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Review Article

# A Review of the PAX Gene Family: Roles in Cancer, Evolution, and Human Pathologies

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**Abstract:** This review paper, conducted between January and March 2025 and based on a comprehensive analysis of previous studies, investigates the function of members of the PAX gene family in human illnesses. PAX genes serve as critical regulators in the development of various tissues and organs, and mutations in these genes have been linked to a broad spectrum of genetic disorders and cancers. The research focused on the functions of individual PAX genes and their associations with disease phenotypes. For instance, mutations in PAX9 are linked to tooth agenesis, with the severity of dental anomalies depending on the mutation's impact on DNA-binding capacity. Mutations in PAX2 have been associated with renal and ocular malformations, notably papillorenal syndrome, characterized by renal hypoplasia and optic nerve defects. Additionally, PAX4 and PAX6 are essential for the differentiation of pancreatic endocrine cells, and their mutations are implicated in various forms of diabetes. Moreover, aberrant expression of PAX genes is observed in several cancer types. PAX3 and PAX7 expression correlates with melanoma and sarcoma progression, while PAX2 and PAX8 are frequently expressed in Wilms tumor, a pediatric kidney cancer. These genes can influence tumor initiation, progression, or resistance mechanisms, though their exact oncogenic roles remain to be fully defined. The findings highlight the necessity for detailed characterization of PAX gene isoforms, mutation effects, and tissue-specific functions. Future investigations should also address the roles of PAX genes in adult tissue regeneration and further elucidate their contributions to developmental disorders and cancer biology.

**Keywords:** PAX Genes.



## 1.1 INTRODUCTION

The finding of PAX genes originated in 1986, subsequent to the successful cloning of the paired (prd) gene in Drosophila [1]. Soon later, it was discovered that a variety of taxa, including fish, amphibians, birds, and mammals, had homologous PAX genes. In both humans and other vertebrates, PAX genes play a critical role in organogenesis. Acting as transcription factors, their expression is tightly regulated—both spatially and temporally—being limited to specific cell populations during defined developmental stages. Mutations in PAX genes have been associated with numerous congenital disorders and malignancies [1].

This review provides a comprehensive overview of the structural characteristics and functional roles of PAX genes, with particular attention to how genetic alterations contribute to disease pathogenesis. A central emphasis is placed on investigating potential therapeutic strategies targeting members of the PAX gene family. An unlimited search of the PubMed database, completed in January 2024, using keywords such as "paired box," "PAX," "paired domain," "master regulator," "cancer," and "development," yielded relevant studies. The selection of studies was focused on their long-term repeatability, methodological rigor, and suitability of their experimental controls.

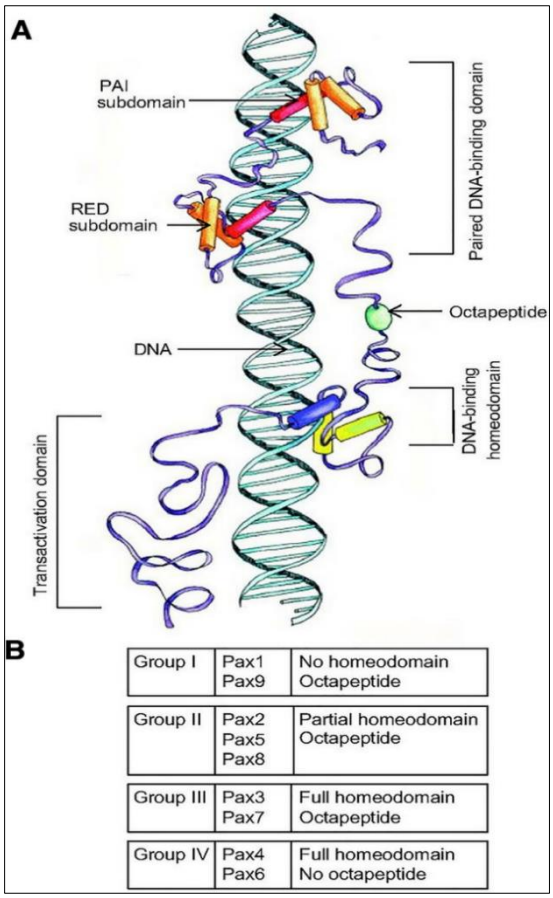


**Figure 1: Structural Features of Paired-Box (PAX) Proteins. a) PAX proteins are defined by the presence of a conserved paired DNA-binding domain, which consists of two distinct subdomains: the RED and PAI subdomains. b) The inclusion—either partial or complete—of additional domains such as the homeodomain (a second DNA-binding domain) and/or the octapeptide linker allows the classification of PAX proteins into four structural groups: Group 1, Group 2, Group 3, and Group 4. Reprinted with permission from Blake and Ziman (2014) [2]**

### 1.2 The PAX Genes Evolutionary Origins and Structural

It was widely known that "homeotic" genes play a crucial role in regulating the patterning of many body segments before the PAX gene family was characterized. These genes control the development of complete organs or anatomical structures in Drosophila, and mutations in these genes commonly result in severe congenital abnormalities. Additionally, specific regions within these genes exhibit sequence similarity to loci found in other metazoan species, highlighting their evolutionary conservation and critical function in developmental regulation [2]. An important accomplishment was the cloning of the prd gene in Drosophila, since it was later found that mammals, such as mice, harbored a corresponding gene known as *Pax1*. Similarly, homologous genes, including *PAX1*, were identified within the human genome [3,4].

The fact that many creatures have orthologs of PAX genes is now well known. These comprise both evolutionarily archaic species like Amphimedon queenslandica, a sponge native to the Great Barrier Reef that is frequently used in evolutionary studies, and well-known model systems like Xenopus, Caenorhabditis elegans, and Danio rerio [5]. In humans, nine unique PAX genes have been discovered. Comparative analyses based on amino acid sequences and phylogenetic relationships have been conducted to study these proteins, as depicted in Figure 1. The phylogenetic tree in Figure 1 organizes the PAX gene family into four structural categories (I–IV), which will be explored in more detail in the subsequent section [6].

All known PAX genes are thought to have originated from a single ancestral proto-PAX gene, which likely gained its characteristic paired domain through the integration of a Tc1/mariner transposable element over 540 million years ago—around the time of the Cambrian explosion, when metazoan diversity expanded rapidly [7,8]. Furthermore, some research suggests that the paired domain may have emerged even earlier, as indicated by the presence of PAX-like gene sequences in *Giardia lamblia*, an intestinal protozoan parasite [9].

Two main theories have been suggested to explain the emergence of the proto-PAX gene, each grounded in a different mechanism of Tc1/mariner transposon insertion. According to one theory, a gene

that resembles PAXB—named for its similarity to the PAXB gene found in cnidarians and sponges—was created when a genomic region that originally contained a homeodomain and an octapeptide motif later acquired a paired domain via transposon activity [10]. The second idea, on the other hand, contends that the paired domain was added later to the proto-PAX gene, which initially had the octapeptide motif, homeodomain, and another unidentified sequence. The primary factor in differentiating between these two situations is whether the ancestral metazoan genome more closely resembles that of sponges or cnidarians.

Within mammalian PAX genes, structural classifications indicate evolutionary divergence: Groups I and III show closer affinity to the PAXD-like lineage, whereas Groups II and IV are more closely aligned with the PAXB-like lineage. The diversification and expansion of the PAX gene family in humans are believed to have arisen through multiple gene duplication events, including whole-genome duplications, following the emergence of the proto-PAX gene.

**Table 1. This table summarizes the currently annotated human PAX protein isoforms. For each PAX gene, both the longest and shortest isoforms are listed to demonstrate the range of isoform lengths observed within and among the four structural groups. It is important to emphasize that not all isoforms are expressed in adult human tissues. The data were compiled from all protein isoforms annotated in the NCBI RefSeq database for each human PAX gene. Isoform names correspond to their official RefSeq designations [10].**

| Subgroup | Gene | Isoform | Longest Isoform | Shortest Isoform |
|---|---|---|---|---|
| Group I | *PAX1* | 1, 2 | 1 (534) | 2 (457) |
| Group I Group II | *PAX9* | - | 341 | - |
| | *PAX2* | a–g (7) | e (432) | g (102) |
| Group II Group III | *PAX5* | 1–11 | 1 (391) | 6 (220) |
| | *PAX8* | A, C, D, E (4) | A (450) | E (287) |
| | *PAX3* | a, b, c, d, e, g, h, i | e (505) | b (206) |
| Group III Group IV | *PAX7* | 1–3 | 1 (520) | 3 (505) |
| | *PAX4* | 1, 2 | 1 (351) | 2 (348) |
| Group IV | *PAX6* | a–o (15) | e (503) | o (221) |

### 1.3 PAX Protein Structure

The human PAX gene family consists of nine transcription factors, each sharing conserved structural features and categorized into distinct subgroups depending on the presence or absence of specific functional domains (Figure 2). A hallmark of all PAX proteins is the N-terminal paired domain—a 128-amino-acid DNA-binding region that was first discovered in *Drosophila* due to sequence similarities between the *prd* and *gsb* loci [11]. The PAI and RED subdomains, two helix-turn-helix motifs that make up this domain, are both necessary for DNA-binding activity (Figure 3) [11].

All PAX family members have a C-terminal transactivation domain in addition to the paired domain, which acts as a docking site for transcriptional co-regulators. The presence or absence of two more components further informs the categorization of PAX proteins into distinct subgroups. The first is the octapeptide motif—an eight-residue sequence present in Groups I, II, and III—that plays a role in transcriptional repression by promoting the recruitment of corepressor proteins [12]. The second element, the homeodomain, acts as a secondary DNA-binding region and is found in Groups II, III, and IV. In Group II, however, the homeodomain is partially truncated, which diminishes its DNA-binding efficiency. Nonetheless, this shortened version retains the ability to engage in protein–protein interactions, similar to those mediated by the full-length domain [13].

The complete homeodomain, characterized by a helix-turn-helix structure, generally binds DNA as a dimer. In certain contexts, it cooperates with the paired domain to specifically recognize neighboring DNA sequences [14].

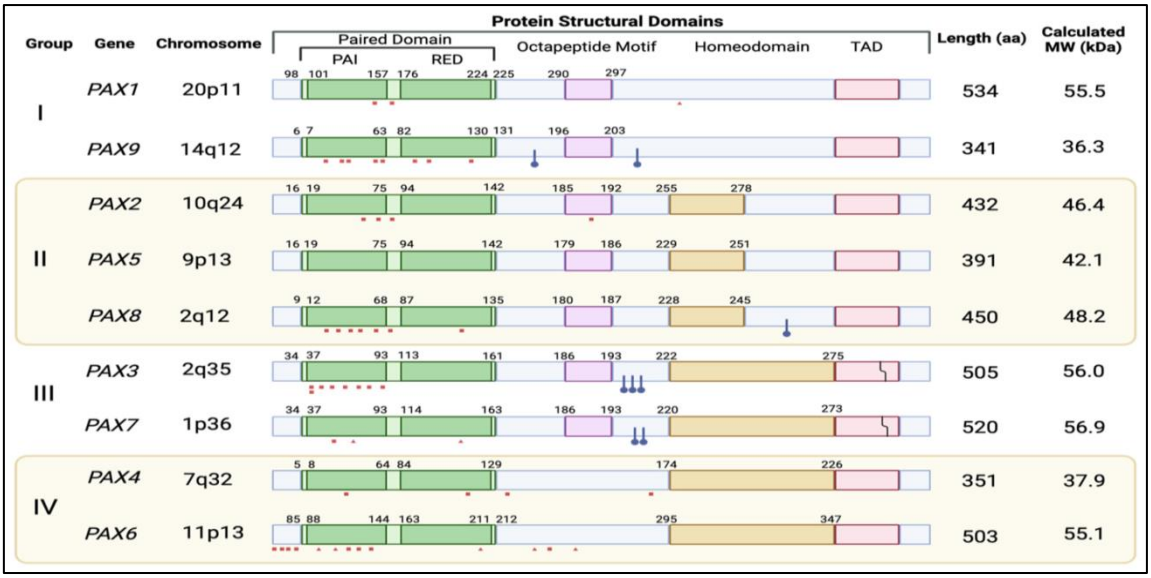


**Figure 2: Structural Grouping of Human PAX Proteins. Each human PAX protein contains an N-terminal paired domain for DNA binding. Additional structural motifs—including the octapeptide, partial or full homeodomain, and C-terminal transactivation domain—define subgroup classifications (I–IV). Disease-associated missense and nonsense mutations are marked in red, phosphorylation sites in blue, and fusion breakpoints (PAX3::FOXO1, PAX7:FOXO1) in alveolar rhabdomyosarcoma are indicated with jagged lines. Longest isoforms shown; figure not to scale [12]**

## 2. PAX Gene Family Role in Regulation of Gene Expression

PAX transcription factors are subject to multiple layers of regulation, including post-translational modifications, protein–protein interactions, and proteolytic degradation. At the RNA level, their expression can be modulated by mechanisms such as alternative splicing and microRNA (miRNA)-mediated repression, both of which contribute to the diversity of PAX isoforms. Despite their frequent role as master regulators, PAX genes themselves are controlled by upstream transcription factors and can also participate in autoregulatory feedback loops. These regulatory pathways are often interconnected, collectively shaping the expression dynamics and functional roles of each PAX family member. While a comprehensive account of all known regulatory mechanisms is beyond the scope of this work, selected examples will be highlighted—particularly those essential for normal development, implicated in disease states, or of potential interest for therapeutic targeting.

### 2.1 PAX Genes Upstream Transcriptional Regulation

The regulation of PAX gene expression involves various transcription factors, including autoregulation by other PAX family members. Specifically, Group II PAX genes, which include PAX2, PAX5, and PAX8, are essential for the development of the central nervous system (CNS). The transcription factors OCT3 and OCT4 cause the neural plate to express PAX2 during gastrulation, which aids in the development of the midbrain–hindbrain barrier. In turn, PAX2 activates the transcription of PAX5 and PAX8, which subsequently regulate downstream target genes essential for both the establishment of this neural boundary and the maintenance of PAX2/5/8 expression [12]. This cascade illustrates the complex transcriptional regulatory networks that control PAX gene activity throughout embryonic development. Upstream regulators have the ability to stimulate a single PAX gene, which can then set off feedback loops that maintain its own expression by inducing the production of additional PAX genes and downstream targets.

### 2.2 MicroRNA Regulation of PAX Genes

Numerous microRNAs (miRNAs), many of which exhibit tissue-specific expression profiles, strictly govern the timing of PAX gene expression during embryonic development. For instance, as the myotome develops into skeletal muscle, miR-1 and miR-206 are noticeably increased, suppressing PAX3 expression throughout this developmental stage [13]. Dysregulation of these miRNAs has been implicated in disease states, affecting normal PAX gene regulation. In rhabdomyosarcoma, levels of both miR-1 and miR-206 are significantly reduced compared to those in healthy skeletal muscle tissue [14]. Experimental overexpression of these miRNAs results in decreased PAX3 protein levels in embryonal rhabdomyosarcoma. Conversely, in alveolar rhabdomyosarcoma, the oncogenic PAX3:FOXO1 fusion protein escapes this regulation due to the loss of its 3′ untranslated region (3′UTR), which normally serves as the binding site for these miRNAs [15].

### 2.3 Alternative Splicing Mechanisms and the Generation of PAX Gene Isoforms

Alternative splicing represents a key post-transcriptional process through which a single gene can produce multiple mRNA transcripts. While some of these variants may code for structurally similar proteins, others give rise to isoforms with differences in domain

composition and functional capacity. Additionally, protein diversity can arise through the utilization of distinct transcription start sites, leading to mRNA variants that are similar but not identical. In the human genome, eight out of the nine PAX genes exhibit transcript variability through either alternative splicing or the use of alternative start sites. The number of resulting isoforms ranges from two in PAX1 and PAX4 to up to fifteen in PAX6 (Table 1). These isoforms display differences in domain architecture, influencing their interactions with other proteins and with DNA. Since not all isoforms have been detected in adult tissues, it is presumed that some function primarily during specific stages of embryonic development [16]. Moreover, certain PAX genes such as PAX3 and PAX7 produce multiple isoforms simultaneously, both in the embryo and in tumors like rhabdomyosarcoma [17,18]. Alternative splicing frequently alters the C-terminal region of PAX proteins, with notable effects on the transactivation domain [19].

## 3. Functional Roles of PAX Genes Throughout Developmental Processes

All nine PAX transcription factors have been shown to play critical roles in directing the development and differentiation of specific tissues during embryogenesis (Table 2, Figure 4). Due to their pivotal functions, they are often referred to as "master regulators." These proteins share key regulatory characteristics, such as elevated expression within their target tissues, the ability to enhance their own transcription through positive feedback mechanisms, strong binding affinity for regulatory regions of tissue-specific genes, and the dual capacity to activate lineage-defining genes while suppressing those involved in alternative developmental pathways [20].

This precise control of gene expression is frequently achieved through interactions with transcriptional co-activators—such as p300 and components of the Mediator complex—as well as co-repressors like the Polycomb group proteins [21]. A well-known example of a master regulator outside the PAX family is NKX2-5, a transcription factor crucial for heart development. Initially identified in *Drosophila* as *tinman*, a gene whose loss prevents heart formation during embryogenesis [22], *Nkx2-5* is highly expressed in murine cardiac progenitor cells and remains active throughout their progression into mature cardiomyocytes [23]. This factor also regulates its own expression by binding to its cis-regulatory elements [24], and it is thought to orchestrate the activity of hundreds of target genes essential for heart development and morphogenesis [25].

The regulatory properties of several PAX protein family members are similar. For instance, PAX6 binds to enhancer regions of genes necessary for lens development in the developing mouse eye, where it is strongly expressed [26,27]. It also participates in an autoregulatory feedback mechanism that helps maintain its own transcriptional activity [28]. In order to maintain eye identity in Drosophila, PAX6 works with Polycomb group (PcG) proteins to prevent unwarranted cell fate modifications, such as the conversion of ocular tissue into wing components [29].

The developmental functions of PAX genes will be explored further in the following sections, with an emphasis on their roles in tissue specification. Much of the current understanding of PAX-driven developmental processes stems from animal studies, especially in murine models. Where applicable, the defining features of master regulatory behavior will be highlighted in relation to PAX gene function.

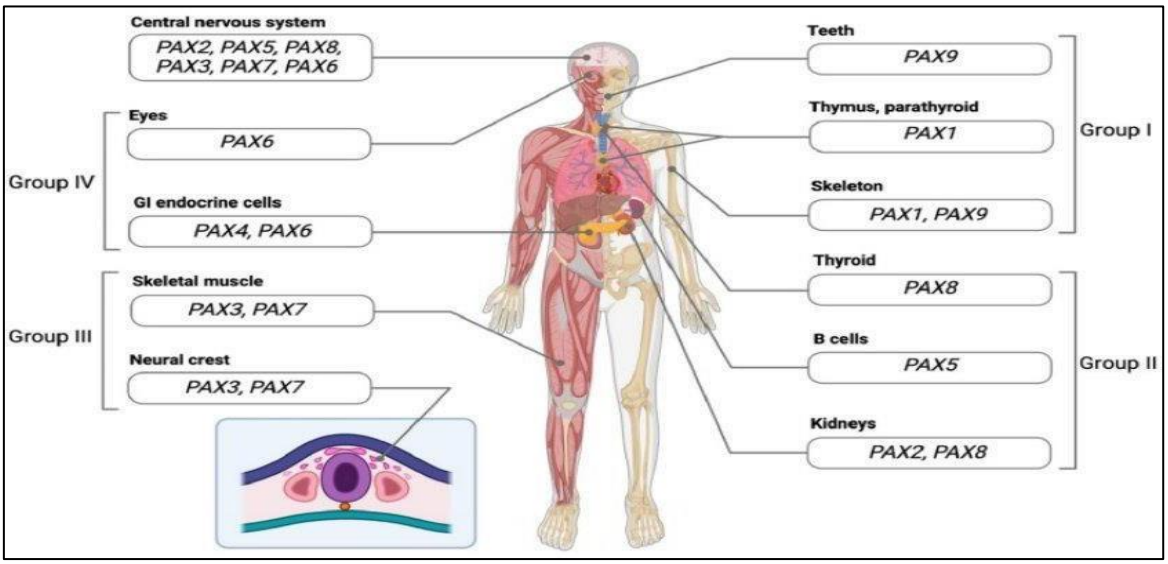


**Figure 3: Developmental Functions of PAX Genes. PAX genes are involved in the development of various human tissues and organs, often with overlapping roles across different systems. This illustration highlights selected examples of cell types, tissues, and organs influenced by PAX gene activity [11]**

### 3.1 Contributions of PAX1 and PAX9 to Skeletal Formation and Development

In particular, the axial skeleton, teeth, and craniofacial region are shaped by Group I PAX genes, which play a crucial role in skeletal development. In developing mouse embryos, Pax1 and Pax9 are highly expressed in the somites and sclerotome; in adult mice, however, their expression decreases in the vertebral column [31]. Gene knockout models have been used for functional investigations, which have shown that these genes have different, non-overlapping functions while having structural similarities. In mice, three naturally occurring *Pax1* mutant alleles—*undulated* (*un*), *undulated extensive* (*unex*), and *undulated short-tail* (*Uns*)—have been identified and characterized [32]. The *un* and *unex* alleles are hypomorphic and are associated with axial skeletal malformations in homozygous individuals. In contrast, the *Uns* allele, which involves a complete deletion of the *Pax1* gene, results in more pronounced defects; heterozygous mice present with visibly shortened and kinked tails, while homozygous mutants suffer from severe skeletal anomalies that lead to perinatal death [33].

It's interesting to note that Uns mice exhibit more severe skeletal deformities than Pax1-null mice produced by targeted gene deletion. Homozygous *Pax1*-null animals show phenotypes resembling those of *Uns* heterozygotes, whereas heterozygous *Pax1* knockouts do not exhibit noticeable skeletal abnormalities [34]. One possible explanation for this discrepancy is that the genomic deletion in *Uns* mutants may cause ectopic expression of *Nkx2-2* within the sclerotome, possibly via enhancer–promoter interactions involving regulatory regions shared between *Pax1* and *Nkx2-2* [35].

### 3.2 Functional Contributions of PAX2 and PAX8 to Kidney Development

In mouse models, *Pax2* exhibits high expression levels during the formation of the urinary excretory system, but its expression diminishes as the kidneys and urogenital tissues reach full maturity [36]. The Tg8052 transgenic mouse, which carries a heterozygous deletion of *Pax2*, presents with a spectrum of renal abnormalities, including kidney aplasia and hypoplasia [37]. Conversely, *Pax2* knockout mice (*Pax2*^−/−), created through homologous recombination, fail to develop kidneys, ureters, and reproductive organs altogether [38]. In *Xenopus*, *pax8* is strongly expressed during early stages of kidney organogenesis, and its knockdown via translation-blocking morpholinos disrupts pronephric tubule formation [39,40]. While *Pax8*^−/− mice do not show obvious renal defects, they succumb shortly after weaning due to thyroid gland abnormalities [41]. Notably, compound heterozygous mice (*Pax2*^+/−; *Pax8*^+/−) exhibit more pronounced kidney malformations than *Pax2*^+/− mice alone [42]. This observation indicates that two functional copies of *Pax2* can compensate for the absence of *Pax8* in nephrogenesis, whereas a single copy of *Pax8* only partially mitigates the effects of *Pax2* haploinsufficiency.

The transcriptional control of kidney development by *Pax2* and *Pax8* involves not only their DNA-binding capabilities but also interactions with epigenetic modulators. Group II PAX proteins such as PAX2 have been shown to interact with Groucho family corepressors, especially GRG4 [17]. The PAX2–GRG4 complex promotes trimethylation of histone H3 on lysine 27 (H3K27me3), a histone alteration connected to gene regulation and chromatin condensation [58]. In contrast, this repressive modification can be reversed when phosphorylated PAX2 recruits coactivators like PTIP and Trithorax group proteins, leading to trimethylation of histone H3 at lysine 4 (H3K4me3), which correlates with open chromatin and active transcription [34]. These epigenetic mechanisms are vital for the initiation and maintenance of kidney-specific gene expression programs [43]. In summary, although *Pax2* and *Pax8* have overlapping functions in renal development, precise regulation of their gene dosage is essential for normal kidney morphogenesis.

### 3.3 The Central Role of PAX5 in B Cell Lineage Commitment and Differentiation

The development of B lymphocytes from hematopoietic stem cells involves multiple tightly regulated stages. During the earliest phase of B cell development, Surface proteins like B220 are expressed when hematopoietic stem cells develop into pre-pro B cells, an isoform of CD45 [44]. The initiation of *PAX5* expression is critical for B cell lineage commitment, as it drives the transcription of numerous B cell–specific genes, including *CD19*, and enhances interleukin-7 (IL-7) signaling. At the pre–pro B cell stage, rearrangement of the immunoglobulin heavy chain (*IgH*) through V(D)J recombination is required for the formation of the pre–B cell receptor (pre-BCR), facilitating the transition to the pre–B cell stage. Successful immunoglobulin light chain (Igl) gene recombination in pre-B cells produces the VJ complex, which assembles a functional B cell receptor (BCR) [45]. Sustained expression of both *PAX5* and IL-7 is essential for proper progression through these developmental stages.

Although Pax5-null (Pax5−/−) mice are not embryonically lethal, most do not survive past the perinatal stage, and those that do completely lack B lineage cells [46]. Because Pax5-deficient hematopoietic stem cells are unable to initiate B cell differentiation, they have been used in experimental systems to restore T cell populations—but not B cells—in Rag2−/− mice, which are otherwise incapable of generating either lymphocyte lineage [47]. In the context of B cell development, PAX5 functions as a classical master regulator, being expressed robustly from the pro-B cell stage and maintained throughout B cell maturation. It exerts control over lineage-specific gene networks by

binding regulatory DNA elements and promoting transcription, partly through recruitment of the coactivator p300 [48]. As a Group II PAX protein, PAX5 also collaborates with Groucho family corepressors to inhibit genes in non-B-cell lineages, strengthening the identity of B cells [17].

### 3.4 PAX8 as a Master Regulator of Thyroid Follicular Cell Differentiation

The two main cell types that make up the thyroid gland are parafollicular cells, which release calcitonin, and follicular cells, which produce thyroxine. Both cell lineages originate from an endodermal pool of thyroid progenitor cells that express PAX8, according to recent research. Functional investigations, however, show that PAX8 is uniquely necessary for follicular cells to fully mature and differentiate [49,50]. Pax8 is extensively expressed during thyroid development in mouse models, and mice lacking Pax8 (Pax8^−/−) stop developing a mature gland at the thyroid bud stage [51,52]. Moreover, mouse embryonic stem cells that express Pax8 and Nkx2-1 ectopically differentiate into cells that resemble thyroid follicles [53]. The transcription of several important genes essential for thyroid cell identity and function, such as those producing thyroglobulin, thyroperoxidase, and the sodium/iodide symporter (NIS), is regulated by PAX8, in accordance with its function as a master regulator [54].

### 3.5 PAX3 and PAX7 in the Specification, Migration, and Survival of Myogenic Progenitors

During embryonic development, the paraxial mesoderm forms somites, which further differentiate into the sclerotome and dermomyotome. Myoblasts produced by the dermomyotome aid in the growth of limb muscles. Pax3 is extensively expressed in the dermomyotome and somites of mice, and it remains active during the myoblast differentiation and migration phases into the limb buds [55]. The *splotch* (*Sp*) mutant mouse, which carries mutations in the *Pax3* homeodomain, exhibits severe defects in skeletal muscle formation, especially in the shoulder and limb regions [56]. Critical myogenic regulatory factors like *Myog* and *Myf5* are not expressed in these mutants, and their limb myoblasts have noticeably decreased migratory capacity [57]. Even when Sp mutants' somites induce MyoD expression, the impacted cells quickly undergo apoptosis. Together, these results underscore the vital function of *Pax3* in directing myogenic lineage specification as well as ensuring progenitor cell survival during early muscle formation [58].

### 3.6 Functional Roles of PAX3 and PAX7 in the Specification and Migration of Neural Crest Cells

The neural crest represents a transient, multipotent population of cells originating from the embryonic ectoderm after neuroectoderm differentiation and neurulation [59]. Neural crest cells, which are first found between the neural tube and the surface ectoderm, go through an epithelial-to-mesenchymal transition (EMT) that helps them migrate and eventually differentiate into a range of cell types, including melanocytes, Schwann cells, ganglia, and smooth muscle cells [60]. Pax3 plays a key role in the development of dorsal root ganglion neurons in mice by being highly expressed in neural crest cells during the early stages of development and remaining active as these cells migrate and differentiate [61]. As mentioned earlier, mutations in *Pax3* found in homozygous *splotch* (*Sp*) mutant mice lead to disrupted neural crest migration and defective neural tube closure. These defects cause the absence of enteric ganglia and congenital heart malformations, culminating in embryonic lethality [62,63].

On the other hand, Pax7^−/− mice have a somewhat milder phenotype; they live past birth but typically pass away soon after weaning [64]. Pax7's more restricted role inside the cephalic neural crest, which supports craniofacial components like neurons, glial cells, cartilage, and connective tissue, is probably the reason for this milder result. As a result, Pax7^−/−mice have abnormalities in the maxilla, serous glands, and nasal capsules, but no discernible abnormalities in the development of the heart or enteric ganglia [65]. Similar to observations in myogenesis, partial functional overlap between *Pax3* and *Pax7* may account for compensatory effects seen in single-gene knockouts. Nonetheless, simultaneous deletion of both genes (*Pax3*^−/−; *Pax7*^−/−) produces a substantially more severe phenotype compared to either mutation alone.

### 3.7. Functional Roles of PAX4 and PAX6 in Pancreatic Endocrine Lineage Specification and Differentiation

The pancreatic islets of Langerhans comprise five distinct endocrine cell types: alpha cells that secrete glucagon, beta cells producing insulin, delta cells responsible for somatostatin secretion, pancreatic polypeptide (PP) cells, and epsilon cells that release ghrelin. The differentiation of endocrine progenitors into these specialized cell types is primarily governed by the transcription factors PAX4 and PAX6, although other regulatory factors also influence gastrointestinal endocrine cell specification. Alpha and epsilon cell populations dramatically rise in Pax4^−/−mice, whereas beta and delta cell development is stopped [66]. These animals die soon after birth due to severe hyperglycemia resulting from the lack of insulin-producing beta cells. Conversely, Pax6^−/− mice completely lack alpha cells, and the remaining beta, delta, and PP cells exhibit disorganized structure, failing to establish proper islet architecture [67].

Mice deficient in both Pax4 and Pax6 (Pax4^−/−; Pax6^−/−) lack all mature pancreatic endocrine cell types [68]. Significantly, Pax6 is still present in adult endocrine cells, where it plays a critical role in preserving beta cell identity by encouraging the production of genes unique to beta cells and suppressing

transcriptional programs linked to other endocrine lineages [69].

### 3.8 PAX6 Function in Ocular Morphogenesis

The cornea and lens form from the surface ectoderm, whereas the retina, iris, and ciliary body originate from the neural plate, making the eye a highly specialized organ made up of multiple unique structures [70]. Notably, the complex developmental processes governing eye formation are predominantly regulated by a single gene, *PAX6*, which exemplifies the characteristics of a master regulatory gene. As previously mentioned, *PAX6* exhibits hallmark features of master regulators, including robust expression in developing ocular tissues, autoregulatory mechanisms that sustain its own transcription, binding to regulatory regions of multiple downstream target genes, and the dual capacity to activate eye-specific genes while repressing genes linked to alternative cell lineages [71]. The *eyeless* mutation was initially described in *Drosophila* over a century ago, predating the identification of the *prd* gene. Subsequent research established that the *eyeless* locus in *Drosophila* is homologous to *Pax6* in mice (also known as *small eye*) and the human *PAX6* gene. This discovery underscored the profound evolutionary conservation of genetic mechanisms controlling eye development across diverse species, despite significant morphological and functional differences between insect and mammalian eyes.

**Table 2. Developmental Functions and Related Disorders of PAX Gene Family Subgroups [24].**

| Subgroup | Gene | Aliases | Developmental Role(s) | Associated Disorder(s) |
|---|---|---|---|---|
| Group I | **PAX1** | HuP48 | The axial and appendicular skeleton, thymus, and parathyroid gland. | Otofaciocervical syndrome-2 (OTFCS2) |
| | **PAX9** | - | Axial and craniofacial skeleton, teeth | Selective tooth agenesis-3 (STHAG3) |
| Group II | **PAX2** | - | Kidney, CNS | Papillorenal syndrome (PAPRS), focal segmental glomerulosclerosis-7 (FSGS7) |
| | **PAX5** | BSAP | CNS, B cells | - |
| | **PAX8** | - | Kidney, CNS, thyroid | Congenital hypothyroidism |
| Group III | **PAX3** | HuP2 | Skeletal muscle, neural crest, CNS | Waardenburg syndrome (Types 1 and 3) and craniofacial-deafness-hand syndrome (CDHS). |
| | **PAX7** | HuP1, RMS2 | Skeletal muscle, neural crest, CNS | Congenital myopathy-19 (CMYP19) |
| Group IV | **PAX4** | - | GI endocrine cells | Maturity-onset diabetes of the young (Type 9, MODY9), type 2 diabetes mellitus, and ketosis-prone diabetes. |
| | **PAX6** | MGDA, WAGR | GI endocrine cells, eye, CNS | Aniridia, anterior segment dysgenesis type 5 (ASGD5), foveal hypoplasia type 1 (FVH1), and keratitis. |

## 4. Implications of PAX Gene Dysregulation in Human Developmental Disorders and Cancer

A variety of genetic illnesses are linked to abnormalities in PAX genes because of their crucial functions in human development (Table 2). The clinical severity of these conditions frequently corresponds to the nature and extent of structural disruption within the encoded protein, as well as the zygosity of the mutation. Many *PAX*-related phenotypes exhibit gene dosage sensitivity, with homozygous mutations typically producing more severe outcomes than heterozygous variants. These conditions are outlined in the sections that follow, together with information on how they are inherited and the structural and functional effects of the involved PAX gene mutations [24].

### 4.1 PAX9 and Its Role in Tooth Agenesis

In several families, autosomal dominant tooth agenesis has been linked to mutations in the PAX9 gene [72]. The clinical spectrum includes oligodontia, which involves the lack of six or more teeth, and hypodontia, which is defined by the absence of less than six permanent teeth. While certain missense mutations and truncating insertions have been found in families presenting with hypodontia, the majority of frameshift and missense mutations affecting the paired domain of PAX9 are largely associated with oligodontia [73]. The degree to which these mutations affect the PAX9 protein's ability to bind DNA seems to be correlated with the severity of tooth agenesis. For example, mutations like R26W and L21P completely eliminate DNA-binding

ability and are linked to more severe clinical manifestations, while variants like K19E and G51S maintain partial binding affinity for paired box motifs and are linked to lesser dental abnormalities.

### 4.2 Pathogenic Roles of PAX Genes in Congenital Renal and Ocular Malformations

Mutations in the *PAX2* gene have been associated with a range of renal and ocular abnormalities. Papillary syndrome (PAPRS), an autosomal dominant condition brought on by heterozygous mutations including frameshift, splice site, and nonsense variants within PAX2, is a well-known example [74]. These mutations frequently result in shortened PAX2 proteins that lack the C-terminal transactivation domain entirely or in part. Furthermore, PAPRS has also been linked to missense mutations and in-frame insertions that impact the paired domain. Clinically, PAPRS is characterized by optic nerve colobomas, which can manifest as morning glory disc abnormalities, and renal hypoplasia, which can develop into end-stage renal disease [75].

Focal segmental glomerulosclerosis-7 (FSGS7) is another condition associated with heterozygous PAX2 mutations. It is characterized by segmental scarring of the renal glomeruli, which can lead to proteinuria and possibly end-stage renal failure. FSGS7 typically exhibits less severe symptoms than PAPRS and is often brought on by heterozygous missense mutations in the paired domain that lower PAX2's DNA-binding affinity. Heterozygous nonsense mutations in PAX2 have been linked to more severe FSGS7 symptoms.

### 4.3. Contribution of PAX gene Mutation in Diabetes

Although the A1168C polymorphism in the *PAX4* gene does not appear to play a major role in the overall genetic susceptibility to islet autoantibody-negative ketosis-prone diabetes (KPD) in the Chinese Han population, evidence suggests that this variation may be associated with an increased risk in specific subgroups, particularly in male patients and individuals diagnosed before the age of 20[76].

Mutations in the PAX4 gene have been implicated in various forms of diabetes. In a study involving over 300 Japanese individuals, The R121W mutation in *PAX4*, identified in both heterozygous and homozygous states, was detected in approximately 2% of individuals diagnosed with type 2 diabetes but was absent in healthy control groups. Additionally, people with maturity-onset diabetes of the young (MODY), a subtype of diabetes that clinically resembles adult type 2 diabetes but appears earlier in life, have been found to have missense mutations in *PAX4*. Notably, the R164W mutation, situated within the homeodomain, disrupts *PAX4*'s capacity to regulate the promoters of insulin and glucagon genes, thereby compromising its transcriptional activity [77].

## CONCLUSIONS

The PAX gene family has long been regarded as important regulators of human development and sickness. Recent improvements in understanding their biological actions, together with advancements in drug development technologies, have brought therapies targeting PAX proteins closer to becoming a reality. Future discoveries will rely on a thorough understanding of the functional distinctions among PAX family members, the impact of structural variants and isoforms, and the influence of specific cellular and tissue contexts on their activity. Future research priorities include understanding the roles of PAX genes in adult tissues, particularly in tissue regeneration and repair following injury. Furthermore, studies should look at the timing of PAX gene expression, tissue-specific distribution, and the functional importance of different isoforms. More research is also needed to understand the molecular mechanisms by which some PAX gene mutations cause developmental problems. Finally, the specific impact of wild-type PAX gene expression in cancer is uncertain; these genes may play roles in tumor initiation or progression, function as tumor suppressors, or be produced secondary to other oncogenic signals without directly driving carcinogenesis.

## REFERENCES

1. Deutsch, U., Dressler, G. R., & Gruss, P. (1988). Pax 1, a member of a paired box homologous murine gene family, is expressed in segmented structures during development. Cell, 53, 617–625.
2. Burri, M., Tromvoukis, Y., Bopp, D., Frigerio, G., & Noll, M. (1989). Conservation of the paired domain in metazoans and its structure in three isolated human genes. EMBO Journal, 8, 1183–1190.
3. Kilchherr, F., Baumgartner, S., Bopp, D., Frei, E., & Noll, M. (1986). Isolation of the paired gene of *Drosophila* and its spatial expression during early embryogenesis. *Nature*, *321*, 493–499.
4. Thompson, B., Davidson, E. A., Liu, W., Nebert, D. W., Bruford, E. A., Zhao, H., Dermitzakis, E. T., Thompson, D. C., & Vasiliou, V. (2021). Overview of PAX gene family: Analysis of human tissue-specific variant expression and involvement in human disease. Human Genetics, 140(3), 381–400. https://doi.org/10.1007/s00439-020-02212-9
5. Paixão-Côrtes, V. R., Salzano, F. M., & Bortolini, M. C. (2015). Origins and evolvability of the PAX family. *Seminars in Cell & Developmental Biology*, *44*, 64–74.
6. Balczarek, K. A., Lai, Z. C., & Kumar, S. (1997). Evolution of functional diversification of the paired box (Pax) DNA-binding domains. *Molecular Biology and Evolution*, *14*, 829–842.
7. Huerta-Cepas, J., Serra, F., & Bork, P. (2016). ETE 3: Reconstruction, analysis, and visualization of phylogenomic data. *Molecular Biology and Evolution*, *33*, 1635–1638.

8. Katoh, K., Kuma, K.-I., Toh, H., & Miyata, T. (2005). MAFFT version 5: Improvement in accuracy of multiple sequence alignment. *Nucleic Acids Research*, *33*, 511–518.
9. Nguyen, L.-T., Schmidt, H. A., von Haeseler, A., & Minh, B. Q. (2015). IQ-TREE: A fast and effective stochastic algorithm for estimating maximum-likelihood phylogenies. *Molecular Biology and Evolution*, *32*, 268–274.
10. Breitling, R., & Gerber, J. K. (2000). Origin of the paired domain. *Development Genes and Evolution*, *210*, 644–650.
11. Shaw, T., Barr, F. G., & Üren, A. (2024). The PAX genes: Roles in development, cancer, and other diseases. Cancers, 16(5), 1022. https://doi.org/10.3390/cancers16051022
12. Bopp, D., Burri, M., Baumgartner, S., Frigerio, G., & Noll, M. (1986). Conservation of a large protein domain in the segmentation gene paired and in functionally related genes of Drosophila. Cell, 47(6), 1033–1040. https://doi.org/10.1016/0092-8674(86)90818-4
13. Baumgartner, S., Bopp, D., Burri, M., & Noll, M. (1987). Structure of two genes at the gooseberry locus related to the paired gene and their spatial expression during Drosophila embryogenesis. Genes & Development, 1, 1247–1267.
14. Codutti, L., van Ingen, H., Vascotto, C., Fogolari, F., Corazza, A., Tell, G., Quadrifoglio, F., Viglino, P., Boelens, R., & Esposito, G. (2008). The solution structure of DNA-free Pax-8 paired box domain accounts for redox regulation of transcriptional activity in the PAX protein family. Journal of Biological Chemistry, 283, 33321–33328.
15. Xu, H. E., Rould, M. A., Xu, W., Epstein, J. A., Maas, R. L., & Pabo, C. O. (1999). Crystal structure of the human Pax6 paired domain-DNA complex reveals specific roles for the linker region and carboxy-terminal subdomain in DNA binding. *Genes & development*, *13*(10), 1263–1275. https://doi.org/10.1101/gad.13.10.1263
16. Lechner, M. S., & Dressler, G. R. (1996). Mapping of Pax-2 transcription activation domains. Journal of Biological Chemistry, 271, 21088–21093.
17. Eberhard, D., Jiménez, G., Heavey, B., & Busslinger, M. (2000). Transcriptional repression by Pax5 (BSAP) through interaction with corepressors of the Groucho family. EMBO Journal, 19, 2292–2303.
18. Birrane, G., Soni, A., & Ladias, J. A. A. (2009). Structural basis for DNA recognition by the human PAX3 homeodomain. Biochemistry, 48, 1148–1155.
19. Corry, G. N., & Underhill, D. A. (2005). Pax3 target gene recognition occurs through distinct modes that are differentially affected by disease-associated mutations. Pigment Cell Research, 18, 427–438.
20. Madej, T., Lanczycki, C. J., Zhang, D., Thiessen, P. A., Geer, R. C., Marchler-Bauer, A., & Bryant, S. H. (2014). MMDB and VAST+: Tracking structural similarities between macromolecular complexes. Nucleic Acids Research, 42, D297–D303.
21. Curto, G. G., Gard, C., & Ribes, V. (2015). Structures and properties of PAX linked regulatory networks architecting and pacing the emergence of neuronal diversity. *Seminars in Cell & Developmental Biology*, *44*, 75–86. https://doi.org/10.1016/j.semcdb.2015.08.003
22. Goljanek-Whysall, K., Sweetman, D., Abu-Elmagd, M., Chapnik, E., Dalmay, T., Hornstein, E., & Münsterberg, A. (2011). MicroRNA regulation of the paired-box transcription factor Pax3 confers robustness to developmental timing of myogenesis. *Proceedings of the National Academy of Sciences*, *108*(29), 11936–11941. https://doi.org/10.1073/pnas.1105362108
23. Li, L., Sarver, A. L., Alamgir, S., & Subramanian, S. (2012). Downregulation of microRNAs miR-1, -206 and -29 stabilizes PAX3 and CCND2 expression in rhabdomyosarcoma. *Laboratory Investigation*, *92*(4), 571–583. https://doi.org/10.1038/labinvest.2011.190
24. Lang, D., Powell, S. K., Plummer, R. S., Young, K. P., & Ruggeri, B. A. (2007). PAX genes: roles in development, pathophysiology, and cancer. *Biochemical pharmacology*, *73*(1), 1–14. https://doi.org/10.1016/j.bcp.2006.06.024
25. Du, S., Lawrence, E. J., Strzelecki, D., Rajput, P., Xia, S. J., Gottesman, D. M., & Barr, F. G. (2005). Co-expression of alternatively spliced forms of PAX3, PAX7, PAX3-FKHR and PAX7-FKHR with distinct DNA binding and transactivation properties in rhabdomyosarcoma. *International Journal of Cancer*, *115*(1), 85–92. https://doi.org/10.1002/ijc.20874.
26. Pritchard, C., Grosveld, G., & Hollenbach, A. D. (2003). Alternative splicing of Pax3 produces a transcriptionally inactive protein. *Gene*, *305*, 61–69. https://doi.org/10.1016/S0378-1119(02)01134-5
27. Sasamoto, Y., Hayashi, R., Park, S.-J., Saito-Adachi, M., Suzuki, Y., Kawasaki, S., Quantock, A. J., Nakai, K., Tsujikawa, M., & Nishida, K. (2016). PAX6 isoforms, along with reprogramming factors, differentially regulate the induction of cornea-specific genes. *Scientific Reports*, *6*, 20807. https://doi.org/10.1038/srep20807
28. Miller, P. J., Dietz, K. N., & Hollenbach, A. D. (2008). Identification of serine 205 as a site of phosphorylation on Pax3 in proliferating but not differentiating primary myoblasts. *Protein Science*, *17*(11), 1979–1986. https://doi.org/10.1110/ps.035899.108
29. Dietz, K. N., Miller, P. J., & Hollenbach, A. D. (2009). Phosphorylation of serine 205 by the protein kinase CK2 persists on Pax3-FOXO1, but not Pax3, throughout early myogenic differentiation. *Biochemistry*, *48*(49), 11786–11795. https://doi.org/10.1021/bi9012849
30. Cao, X., Kambe, F., Lu, X., Kobayashi, N., Ohmori, S., & Seo, H. (2005). Glutathionylation of two

cysteine residues in paired domain regulates DNA binding activity of Pax-8. *Journal of Biological Chemistry*, *280*(27), 25901–25906. https://doi.org/10.1074/jbc.M502314200

31. Schäfer, B. W., Czerny, T., Bernasconi, M., Genini, M., & Busslinger, M. (1994). Molecular cloning and characterization of a human PAX-7 cDNA expressed in normal and neoplastic myocytes. *Nucleic Acids Research*, *22*(21), 4574–4582. https://doi.org/10.1093/nar/22.21.4574
32. Verger, A., & Duterque-Coquillaud, M. (2002). When Ets transcription factors meet their partners. *BioEssays*, *24*(4), 362–370. https://doi.org/10.1002/bies.10075
33. Patel, S. R., Kim, D., Levitan, I., & Dressler, G. R. (2007). The BRCT-domain containing protein PTIP links PAX2 to a histone H3, lysine 4 methyltransferase complex. *Developmental Cell*, *13*(4), 580–592. https://doi.org/10.1016/j.devcel.2007.08.009
34. Lee, T. I., & Young, R. A. (2013). Transcriptional regulation and its misregulation in disease. *Cell*, *152*(6), 1237–1251. https://doi.org/10.1016/j.cell.2013.02.014
35. Bodmer, R. (1993). The gene tinman is required for specification of the heart and visceral muscles in *Drosophila*. *Development*, *118*, 719–729. https://doi.org/10.1242/dev.118.3.719
36. Lints, T. J., Parsons, L. M., Hartley, L., Lyons, I., & Harvey, R. P. (1993). Nkx-2.5: A novel murine homeobox gene expressed in early heart progenitor cells and their myogenic descendants. *Development*, *119*, 969–979. https://doi.org/10.1242/dev.119.3.969
37. He, A., Kong, S. W., Ma, Q., & Pu, W. T. (2011). Co-occupancy by multiple cardiac transcription factors identifies transcriptional enhancers active in heart. *Proceedings of the National Academy of Sciences*, *108*(14), 5632–5637. https://doi.org/10.1073/pnas.1016959108
38. Bouveret, R., Waardenberg, A. J., Schonrock, N., Ramialison, M., Doan, T., de Jong, D., Bondue, A., Kaur, G., Mohamed, S., Fonoudi, H., *et al.,* (2015). NKX2-5 mutations causative for congenital heart disease retain functionality and are directed to hundreds of targets. *eLife*, *4*, e06942. https://doi.org/10.7554/eLife.06942
39. 39.Bouveret, R., Waardenberg, A. J., Schonrock, N., Ramialison, M., Doan, T., de Jong, D., Bondue, A., Kaur, G., Mohamed, S., Fonoudi, H., Chen, C. M., Wouters, M. A., Bhattacharya, S., Plachta, N., Dunwoodie, S. L., Chapman, G., Blanpain, C., & Harvey, R. P. (2015). NKX2-5 mutations causative for congenital heart disease retain functionality and are directed to hundreds of targets. *eLife*, *4*, e06942. https://doi.org/10.7554/eLife.06
40. Walther, C., & Gruss, P. (1991). Pax-6, a murine paired box gene, is expressed in the developing CNS. *Development*, *113*(4), 1435–1449. https://doi.org/10.1242/dev.113.4.1435
41. Wolf, L. V., Yang, Y., Wang, J., Xie, Q., Braunger, B., Tamm, E. R., Zavadil, J., & Cvekl, A. (2009). Identification of pax6-dependent gene regulatory networks in the mouse lens. *PLoS ONE, 4*(3), e4159. https://doi.org/10.1371/journal.pone.0004159
42. Grindley, J. C., Davidson, D. R., & Hill, R. E. (1995). The role of Pax-6 in eye and nasal development. *Development, 121*(5), 1433–1442. https://doi.org/10.1242/dev.121.5.1433
43. Zhu, J., Ordway, A. J., Weber, L., Buddika, K., & Kumar, J. P. (2018). Polycomb group (PcG) proteins and Pax6 cooperate to inhibit in vivo reprogramming of the developing Drosophila eye. *Development, 145*, dev160754. https://doi.org/10.1242/dev.160754
44. Neubüser, A., Koseki, H., & Balling, R. (1995). Characterization and developmental expression of Pax9, a paired-box-containing gene related to Pax1. *Developmental Biology, 170*(2), 701–716. https://doi.org/10.1006/dbio.1995.1241
45. Wallin, J., Wilting, J., Koseki, H., Fritsch, R., Christ, B., & Balling, R. (1994). The role of Pax-1 in axial skeleton development. *Development, 120*(5), 1109–1121. https://doi.org/10.1242/dev.120.5.1109
46. Wilm, B., Dahl, E., Peters, H., Balling, R., & Imai, K. (1998). Targeted disruption of Pax1 defines its null phenotype and proves haploinsufficiency. *Proceedings of the National Academy of Sciences, 95*(15), 8692–8697. https://doi.org/10.1073/pnas.95.15.8692
47. Kokubu, C., Wilm, B., Kokubu, T., Wahl, M., Rodrigo, I., Sakai, N., Santagati, F., Hayashizaki, Y., Suzuki, M., Yamamura, K.-I., *et al.,* (2003). Undulated short-tail deletion mutation in the mouse ablates Pax1 and leads to ectopic activation of neighboring Nkx2-2 in domains that normally express Pax1. *Genetics, 165*(1), 299–307. https://doi.org/10.1093/genetics/165.1.299
48. Peters, H., Wilm, B., Sakai, N., Imai, K., Maas, R., & Balling, R. (1999). Pax1 and Pax9 synergistically regulate vertebral column development. *Development, 126*(23), 5399–5408. https://doi.org/10.1242/dev.126.23.5399
49. Peters, H., Neubüser, A., Kratochwil, K., & Balling, R. (1998). Pax9-deficient mice lack pharyngeal pouch derivatives and teeth and exhibit craniofacial and limb abnormalities. *Genes & Development, 12*(17), 2735–2747. https://doi.org/10.1101/gad.12.17.2735
50. Li, R., Chen, Z., Yu, Q., Weng, M., & Chen, Z. (2019). The function and regulatory network of Pax9 gene in palate development. *Journal of Dental Research, 98*(3), 277–287. https://doi.org/10.1177/0022034518815509
51. Dressler, G. R., Deutsch, U., Chowdhury, K., Nornes, H. O., & Gruss, P. (1990). Pax2, a new murine paired-box-containing gene and its expression in the developing excretory system. *Development, 109*(4), 787–795. https://doi.org/10.1242/dev.109.4.787

52. Keller, S. A., Jones, J. M., Boyle, A., Barrow, L. L., Killen, P. D., Green, D. G., Kapousta, N. V., Hitchcock, P. F., Swank, R. T., & Meisler, M. H. (1994). Kidney and retinal defects (Krd), a transgene-induced mutation with a deletion of mouse chromosome 19 that includes the Pax2 locus. *Genomics, 23*(2), 309–320. https://doi.org/10.1006/geno.1994.1519
53. Torres, M., Gómez-Pardo, E., Dressler, G. R., & Gruss, P. (1995). Pax-2 controls multiple steps of urogenital development. *Development, 121*(12), 4057–4065. https://doi.org/10.1242/dev.121.12.4057
54. Carroll, T. J., & Vize, P. D. (1999). Synergism between Pax-8 and lim-1 in embryonic kidney development. *Developmental Biology, 214*(1), 46–59. https://doi.org/10.1006/dbio.1999.9394
55. Buisson, I., Le Bouffant, R., Futel, M., Riou, J.-F., & Umbhauer, M. (2015). Pax8 and Pax2 are specifically required at different steps of Xenopus pronephros development. *Developmental Biology, 397*(2), 175–190. https://doi.org/10.1016/j.ydbio.2014.10.003
56. Mansouri, A., Chowdhury, K., & Gruss, P. (1998). Follicular cells of the thyroid gland require Pax8 gene function. *Nature Genetics, 19*(1), 87–90. https://doi.org/10.1038/ng0598-87
57. Asher, J. H., Jr., Sommer, A., Morell, R., & Friedman, T. B. (1996). Missense mutation in the paired domain of PAX3 causes craniofacial-deafness-hand syndrome. *Human Mutation, 7*(1), 30–35. https://doi.org/10.1002/(SICI)1098-1004(1996)7:1<30::AID-HUMU5>3.0.CO;2-8
58. Feichtinger, R. G., Mucha, B. E., Hengel, H., Orfi, Z., Makowski, C., Dort, J., D'Anjou, G., Nguyen, T. T. M., Buchert, R., Juenger, H., *et al.,* (2019). Biallelic variants in the transcription factor PAX7 are a new genetic cause of myopathy. *Genetics in Medicine, 21*(11), 2521–2531. https://doi.org/10.1038/s41436-019-0493-8
59. Shimajiri, Y., Sanke, T., Furuta, H., Hanabusa, T., Nakagawa, T., Fujitani, Y., Kajimoto, Y., Takasu, N., & Nanjo, K. (2001). A missense mutation of Pax4 gene (R121W) is associated with type 2 diabetes in Japanese. *Diabetes, 50*(12), 2864–2869. https://doi.org/10.2337/diabetes.50.12.2864
60. Plengvidhya, N., Kooptiwut, S., Songtawee, N., Doi, A., Furuta, H., Nishi, M., Nanjo, K., Tantibhedhyangkul, W., Boonyasrisawat, W., Yenchitsomanus, P.-T., *et al.,* (2007). PAX4 mutations in Thais with maturity onset diabetes of the young. *The Journal of Clinical Endocrinology & Metabolism, 92*(7), 2821–2826. https://doi.org/10.1210/jc.2007-0241
61. 61.Mauvais-Jarvis, F., Smith, S. B., Le May, C., Leal, S. M., Gautier, J.-F., Molokhia, M., Riveline, J.-P., Rajan, A. S., Kevorkian, J.-P., Zhang, S., *et al.,* (2004). PAX4 gene variations predispose to ketosis-prone diabetes. *Human Molecular Genetics, 13*(24), 3151–3159. https://doi.org/10.1093/hmg/ddh327
62. 62.Robinson, D. O., Howarth, R. J., Williamson, K. A., van Heyningen, V., Beal, S. J., & Crolla, J. A. (2008). Genetic analysis of chromosome 11p13 and the PAX6 gene in a series of 125 cases referred with aniridia. *American Journal of Medical Genetics Part A, 146A*(5), 558–569. https://doi.org/10.1002/ajmg.a.32150
63. 63.Singh, S., Chao, L. Y., Mishra, R., Davies, J., & Saunders, G. F. (2001). Missense mutation at the C-terminus of PAX6 negatively modulates homeodomain function. *Human Molecular Genetics, 10*(9), 911–918. https://doi.org/10.1093/hmg/10.9.911
64. 64.Jordan, T., Hanson, I., Zaletayev, D., Hodgson, S., Prosser, J., Seawright, A., Hastie, N., & van Heyningen, V. (1992). The human PAX6 gene is mutated in two patients with aniridia. *Nature Genetics, 1*(4), 328–332. https://doi.org/10.1038/ng0692-328
65. 65.Solomon, B. D., Pineda-Alvarez, D. E., Balog, J. Z., Hadley, D., Gropman, A. L., Nandagopal, R., Han, J. C., Hahn, J. S., Blain, D., Brooks, B., *et al.,* (2009). Compound heterozygosity for mutations in PAX6 in a patient with complex brain anomaly, neonatal diabetes mellitus, and microophthalmia. *American Journal of Medical Genetics Part A, 149A*(11), 2543–2546. https://doi.org/10.1002/ajmg.a.33071
66. Mirzayans, F., Pearce, W. G., MacDonald, I. M., & Walter, M. A. (1995). Mutation of the PAX6 gene in patients with autosomal dominant keratitis. *American Journal of Human Genetics, 57*(3), 539–548.
67. Hanson, I. M., Fletcher, J. M., Jordan, T., Brown, A., Taylor, D., Adams, R. J., Punnett, H. H., & van Heyningen, V. (1994). Mutations at the PAX6 locus are found in heterogeneous anterior segment malformations including Peters' anomaly. *Nature Genetics, 6*(2), 168–173. https://doi.org/10.1038/ng0294-168
68. Robson, E. J. D., He, S.-J., & Eccles, M. R. (2006). A PANorama of PAX genes in cancer and development. *Nature Reviews Cancer, 6*(1), 52–62. https://doi.org/10.1038/nrc1777
69. Huang, J., Tan, Z.-R., Yu, J., Li, H., Lv, Q.-L., Shao, Y.-Y., & Zhou, H.-H. (2017). DNA hypermethylated status and gene expression of PAX1/SOX1 in patients with colorectal carcinoma. *OncoTargets and Therapy, 10*, 4739–4751. https://doi.org/10.2147/OTT.S146271
70. Kan, Y.-Y., Liou, Y.-L., Wang, H.-J., Chen, C.-Y., Sung, L.-C., Chang, C.-F., & Liao, C.-I. (2014). PAX1 methylation as a potential biomarker for cervical cancer screening. *International Journal of Gynecological Cancer, 24*(5), 928–934. https://doi.org/10.1097/IGC.0000000000000113
71. Gerber, J.-K., Richter, T., Kremmer, E., Adamski, J., Höfler, H., Balling, R., & Peters, H. (2002). Progressive loss of PAX9 expression correlates with increasing malignancy of dysplastic and cancerous

epithelium of the human oesophagus. *The Journal of Pathology, 197*(3), 293–297. https://doi.org/10.1002/path.1093

72. Tung, C. S., Mok, S. C., Tsang, Y. T. M., Zu, Z., Song, H., Liu, J., Deavers, M. T., Malpica, A., Wolf, J. K., Lu, K. H., *et al.,* (2009). PAX2 expression in ovarian cancer. *Modern Pathology, 22*(3), 402–409. https://doi.org/10.1038/modpathol.2008.190
73. Morrison, A. M., Jäger, U., Chott, A., Schebesta, M., Haas, O. A., & Busslinger, M. (1998). Deregulated PAX-5 transcription from a translocated IgH promoter in marginal zone lymphoma. *Blood, 92*(11), 3865–3873. https://doi.org/10.1182/blood.V92.11.3865.415k20_3865_3873
74. Alur, R. P., Vijayasarathy, C., Brown, J. D., Mehtani, M., Onojafe, I. F., Sergeev, Y. V., Boobalan, E., Jones, M., Tang, K., Liu, H., Xia, C. H., Gong, X., & Brooks, B. P. (2010). Papillorenal syndrome-causing missense mutations in PAX2/Pax2 result in hypomorphic alleles in mouse and human. *PLoS genetics*, *6*(3), e1000870. https://doi.org/10.1371/journal.pgen.1000870
75. Cazzaniga, G., Daniotti, M., Tosi, S., Giudici, G., Aloisi, A., Pogliani, E., Kearney, L., & Biondi, A. (2001). The paired box domain gene PAX5 is fused to ETV6/TEL in an acute lymphoblastic leukemia case. *Cancer Research, 61*(12), 4666–4670.
76. Zhou, M., Zhang, Y., Zhang, D., Lin, J., Wang, J., Zhou, H., & Zhou, Z. (2010). *Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences*, *35*(3), 215–221. https://doi.org/10.3969/j.issn.1672-7347.2010.03.005
77. Mullighan, C. G., Goorha, S., Radtke, I., Miller, C. B., Coustan-Smith, E., Dalton, J. D., Girtman, K., Mathew, S., Ma, J., Pounds, S. B., *et al.,* (2007). Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. *Nature, 446*(7137), 758–764. https://doi.org/10.1038/nature05634