEM M. EL-HODIRI*[,1,2]

Graduate Program in Molecular, Cellular and Developmental Biology, College of Biological Sciences, The Ohio State University, [1]Center for Molecular and Human Genetics, Columbus Children's Research Institute and [2]Department of Pediatrics, College of Medicine and Public Health, The Ohio State University, Columbus, OH, USA.

ABSTRACT Nr2e3 is a nuclear hormone receptor that is involved in rod photoreceptor differentiation. The *Nr2e3* gene was previously identified in humans, mice, zebrafish and chicken. In all species, *Nr2e3* expression is restricted to the retina and is believed to have a role in rod photoreceptor specification and maintenance. Here we report the identification and characterization of the *Xenopus Nr2e3*. We found that *Nr2e3* is primarily expressed in developing rod photoreceptors. In contrast to other species, *Nr2e3* is also expressed in the notochord and pineal gland during *Xenopus laevis* development.

KEY WORDS: *Nr2e3, nuclear hormone receptor, photoreceptor, retina, pineal gland, notochord, Xenopus*

Nr2e3 belongs to the superfamily of nuclear hormone receptors that function as ligand-dependent transcription factors (Escriva *et al.*, 2000, Kobayashi *et al.*, 1999). Nuclear receptors all share three canonical domains: an N-terminal variable domain, a zinc finger DNA binding domain (DBD) and a ligand binding domain (LBD) (Escriva *et al.*, 2000, Zhao *et al.*, 1998). Despite their common structure, nuclear receptors have distinct functions in different tissues (Escriva *et al.*, 2000, Giguere, 1999, Kobayashi *et al.*, 1999).

Many of the nuclear receptors identified to date, including Nr2e3, lack a known ligand and are thus named orphan nuclear receptors (Giguere, 1999). The superfamily of orphan nuclear receptors includes *COUP TF I* (*Nr2f1*), *COUP TF II* (*Nr2f2*) and *Tlx* (*Nr2e1*), a homolog of the *Drosophila* terminal/gap gene *tailless* (Chen *et al.*, 2005, Kobayashi *et al.*, 1999). *Nr2e3* was initially identified for its sequence similarity to *Tlx* (*Nr2e1*) (Kobayashi *et al.*, 1999).

Nr2e3 expression was found to be restricted to the retina and observed only in the outer nuclear layer (ONL) where the nuclei of photoreceptors are located (Chen *et al.*, 2005, Kobayashi *et al.*, 1999). It was initially observed in the human retina that *Nr2e3* is specifically expressed in rod photoreceptors (Bumsted O'Brien *et al.*, 2004) and later the same pattern of expression was observed in the rodent retina (Cheng *et al.*, 2004).

In the embryonic mouse retina, *Nr2e3* expression is observed early in rod precursors between E18.0-18.5, before the expression of any rod differentiation markers (Chen *et al.*, 2005, Cheng *et al.*, 2004). Similarly, in the developing zebrafish retina *Nr2e3* expression becomes restricted to rod photoreceptors by 4 days post-fertilization (dpf), although transient expression of *Nr2e3* was detected in both cone and rod photoreceptors at 2 dpf (Chen *et al.*, 2005). Functionally, Nr2e3 has been established to be a transcriptional activator of rod photoreceptor genes (Cheng *et al.*, 2004, Peng *et al.*, 2005). Nr2e3 heterodimerizes with Nr1d1 and in conjunction with Crx and Nrl, regulates the activity of the *Rhodopsin* promoter (Cheng *et al.*, 2004).

Enhanced S-cone syndrome (ESCS) is an autosomal recessive hereditary disease in which the S-cones (blue) are hypersensitive (Jacobson *et al.*, 1991, Marmor *et al.*, 1990). The hypersensitivity of S-cones in ESCS is due to a greater number of S-cones than the more normally abundant L or M-cones (Hood *et al.*, 1995). In humans, different mutations in *NR2E3* have been correlated with ESCS (Haider *et al.*, 2000, Hayashi *et al.*, 2005, Milam *et al.*, 2002, Nakamura *et al.*, 2002, Nakamura *et al.*, 2004, Sharon *et al.*, 2003, Wright *et al.*, 2004), although mutations in *NRL* have also been correlated with ESCS (Wright *et al.*, 2004). In many of the cases where the *NR2E3* gene is mutated, an increased number of S-cones, retinal dysplasia and degeneration was observed (Haider *et al.*, 2000). Mice harboring the naturally occurring *rd7* mutation also exhibit retinal dysplasia and degeneration (Akhmedov *et al.*, 2000, Haider *et al.*, 2001), reminiscent of the phenotype of the mutations observed in humans. Later studies showed that *rd7* mice harbor a deletion encompassing exons 4 and 5 of the *Nr2e3* message (Akhmedov *et al.*, 2000, Haider *et al.*, 2001)

***Address correspondence to:** Heithem M. El-Hodiri, PhD. Center for Molecular and Human Genetics, Columbus Children's Research Institute, 700 Children's Drive, Columbus, OH 43205, USA. Fax: +1-614-722-2817. e-mail: elh@ccri.net

0214-6282/2007/$30.00

Printed in Spain
www.intjdevbiol.com

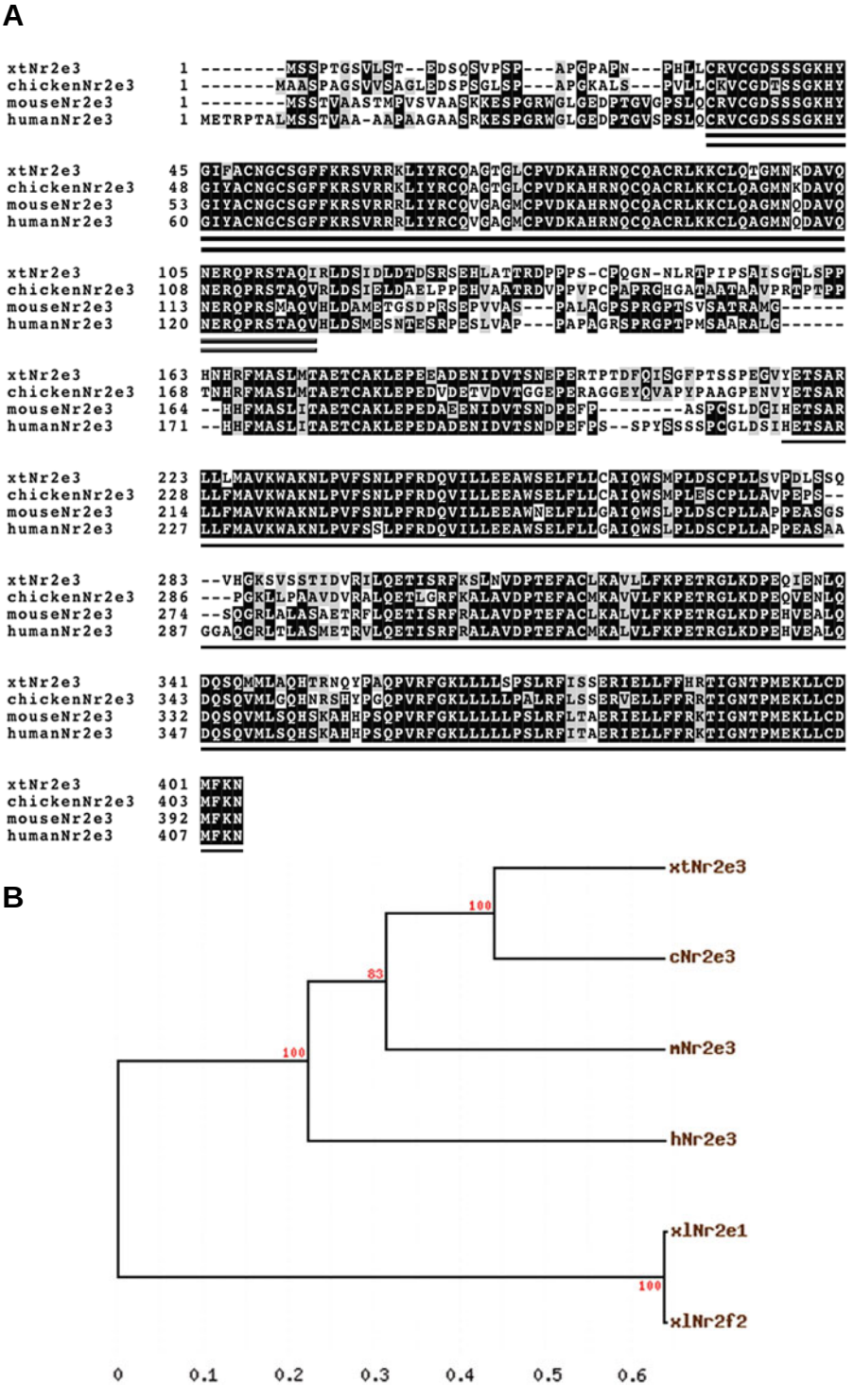


Fig. 1. Amino acid sequence comparison of Nr2e3 between different species. (A) *The sequence of the* Xenopus tropicalis Nr2e3 (xtNr2e3) *gene product (Accession number: DQ906161) is compared to that of the chicken, mouse and human. Single underline denotes the conserved ligand binding domain (LBD) and the double underline denotes the conserved DNA binding domain (DBD).* **(B)** *Phylogenic analysis of xtNr2e3 and the related orphan nuclear receptors Nr2e1 (Tlx) and Nr2f2 (COUP TF II). Phylogenetic analysis was performed from ClustalW alignment using the Phylip tree format in the Tree Top program (http://www.genebee.msu.su/services/phtree_reduced.html). Species abbreviations: xt,* Xenopus tropicalis; *c, chicken; m, mouse; h, human; xl,* Xenopus laevis.

and causes excess cone cell proliferation (Akhmedov *et al.*, 2000, Haider *et al.*, 2001).

Here we report for the first time the identification and characterization of the *Xenopus tropicalis Nr2e3* ortholog. We also examine the expression pattern of *Nr2e3* during *Xenopus laevis* development.

Results and Discussion

The predicted *X. tropicalis* Nr2e3 (xtNr2e3) gene product is most similar (76%) to the published chicken Nr2e3 protein (Figure 1A), but also has a high degree of sequence conservation with the mouse (68%) and human (67%) Nr2e3 proteins (Figure 1A). *xtNr2e3* encodes both a canonical DBD and LBD that are found throughout the orphan nuclear receptor superfamily of proteins (Figure 1A). In a phylogenetic analysis, xtNr2e3 is clustered with Nr2e3 from other species and it is excluded from the *X. laevis* Nr2e1 (Tlx) and Nr2f2 branches (Figure 1B). These findings suggest that our isolated clone encodes the frog ortholog of Nr2e3, since it is most closely related to the other vertebrate Nr2e3 gene products.

During *X. laevis* development, the expression of *Nr2e3* is first observed at stage 30/31 in the center of the eye (Figure 2A). In sections taken from the wholemount *in situ* embryos, *Nr2e3* expression can be confirmed to be present in the central retina (Figure 2H). This pattern of *Nr2e3* expression is consistent with the development of the retina in a central-to-peripheral manner (Rapaport and Stone, 1984, Stone *et al.*, 1985), with photoreceptor cell birth following the same pattern of development (Chang and Harris, 1998, Rapaport *et al.*, 2001). At stage 33/34, *Nr2e3* expression is no longer observed in the central retina, but is expressed strongly in the developing peripheral retina (Figure 2B). By stage 35/36, *Nr2e3* expression is observed only in the neural retina and is clearly excluded from the lens (Figure 2C arrow). This expression pattern differs from that of *Tlx (Nr2e1)*, which is expressed in the retina, forebrain and midbrain between stages 30/31 to 35/36 (Figure 2 D-F) (Hollemann *et al.*, 1998). *Nr2e3* expression was also observed in the pineal gland (Figure 2 A-C arrowheads). The pineal gland contains photoreceptor-like cells (Vigh *et al.*, 2002) and the expression of *Nr2e3* in this organ is similar to the expression of *Rx* in the pineal gland at this stage (Figure 2G arrow) (Casarosa *et al.*, 1997, Mathers *et al.*, 1997). In addition, *Nr2e3* expression was also detected in the

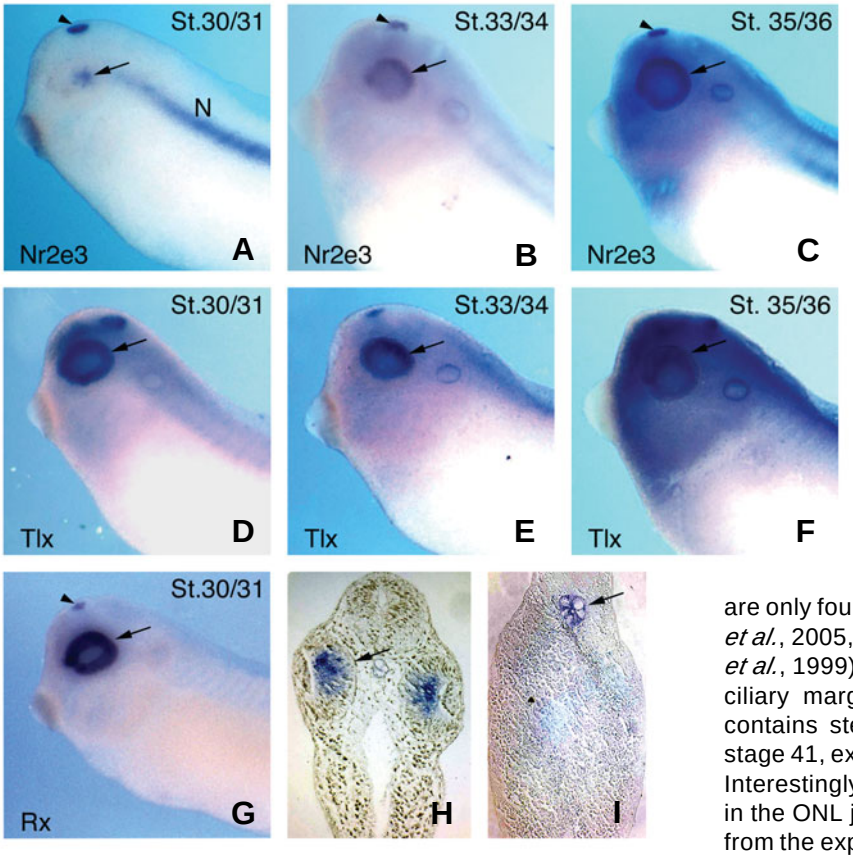
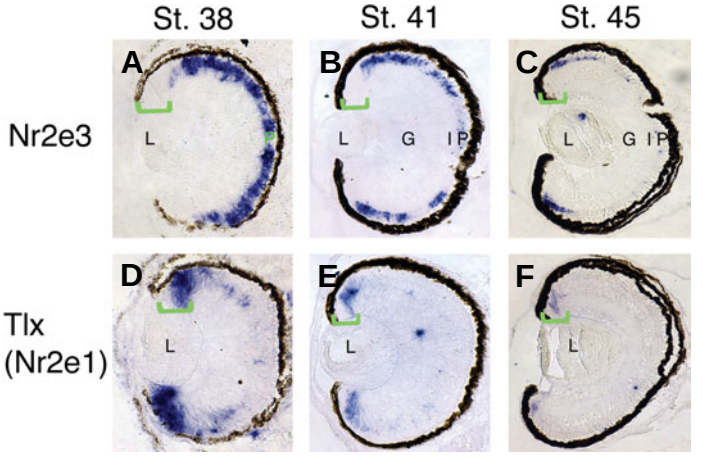


Fig. 2. Expression of *Nr2e3* in *X. laevis* embryos during development. (A-H) *Lateral views of embryos subjected to wholemount* in situ *hybridization using antisense riborprobes specific for* Nr2e3 **(A-C)**, Tlx **(D-F)**, *or* Rx **(G)**. *Arrow denotes retinal expression and the arrowhead denotes pineal gland expression. (H, I) Transverse sections of an embryo at stage 30/31 after wholemount* in situ *hybridization.* **(H)** *Transverse section through the head showing retinal expression (arrow).* **(I)** *Transverse section around the gut area showing strong notochord expression (arrow). In (A-G), riboprobes and developmental stages are indicated in the lower left and upper right corner of each panel, respectively.*

notochord of the developing embryos (Figure 2 A-C, I-arrow). Expression of *Nr2e3* in pineal gland and notochord has not been reported in other species.

To further analyze the expression of *Nr2e3* in the developing retina at later developmental stages, we performed *in situ* hybridization on retinal sections of embryos at stages 38, 41 and 45 (Figure 3). At stage 38, when the retina is not yet obviously laminated, *Nr2e3* expression is very robust in the photoreceptor layer (Figure 3A), consistent with the previous observation that *Nr2e3* transcripts are only found in photoreceptors (Akhmedov *et al.*, 2000, Chen *et al.*, 2005, Haider *et al.*, 2000, Haider *et al.*, 2001, Kobayashi *et al.*, 1999). However, *Nr2e3* expression is excluded from the ciliary marginal zone (CMZ), the region of the retina that contains stem cells and retinal progenitors (Figure 3A). By stage 41, expression of *Nr2e3* is apparent throughout the ONL. Interestingly, by stage 45, *Nr2e3* expression was only observed in the ONL just adjacent to the CMZ (Figure 3C), which differs from the expression of *Nr2e3* in the rodent and zebrafish retina where *Nr2e3* is expressed throughout the ONL once photoreceptors have differentiated and matured (Chen *et al.*, 2005, Cheng *et al.*, 2004). In contrast, *Tlx* expression is restricted to the CMZ, where *Nr2e3* is absent (Figure 3 D-F). *Tlx* expression decreases as development progresses (Figure 3D-3F).

Double *in situ* hybridization showed overlapping expression of *Nr2e3* and *Rhodopsin* in the ONL at stage 45 (Figure 4A, B arrow). *Nr2e3* expression is observed in the photoreceptor cell body, since Nr2e3 transcripts are restricted to photoreceptors (Akhmedov *et al.*, 2000, Chen *et al.*, 2005, Haider *et al.*, 2001, Kobayashi *et al.*, 1999). Interestingly, co-expression of *Rhodopsin* and *Nr2e3* is observed in rods at the periphery of the neural retina, but excluding the CMZ (Figure 4B). *Nr2e3* is expressed in rod precursors before differentiation and prior to expression



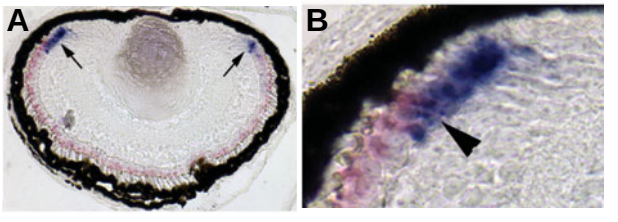


Fig. 3. (Left) *Nr2e3* and *Tlx (Nr2e1)* expression in retinal sections. In situ *hybridization using paraffin sections of embryos at various stages during* X. laevis *development probed for* Nr2e3 **(A-C)** *and* Tlx (Nr2e1) **(D-F)** *expression.* Nr2e3 *is expressed in the neural retina, but not in the CMZ (A-C). Retinal expression of* Tlx *is restricted to the CMZ by stage 45 (arrows in (D-F). Retinal layers and the lens are labeled with a letter abbreviation: L, lens; G, ganglion cell layer; I, inner nuclear layer; P, photoreceptor layer.*

Fig. 4. (Right) Co-expression of *Nr2e3* and *Rhodopsin* in rods. (A) *Double* in situ *hybridization for* Nr2e3 *(purple) and* Rhodopsin *(red) in a section of an eye from a stage 45 embryo. Arrows denote the overlap between* Nr2e3 *and* Rhodopsin *expression.* **(B)** *Higher magnification (optical and digital) of the picture in (A) showing the region of overlap between* Nr2e3 *and* Rhodopsin *expression (arrowhead).*

of *Rhodopsin*, which is first detected at stage 33/34 in *Xenopus laevis* (Chang and Harris, 1998).

Materials and Methods

Isolation and cloning of the X. tropicalis Nr2e3 *ortholog*

A BLAT search of the *Xenopus tropicalis* genome in the DOE Joint Genome Institute (JGI) website (http://www.jgi.doe.gov/) yielded a genomic locus for the *Nr2e3* gene (Scaffold 103: 742787-749884). By sequence comparison of the intron and exon arrangements of the chicken *Nr2e3*, primers (5'- caatgagttctcccacaggatc; 3'- gatttagttcttgaacatatcacaaag) were designed against the first exon and last exon predicted by the BLAT search. Total mRNA was purified from heads isolated from stage 38 *Xenopus tropicalis* tadpoles (NASCO Sciences; Fort Atkinson, WI, USA) using TRIZOL (Invitrogen). RT-PCR was performed from the total RNA using the SuperScript One Step RT PCR Kit (Invitrogen). The amplified product was subcloned (TOPO TA Kit, Invitrogen), sequenced and confirmed to be full length *Nr2e3* (Submitted to PubMed; accession number: DQ906161). *Nr2e3* sequences were aligned using the ClustalW program from the European Bioinformatics Institute (EBI) website (http://www.ebi.ac.uk/clustalw/).

In situ *hybridization*

The *Nr2e3* probe used for wholemount *in situ* hybridization was generated from a *Xenopus laevis* expressed sequence tag (EST) (Accession number: CD328661) that was identified by its degree of sequence homology to the chicken Nr2e3 gene product in a BLAST search. To generate the riboprobe the Nr2e3est/pCMV-Sport6-ccdb plasmid was cut with using NotI and EcoRI restriction enzymes (New England Biolabs) to release the predicted coding sequence from the EST. The excised coding region from the Nr2e3est/pCMV-Sport6-ccdb plasmid was then cloned into the NotI and EcoRI sites of pBlueScriptII KS to generate the plasmid Nr2e3cds/pBlueScript. Nr2e3cds/pBlueScript was then linearized with EcoRI (New England Biolabs) and the antisense riboprobe made using T7 RNA polymerase plus (Ambion). Antisense riboprobes for *Rhodopsin*, *Tlx, Rx* were generated as described previously (Hollemann *et al.*, 1998, Mathers *et al.*, 1997, Pan *et al.*, 2006, Zuber *et al.*, 2003).

Embryos were generated by *in vitro* fertilization (Sive *et al.*, 2000), staged and fixed as described previously (Nieuwkoop and Faber, 1994, Sive *et al.*, 2000). Wholemount *in situ* was performed using whole embryos as previously described using digoxigenin-labeled antisense riboprobes (Sive *et al.*, 2000, Turner and Weintraub, 1994). Briefly, hybridization and post-hybridization washes were performed at 65°C and after color reaction in BM-Purple (Roche) the embryos were post-fixed in Modified Bouin's fixative (picric acid was omitted), dehydrated and bleached (Seufert *et al.*, 2005, Shimamura *et al.*, 1994). For section *in situ* hybridization, paraffin sections (8 μm) of retinas were processed using digoxigenin-labeled antisense riboprobes as previously described (Shimamura *et al.*, 1994, Viczian *et al.*, 2003). Double section *in situ* hybridization was performed using digoxigenin-labeled *Nr2e3* and fluorescein-labeled *Rhodopsin* antisense riboprobes (2 μg/ml each). After hybridization, the retinal sections were incubated with anti-digoxigenin-AP antibody overnight (Roche), followed by the color reaction with BM Purple (Roche). After color development, sections were subjected to post-hybridization washes (beginning after RNase treatment) and incubated with anti-fluorescein-AP antibody (Roche) overnight. Rhodopsin expression was visualized using Vector Red alkaline phosphatase substrate (Vector Laboratories).

Acknowledgements

We would like to thank Michael E. Zuber who kindly provided us with the Xenopus Tlx *plasmid. We would also like to thank Holly Moose and Lisa Kelly for critical reading of this manuscript. Also, we want to thank Srivamsi Nekkalapudi and Lisa Kelly for expert technical assistance and Yi Pan for providing the* Xenopus tropicalis *cDNA. Lastly, we thank Vera McIlvain for helpful discussions and the sharing of unpublished results. This work was supported by NIH/NEI grant EY015480 to HME.*

References

AKHMEDOV, N.B., PIRIEV, N.I., CHANG, B., RAPOPORT, A.L., HAWES, N.L., NISHINA, P.M., NUSINOWITZ, S., HECKENLIVELY, J.R., RODERICK, T.H., KOZAK, C.A. *et al.* (2000). A deletion in a photoreceptor-specific nuclear receptor mrna causes retinal degeneration in the rd7 mouse. *Proc Natl Acad Sci USA* 97: 5551-6.

BUMSTED O'BRIEN, K.M., CHENG, H., JIANG, Y., SCHULTE, D., SWAROOP, A. and HENDRICKSON, A.E. (2004). Expression of photoreceptor-specific nuclear receptor nr2e3 in rod photoreceptors of fetal human retina. *Invest Ophthalmol Vis Sci* 45: 2807-12.

CASAROSA, S., ANDREAZZOLI, M., SIMEONE, A. and BARSACCHI, G. (1997). Xrx1, a novel xenopus homeobox gene expressed during eye and pineal gland development. *Mech Dev* 61: 187-98.

CHANG, W.S. and HARRIS, W.A. (1998). Sequential genesis and determination of cone and rod photoreceptors in xenopus. *J Neurobiol* 35: 227-44.

CHEN, J., RATTNER, A. and NATHANS, J. (2005). The rod photoreceptor-specific nuclear receptor nr2e3 represses transcription of multiple cone-specific genes. *J Neurosci* 25: 118-29.

CHENG, H., KHANNA, H., OH, E.C., HICKS, D., MITTON, K.P. and SWAROOP, A. (2004). Photoreceptor-specific nuclear receptor nr2e3 functions as a transcriptional activator in rod photoreceptors. *Hum Mol Genet* 13: 1563-75.

ESCRIVA, H., DELAUNAY, F. and LAUDET, V. (2000). Ligand binding and nuclear receptor evolution. *Bioessays* 22: 717-27.

GIGUERE, V. (1999). Orphan nuclear receptors: From gene to function. *Endocr Rev* 20: 689-725.

HAIDER, N.B., JACOBSON, S.G., CIDECIYAN, A.V., SWIDERSKI, R., STREB, L.M., SEARBY, C., BECK, G., HOCKEY, R., HANNA, D.B., GORMAN, S. *et al.* (2000). Mutation of a nuclear receptor gene, nr2e3, causes enhanced s cone syndrome, a disorder of retinal cell fate. *Nat Genet* 24: 127-31.

HAIDER, N.B., NAGGERT, J.K. and NISHINA, P.M. (2001). Excess cone cell proliferation due to lack of a functional nr2e3 causes retinal dysplasia and degeneration in rd7/rd7 mice. *Hum Mol Genet* 10: 1619-26.

HAYASHI, T., GEKKA, T., GOTO-OMOTO, S., TAKEUCHI, T., KUBO, A. and KITAHARA, K. (2005). Novel nr2e3 mutations (r104q, r334g) associated with a mild form of enhanced s-cone syndrome demonstrate compound heterozygosity. *Ophthalmology* 112: 2115.

HOLLEMANN, T., BELLEFROID, E. and PIELER, T. (1998). The xenopus homologue of the drosophila gene tailless has a function in early eye development. *Development* 125: 2425-32.

HOOD, D.C., CIDECIYAN, A.V., ROMAN, A.J. and JACOBSON, S.G. (1995). Enhanced s cone syndrome: Evidence for an abnormally large number of s cones. *Vision Res* 35: 1473-81.

JACOBSON, S.G., ROMAN, A.J., ROMAN, M.I., GASS, J.D. and PARKER, J.A. (1991). Relatively enhanced s cone function in the goldmann-favre syndrome. *Am J Ophthalmol* 111: 446-53.

KOBAYASHI, M., TAKEZAWA, S., HARA, K., YU, R.T., UMESONO, Y., AGATA, K., TANIWAKI, M., YASUDA, K. and UMESONO, K. (1999). Identification of a photoreceptor cell-specific nuclear receptor. *Proc Natl Acad Sci USA* 96: 4814-9.

MARMOR, M.F., JACOBSON, S.G., FOERSTER, M.H., KELLNER, U. and WELEBER, R.G. (1990). Diagnostic clinical findings of a new syndrome with night blindness, maculopathy and enhanced s cone sensitivity. *Am J Ophthalmol* 110: 124-34.

MATHERS, P.H., GRINBERG, A., MAHON, K.A. and JAMRICH, M. (1997). The rx homeobox gene is essential for vertebrate eye development. *Nature* 387: 603-7.

MILAM, A.H., ROSE, L., CIDECIYAN, A.V., BARAKAT, M.R., TANG, W.X., GUPTA, N., ALEMAN, T.S., WRIGHT, A.F., STONE, E.M., SHEFFIELD, V.C. *et al.* (2002). The nuclear receptor nr2e3 plays a role in human retinal photoreceptor

differentiation and degeneration. *Proc Natl Acad Sci USA* 99: 473-8.

NAKAMURA, M., HOTTA, Y., PIAO, C.H., KONDO, M., TERASAKI, H. and MIYAKE, Y. (2002). Enhanced s-cone syndrome with subfoveal neovascularization. *Am J Ophthalmol* 133: 575-7.

NAKAMURA, Y., HAYASHI, T., KOZAKI, K., KUBO, A., OMOTO, S., WATANABE, A., TODA, K., TAKEUCHI, T., GEKKA, T. and KITAHARA, K. (2004). Enhanced s-cone syndrome in a japanese family with a nonsense nr2e3 mutation (q350x). *Acta Ophthalmol Scand* 82: 616-22.

NIEUWKOOP, P.D. and FABER, J. (1994). *Normal table of xenopus laevis (daudin).* Garland Publishing, Inc., New York.

PAN, Y., NEKKALAPUDI, S., KELLY, L.E. and EL-HODIRI, H.M. (2006). The rx-like homeobox gene (rx-l) is necessary for normal photoreceptor development. *Invest Ophthalmol Vis Sci* 47: 4245-4253.

PENG, G.H., AHMAD, O., AHMAD, F., LIU, J. and CHEN, S. (2005). The photoreceptor-specific nuclear receptor nr2e3 interacts with crx and exerts opposing effects on the transcription of rod versus cone genes. *Hum Mol Genet* 14: 747-64.

RAPAPORT, D.H., PATHEAL, S.L. and HARRIS, W.A. (2001). Cellular competence plays a role in photoreceptor differentiation in the developing xenopus retina. *J Neurobiol* 49: 129-41.

RAPAPORT, D.H. and STONE, J. (1984). The area centralis of the retina in the cat and other mammals: Focal point for function and development of the visual system. *Neuroscience* 11: 289-301.

SEUFERT, D.W., PRESCOTT, N.L. and EL-HODIRI, H.M. (2005). Xenopus aristaless-related homeobox (xarx) gene product functions as both a transcriptional activator and repressor in forebrain development. *Dev Dyn* 232: 313-24.

SHARON, D., SANDBERG, M.A., CARUSO, R.C., BERSON, E.L. and DRYJA, T.P. (2003). Shared mutations in nr2e3 in enhanced s-cone syndrome, goldmann-favre syndrome and many cases of clumped pigmentary retinal degeneration. *Arch Ophthalmol* 121: 1316-23.

SHIMAMURA, K., HIRANO, S., MCMAHON, A.P. and TAKEICHI, M. (1994). Wnt-1-dependent regulation of local e-cadherin and alpha n-catenin expression in the embryonic mouse brain. *Development* 120: 2225-34.

SIVE, H.L., GRAINGER, R.M. and HARLAND, R.M. (2000). *Early development of xenopus laevis: A laboratory manual.* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

STONE, J., EGAN, M. and RAPAPORT, D.H. (1985). The site of commencement of retinal maturation in the rabbit. *Vision Res* 25: 309-17.

TURNER, D.L. and WEINTRAUB, H. (1994). Expression of achaete-scute homolog 3 in xenopus embryos converts ectodermal cells to a neural fate. *Genes Dev* 8: 1434-47.

VICZIAN, A.S., VIGNALI, R., ZUBER, M.E., BARSACCHI, G. and HARRIS, W.A. (2003). Xotx5b and xotx2 regulate photoreceptor and bipolar fates in the xenopus retina. *Development* 130: 1281-94.

VIGH, B., MANZANO, M.J., ZADORI, A., FRANK, C.L., LUKATS, A., ROHLICH, P., SZEL, A. and DAVID, C. (2002). Nonvisual photoreceptors of the deep brain, pineal organs and retina. *Histol Histopathol* 17: 555-90.

WRIGHT, A.F., REDDICK, A.C., SCHWARTZ, S.B., FERGUSON, J.S., ALEMAN, T.S., KELLNER, U., JURKLIES, B., SCHUSTER, A., ZRENNER, E., WISSINGER, B. *et al.* (2004). Mutation analysis of nr2e3 and nrl genes in enhanced s cone syndrome. *Hum Mutat* 24: 439.

ZHAO, Q., KHORASANIZADEH, S., MIYOSHI, Y., LAZAR, M.A. and RASTINEJAD, F. (1998). Structural elements of an orphan nuclear receptor-DNA complex. *Mol Cell* 1: 849-61.

ZUBER, M.E., GESTRI, G., VICZIAN, A.S., BARSACCHI, G. and HARRIS, W.A. (2003). Specification of the vertebrate eye by a network of eye field transcription factors. *Development* 130: 5155-67.

Received: 4th October 2006
Reviewed by Referees: 19th October 2006
Modified by Authors and Accepted for Publication: 19th October 2006
Published Online: X April 2007
Edited by: Thomas D. Sargent

Previously published, related *Int. J. Dev. Biol. articles*

See our Special Issue on *Eye Development* edited by J. Piatigorsky and R. Granger at:
http://www.ijdb.ehu.es/web/contents.php?vol=48&issue=8-9

The signal transducing photoreceptors of plants
Keara A. Franklin, Victoria S. Larner and Garry C. Whitelam
Int. J. Dev. Biol. (2005) 49: 653-664

Xenopus laevis FoxE1 is primarily expressed in the developing pituitary and thyroid
Heithem M. El-Hodiri, Daniel W. Seufert, Srivamsi Nekkalapudi, Nichole L. Prescott, Lisa E. Kelly and Milan Jamrich
Int. J. Dev. Biol. (2005) 49: 881-884

Regulation of vertebrate eye development by Rx genes
Travis J. Bailey, Heithem El-Hodiri, Li Zhang, Rina Shah, Peter H. Mathers and Milan Jamrich
Int. J. Dev. Biol. (2004) 48: 761-770

A moving wave patterns the cone photoreceptor mosaic array in the zebrafish retina
Pamela A. Raymond and Linda K. Barthel
Int. J. Dev. Biol. (2004) 48: 935-945

Genetics of photoreceptor development and function in zebrafish
Motokazu Tsujikawa and Jarema Malicki
Int. J. Dev. Biol. (2004) 48: 925-934

Historical perspective on the development and evolution of eyes and photoreceptors
Walter J. Gehring
Int. J. Dev. Biol. (2004) 48: 707-717

Evolution of eyes and photoreceptor cell types.
Detlev Arendt
Int. J. Dev. Biol. (2003) 47: 563-571

Evolution and developmental expression of nuclear receptor genes in the ascidian Herdmania.
Christine Devine, Veronica F Hinman and Bernard M Degnan
Int. J. Dev. Biol. (2002) 46: 687-692

Expression of the mediators of dioxin toxicity, aryl hydrocarbon receptor (AHR) and the AHR nuclear translocator (ARNT), is developmentally regulated in mouse teeth.
Carin Sahlberg, Raimo Pohjanvirta, Yuguang Gao, Satu Alaluusua, Jouko Tuomisto and Pirjo-Liisa Lukinmaa
Int. J. Dev. Biol. (2002) 46: 295-300