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cord, and rhombic lip. We conclude that Math5-GFP mice are a useful tool to study optic projections in the brain. Furthermore, we propose that 3′ regulatory elements restrict Math5 expression to the retina and cochlear nucleus.

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Paired-less Pax6 has a role in eye development

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Pax6, a member of the paired-family of transcription factors, is required for development of the eye. Recent studies have shown that Pax6 affects cell proliferation, cell fate decisions, and patterning. These diverse functions appear to be mediated by different isoforms of the Pax6 protein. Three isoforms of the Pax6 protein have been reported in mammals. The canonical form contains the paired domain (PD), paired-type homeodomain (HD), and a transactivation domain (PST). This isoform is expressed in most cells that express Pax6. The second isoform contains a 14 amino acid insertion in the N-terminal subunit of the PD. The third isoform lacks the paired-domain (Pax6ΔPD); however, little is known about where this isoform is expressed or its normal function in vivo. To investigate the role of Pax6ΔPD, we used a Pax6 BAC transgene that we developed to over-express this isoform in those cells that normally express it. Over-expression of Pax6ΔPD causes a severe microphthalmic phenotype in wild-type mice carrying 18 copies of the transgene. A similar phenotype was observed in Small eye mice carrying 8–10 copies of the transgene. Microphthalmic eyes appear to lack lenses and exhibit several morphological defects. Analysis of lens development in these mice revealed that the lens degenerated via apoptotic cell death between e12.5 and e15. These results suggest a role for Pax6ΔPD in eye development, which may be different than that ascribed to canonical Pax6.

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Function of Lmx1b in the development of ocular anterior segment

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The anterior segment (AS) of murine eye is important for normal ocular function. Malformation or dysfunction of AS can lead to many ocular diseases, the most common of which is glaucoma. It has been demonstrated that mutations of a gene encoding a LIM homeodomain transcription factor LMX1B cosegregate with the glaucoma associated with a congenital disease called nail patella syndrome. Our studies on homozygous mutant mice of Lmx1b, the mouse orthologue of human LMX1B, have determined that Lmx1b is required for development of multiple tissues of the AS. Lmx1b is expressed in the periocular mesenchyme (PM). Our fate mapping experiments showed that the neural crest is the major contributor of PM and suggested that Lmx1b is expressed in neural-crest-derived PM. To determine whether Lmx1b plays a specific role in the neural crest precursors, we generated neural-crest-specific Lmx1b knockout mice and found that Lmx1b is required for the specification of cornea. Lmx1b is not only expressed in the eye during embryogenesis but is also maintained in the adult iris, cornea and trabecular meshwork (TM). To elucidate the role of Lmx1b in the TM development, we generated PM-specific Lmx1b knockout mice and determined that Lmx1b is required in the PM for the formation of TM. We will also employ conditional gene targeting methods to examine whether Lmx1b functions in the adult eye to regulate the extracellular matrix composition of the TM. Our studies will advance the understanding of molecular mechanisms that leads to glaucoma associated with nail patella syndrome and help in diagnosis and treatment of this disease.

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Long-range regulation of *Hoxa13* in limb development

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The posterior HoxA and HoxD genes are essential in appendicular development. Prior studies have demonstrated that a “distal limb enhancer”, remotely located upstream of the HoxD complex, is required to drive embryonic autopod expression of the posterior Hox genes as well as the two additional non-Hox genes in the region: Evx2 and Lnp. Our work demonstrates a similar mode of regulation for Hoxa13 and four upstream genes: Evx1, Hibadh, Tax1bp, and Jaz1. These genes all show embryonic (E11.5–E13.5) distal limb and genital bud expression, suggesting the existence of a nearby enhancer influencing the expression of a domain of genes. Comparative sequence analysis between homologous human and mouse genomic sequence upstream of Hoxa13 revealed a remote 2.25 kb conserved non-coding sequence (mmA13CNS) within the fourth intron of the Hibadh gene. mmA13CNS shares a common 131 bp core identity within a conserved non-coding sequence upstream of Hoxd13, which is located within the previously identified “distal limb enhancer” critical region. To test the function of this conserved sequence, we created both mmA13CNS-Hsp68-lacZ and mmA13CNS-Bglobin-lacZ transgenic mice. mmA13CNS directed a wide range of tissue expression including the central nervous system, limb, and genital bud. Limb and genital bud expression directed by mmA13CNS is not identical to the patterns exhibited by Hoxa13/Evx1/Hibadh/Tax1bp1/Jaz1, suggesting that mmA13CNS is not sufficient to fully recapitulate their expression in those tissues