Planar cell polarity pathway in kidney development, function and disease

Elena Torban[1,2]✉ *and Sergei Y. Sokol*[3]✉

Abstract | Planar cell polarity (PCP) refers to the coordinated orientation of cells in the tissue plane. Originally discovered and studied in *Drosophila melanogaster*, PCP is now widely recognized in vertebrates, where it is implicated in organogenesis. Specific sets of PCP genes have been identified. The proteins encoded by these genes become asymmetrically distributed to opposite sides of cells within a tissue plane and guide many processes that include changes in cell shape and polarity, collective cell movements or the uniform distribution of cell appendages. A unifying characteristic of these processes is that they often involve rearrangement of actomyosin. Mutations in PCP genes can cause malformations in organs of many animals, including humans. In the past decade, strong evidence has accumulated for a role of the PCP pathway in kidney development including outgrowth and branching morphogenesis of ureteric bud and podocyte development. Defective PCP signalling has been implicated in the pathogenesis of developmental kidney disorders of the congenital anomalies of the kidney and urinary tract spectrum. Understanding the origins, molecular constituents and cellular targets of PCP provides insights into the involvement of PCP molecules in normal kidney development and how dysfunction of PCP components may lead to kidney disease.

Insect cuticle
An extracellular layer that covers the external surface of the epidermis in many insects.

[1]*McGill University, Montreal, Quebec, Canada.*

[2]*McGill University Health Center Research Institute, Montreal, Quebec, Canada*

[3]*Department of Cell, Developmental and Regenerative Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.*

✉*e-mail: elena.torban@mcgill.ca; sergei.sokol@mssm.edu*

https://doi.org/10.1038/s41581-021-00395-6

In contrast to apical–basal polarity, which refers to the asymmetry between the top and bottom surfaces of cells and is easily appreciated, particularly for epithelial cells, planar cell polarity (PCP) refers to the coordinated orientation of cells within a plane of tissue; that is, in the direction perpendicular to the apical–basal axis. PCP has long been recognized for its role in establishing the polarized arrays of bristles or hairs on the insect cuticle[1]. Early genetic screens in the fruit fly, *Drosophila melanogaster*, identified mutants characterized by disorganized wing hairs or photoreceptors[2,3], and led to the identification of a set of conserved 'core' PCP genes[4]. These genes include *Frizzled* (*fz*/*Fzd* for the *Drosophila* and vertebrate homologue, respectively), *Dishevelled* (*dsh*/*Dvl*), *Flamingo* (also known as *Starry night* (*fmi* or *stan*/*Celsr*)), *Van Gogh* or *Strabismus* (*vang* or *stbm*/*Vangl*), *Prickle* (*pk*/*Pk*) and *Diego* (*dgo*/*Diversin* or *Inversin* (*Inversin* is also known as *NPHP2*))[5,6]. The unifying characteristic of these genes is that their encoded proteins are organized into complexes that exist at opposing faces of epithelial cells[4]. For example, in the *Drosophila* wing, the Van Gogh–Prickle complex is present at the proximal side of the cell, whereas the Frizzled–Dishevelled–Diego complex is located distally[5,7,8] (FIG. 1). An exception is Flamingo, which partners with both the proximal Van Gogh–Prickle complex and the distal Frizzled-Dishevelled complex[9,10]. Core PCP constituents are interdependent so that mutations in any one of them disrupt the localization of other core PCP proteins. The asymmetric localization of PCP protein complexes is crucial for establishing polarity along the epithelial plane and serves as a marker of PCP signalling activity within the cell.

PCP has been associated with specific signalling pathways that regulate cell shape and behaviour. Although PCP as a phenomenon refers to the subcellular asymmetry that extends throughout a tissue and can be conferred by diverse mechanisms, in this Review we largely discuss the pathway mediated by core PCP proteins and their partners. In addition to the core PCP proteins, this pathway includes a large number of other players. For example, mutations in the *Drosophila* genes *ft*/*Fat*, *ds*/*Dchs* and *ft*/*Fjt1*, encoding the atypical cadherins Fat, Dachsous and the Golgi kinase Four-jointed[11–14] produce long-range defects in tissue polarization. Initial analyses of *ft* and *ds Drosophila* mutants suggested that the encoded proteins function as upstream regulators of core PCP genes; however, existing genetic evidence is also consistent with an independent role in the regulation of PCP, at least in some contexts[15].

The upstream mechanisms that regulate the asymmetric organization of core proteins may involve molecular gradients and mechanical cues, although these mechanisms remain to be fully determined. Once the

Key points

- Planar cell polarity (PCP) refers to the coordinated organization of cells or cell components across a tissue plane as exemplified by the uniform patterns of scales on fish, trichomes (small hairs) on *Drosophila* wings or stereocilia in the mammalian inner ear.
- Evolutionarily conserved PCP proteins function in specialized signalling pathways to coordinate changes in cell shape and behaviour through processes that commonly involve actomyosin activation; these PCP-dependent changes in cell morphology control tissue morphogenesis.
- PCP proteins exhibit asymmetric subcellular localization along the tissue plane.
- Functions of vertebrate homologues of *Drosophila* PCP components in PCP signalling are often unclear owing to gene redundancy and/or their involvement in non-PCP-related processes.
- Given the essential roles of PCP proteins in morphogenetic processes, mutations in genes that encode PCP components can cause congenital malformations in multiple organs and tissues, including the kidney. Defective PCP signalling influences ureteric bud outgrowth and branching, nephron progenitor cell renewal and differentiation, and podocyte development. In mouse PCP mutants, renal tubules are dilated but no cysts form.

asymmetric distribution of core PCP proteins has been established, a set of downstream molecules encoded by PCP 'effector' genes induces changes in cytoskeletal organization, cell adhesion and vesicular trafficking that drive directional movement and patterned tissue growth during organogenesis. For example, the PCP effectors Fuzzy (encoded by *fy*/*Fuz*)[16]), Inturned (*in*/*In*)[17], Fritz (*frt*/*Wdpcp*)[18] and Multiple wing hairs (*mwh*; vertebrate homologue is unknown)[3,19] control the planar polarity of actin-based hairs, specifying the position and orientation of a single hair on each wing cell (FIG. 1a). In addition, housekeeping molecules, such as myosins, protein kinases and small GTPases, act downstream of Frizzled–Dishevelled complexes to control cell shape and behaviour; however, they may also regulate morphogenesis independently of core PCP components[20–23]. An increasing body of evidence suggests that the initial classification of global, core and effector PCP genes does not fully reflect the complexity of the PCP pathway. For example, available data suggest that Myosin II and other 'downstream' PCP effectors also act upstream of the core PCP proteins to influence their localization[24,25]. This feedback regulation is an essential feature of PCP signalling.

Another layer of complexity derives from the evolution of PCP homologues. Although only two *fz* and *ft* genes and single copies of other core PCP genes exist in *Drosophila*, vertebrate genomes contain at least ten *Fzd*[26], four *Pk*, two *Vangl*[27], three *Celsr* and three *Dvl*, as well as four *Fat* and two *Dchs* genes. As a result, analyses of PCP in vertebrates may be hampered by genetic redundancies and overlapping functional drift. In contrast, the mammalian PCP effectors *In*, *Fuz* and *Wdpcp* are encoded by single-copy genes (reviewed elsewhere[6]). Mutations in *Drosophila* orthologues of some vertebrate genes that contribute to PCP, such as *Daam1* (REF.[28]), *Shroom3* (REFS[29,30]) and non-canonical receptor tyrosine kinases *Ror1/2* (REFS[31,32]), *Ryk*[33,34] and *Ptk7* (REF.[35]), lack obvious PCP phenotypes. Other vertebrate PCP regulators have acquired novel functions, such as the regulation of ciliogenesis, that may indirectly relate to PCP signalling (reviewed elsewhere[36]). Therefore, one goal of future studies is to understand whether the PCP molecules define a specific signalling pathway that orchestrates planar polarity or whether they also participate in a variety of events that are unrelated to PCP.

Importantly, loss of PCP signalling disturbs key morphogenetic processes such as cell migration, cell intercalation, constriction of apical surfaces and oriented cell division[37–39]. Other vertebrate-specific processes that require PCP components and contribute to three-dimensional body architecture include the generation and proper functioning of motile and primary cilia as well as left–right patterning[40–45]. Thus, PCP signalling provides cells in a tissue with directional information that is needed for collective cell behaviours during organogenesis.

A body of evidence accumulated over the past 10–15 years supports a role of the PCP pathway in kidney development. For example, mutations in PCP genes are associated with congenital anomalies of the kidney and urinary tract (CAKUT) in mice and humans[46] (Supplementary Table 1). This Review describes the origins of PCP signalling, its activity and cellular targets, with a particular emphasis on the function of the PCP pathway in normal kidney development and the consequences of PCP misregulation for kidney disease.

Origins of PCP

Phenotypic analyses of mouse and zebrafish embryos carrying mutations in PCP genes have revealed essential roles for PCP components in various morphogenetic processes, including neural tube closure and cardiac morphogenesis (reviewed elsewhere[6]). However, despite intense research over the past three decades, the mechanisms by which PCP is established remains unclear. The finding that planar polarity can be visualized at the cellular level via the asymmetric distribution of proteins or cell structures[6] suggests that the orientation of individual cells in embryonic tissues might originate from the intrinsic polarity of the zygote. However, PCP normally emerges rather late in embryonic development and exists within large tissues that are comparable to the size of an embryo, for example, in the vertebrate skin along the anterior–posterior body axis. These findings suggest that PCP forms in response to one or more long-range cues that are sensed and interpreted within each cell of the tissue. The small differences between individual cells are then amplified to allow robust planar polarization.

Global PCP cues

Molecular gradients are traditionally invoked to explain long-range cues for establishing PCP. These could be gradients of transcriptional or enzymatic activity, cell–cell adhesion molecules, extracellular matrix (ECM) signals, or diffusible growth factors. Secreted Wnt proteins have long been considered excellent candidates for this role, due to their apparent ability to trigger the enrichment of Frizzled receptors at the nearest surface of each responding cell[26,47] (BOX 1). In support of this notion, Wnt ligands are essential for PCP, serving as directional guidance cues in both *Drosophila* and vertebrates[32,48–51]. Nevertheless, the involvement of Wnt ligands in PCP,

Functional drift
Acquisition of a diverse function or functions by homologous genes.

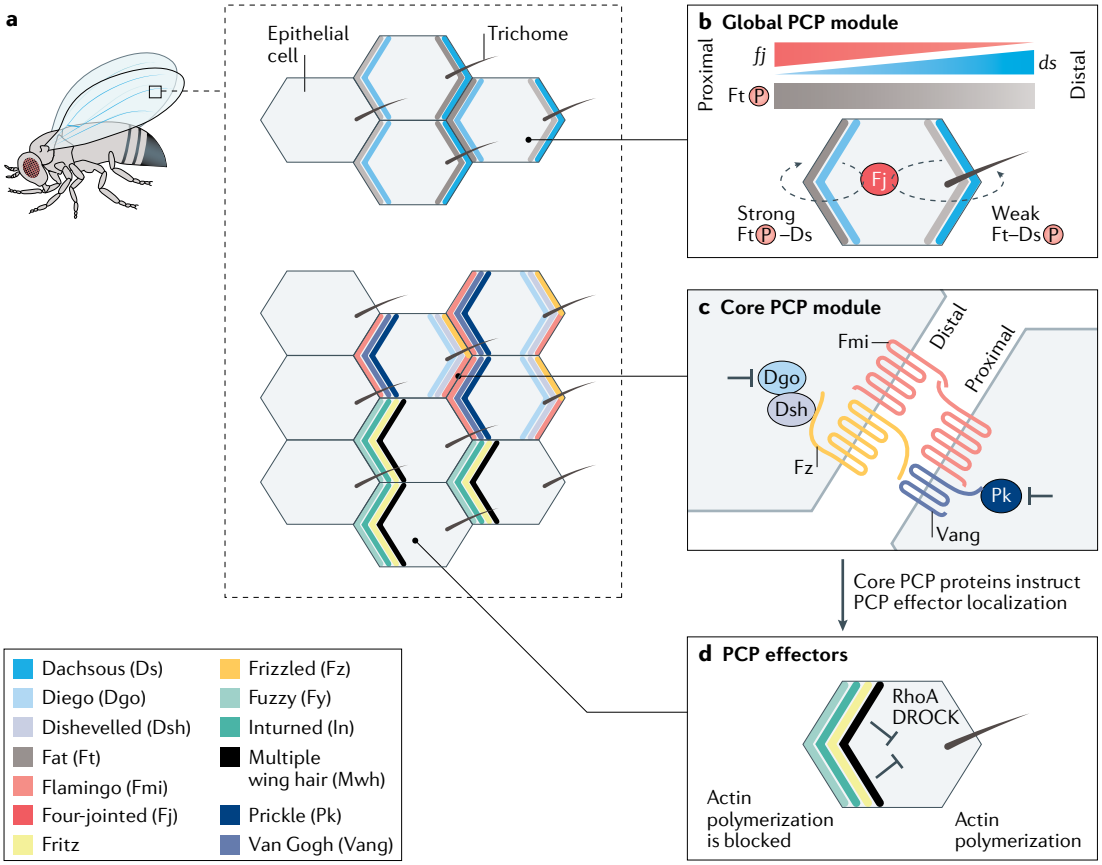

Fig. 1 | **Planar cell polarity in *Drosophila* wing. a** | Instructed by long-range cues, hexamer-shaped wing cells generate a single actin-based trichome (hair) at the most distal aspect of each cell. Formation of the single trichome and its precise localization is controlled by specific subsets of planar cell polarity (PCP) proteins that are distributed asymmetrically to the distal or proximal side of each cell. **b** | *ft* mRNA (which encodes Fat) is evenly expressed along the wing tissue, whereas *ds* (encoding Dachsous) is expressed in a distal-to-proximal gradient and *fj* (encoding the Four-jointed kinase) is expressed in a proximal-to-distal gradient. Four-jointed phosphorylates both Fat (with stronger phosphorylation at the proximal side) and Dachsous (with stronger phosphorylation at the distal side). The phosphorylation of Fat translates into strong Fat–Dachsous protein–protein interactions at the proximal side, whereas phosphorylation of Dachsous weakens Fat–Dachsous interactions at the distal side, thereby generating a shallow gradient of Fat–Dachsous adhesion across the tissue plane. **c** | Within *Drosophila* wing cells, core PCP protein complexes are distributed asymmetrically, with Van Gogh–Prickle (encoded by *vang* and *pk*, respectively) located at the proximal end and Frizzle–Dishevelled–Diego (encoded by *fz*, *dsh* and *dgo*, respectively) located at the distal end. The cadherin Flamingo (encoded by *fmi*) is localized at both the proximal and distal ends and forms homodimers with the extracellular domains of molecules expressed by adjacent cells. Interactions between Flamingo and Van Gogh or Flamingo and Frizzled, as well as between extracellular domains of Van Gogh and Frizzled expressed on surfaces of neighbouring cells, stabilize Van Gogh–Prickle and Frizzled–Dishevelled complexes on the opposite cell membranes. Inside the cell, mutual antagonism between Prickle and Dishevelled creates 'exclusion' zones where the proteins of the opposite core PCP complex cannot function. **d** | Core PCP proteins control localization of PCP effectors via direct interactions (for example, Van Gogh interacts with Inturned and Fuzzy (encoded by *in* and *fy*, respectively)). In *Drosophila* wing cells, PCP effectors inhibit the generation of trichome at the proximal side of the cell, whereas positive actin regulators, such as RhoA GTPase and *Drosophila* RhoA kinase (DROCK) accumulate at the distal side of the cell where they promote actin polymerization and hair formation.

especially in *Drosophila*, remains a topic of debate[52–54] given the challenge of conclusively demonstrating a role for Wnt ligands in PCP. For example, gradients of morphogens, including Wnt ligands, may influence PCP indirectly, by affecting growth and tissue shape, which, in turn, might modulate the PCP vector[55,56]. Alternatively, an initial positional cue in early embryogenesis might propagate through the developing tissue through interactions between neighbouring cells. Further research is needed to delineate which of these mechanisms is involved.

Gradients of cell adhesion molecules are an alternative to the diffusible factor hypothesis. This idea is consistent with the demonstration of opposing RNA and protein expression gradients for the atypical cadherin Dachsous and Four-jointed in the *Drosophila* wing (reviewed elsewhere[14,57]). Four-jointed differentially phosphorylates the extracellular domains of Fat and Dachsous on each side of the cell, thereby increasing the affinity of Fat for Dachsous on one face and decreasing the affinity of Dachsous for Fat on the other. Thus, Four-jointed enables neighbouring cells to polarize across the tissue (FIG. 1b).

Box 1 | **Wnt signalling and PCP**

Wnt pathways promote cell proliferation, cell movements and cell fate specification during embryonic development[233]. Activation of the canonical Wnt–β-catenin pathway leads to stabilization of β-catenin in the nucleus and target gene activation. Wnt proteins also activate non-canonical pathways that are independent of β-catenin but can modulate core planar cell polarity (PCP) components (e.g. Frizzled, Dishevelled, Prickle and Van Gogh) to trigger changes in cell shape and behaviour. Non-canonical Wnt signalling is often referred to as the 'Wnt–PCP pathway', based on several experimental observations. First, the core PCP component Frizzled is a Wnt ligand receptor[26]. Second, Dishevelled functions as a core PCP protein and as an obligatory player in the Wnt–β-catenin pathway. Third, some Wnt proteins and core PCP pathway components regulate cilia functions and left–right patterning[36,234]. Finally, both Wnt and PCP signalling affect the localization and/or activity of apicobasal polarity components, such as apical Par proteins and the basolateral determinants Lgl and Scrib[73,76].

Although available evidence suggests that Wnt proteins can regulate PCP, the molecular mechanism underlying this function is still unknown. Both canonical and noncanonical Wnt pathways, as well as core PCP protein stabilization, are accompanied by phosphorylation of Dishevelled, but the modulation of cell shape and polarity involves RhoA GTPase, ROCK and Myosin activities, rather than β-catenin. Phosphorylation of Dishevelled promotes its association with the formin protein Daam1 and leads to upregulation of RhoA and ROCK activity, followed by phosphorylation of Myosin II[28,235–237]. Alternatively, in mouse limb buds, phosphorylation of Van Gogh-like 2 by Casein kinase I is initiated in response to Wnt5a; the receptor tyrosine kinase, Ror2, may be a key regulator of Van Gogh-like 2 localization[32]. The segregation of core protein complexes to opposite cell faces is achieved through positive and negative feedback loops to define cell and tissue polarity[6,238].

Many Wnt proteins are expressed in the kidney in a precise temporal and spatial manner and are known to be the major regulators of kidney development and thus, crosstalk between Wnt and PCP pathways is operational during different stages of kidney development.

Gradients of Fat and Dachsous activity in the Drosophila wing were originally thought to fine-tune core PCP module-mediated signalling[11], but evidence from genetic studies now suggests that the Fat–Dachsous pathway might also act independently of the core PCP module, in a context-restricted manner[58,59]. Notably, Fat–Dachsous signalling not only regulates PCP but also affects cell and tissue growth by controlling the Hippo pathway through a PCP-independent mechanism[14,57].

Mechanical strain across the tissue might also serve as a global PCP cue[56,60]. In the *Drosophila* wing, mechanical stress generated by the contraction at the hinge region has been suggested to promote the alignment of polarized cells[56]. Similarly, the force generated during blastopore closure in gastrulating frog embryos is thought to align microtubules in frog ectoderm[60]. Consistent with this notion, artificially generated mechanical strain triggers microtubule polarization and altered PCP in frog ectoderm[60]. Similarly, mouse skin explants subjected to uniaxial stretch induce polarization of Celsr1, according to the direction of tissue deformation[61]. Together, these studies suggest that PCP relies on mechanical forces. This hypothesis is further supported by the observation that Myosin II and Rho-associated kinase (Rock) — two proteins that activate contractility of the actomyosin network and were initially considered to be PCP effectors[20] — also function as key regulators of Van Gogh-like 2 localization during neural tube closure in *Xenopus*[25] and PCP during *Drosophila* germband extension[62,63]. Whether the mechanical forces that regulate PCP originate within or outside the polarizing cells is unknown and warrants further investigation.

Germband extension
A morphogenetic process similar to vertebrate convergent extension, in which the segmented trunk of an insect embryo (germband) elongates along the anteroposterior axis and narrows along the dorsoventral axis.

Local PCP amplification

Regardless of the global PCP cues, PCP is amplified at the cellular level by feedback interactions among core PCP proteins in the cytoplasm and at the cell surface. At the initial stages of PCP development, core PCP complexes are located within clusters in cells that lack visible tissue polarity. These clusters are stabilized by molecular interactions within each protein complex, so that Prickle associates with Van Gogh[7,64] and Dishevelled is recruited by Frizzled[65]. A process then occurs wherein the cytoplasmic constituents of opposing PCP complexes antagonize each other within the same cell[66], whereas transmembrane PCP components positively reinforce the presence of complementary PCP components across the junction of two neighbouring cells[10,67,68]. These signalling interactions, which are both positive and negative, often rely on post-translational modifications of core PCP proteins, of which phosphorylation is the most common. For example, Van Gogh and Dishevelled are phosphorylated in response to Wnt signals, and these modifications seem to be essential for establishing PCP in the mouse limb and frog neural plate[25,32] and are conserved in *Drosophila*[69,70]. Together, these mechanisms lead to the *asymmetric distribution* of core PCP proteins — a hallmark of active PCP signalling.

The enrichment of PCP complexes in the apical cell compartment by apicobasal polarity proteins may be essential for PCP signalling[25,71]. For example, the apical protein Par3 is planar polarized in the *Xenopus* neural plate and recruits Prickle 3 to the apical surface to promote anterior PCP complex formation[72]. Interference with Par3 activity or with the binding between Par3 and Prickle 3 disturbs PCP in the neural plate. Notably, mutations of the basolateral determinant Scribble cause neural tube defects (NTDs) that are prototypical of core PCP mutants[73,74]. Although many physical and functional interactions between apicobasal and PCP proteins have been reported[75–77], the extent of crosstalk between different polarity modules remains to be fully determined.

The Frizzled–Dishevelled and Van Gogh–Prickle complexes are not usually present in the same location within a cell, suggesting that they are mutually antagonistic[8,66,67]. In *Drosophila* wing, the Van Gogh–Prickle complex is located proximally, whereas the Frizzle–Dishevelled complex accumulates distally (FIG. 1c). This localization process often involves proteasome-mediated degradation of one core PCP component, triggered by its interaction with a protein from the opposing PCP complex[78–80]. Specifically, the Cullin1 and Smurf1 E3 ubiquitin ligases regulate Prickle turnover in flies and mice, respectively, in a manner dependent on Frizzled and Dishevelled[78,79]. Alternatively, intracellular partitioning can be achieved by vesicular trafficking of PCP components[23,81–84]. Directional microtubule-dependent vesicular trafficking of Frizzled and Dishevelled to one side of the cell has been reported in *Drosophila*[85]. Moreover, Flamingo is internalized more rapidly in cells with mutant rather than wild-type *fz* or *vang*[80], indicating that Frizzled–Flamingo and Van Gogh–Flamingo complexes are selectively stabilized at the relevant junctions and resistant to endocytosis.

The importance of vesicular trafficking is highlighted by the requirement of basic components of the endocytic machinery — such as Rabs, Arfs and the clathrin adaptor AP-1 — for PCP[23,81,86].

The mutations of PCP components in *Drosophila* cell clones often affect the polarity of adjacent wild-type tissue — a phenomenon termed 'domineering nonautonomy'[87,88]. This process is thought to reflect the formation of molecular bridges between the interacting cells owing to positive feedback. For example, the extracellular domain of Frizzled on the distal side of one cell interacts with the extracellular loops of Van Gogh (probably in association with Flamingo) on the proximal side of the neighbouring cell, thereby coordinating polarity of individual cells in a tissue plane[10,67] (FIG. 1c). The asymmetric bridges may amplify PCP signalling by increasing the anisotropic adhesion of neighbouring cells through the activities of the cadherin proteins Flamingo, Fat and Dachsous.

PCP signalling targets and mechanisms

In a complex morphogenetic process, the establishment of asymmetric PCP protein localization serves to coordinate various cell behaviours. Below we describe specific cellular targets of PCP signalling that mediate this coordination.

Intracellular targets of PCP

Actomyosin complexes are key cellular targets of the PCP pathway and are crucial for cell contractility, directional membrane fusion and trafficking events that underlie the regulation of cell shape and motility. In *Drosophila* embryos, Myosin II activity is critical for establishing the polarity of actin hairs in the wing as well as PCP during germband extension. In vertebrate embryos, actomyosin dynamics mediate most if not all the effects of PCP signalling on morphogenetic behaviours, including mediolateral and radial cell intercalations, apical constriction and oriented cell divisions. The core proteins may control the localization of RhoA and ROCK — PCP effectors that are involved in actomyosin contractility, trichome generation in *Drosophila* and gastrulation in vertebrates (FIG. 1d). Moreover, several PCP effectors have been directly linked to actomyosin dynamics. Multiple wing hairs is a PCP effector and a formin-like protein that negatively controls actin polymerization during hair formation in the wing and legs of *Drosophila*[89,90]. Inturned possibly affects actin polymerization by associating with another formin protein, Daam1 (REF.[91]). The WD40 domain protein Fritz/Wdpcp[18] regulates the localization of the GTP-binding protein septin and F-actin[92,93]. Depletion of different PCP proteins in vertebrate tissues leads to reduced amounts of F-actin and decreased phosphorylation of regulatory myosin light chain (MLC)[94]. For example, a reduction in phospho-MLC has been observed in *Ptk7*-knockout mouse embryos[95,96]. Beyond actomyosin, non-centrosomal microtubules frequently align in a polarized manner in epithelial tissues and can mediate directional trafficking of PCP components[85,97]. In frog ectoderm, this alignment has been associated with core PCP signalling[60]. In the fly, the directionality of apical microtubule arrays is instructed by Prickle isoforms[98,99]. Inactivation of *ft* and *ds* in *Drosophila* also leads to a loss of microtubule alignment and subsequent developmental phenotypes[12,97].

Vesicular trafficking is another major intracellular target of PCP signalling[22,23,84,86]. Both core PCP proteins and their putative effectors have been reported to influence Rab-dependent trafficking processes[22,23,84,100]. Fuzzy contains a LONGIN domain — a common feature of SNARE proteins — that has been implicated in membrane fusion events[101,102]. Consistent with the role for Fuzzy in PCP signalling, mouse embryos that lack Fuzzy function develop NTDs[103].

PCP signalling is also involved in the remodelling of cell junctions, which can affect cell movements within a tissue. In this context, PCP proteins have been physically linked to proteins such as the Par proteins, Lethal giant larvae and Scribble, which are involved in the regulation of apical and basolateral polarity as well as the formation and maintenance of junctional complexes[72,73,76]. The rearrangement of cell junctions through these interactions promotes cell intercalations leading to morphological tissue changes. Furthermore, PCP signalling probably affects cell adhesion through binding of Van Gogh and Frizzled to the atypical cadherin Flamingo. The association of Van Gogh and Frizzled with classical cadherins has also been described[22,104]. The interaction of the atypical cadherins Fat and Dachsous with each other may also modulate adhesion strength between polarized cells in the plane of the tissue.

Regulation of coordinated cell behaviours

Although PCP proteins can control the shape and motility of individual cells (for example, cell elongation and oriented cell divisions[31,105] (FIG. 2a)), the primary function of PCP signalling is to regulate collective cell behaviours. Importantly, all of these events involve Myosin II regulation. One process controlled by the PCP pathway is convergent extension[106,107]. This process involves the elongation of neighbouring cells in the direction perpendicular to the axis of extension through the formation of mediolaterally directed actin-based protrusions and is followed by cell intercalation, resulting in a longer and narrower tissue array (FIG. 2b). These mediolateral intercalations are blocked in embryos that are deficient in PCP signalling[38,39,108], leading to abnormal cell protrusive activity and junction remodelling. However, better understanding of the mechanisms underlying convergent extension is hampered by the observation that overexpression and deletion of PCP components often produce morphologically similar phenotypes (reviewed elsewhere[37]). Moreover, since cell movements that result from convergent extension might also be disrupted by defects in cell adhesion or growth factor signalling that are unrelated to PCP, the interpretation of these phenotypes can be ambiguous. Of note, in contrast to mediolateral intercalations, radial intercalations — such as those involved in lumen formation during tubulogenesis in multilayered epithelia (for example, of the midgut or mammary gland)[109,110] or in early epiboly of *Xenopus* embryos — are oriented along the apicobasal axis and require functional PCP components[111].

Non-centrosomal microtubules
Microtubular arrays that do not originate from the centrosome. In many polarized epithelia non-centrosomal microtubules are aligned along the apical–basal axis with their minus ends oriented towards the apical surface.

SNARE proteins
A diverse group of proteins that enable docking and fusion of cargo vesicles with the target membrane such as plasma or ciliary membrane.

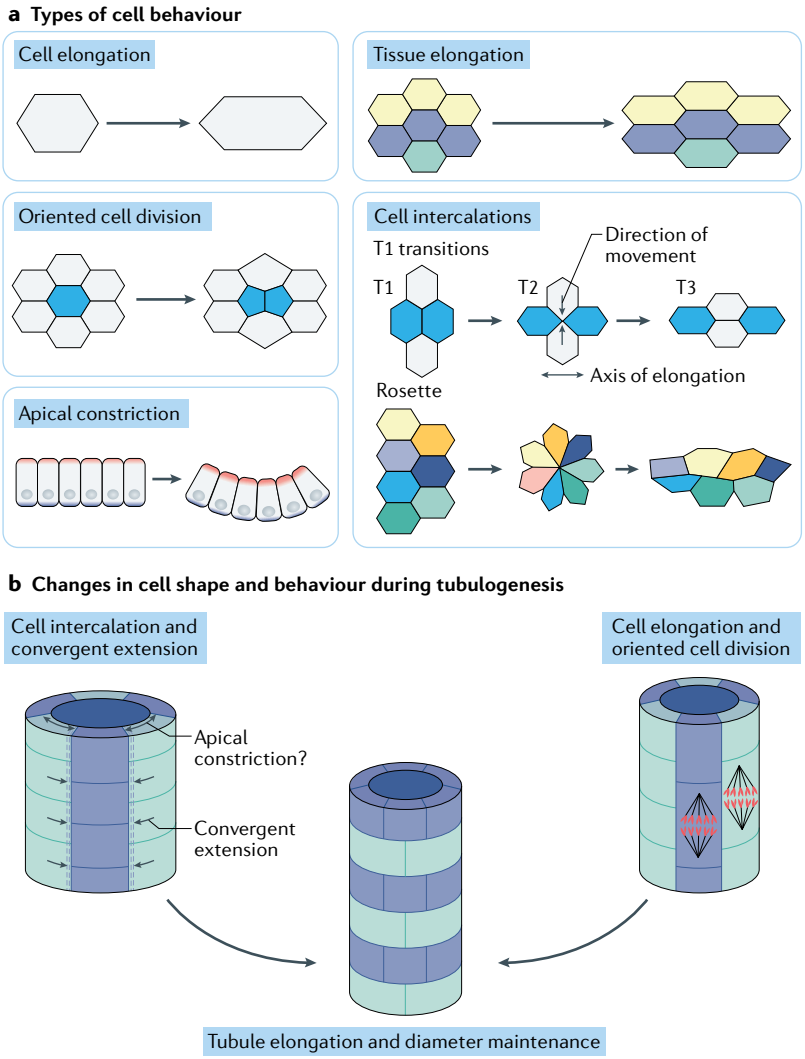

Fig. 2 | **Cell behaviours during morphogenesis. a** | A number of individual and collective cell behaviours can affect tissue architecture during morphogenesis. Cell and tissue elongation promote organ extension whereas oriented cell divisions orchestrate branching events. Cell intercalations typically involve four neighbouring cells (T1–T3 transitions) or the formation of more complex rosette intermediates consisting of five or more cells. In the case of T1–T3 transitions, the transition from T1 to T2 results in shrinkage of one cell junction and the formation of a new cell–cell contact in the vertex of the four cells, whereas the T2 to T3 transition leads to the extension of a new cell–cell junction. By contrast, rosettes involve the participation of more cells in the process of junction shrinking and extension. Apical constriction affects the curvature of the folding tissue and can promote exchanges of neighbouring cells. **b** | Examples of cell behaviour relevant to the formation of kidney tubules. Both cell elongation and oriented cell divisions can stimulate tubule lengthening. Cell intercalations that accompany convergent extension rely on the elongation and polarization of cells in the mediolateral direction perpendicular to the tubular axis. Both cell intercalation and, possibly, apical constriction reduce tubule diameter and lead to tubule elongation. Oriented cell divisions enable the incorporation of a daughter cell along the tubular axis, also facilitating tubule lengthening.

PCP signalling also seems to be involved in at least some instances of apical constriction (FIG. 2a) — a process that involves shortening of apical cell junctions[94,112] and is a major cell behaviour that is responsible for the formation of neural folds in vertebrates (reviewed elsewhere[113]). Actomyosin contractility has key roles in both apical constriction and convergent extension; however, it is currently unknown why activation of Myosin II causes some cells to converge and extend but leads to apical constriction of other cells. One suggestion is that differential phosphorylation of MLC may regulate the extent of actomyosin rearrangement at different locations, such as in apical versus basolateral cell junctions, as has been observed in an ascidian embryo[114]. Although PCP signalling takes place both apically and basolaterally, its spatially restricted mechanisms remain to be further clarified[107,115,116].

Oriented cell divisions align the mitotic spindles in dividing cells with the axis of tissue elongation (FIG. 2b). Oriented cell divisions have been linked to PCP signalling in both *Drosophila* and vertebrates[117–120]. In zebrafish embryos, PCP signalling-dependent oriented cell divisions rather than convergent extension has been suggested to be a primary cause of body axis elongation[119,120]. In support of this view, mutations in PCP components affect oriented cell divisions in many model systems[118,121,122]. Although oriented cell division phenotypes are frequently interpreted as a sign of deficient PCP signalling, dysfunction of apicobasal polarity components (reviewed elsewhere[109,123]) or IFT proteins[124] can also lead to randomized oriented cell divisions.

PCP components and cilia

Cilia are specialized organelles located at the apical surface of most cells where they generate directional fluid movements (in the case of motile cilia) or detect environmental cues that coordinate cellular behaviours during tissue morphogenesis or homeostasis (in the case of primary cilia)[125]. The PCP effectors Fuzzy, Inturned and Fritz are critical for the formation of both motile cilia in *Xenopus* epidermis[101,126] and primary cilia in frog and mouse tissues[93,102,127]. Loss of these PCP effectors results in shortened, sparse cilia and disturbance of Sonic hedgehog (Shh)[101,128] or Wnt signalling[129]. PCP effectors have been suggested to promote intraflagellar transport, possibly by regulating the localization of septin[92,93] needed to support the formation of the ciliary transition zone[130]. A 2019 study discovered that Fuzzy and Inturned function as heteromeric guanine nucleotide exchange factors for Rab23 (REF.[131]) — a Rab GTPase that is involved in ciliary trafficking — directly linking these PCP effectors to membrane trafficking and ciliogenesis.

The involvement of core PCP proteins in cilia biology is more complex. Some PCP proteins, such as Van Gogh homologues, do not seem to contribute to the formation of primary cilia, but their loss affects the function of motile cilia in the mouse node[40], the gastrocoel roof plate in *Xenopus*[43] and in the Kupffer vesicle in zebrafish[42]. In these tissues, the sole motile cilium on each cell is posteriorly tilted, enabling a leftward directional movement of extra-embryonic fluid that serves to establish left–right asymmetry in embryos[41]. Lack of functional *Vangl1* and *Vangl2* genes results in disorganized ciliary beating and randomized left–right asymmetry[40]. Mutations in *Celsr1*, *Vangl2* or *Fzd3* disrupt both the radial (location within the cell) and planar (uniform tilting) polarization of motile multicilia on mouse ependymal cells, associated with disorganization of actin and the microtubule cytoskeleton[132]. Some studies have linked PCP proteins

Neural folds
Elevated structures in the flanking areas of the neural plate that bend towards each other and fuse to form the neural tube.

Mouse node
Cell population at the distal tip (anterior primitive streak) of the gastrulating mouse embryo that secretes signalling factors regulating cell movements and the body axes.

Gastrocoel roof plate
A transient patch of ciliated endodermal cells in frog embryos that controls left–right patterning.

Kupffer vesicle
A transient ciliated organ at the posterior end of the zebrafish embryo that is required for left–right patterning, similar to the frog gastrocoel roof plate and mouse posterior node.

Centrosome
A microtubule-based organelle that consists of two centrioles and functions to regulate cell divisions and ciliary growth.

to the centrosome and/or the basal body, which serves as a template for growing cilia[133]. Interestingly, mutations in *Celsr2* or *Celsr3* affect the assembly of ependymal cilia through the loss of centrosomal and basal body structures, causing lethal hydrocephalus in mice[134]. Vertebrate homologues of Dgo — Inversin and Diversin — as well as Dishevelled 2 and Prickle 3 are all detected in the basal body of *Xenopus* or mammalian cells[135–137], where they may be required for the maintenance of normal centrosome and/or basal body structure and cilia formation[44,45,138–140]. To what extent these proteins are involved in core PCP signalling and whether their centrosomal and ciliary functions are relevant for PCP is unclear. As discussed below, mutation of these proteins can induce kidney anomalies that, in some cases, might be attributed to ciliary dysfunction (BOX 2).

PCP signalling and kidney development

As described above, PCP signalling controls various intracellular processes and collective cell behaviours that are necessary for normal morphogenesis and the maintenance of various tissues. Below, we detail the role of PCP signalling in kidney development and how mutations in genes encoding various PCP constituents can lead to diverse kidney defects in mice and humans.

Overview of mammalian kidney development

The development of the mammalian 'metanephric' kidney starts at embryonic (E) day 9.5 in mice and at the fifth week of gestation in humans, when a portion of the intermediate mesoderm on each side of the spinal cord undergoes mesenchymal-to-epithelial transition to form an epithelial tube, known as the nephric duct (also known as the Wolffian duct), which is paralleled by a column of nephric cord[141]. As development proceeds, the nephric duct induces progenitor cells within the nephric cord to convert into tubules and glomerulus-like structures sequentially forming the pronephros and then, more caudally, the mesonephros. Although the pronephros and the mesonephros are transient structures in mammals, the genetic programmes that govern their development are similar to the events that underlie development of the metanephric kidney — the final functional kidney in higher vertebrates, including mammals. Because of its simplicity, the *Xenopus* pronephros, which contains only a single nephron, has been an informative model of processes involved in formation of the metanephric kidney[142]. The mammalian kidney is induced when caudal extension of the nephric duct reaches the hindlimb level (FIG. 3). There, signals from the nephric cord-derived metanephric mesenchyme stimulate lateral outgrowth of the ureteric bud (UB) from the nephric duct[143,144]; the descending nephric duct subsequently gives rise to the reproductive system in males or degenerates in females[145]. As the UB contacts the metanephric mesenchyme, it branches repeatedly to form a tree-like collecting system; a distal part of the collecting tree coalesces to form the renal pelvis and ureter. In a reciprocal fashion, Wnt molecules secreted from each tip of the UB induce nearby cells in the metanephric mesenchyme to condense into a cap mesenchyme[141], which contains nephron progenitor cells (NPCs). In response to the inductive UB signals, the NPCs undergo mesenchyme-to-epithelial transition and are transformed into a polarized epithelium that lines an early renal vesicle with a central lumen. The renal vesicle twists and elongates to form a comma and then an S-shaped body, as specialized segments of the nephron emerge. Interaction of the S-shaped body with blood vessels at its proximal end leads to formation of a glomerulus. At its distal end, the S-shaped body fuses with its parent UB tip to form a continuous lumen that leads to a common collecting duct. The glomerular filtrate begins to flow at about E15 in mice when the ureter connects with the bladder. Fluid flow may provide mechanical cues that further orient tubular epithelial cells[146].

Metanephric mesenchyme not immediately adjacent to the UB tip forms renal stroma that supports specification of the NPCs, the development of nephrons and renal vasculature[147,148]. Cycles of UB branching, local nephrogenesis and vascular recruitment are reiterated until ~38 weeks of gestation in humans, generating a total of about one million nephrons per kidney[149]. In small rodents, such as mice and rats, nephrogenesis continues until postnatal (P) day P7–P10 generating ~10,000–40,000 nephrons per kidney[150]. Although no new nephrons are formed thereafter, postnatal proliferation of tubule cells drives tubule elongation and establishes the final anatomy and function of the renal cortex and medulla.

Development of the mammalian kidney is controlled by a hierarchical gene regulatory network that governs precise spatial and temporal changes in cell fate, shape, polarity, proliferation, adhesion, directional cell movements and the expression of specific genes[141,151]. Mutations in the key developmental genes that regulate

Box 2 | **PCP and the kidney**

The human kidney has a highly complex architecture: each comprises about one million nephrons and is populated by more than 20 cell types. Each nephron forms an ultrafiltrate of plasma that flows through a series of specialized tubule segments that absorb or secrete small molecules and electrolytes to regulate electrolyte and fluid homeostasis. The kidneys also produce growth factors and hormones that regulate various physiological processes. Extensive changes in the polarity, shape, adhesion and division of cells during embryonic development enable collective cell behaviours that arrange and shape tubular segments. Pathways that regulate apical–basal and planar cell polarity in combination with cues from mechanical forces establish the cell arrangements and tissue coordinates that orchestrate morphogenesis.

Mutations in PCP genes have been associated with congenital anomalies of the kidney and urinary tract (CAKUT), including small, unilateral or horseshoe-shaped kidneys and polycystic kidney disease[155,181,227]. Collectively, CAKUT represent a common group of human congenital defects, but only one third of the causative genes have been identified. Pathogenic mutations in several PCP genes have also been well-documented in patients with neural tube defects (NTDs) (reviewed elsewhere[220]). Notably, NTDs are frequently associated with CAKUT, such as small or horseshoe kidneys[155]. Consistent with a causative role of mutant PCP genes in CAKUT and NTDs, mice with mutations in the PCP genes *Vangl2*, *Ptk7* or *Celsr1* exhibit neural tube and kidney abnormalities[35,155,158,188].

For many years, defective PCP signalling was thought to initiate cystogenesis in the developing kidney, a key feature of polycystic kidney disease (PKD)[205,239]. However, a body of experimental data indicates that loss of core PCP genes leads to transient embryonic increases in nephric tubule diameter but does not result in postnatal kidney cysts[171,204]. These observations largely refute the popular view that PCP defects are key to the pathogenesis of PKD in humans.

these events lead to a wide spectrum of anomalies including complete renal agenesis, hypoplastic or dysplastic kidneys and enlarged cystic kidneys (reviewed elsewhere[152,153]). These diverse anomalies — collectively referred to as CAKUT — occur in 1 in 500 children worldwide[153]. The complexity of the processes underlying kidney development makes it challenging to understand the molecular and cellular mechanisms that cause such diverse CAKUT phenotypes; however, available evidence suggests a role for dysregulated PCP signalling in at least some instances.

PCP components in the kidney

Many vertebrate homologues of *Drosophila* PCP genes are expressed in the developing mouse kidney. Core PCP components Van Gogh-like 1 and Van Gogh-like 2, Prickle1, Celsr1 as well as Protein tyrosine kinase 7 (Ptk7) are all present in emerging nephrons and in UB-derived structures[154,155], as supported by expression data in the Genitourinary Development Molecular Anatomy Project (GUDMAP) database. *Fat1* (a close homologue of *Drosophila Ft2*, which regulates PCP during oogenesis[156]) is detected in the mouse UB[157] and, together with Van Gogh-like 2, is highly expressed in developing podocytes; *Fat1* persists in differentiated podocytes[158,159]. *Fat4* (the closest homologue of *Drosophila* gene *ft*) is found in the stroma surrounding the cap mesenchyme whereas its ligand *Dchs1* is expressed in progenitor cells at the outer edge of the cap mesenchyme[160,161].

Several *Wnt* and *Fzd* genes are also expressed during mammalian kidney development, but defining the most important ligand–receptor pairs has proven difficult. In various cellular contexts, Wnt and Frizzled family members function in distinct canonical Wnt–β-catenin or PCP pathways, depending on the involvement of specific co-receptors[162,163]. The Wnt–β-catenin pathway has critical roles in kidney development and disease (BOX 1), as reviewed elsewhere[163,164]. Among the Wnt ligands that may signal through the PCP pathway, Wnt5a acts via its co-receptors Ror1 and Ror2 (REF.[165]) and is expressed in a caudally increasing gradient in the intermediate mesenchyme[166,167]. Wnt11 is restricted exclusively to the

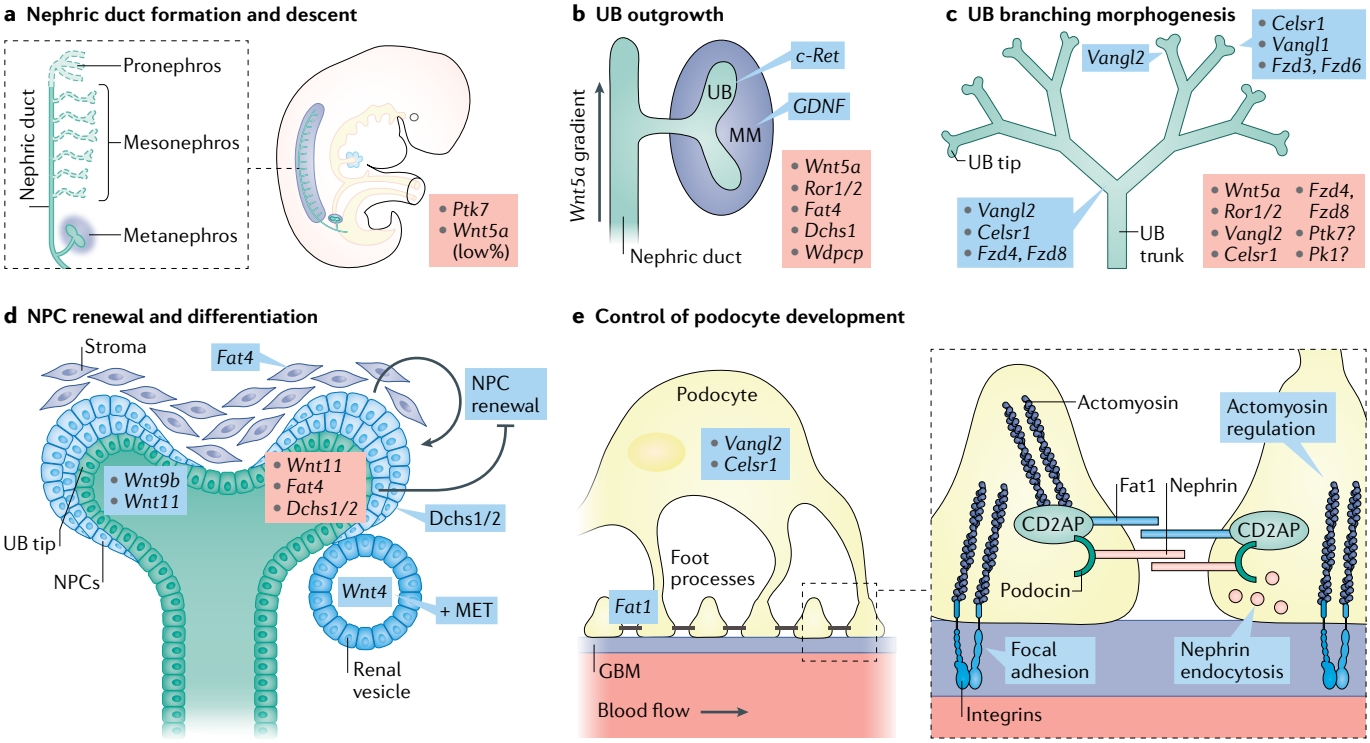

Fig. 3 | **PCP signalling in kidney development. a** | Formation of the nephric duct (also known as the Wolffian duct) is affected by mutations in certain PCP genes, including *Ptk7* and *Wnt5a*. **b** | Outgrowth of the ureteric bud (UB) from the nephric duct is largely controlled by c-Ret (expressed in the nephric duct at the time of UB formation) and its ligand GDNF (expressed in cells of the metanephric mesenchyme (MM)). Loss of, or mutations in, several PCP genes including *Wnt5a*, *Ror1* and *Ror2*, *Fat4*, *Dchs1* and *Wdpcp* (listed in the pink box) lead to abnormal UB outgrowth in both humans and mice, resulting in renal agenesis or kidney duplication. **c** | UB branching morphogenesis depends on timely and spatially coordinated changes in cell shape and movements. Expression of the PCP genes *Vangl1*, *Vangl2*, *Celsr1*, *Fzd3*, *Fzd4*, *Fzd6* and *Fzd8* has been detected in the UB tip and trunk (listed in the blue boxes). Mutations in PCP genes, including *Wnt5a*, *Ror1* and *Ror2*, *Vangl2*, *Celsr1*, *Fzd4* and *Fzd8*, and perhaps *Ptk7* and *Pk1*, affect UB branching, branch shape and branching angles (pink box). **d** | Nephron progenitor cell (NPC) renewal and differentiation depend on the crosstalk between stroma and UB tip. Wnt9b secreted from the cells of the UB tip induces both NPC fate in the cells adjacent to the UB tip and Wnt4 expression in the pre-tubular aggregates; Wnt4 drives mesenchyme-to-epithelial transition in the early nephrogenic structures. Loss of *Wnt11* gene affects NPC attachment to the UB tip cells causing premature depletion of NPCs. Loss of *Fat4* in the stroma or *Dchs1 or Dchs2* in NPCs leads to NPC expansion; however, the specific role(s) of these genes in NPC specification and behaviour are unclear. **e** | Formation of the glomerular filtration barrier requires interdigitation of podocyte foot processes along the glomerular capillary. Loss of the core PCP genes *Vangl2* and *Celrs1* affects podocyte differentiation and glomerular maturation; Vangl2 controls nephrin internalization. Mutations in *Fat1* cause widespread disruption of slit diaphragm complexes and diffuse foot process effacement in mice and humans. GBM, glomerular basement membrane.

Paralogs
Homologous genes that originate in the same species as a result of gene duplication.

Multicellular rosette
A group of five or more cells exhibiting coordinated behaviours, including the formation of a transient single contact (vertex), that result in tissue convergence and extension.

UB tip[168]. In contrast, Wnt9b is expressed in both the UB tip and the UB trunk, whereas Wnt7b is found only in the UB trunk[169,170]. Frizzled 3, 4, 6 and 8 are detected in the UB-derived collecting duct[171,172]. Thus, the distribution of specific Wnt and Frizzled family members suggests that both short-range and long-range signals may orchestrate PCP in the developing nephron.

The expression of numerous PCP gene paralogs in the kidney further complicates interpretation of their specific roles in nephrogenesis. The asymmetric distribution of PCP proteins in renal tubule cells indicates that the PCP pathway must be operative[171]: Frizzled 3 and Frizzled 6 are localized at the distal side of epithelial cells whereas Van Gogh-like 1 is sequestered at the proximal side of E18.5–P1 mouse renal tubules (FIG. 4). This pattern of expression suggests that PCP signalling is active during embryonic and early postnatal kidney development.

PCP components and the initiation of kidney development. Careful analysis of the elongating nephric duct in amphibians, fish and mice has revealed cell behaviour consistent with convergent extension, implying planar polarization of the nephric duct cells[173,174]. Use of membrane-bound GFP to trace cell behaviour in the proximal part of the pronephric duct in *Xenopus* tadpoles revealed that duct convergence and extension is driven through a multicellular rosette-based mechanism[175]. In this process, rosettes are formed by four to eight tubule epithelial cells, in which the long apical cell surfaces forming the wider rosette axis are oriented perpendicular to the tubule plane. This step is followed by shrinking of the rosette's wide axis. Subsequent stretching of apical surfaces of rosette cells occurs at the 90° angle, turning the rosette along its tubular structure, and thereby elongating the tubule longitudinally while narrowing its diameter. The coordinated constriction and stretching of apical cell surfaces lead to elongation of the kidney tubules (FIG. 2). Importantly, expression of a mutant form of Dishevelled (Xdd1) that can inhibit PCP signalling[38] disrupted directional rosette resolution and resulted in the formation of wider and shorter proximal pronephros[175].

Another study implicated the mouse PCP gene *Ptk7* in elongation of the nephric duct after UB outgrowth, as the duct becomes a part of the male reproductive system[176]. Loss of *Ptk7* affected convergent extension in rapidly proliferating Wolffian duct cells, leading to the formation of a short, less coiled duct that affected sperm motility. Of note, *Ptk7*-knockout mice form kidneys, indicating that the nephric duct does appropriately descend and that UB outgrowth has occurred[35], although these kidneys are hypoplastic.

Wnt9b located at the tip of the UB induces metanephric mesenchymal cells to become nephrogenic progenitors[177]. Triggered by Wnt9b, progenitors form pre-tubular aggregates and start expressing Wnt4 that controls mesenchyme-to-epithelial transition necessary for subsequent nephron development[178,179]. Loss of Wnt4 prevents differentiation of renal epithelia and precludes nephron formation[178]. Interestingly, Wnt4 controls mesenchyme-to-epithelial transition in a β-catenin-independent manner[180], yet its association with PCP signalling has not been directly investigated.

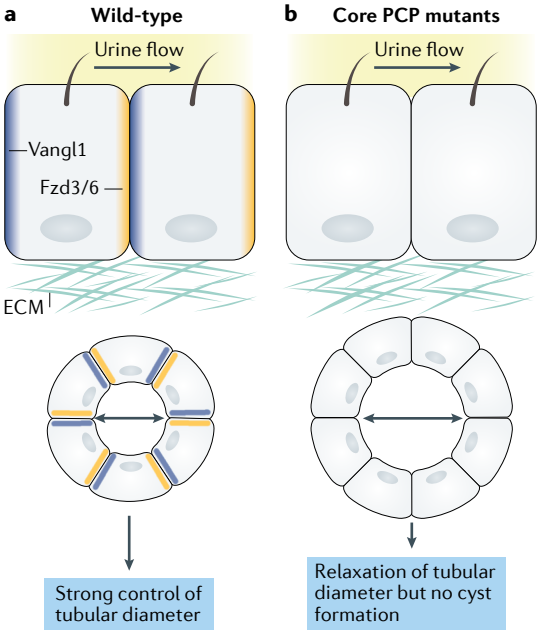

Fig. 4 | **The relationship between PCP and cystogenesis.** **a** | Tubule formation requires changes in cell shape, dynamic remodelling of the extracellular matrix (ECM)–cell attachments, directional cell movements and oriented cell divisions to enable tubule elongation and narrowing. Core planar cell polarity (PCP) proteins Van Gogh-like 1 (Vangl1) and Frizzled 3 (Fzd3) or Fzd 6 are asymmetrically distributed to either the proximal or the distal side of wild-type developing tubule — a sign of active PCP signalling. **b** | Various mechanisms have been suggested to contribute to cyst formation in kidney tubules, including the loss of cilia and/or ciliary function, increased proliferation of tubule epithelial cells, dysregulated ECM–cell signalling or abnormalities in apical–basal polarity (not shown). Lack of PCP protein function has also been suggested to contribute to cystogenesis; however, despite a body of experimental data showing that core PCP proteins are polarized along the tubular axis in the developing kidneys, and that PCP signalling tightly controls the tubular diameter via convergent extension and oriented cell division, available evidence suggests that loss of core PCP genes, such as *Vangl2* and *Fzd3* or *Fzd6*, does not lead to cyst formation.

Mice with deletion of *Wnt5a* can exhibit a range of kidney phenotypes, including duplex kidneys (common), hypoplasia hydronephrosis, or unilateral or bilateral renal agenesis (rare)[166,167,181]. Loss of the Wnt5a co-receptor Ror2 in collecting ducts leads to duplex kidneys in ~50% of homozygous embryos, whereas >85% of mice with $Ror2^{+/-}$;$Wnt5a^{+/-}$ double heterozygous mutations exhibit duplex kidneys, or unilateral or bilateral kidney agenesis, suggesting interaction between Wnt5a and Ror2 in kidney development. *Ror1* also interacts genetically with *Wnt5a*, with double heterozygous mutants exhibiting ureter duplication and ectopic kidney formation[182]. The kidney phenotypes observed in mice with *Wnt5a* and *Ror1* or *Ror2* mutations are consistent with defective UB outgrowth, indicating aberrant GDNF–c-Ret signalling[183,184]. GDNF, derived from the metanephric mesenchyme, normally acts to restrict expression of its receptor, c-Ret, in the nephric

duct to the site of future UB outgrowth[144]. Ureter duplication in mice with *Wnt5a* and *Ror1* or *Ror2* mutations is linked to elevated ectopic expression of GDNF, which, in turn, expands c-Ret expression domain and leads to additional UB outgrowth[167,185]. Duplex kidneys have also been reported in up to ~40% of *Fat4*$^{-/-}$ embryos and in ~70% of double homozygous *Fat4*$^{-/-}$;*Fjx1*$^{-/-}$ embryos (*Fjx1* is a vertebrate homologue of the *Drosophila fj* gene)[186]. Detailed studies have revealed that the duplex kidney defect in *Fat4*$^{-/-}$ kidneys is also caused by excessive GDNF–c-Ret signalling and is rescued by genetic removal of one *Gdnf* allele[186]. Unexpectedly, the extracellular domains of Fat4 and c-Ret have been found to physically interact, providing an additional level of Fat4–c-Ret regulation[186]. Mice with mutations in the PCP effector gene *Wdpcp* also have ectopic kidneys[93]; however, the mechanisms underlying this phenotype have not been elucidated. Together, the available data suggest that PCP molecules may control the location or activity of growth factors that drive early kidney development and that loss of PCP components may induce defects in nephric duct patterning and UB outgrowth. Whether these PCP components participate in PCP signalling as a single molecular pathway or act independently during kidney development remains to be addressed.

PCP components and branching morphogenesis. UB branching is central to kidney development and requires coordinated changes in cell behaviour (reviewed elsewhere[144]). Governed primarily by the GDNF–c-Ret and FGF signalling pathways, cells at the tip of each branch of the UB rapidly proliferate to form a UB ampoule[144,187]. Dichotomous branching of the ampoule requires remodelling of the cytoskeleton, cell–cell junctions and cell– ECM adhesion processes, culminating in profound cell shape changes. Several mouse PCP mutants exhibit defective branching morphogenesis, confirming that PCP signalling is required for cell behaviours implicated in UB bifurcation[155,188]. Hypodysplastic kidneys with fewer UB branches were found at E13.5 in homozygous *Vangl2*$^{Lp/Lp}$ '*Looptail*' and *Celsr1* '*crash*' mutants; this phenotype was more severe in double heterozygous *Vangl2*$^{Lp/+}$;*Celsr1*$^{Crsh/+}$ embryos[188], confirming that these two genes interact during kidney development as they do in the development of the neural tube and inner ear[73]. Use of optical projection tomography and 3D reconstruction has revealed that UB branching is particularly affected in the caudal aspects of E13.5 *Vangl2*$^{Lp/Lp}$, *Celsr1*$^{Crsh/Crsh}$ and *Vangl2*$^{Lp/+}$;*Celcr1*$^{Crsh/+}$ kidneys[188], although the mechanism or mechanisms underlying this predilection are unclear and may reflect shortening of the embryonic rostral–caudal axis due to deficient convergent extension in these mutants[73,189]. *Vangl2*$^{Lp/Lp}$ and *Celsr1*$^{Crsh/Crsh}$ mice also display reduced branching morphogenesis of the lung as a consequence of defective cytoskeletal remodelling[190]. Actin polymerization defects have been reported in *Vangl2*$^{Lp/Lp}$ proximal tubule cells[155], suggesting that widespread actomyosin deregulation in *Vangl2*$^{Lp/Lp}$ embryos may contribute to reduced UB branching. Importantly, Van Gogh-like 2 interacts with several PCP components, including Dishevelled[191] and Ptk7, which have been linked to the regulation of actomyosin contractility. Dishevelled activates the formin protein Daam1, which nucleates actin monomers and promotes actin polymerization[28], and downregulation of Daam1 in *Xenopus* embryos disrupts pronephric tubulogenesis[192]. *Ptk7* interacts genetically with *Vangl2*, and as mentioned earlier, mice lacking *Ptk7* develop renal hypoplasia[35]. Ptk7 activates Src–ROCK2 signalling and modulates Myosin II contractility at cell–cell junctions in inner ear cells[95,96]; however, whether renal hypoplasia in *Ptk7*$^{-/-}$ mice is caused by actomyosin dysregulation in cells of the UB is unclear.

In addition, the PCP proteins remodel junctional complexes and the ECM in flies[22,193] and zebrafish[194,195]. Similar mechanisms may underlie the hypoplastic phenotype of *Wnt5a* mouse mutants, for example, through UB branching defects associated with a disorganized basement membrane and reduced expression of laminin and type IV collagen in collecting duct cells[181]. Collectively, the available studies indicate that PCP signalling has a central role in organizing cell shape changes and coordinating cell movements involved in branching morphogenesis in the developing kidney.

PCP components and nephron progenitor cells. The pool of NPCs in the cap mesenchyme around each UB tip requires crosstalk between the UB and its surrounding stroma[196,197]. In the absence of *Wnt11* in the UB tips, NPCs lose their stable attachments to the UB tip cells, and the polarized distribution of several markers is detected[198]. These events lead to the dispersion of NPCs from their niche and premature NPC exhaustion, resulting in deficient UB branching and renal hypoplasia. Loss of *Fat4*, which is normally expressed in the stroma, results in a dramatic expansion of the NPC pool at E12.5–E13.5 (REFS[197,199]), indicating that Fat4 non-autonomously inhibits NPC renewal (FIG. 3). Similarly, loss of the Fat4 ligands, Dachsous 1 and/or and Dachsous 2, also expands the NPC pool[160,161]. The abnormal cap mesenchyme compartment in *Fat4*$^{-/-}$ or *Dchs1*$^{-/-}$ mice might affect UB branching by disturbing NPC-derived cues. Indeed, these mutants exhibit reduced UB branch number and an abnormal shape and orientation of branches[161]. However, the signalling events that contribute to NPC expansion have not yet been fully elucidated. *Vangl2*$^{Lp/Lp}$ mutant kidneys have normal numbers of NPCs and the loss of one *Vangl2* allele in the *Fat4*$^{-/-}$ kidneys does not exacerbate the *Fat4*$^{-/-}$ NPC phenotype[160]. These findings argue against involvement of the core PCP pathway in controlling NPC pool size. Fat proteins are able to activate both the PCP and Hippo pathways in various cellular contexts[14]. However, genetic deletion of a *Yap* allele (downstream effector of Hippo signalling) did not rescue the expansion of NPCs observed in *Fat4*$^{-/-}$ mice[160], indicating that Hippo signalling is not involved in this process. Canonical Wnt–β-catenin signalling also drives the proliferation of renal NPCs[200], but is unchanged in *Fat4* and *Dchs1/2* mutants[160]. Thus, the core PCP pathway does not seem to control the NPC pool directly; however, the precise events that act downstream of

Fat4–Dachsous signalling to regulate the NPC pool are yet to be identified.

PCP components, tubulogenesis and cyst formation. Lengthening of the kidney tubule predominantly occurs during embryogenesis, but in small rodents, a secondary wave of tubular elongation seems to take place in the early postnatal period. The diameter of different tubule segments is tightly regulated during tubulogenesis. Careful measurement of tubule diameters in hundreds of circular transverse cross-sections of wild-type mouse kidneys from E13.5 to postnatal day P5 demonstrated that tubules become progressively narrower until late gestation, after which the tubule diameter is fixed[169]. The process of tubular narrowing (convergence) occurs through a reduction in the number of cells surrounding each tubular lumen. This is accomplished via directional cell intercalations that also elongate the tubule axis (FIGS 2 and 4). Between E13.5 and E19.5, cell divisions in the tubule are random, and become oriented only after the tubule diameter is established around the time of birth[169]. Their findings led the researchers to propose that tubular elongation is controlled by two temporally distinct, yet mechanistically connected, processes: convergent extension that occurs during narrowing of the embryonic tubule, and oriented cell division once the tubule diameter has been established perinatally. In *Wnt9b*$^{-/-}$ mice, tubules are dilated during the embryonic phase of convergent extension and become cystic postnatally[169]. However, since Wnt9b acts through both β-catenin-dependent and β-catenin-independent pathways[169,200], the mechanisms underlying cystogenesis in *Wnt9b*$^{-/-}$ mice are at this stage unclear. In contrast to kidneys of *Wnt9b*$^{-/-}$ mice, kidneys of *Wnt7b*$^{-/-}$ mice lack normal tubular elongation in the medullary tubules — a defect that has been attributed to dysregulation of oriented cell division[170]. Notably, a similar phenotype has been found in the mice with stroma-specific deletion of β-catenin[170], suggesting a potential paracrine action of Wnt7b through activation of the Wnt–β-catenin pathway in the interstitium.

Mutations in several core PCP genes lead to tubular dilatation and occasional cysts. For example, embryonic kidneys of *Pk1*$^{-/-}$ mice exhibit dilatation of renal cortical tubules in all mutant animals; marked cystic changes occur in ~5% of the mice[201]. Similarly, tubular dilation, moderate cystic kidney disease and medullary zone hypoplasia have been found in *Ptk7*$^{-/-}$ mouse kidneys[202]. E17.5–18.5 *Vangl2*$^{Lp/Lp}$ embryos display dilated proximal tubules and collecting ducts in the cortex, and marked loss of the medullary compartment[155,188,203]. One study demonstrated that tubule diameters of E18.5 *Vangl2*$^{Lp/Lp}$, double *Fz3*$^{-/-}$;*Fz6*$^{-/-}$ and double kidney-specific *Vangl1*$^{-/-}$;*Vangl2*$^{-/-}$ mutants were not as tightly regulated as in control kidneys[171]. Another study confirmed the presence of dilated kidney tubules in E17.5 *Vangl2*$^{Lp/Lp}$ mice and *Vangl2*$^{Δ/Δ}$ mice (with targeted knockout of Vangl2 exon4) as a result of defective convergent extension[204]. Whether rearrangement of multicellular rosettes controls tubule diameter and drives elongation in mammalian renal tubules has not been studied, but abnormal apical cell constriction and reduced phosphorylation of MLC has been reported in tubule epithelial cells from *Vangl2*$^{-/-}$ mice, consistent with such a possibility[204].

A 2006 study demonstrated that tubular elongation is associated with oriented cell division along the tubular plane in wild-type postnatal mice and rats[205]. By measuring angles of mitotic spindles in neonatal mice with renal-specific inactivation of *Hnf1β* (a model of polycystic kidney disease (PKD) and type I diabetes mellitus) and *Pck* rats (another model of PKD resulting from a frameshift mutation in *Pkhd1*), researchers showed that oriented cell division occurs randomly in pre-cystic dilated tubules of these animals, prompting the suggestion that defective planar polarity underlies PKD[205] (FIG. 4). Two years later, another study showed that targeted deletion of *Fat4* leads to tubule dilation and the development of some cysts in E16.5 mouse kidneys via the induction of random oriented cell division[206]. Removal of one *Fat1* copy in *Fat4*$^{-/-}$ mice exacerbated the cystic phenotype[157], confirming that both genes contribute to this phenotype. Importantly, loss of one *Vangl2* allele on a *Fat4*$^{-/-}$ background somewhat exacerbated the severity of cystic tubular dilation[206], implying the potential involvement of these PCP components in tubule morphogenesis and patterning. However, since Fat proteins can also act via the Hippo pathway[14,207], and strong evidence that dysfunction of Hippo signalling causes severe cystogenesis in mice and humans[208,209], the mechanisms underlying the development of kidney cysts in *Fat4*$^{-/-}$ mice may be multifactorial.

The relationship between core PCP genes and cystic kidney disease was re-examined in a 2017 study in which conditional deletion of *Vangl1* and *Vangl2* predominantly in the collecting ducts (using a Kif3a–Cre construct) induced only a mild oriented cell division defect at P1 (REF.[171]). Surprisingly, at 16 weeks of age, the mice displayed only minimally irregular tubules, with a complete absence of cysts, arguing against a role for disrupted PCP signalling in cyst formation. Moreover, cells lining cysts in conditional *Kif3a*$^{-/-}$ mice (a model of defective ciliogenesis), or in ubiquitous *Pkhd*$^{-/-}$ mice displayed an asymmetric distribution of Van Gogh-like 1 and Frizzled 6 proteins, indicating that cystogenesis occurs in these models despite normal activity of core PCP components[171]. In line with these findings, a 2020 study found that mutant mice with Hoxb7–Cre-driven excision of *Vangl2* (to target gene excision to the nephric duct and collecting duct) had tubular dilatation and cysts at E17.5 and some residual tubular dilatation at P1. However, any tubule defects disappeared by P7 (REF.[204]) (FIG. 4). Overall, the findings of these studies are consistent with a role for the core PCP pathway in establishing tubular diameter via convergent extension, but do not provide conclusive insights into the contribution of PCP components to cystogenesis, with available data suggesting that molecular mechanisms in addition to PCP signalling operate around the time of birth to maintain renal tubule diameter.

The driver of the perinatal switch from convergent extension to oriented cell division and the PCP-independent mechanisms that control tubule diameter are unknown, but one possibility is that postnatal ECM

remodelling contributes to these processes as has been shown for postnatal lung and heart development[210,211]. Such remodelling might alter the tension between ECM and tubular cells, modulating both cell shape and cell movements required for convergent extension[212]. With the onset of tubular flow at E15 in mice, mechanical forces on the primary cilium may also provide positional information that modulates the ECM[213]. Although PCP signalling seems to control oriented cell division, loss of cilia (as in the *Ift88* zebrafish mutant[124]) or ciliary function (as in *Pck* rats[205]) also leads to randomization of mitotic spindle orientation in the developing neural tube and kidney tubule cells, respectively. However, loss of oriented cell division alone does not seem to be sufficient for cyst initiation. For example, dysregulation of oriented cell division in the *Pkhd1*$^{-/-}$ mouse does not cause cystic transformation whereas oriented cell division is normal in the dilated tubules prior to cyst formation in the *Pkd1*$^{-/-}$ and *Pkd2*$^{-/-}$ mice[214]. Notably, the protein encoded by *Pkd1*, polycystin 1, binds to and stabilizes the junctional apical complex Par3–aPKC to regulate cell intercalations and cell polarity in developing mouse kidney tubules[215]. Thus cilia-mediated processes may instruct both convergent extension and oriented cell divisions within the kidney tubules independently of core PCP components.

PCP components and glomerular development. Tubular fluid, an ultrafiltrate of blood, is generated by intracapillary pressure, which drives plasma through specialized sieve-like cell–cell junctions between podocytes. During nephrogenesis, podocyte precursor cells initially appear cuboidal but rapidly develop actin-based projections called foot processes that envelop the underlying capillary. Foot processes from neighbouring podocytes interdigitate along the capillary in the plane tangential to blood flow. Podocyte cell–cell junctions, initially found at the apical surface, descend towards the basal aspect of the cell to form highly specialized slit diaphragms linked to the intracellular actin cytoskeleton. Each foot process is anchored via focal adhesions to the underlying glomerular basement membrane. Critically, the highly polarized architecture of mature podocytes depends on the actin cytoskeleton (FIG. 3).

Among the many fly PCP gene homologues expressed in mammalian podocytes[216], the gene for the giant cadherin *Fat1* is detected at an early stage, as NPCs differentiate into podocyte precursors[217]. Depletion of *Fat1* in cultured podocytes reduces their adhesion and motility by decreasing the activity of the actin regulators Rac1 and Cdc42, indicating an involvement of Fat1 in actin regulation[218]. Fat1 is a component of the slit diaphragm complex. Consistent with this role, *Fat1*$^{-/-}$ mice die shortly after birth owing to a complete lack of slit diaphragms and widespread loss of foot processes[159]. In rats recovering from puromycin aminonucleoside-induced nephrosis, elevated levels of Fat1 were found in the newly formed contacts between podocytes[217], suggesting a role in recovery from injury, possibly through regulation of the actin cytoskeleton and foot process assembly.

Van Gogh-like 2 is highly expressed at the basolateral surface of mouse podocyte precursors as they generate foot processes[158]. Loss of *Vangl2* leads to mislocalization of the major structural slit diaphragm protein, nephrin, at the cell membrane owing to a defect in nephrin internalization[203]. Thus, Van Gogh-like 2 is needed for the normal dynamics of cell junction remodelling and the assembly of slit diaphragms between newly formed foot processes. In addition, depletion of *Vangl2* induces changes in podocyte morphology and reduces the number of filopodia and stress fibres, indicating that Van Gogh-like 2 also regulates the podocyte actin cytoskeleton[203,216]. Glomeruli of embryonic *Vangl2*$^{Lp/Lp}$ mice are immature, with reduced podocyte number and can show collapse of the glomerular tuft[155,158]. By contrast, adult mice with podocyte-specific deletion of *Vangl2* have fewer podocytes per glomerulus than wild-type mice, but do not show any sign of glomerular dysfunction under basal conditions[158]. However, following experimental glomerular injury, these mutant mice develop severe and irreversible glomerular damage[158], suggesting that Van Gogh-like 2 may also contribute to podocyte survival and recovery, potentially through its effects on the actin cytoskeleton and slit diaphragm remodelling.

PCP genes and human kidney disease

Mutations in PCP genes have been identified in a variety of human nephropathies (Supplementary Table 1). Children born with NTDs are at high risk of progressive kidney dysfunction, which for many years, was considered a secondary complication of the associated neurogenic bladder[219]. However, patients with NTD often have a CAKUT phenotype such as renal hypoplasia, or duplex or horseshoe kidneys[155]; these congenital malformations arise in utero, well before bladder dysfunction could alter basic kidney architecture. Mutations in PCP genes have been linked to human NTD[220]. Mouse models with mutations in the corresponding PCP genes (for example, *Vangl2* or *Celsr1* (REFS[189,221])) also demonstrate NTDs. Notably, these mice also display the spectrum of renal anomalies found in patients with NTD. A plausible hypothesis is that the kidney abnormalities seen in these patients are attributable to abnormal PCP signalling.

Several mutations in PCP genes cause Robinow syndrome — a disease that is characterized by pathognomonic facial dysmorphism and skeletal abnormalities[222–226]; hydronephrosis or renal dysplasia have been reported in some patients[227]. A *WNT5a* missense mutation was identified in a patient with a unilateral duplex collecting system without skeletal defects[181], reminiscent of the unilateral kidney duplication phenotype seen in *Wnt5a* mutant mice[167,182]. Mutations in *FAT4* or *DCHS1* cause Van Maldergem syndrome, which is characterized by intellectual disability, craniofacial defects, hearing loss, skeletal malformations and, in some cases, renal hypoplasia[228]; the kidney phenotype is consistent with the kidney anomalies seen in *Fat4*$^{-/-}$ mice[206] and *Dchs1*$^{-/-}$ mice[161]. Homozygous truncating *FAT1* mutations were identified in patients diagnosed with a novel syndrome characterized by ocular abnormalities, nephropathy (glomerular or glomerulotubular sclerosis), syndactyly and facial dysmorphism[229], whereas milder recessive

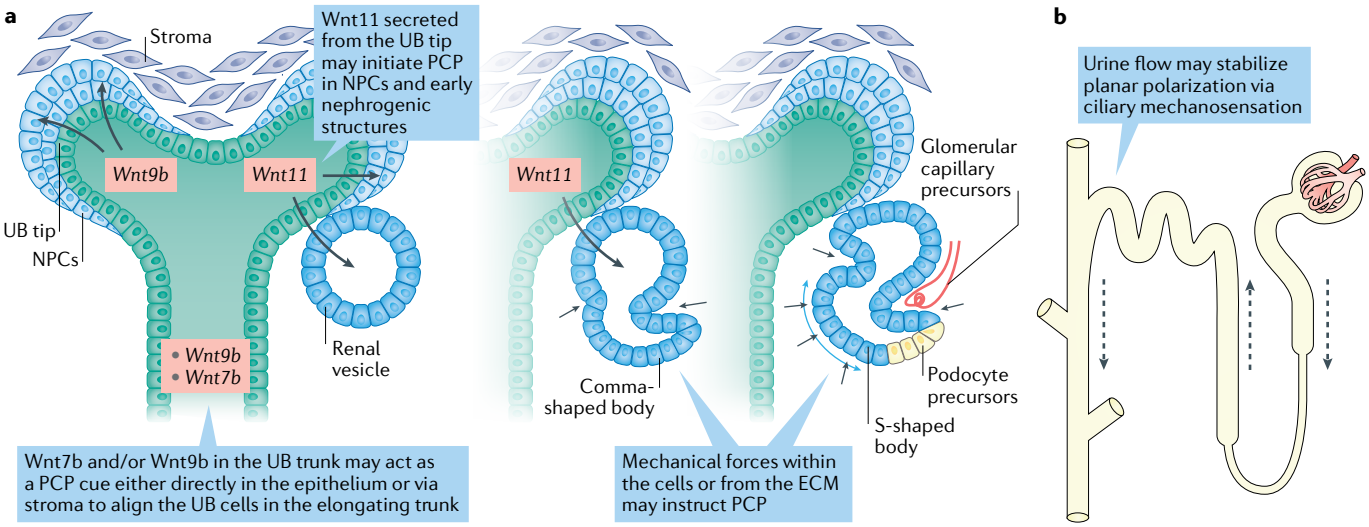

Fig. 5 | **Cues for establishing PCP during kidney development. a** | The origin of planar cell polarity (PCP) in early tubule structures and glomeruli is unknown; however, several molecules may act as cues to initiate PCP in early nephrogenic structures. For example, Wnt11 secreted from the ureteric bud (UB) tip may direct polarized nephron progenitor cell (NPC) behaviours as they epithelize and transform into pre-tubular aggregates and renal vesicles. In the UB trunk, Wnt9b or Wnt7b may act locally or non-autonomously on the stromal cells adjacent to the developing tubule to stabilize the polarity of proliferating UB cells. In addition, mechanical forces within the cells and/or from the extracellular matrix (ECM) may provide polarity cues as the comma-shaped and S-shaped bodies undergo stretching and invagination. **b** | The onset of urine formation at embryonic day 15.0 in the mouse nephron may provide further cues via ciliary mechanosensation to stabilize planar polarization along the growing tubule.

missense mutations were identified in patients with various isolated glomerulopathies. All patients showed podocyte foot process effacement[218] similar to the podocyte abnormalities and lack of slit diaphragm observed in *Fat1*$^{-/-}$ mice[159]. Mutations in the PCP effectors *INTU*, *FUZZY* and *WDPCP* have been found in various ciliopathies, including those with kidney involvement such as renal hypoplasia[126,230,231]. Again, mouse PCP effector mutants faithfully recapitulate many of the phenotypic features observed in patients[93,102,126,232]. Infantile nephronophthisis type 2, which is characterized by the presence of kidney microcysts and interstitial fibrosis, is caused by mutations in *INVERSIN* (also known as *NPHP2*)[231]. This disease is probably caused by complex mechanisms that involve abnormal ciliary functions as well as disrupted canonical and non-canonical Wnt signalling[136].

Conclusions and future directions

PCP signalling is involved in many aspects of kidney development, including outgrowth and branching morphogenesis of the UB, patterning of the glomerulus, and shaping of the proximal and distal nephron segments, as well as postnatal changes that organize and maintain kidney functions. Available evidence suggests that mutations in PCP genes cause a number of human kidney malformations in the CAKUT spectrum; genetic deletion of these same genes in mice induces similar malformations, further implicating the PCP pathway in developmental processes and recovery from injury. However, many of the fundamental properties of the PCP pathway in the kidney are still unclear. The global signals that engage this pathway during nephrogenesis are largely unknown and the mechanisms that coordinate PCP with the cytoskeleton and apicobasal polarity remain to be explored (FIG. 5). The relationships between planar cell organization and the directional flow of tubular fluid and transduction of mechanical signals by primary cilia or the ECM are interesting areas for future study. Although the pathogenesis of PKD does not seem to involve loss of core PCP pathway function, it may involve dysfunction of other PCP pathway components such as Fat or the PCP effector proteins via links to the Hippo pathway or cilia signalling and/or actomyosin dynamics. The existence of multiple PCP gene homologues expressed in the developing kidney, their potential functional redundancies and involvement in the non-PCP-related processes contributes to the difficulties of studying PCP in this organ. For example, polycystin 1 seems to regulate convergent extension and oriented cell division in the kidney tubule through mechanisms that are independent of PCP signalling[215]. Thus, the features characteristic of PCP may be disturbed through PCP-independent mechanisms in some nephropathies. To unravel the mechanisms by which PCP does contribute to kidney development and disease, an approach that combines high-resolution live imaging in model organisms with ex vivo kidney explants or organoids carrying mutant PCP genes is needed. It is clear that more work is warranted to better understand the complexities of morphogenetic processes and PCP protein interactions involved in kidney development and the pathogenesis of the human disease. This Review is just a starting point in that direction.

Published online 5 February 2021

1. Lawrence, P. A. Gradients in the insect segment: the orientation of hairs in the milkweed bug Oncopeltus fasciatus. *J. Exp. Biol.* **44**, 607–620 (1966).
2. Wong, L. L. & Adler, P. N. Tissue polarity genes of Drosophila regulate the subcellular location for prehair initiation in pupal wing cells. *J. Cell Biol.* **123**, 209–221 (1993).
3. Gubb, D. & Garcia-Bellido, A. A genetic analysis of the determination of cuticular polarity during development in Drosophila melanogaster. *J. Embryol. Exp. Morphol.* **68**, 37–57 (1982).
4. Adler, P. N. The frizzled/stan pathway and planar cell polarity in the Drosophila wing. *Curr. Top. Dev. Biol.* **101**, 1–31 (2012).
5. Vladar, E. K., Antic, D. & Axelrod, J. D. Planar cell polarity signaling: the developing cell's compass. *Cold Spring Harb. Perspect. Biol.* **1**, a002964 (2009).
6. Goodrich, L. V. & Strutt, D. Principles of planar polarity in animal development. *Development* **138**, 1877–1892 (2011).
7. Bastock, R., Strutt, H. & Strutt, D. Strabismus is asymmetrically localised and binds to Prickle and Dishevelled during Drosophila planar polarity patterning. *Development* **130**, 3007–3014 (2003).
8. Jenny, A., Reynolds-Kenneally, J., Das, G., Burnett, M. & Mlodzik, M. Diego and Prickle regulate Frizzled planar cell polarity signalling by competing for Dishevelled binding. *Nat. Cell Biol.* **7**, 691–697 (2005).
9. Usui, T. et al. Flamingo, a seven-pass transmembrane cadherin, regulates planar cell polarity under the control of Frizzled. *Cell* **98**, 585–595 (1999).
10. Chen, W. S. et al. Asymmetric homotypic interactions of the atypical cadherin flamingo mediate intercellular polarity signaling. *Cell* **133**, 1093–1105 (2008).
11. Ma, D., Yang, C. H., McNeill, H., Simon, M. A. & Axelrod, J. D. Fidelity in planar cell polarity signalling. *Nature* **421**, 543–547 (2003).
12. Harumoto, T. et al. Atypical cadherins Dachsous and Fat control dynamics of noncentrosomal microtubules in planar cell polarity. *Dev. Cell* **19**, 389–401 (2010).
13. Matakatsu, H. & Blair, S. S. Interactions between Fat and Dachsous and the regulation of planar cell polarity in the Drosophila wing. *Development* **131**, 3785–3794 (2004).
14. Fulford, A. D. & McNeill, H. Fat/Dachsous family cadherins in cell and tissue organisation. *Curr. Opin. Cell Biol.* **62**, 96–103 (2019).
15. Lawrence, P. A. & Casal, J. Planar cell polarity: two genetic systems use one mechanism to read gradients. *Development* **145**, dev168229 (2018).
16. Collier, S. & Gubb, D. Drosophila tissue polarity requires the cell-autonomous activity of the fuzzy gene, which encodes a novel transmembrane protein. *Development* **124**, 4029–4037 (1997).
17. Adler, P. N., Zhu, C. & Stone, D. Inturned localizes to the proximal side of wing cells under the instruction of upstream planar polarity proteins. *Curr. Biol.* **14**, 2046–2051 (2004).
18. Collier, S., Lee, H., Burgess, R. & Adler, P. The WD40 repeat protein fritz links cytoskeletal planar polarity to frizzled subcellular localization in the Drosophila epidermis. *Genetics* **169**, 2035–2045 (2005).
19. Lee, H. & Adler, P. N. The function of the frizzled pathway in the Drosophila wing is dependent on inturned and fuzzy. *Genetics* **160**, 1535–1547 (2002).
20. Winter, C. G. et al. Drosophila Rho-associated kinase (Drok) links Frizzled-mediated planar cell polarity signaling to the actin cytoskeleton. *Cell* **105**, 81–91 (2001).
21. Strutt, D. I., Weber, U. & Mlodzik, M. The role of RhoA in tissue polarity and Frizzled signalling. *Nature* **387**, 292–295 (1997).
22. Classen, A. K., Anderson, K. I., Marois, E. & Eaton, S. Hexagonal packing of Drosophila wing epithelial cells by the planar cell polarity pathway. *Dev. Cell* **9**, 805–817 (2005).
23. Ossipova, O. et al. Role of Rab11 in planar cell polarity and apical constriction during vertebrate neural tube closure. *Nat. Commun.* **5**, 3734 (2014).
24. Wang, Y., Yan, J., Lee, H., Lu, Q. & Adler, P. N. The proteins encoded by the Drosophila planar polarity effector genes inturned, fuzzy and fritz interact physically and can re-pattern the accumulation of "upstream" planar cell polarity proteins. *Dev. Biol.* **394**, 156–169 (2014).
25. Ossipova, O., Kim, K. & Sokol, S. Y. Planar polarization of Vangl2 in the vertebrate neural plate is controlled by Wnt and Myosin II signaling. *Biol. Open* **4**, 722–730 (2015).
26. Bhanot, P. et al. A new member of the frizzled family from Drosophila functions as a Wingless receptor. *Nature* **382**, 225–230 (1996).
27. Murdoch, J. N., Doudney, K., Paternotte, C., Copp, A. J. & Stanier, P. Severe neural tube defects in the loop-tail mouse result from mutation of Lpp1, a novel gene involved in floor plate specification. *Hum. Mol. Genet.* **10**, 2593–2601 (2001).
28. Habas, R., Kato, Y. & He, X. Wnt/Frizzled activation of Rho regulates vertebrate gastrulation and requires a novel Formin homology protein Daam1. *Cell* **107**, 843–854 (2001).
29. McGreevy, E. M., Vijayraghavan, D., Davidson, L. A. & Hildebrand, J. D. Shroom3 functions downstream of planar cell polarity to regulate myosin II distribution and cellular organization during neural tube closure. *Biol. Open* **4**, 186–196 (2015).
30. Hildebrand, J. D. & Soriano, P. Shroom, a PDZ domain-containing actin-binding protein, is required for neural tube morphogenesis in mice. *Cell* **99**, 485–497 (1999).
31. Nishita, M. et al. Filopodia formation mediated by receptor tyrosine kinase Ror2 is required for Wnt5a-induced cell migration. *J. Cell Biol.* **175**, 555–562 (2006).
32. Gao, B. et al. Wnt signaling gradients establish planar cell polarity by inducing Vangl2 phosphorylation through Ror2. *Dev. Cell* **20**, 163–176 (2011).
33. Lu, W., Yamamoto, V., Ortega, B. & Baltimore, D. Mammalian Ryk is a Wnt coreceptor required for stimulation of neurite outgrowth. *Cell* **119**, 97–108 (2004).
34. Andre, P. et al. The Wnt coreceptor Ryk regulates Wnt/planar cell polarity by modulating the degradation of the core planar cell polarity component Vangl2. *J. Biol. Chem.* **287**, 44518–44525 (2012).
35. Lu, X. et al. PTK7/CCK-4 is a novel regulator of planar cell polarity in vertebrates. *Nature* **430**, 93–98 (2004).
36. Adler, P. N. & Wallingford, J. B. From planar cell polarity to ciliogenesis and back: the curious tale of the PPE and CPLANE proteins. *Trends Cell Biol.* **27**, 379–390 (2017).
37. Gray, R. S., Roszko, I. & Solnica-Krezel, L. Planar cell polarity: coordinating morphogenetic cell behaviors with embryonic polarity. *Dev. Cell* **21**, 120–133 (2011).
38. Sokol, S. Y. Analysis of Dishevelled signalling pathways during Xenopus development. *Curr. Biol.* **6**, 1456–1467 (1996).
39. Ybot-Gonzalez, P. et al. Convergent extension, planar-cell-polarity signalling and initiation of mouse neural tube closure. *Development* **134**, 789–799 (2007).
40. Song, H. et al. Planar cell polarity breaks bilateral symmetry by controlling ciliary positioning. *Nature* **466**, 378–382 (2010).
41. Hashimoto, M. et al. Planar polarization of node cells determines the rotational axis of node cilia. *Nat. Cell Biol.* **12**, 170–176 (2010).
42. Borovina, A., Superina, S., Voskas, D. & Ciruna, B. Vangl2 directs the posterior tilting and asymmetric localization of motile primary cilia. *Nat. Cell Biol.* **12**, 407–412 (2010).
43. Antic, D. et al. Planar cell polarity enables posterior localization of nodal cilia and left-right axis determination during mouse and Xenopus embryogenesis. *PLoS ONE* **5**, e8999 (2010).
44. Mochizuki, T. et al. Cloning of inv, a gene that controls left/right asymmetry and kidney development. *Nature* **395**, 177–181 (1998).
45. Yasunaga, T., Itoh, K. & Sokol, S. Y. Regulation of basal body and ciliary functions by diversin. *Mech. Dev.* **128**, 376–386 (2011).
46. Schnell, U. & Carroll, T. J. Planar cell polarity of the kidney. *Exp. Cell Res.* **343**, 258–266 (2016).
47. Adler, P. N., Krasnow, R. E. & Liu, J. Tissue polarity points from cells that have higher Frizzled levels towards cells that have lower Frizzled levels. *Curr. Biol.* **7**, 940–949 (1997).
48. Qian, D. et al. Wnt5a functions in planar cell polarity regulation in mice. *Dev. Biol.* **306**, 121–133 (2007).
49. Gros, J., Serralbo, O. & Marcelle, C. WNT11 acts as a directional cue to organize the elongation of early muscle fibres. *Nature* **457**, 589–593 (2009).
50. Chu, C. W. & Sokol, S. Y. Wnt proteins can direct planar cell polarity in vertebrate ectoderm. *eLife* **5**, e16463 (2016).
51. Wu, J., Roman, A. C., Carvajal-Gonzalez, J. M. & Mlodzik, M. Wg and Wnt4 provide long-range directional input to planar cell polarity orientation in Drosophila. *Nat. Cell Biol.* **15**, 1045–1055 (2013).
52. Navajas Acedo, J. et al. PCP and Wnt pathway components act in parallel during zebrafish mechanosensory hair cell orientation. *Nat. Commun.* **10**, 3993 (2019).
53. Yu, J. J. S. et al. Frizzled-dependent planar cell polarity without secreted Wnt ligands. *Dev. Cell* **54**, 583–592. e5 (2020).
54. Ewen-Campen, B., Comyn, T., Vogt, E. & Perrimon, N. No evidence that Wnt ligands are required for planar cell polarity in drosophila. *Cell Rep.* **32**, 108121 (2020).
55. Sagner, A. et al. Establishment of global patterns of planar polarity during growth of the Drosophila wing epithelium. *Curr. Biol.* **22**, 1296–1301 (2012).
56. Aigouy, B. et al. Cell flow reorients the axis of planar polarity in the wing epithelium of Drosophila. *Cell* **142**, 773–786 (2010).
57. Matis, M. & Axelrod, J. D. Regulation of PCP by the Fat signaling pathway. *Genes Dev.* **27**, 2207–2220 (2013).
58. Casal, J., Lawrence, P. A. & Struhl, G. Two separate molecular systems, Dachsous/Fat and Starry night/Frizzled, act independently to confer planar cell polarity. *Development* **133**, 4561–4572 (2006).
59. Lawrence, P. A., Struhl, G. & Casal, J. Planar cell polarity: one or two pathways? *Nat. Rev. Genet.* **8**, 555–563 (2007).
60. Chien, Y. H., Keller, R., Kintner, C. & Shook, D. R. Mechanical strain determines the axis of planar polarity in ciliated epithelia. *Curr. Biol.* **25**, 2774–2784 (2015).
61. Aw, W. Y., Heck, B. W., Joyce, B. & Devenport, D. Transient tissue-scale deformation coordinates alignment of planar cell polarity junctions in the mammalian skin. *Curr. Biol.* **26**, 2090–2100 (2016).
62. Bertet, C., Sulak, L. & Lecuit, T. Myosin-dependent junction remodelling controls planar cell intercalation and axis elongation. *Nature* **429**, 667–671 (2004).
63. de Matos Simões, S. et al. Rho-kinase directs Bazooka/Par-3 planar polarity during Drosophila axis elongation. *Dev. Cell* **19**, 377–388 (2010).
64. Jenny, A., Darken, R. S., Wilson, P. A. & Mlodzik, M. Prickle and Strabismus form a functional complex to generate a correct axis during planar cell polarity signaling. *EMBO J.* **22**, 4409–4420 (2003).
65. Strutt, H., Warrington, S. J. & Strutt, D. Dynamics of core planar polarity protein turnover and stable assembly into discrete membrane subdomains. *Dev. Cell* **20**, 511–525 (2011).
66. Tree, D. R. et al. Prickle mediates feedback amplification to generate asymmetric planar cell polarity signaling. *Cell* **109**, 371–381 (2002).
67. Wu, J. & Mlodzik, M. The frizzled extracellular domain is a ligand for Van Gogh/Stbm during nonautonomous planar cell polarity signaling. *Dev. Cell* **15**, 462–469 (2008).
68. Loza, O. et al. A synthetic planar cell polarity system reveals localized feedback on Fat4-Ds1 complexes. *eLife* **6**, e24820 (2017).
69. Kelly, L. K., Wu, J., Yanfeng, W. A. & Mlodzik, M. Frizzled-induced Van Gogh phosphorylation by CK1ε promotes asymmetric localization of core PCP factors in Drosophila. *Cell Rep.* **16**, 344–356 (2016).
70. Strutt, H., Gamage, J. & Strutt, D. Reciprocal action of casein kinase Iε on core planar polarity proteins regulates clustering and asymmetric localisation. *eLife* **8**, e45107 (2019).
71. Wu, J., Klein, T. J. & Mlodzik, M. Subcellular localization of frizzled receptors, mediated by their cytoplasmic tails, regulates signaling pathway specificity. *PLoS Biol.* **2**, E158 (2004).
72. Chuykin, I., Ossipova, O. & Sokol, S. Y. Par3 interacts with Prickle3 to generate apical PCP complexes in the vertebrate neural plate. *eLife* **7**, e37881 (2018).
73. Montcouquiol, M. et al. Identification of Vangl2 and Scrb1 as planar polarity genes in mammals. *Nature* **423**, 173–177 (2003).
74. Murdoch, J. N. et al. Disruption of scribble (Scrb1) causes severe neural tube defects in the circletail mouse. *Hum. Mol. Genet.* **12**, 87–98 (2003).
75. Ossipova, O., Dhawan, S., Sokol, S. & Green, J. B. Distinct PAR-1 proteins function in different branches of Wnt signaling during vertebrate development. *Dev. Cell* **8**, 829–841 (2005).
76. Dollar, G. L., Weber, U., Mlodzik, M. & Sokol, S. Y. Regulation of Lethal giant larvae by Dishevelled. *Nature* **437**, 1376–1380 (2005).
77. Djiane, A., Yogev, S. & Mlodzik, M. The apical determinants aPKC and dPatj regulate Frizzled-dependent planar cell polarity in the Drosophila eye. *Cell* **121**, 621–631 (2005).

78. Narimatsu, M. et al. Regulation of planar cell polarity by Smurf ubiquitin ligases. *Cell* **137**, 295–307 (2009).
79. Cho, B., Pierre-Louis, G., Sagner, A., Eaton, S. & Axelrod, J. D. Clustering and negative feedback by endocytosis in planar cell polarity signaling is modulated by ubiquitinylation of prickle. *PLoS Genet.* **11**, e1005259 (2015).
80. Strutt, H. & Strutt, D. Differential stability of flamingo protein complexes underlies the establishment of planar polarity. *Curr. Biol.* **18**, 1555–1564 (2008).
81. Wansleeben, C. et al. Planar cell polarity defects and defective Vangl2 trafficking in mutants for the COPII gene Sec24b. *Development* **137**, 1067–1073 (2010).
82. Merte, J. et al. Sec24b selectively sorts Vangl2 to regulate planar cell polarity during neural tube closure. *Nat. Cell Biol.* **12**, 41–46 (2010).
83. Guo, Y., Zanetti, G. & Schekman, R. A novel GTP-binding protein-adaptor protein complex responsible for export of Vangl2 from the trans Golgi network. *Elife* **2**, e00160 (2013).
84. Mottola, G., Classen, A. K., Gonzalez-Gaitan, M., Eaton, S. & Zerial, M. A novel function for the Rab5 effector Rabenosyn-5 in planar cell polarity. *Development* **137**, 2353–2364 (2010).
85. Shimada, Y., Yonemura, S., Ohkura, H., Strutt, D. & Uemura, T. Polarized transport of Frizzled along the planar microtubule arrays in Drosophila wing epithelium. *Dev. Cell* **10**, 209–222 (2006).
86. Carvajal-Gonzalez, J. M. et al. The clathrin adaptor AP-1 complex and Arf1 regulate planar cell polarity in vivo. *Nat. Commun.* **6**, 6751 (2015).
87. Vinson, C. R. & Adler, P. N. Directional non-cell autonomy and the transmission of polarity information by the frizzled gene of Drosophila. *Nature* **329**, 549–551 (1987).
88. Adler, P. N., Taylor, J. & Charlton, J. The domineering non-autonomy of frizzled and van Gogh clones in the Drosophila wing is a consequence of a disruption in local signaling. *Mech. Dev.* **96**, 197–207 (2000).
89. Lu, Q., Schafer, D. A. & Adler, P. N. The Drosophila planar polarity gene multiple wing hairs directly regulates the actin cytoskeleton. *Development* **142**, 2478–2486 (2015).
90. Yan, J. et al. The multiple-wing-hairs gene encodes a novel GBD-FH3 domain-containing protein that functions both prior to and after wing hair initiation. *Genetics* **180**, 219–228 (2008).
91. Yasunaga, T. et al. The polarity protein Inturned links NPHP4 to Daam1 to control the subapical actin network in multiciliated cells. *J. Cell Biol.* **211**, 963–973 (2015).
92. Kim, S. K. et al. Planar cell polarity acts through septins to control collective cell movement and ciliogenesis. *Science* **329**, 1337–1340 (2010).
93. Cui, C. et al. Wdpcp, a PCP protein required for ciliogenesis, regulates directional cell migration and cell polarity by direct modulation of the actin cytoskeleton. *PLoS Biol.* **11**, e1001720 (2013).
94. Ossipova, O., Chuykin, I., Chu, C. W. & Sokol, S. Y. Vangl2 cooperates with Rab11 and Myosin V to regulate apical constriction during vertebrate gastrulation. *Development* **142**, 99–107 (2015).
95. Lee, J. et al. PTK7 regulates myosin II activity to orient planar polarity in the mammalian auditory epithelium. *Curr. Biol.* **22**, 956–966 (2012).
96. Andreeva, A. et al. PTK7-Src signaling at epithelial cell contacts mediates spatial organization of actomyosin and planar cell polarity. *Dev. Cell* **29**, 20–33 (2014).
97. Matis, M., Russler-Germain, D. A., Hu, Q., Tomlin, C. J. & Axelrod, J. D. Microtubules provide directional information for core PCP function. *eLife* **3**, e02893 (2014).
98. Olofsson, J., Sharp, K. A., Matis, M., Cho, B. & Axelrod, J. D. Prickle/spiny-legs isoforms control the polarity of the apical microtubule network in planar cell polarity. *Development* **141**, 2866–2874 (2014).
99. Ayukawa, T. et al. Dachsous-dependent asymmetric localization of spiny-legs determines planar cell polarity orientation in Drosophila. *Cell Rep.* **8**, 610–621 (2014).
100. Pataki, C. et al. Drosophila Rab23 is involved in the regulation of the number and planar polarization of the adult cuticular hairs. *Genetics* **184**, 1051–1065 (2010).
101. Park, T. J., Haigo, S. L. & Wallingford, J. B. Ciliogenesis defects in embryos lacking inturned or fuzzy function are associated with failure of planar cell polarity and Hedgehog signaling. *Nat. Genet.* **38**, 303–311 (2006).
102. Gray, R. S. et al. The planar cell polarity effector Fuz is essential for targeted membrane trafficking, ciliogenesis and mouse embryonic development. *Nat. Cell Biol.* **11**, 1225–1232 (2009).
103. Seo, J. H. et al. Mutations in the planar cell polarity gene, Fuzzy, are associated with neural tube defects in humans. *Hum. Mol. Genet.* **20**, 4324–4333 (2011).
104. Dos-Santos Carvalho, S. et al. Vangl2 acts at the interface between actin and N-cadherin to modulate mammalian neuronal outgrowth. *eLife* **9**, e51822 (2020).
105. Green, J. L., Inoue, T. & Sternberg, P. W. Opposing Wnt pathways orient cell polarity during organogenesis. *Cell* **134**, 646–656 (2008).
106. Keller, R. Shaping the vertebrate body plan by polarized embryonic cell movements. *Science* **298**, 1950–1954 (2002).
107. Huebner, R. J. & Wallingford, J. B. Coming to consensus: a unifying model emerges for convergent extension. *Dev. Cell* **46**, 389–396 (2018).
108. Wallingford, J. B. et al. Dishevelled controls cell polarity during Xenopus gastrulation. *Nature* **405**, 81–85 (2000).
109. Walck-Shannon, E. & Hardin, J. Cell intercalation from top to bottom. *Nat. Rev. Mol. Cell Biol.* **15**, 34–48 (2014).
110. Smith, P. et al. VANGL2 regulates luminal epithelial organization and cell turnover in the mammary gland. *Sci. Rep.* **9**, 7079 (2019).
111. Ossipova, O. et al. The involvement of PCP proteins in radial cell intercalations during Xenopus embryonic development. *Dev. Biol.* **408**, 316–327 (2015).
112. Sawyer, J. M. et al. Apical constriction: a cell shape change that can drive morphogenesis. *Dev. Biol.* **341**, 5–19 (2010).
113. Nikolopoulou, E., Galea, G. L., Rolo, A., Greene, N. D. & Copp, A. J. Neural tube closure: cellular, molecular and biomechanical mechanisms. *Development* **144**, 552–566 (2017).
114. Sherrard, K., Robin, F., Lemaire, P. & Munro, E. Sequential activation of apical and basolateral contractility drives ascidian endoderm invagination. *Curr. Biol.* **20**, 1499–1510 (2010).
115. Williams, M., Yen, W., Lu, X. & Sutherland, A. Distinct apical and basolateral mechanisms drive planar cell polarity-dependent convergent extension of the mouse neural plate. *Dev. Cell* **29**, 34–46 (2014).
116. Barlan, K., Cetera, M. & Horne-Badovinac, S. Fat2 and Lar define a basally localized planar signaling system controlling collective cell migration. *Dev. Cell* **40**, 467–477.e5 (2017).
117. Bellaiche, Y., Beaudoin-Massiani, O., Stuttem, I. & Schweisguth, F. The planar cell polarity protein Strabismus promotes Pins anterior localization during asymmetric division of sensory organ precursor cells in Drosophila. *Development* **131**, 469–478 (2004).
118. Baena-Lopez, L. A., Baonza, A. & Garcia-Bellido, A. The orientation of cell divisions determines the shape of Drosophila organs. *Curr. Biol.* **15**, 1640–1644 (2005).
119. Gong, Y., Mo, C. & Fraser, S. E. Planar cell polarity signalling controls cell division orientation during zebrafish gastrulation. *Nature* **430**, 689–693 (2004).
120. Ciruna, B., Jenny, A., Lee, D., Mlodzik, M. & Schier, A. F. Planar cell polarity signalling couples cell division and morphogenesis during neurulation. *Nature* **439**, 220–224 (2006).
121. Segalen, M. et al. The Fz-Dsh planar cell polarity pathway induces oriented cell division via Mud/NuMA in Drosophila and zebrafish. *Dev. Cell* **19**, 740–752 (2010).
122. Lake, B. B. & Sokol, S. Y. Strabismus regulates asymmetric cell divisions and cell fate determination in the mouse brain. *J. Cell Biol.* **185**, 59–66 (2009).
123. Nance, J. & Zallen, J. A. Elaborating polarity: PAR proteins and the cytoskeleton. *Development* **138**, 799–809 (2011).
124. Borovina, A. & Ciruna, B. IFT88 plays a cilia- and PCP-independent role in controlling oriented cell divisions during vertebrate embryonic development. *Cell Rep.* **5**, 37–43 (2013).
125. Gerdes, J. M., Davis, E. E. & Katsanis, N. The vertebrate primary cilium in development, homeostasis, and disease. *Cell* **137**, 32–45 (2009).
126. Toriyama, M. et al. The ciliopathy-associated CPLANE proteins direct basal body recruitment of intraflagellar transport machinery. *Nat. Genet.* **48**, 648–656 (2016).
127. Zeng, H., Hoover, A. N. & Liu, A. PCP effector gene Inturned is an important regulator of cilia formation and embryonic development in mammals. *Dev. Biol.* **339**, 418–428 (2010).
128. Heydeck, W., Zeng, H. & Liu, A. Planar cell polarity effector gene Fuzzy regulates cilia formation and Hedgehog signal transduction in mouse. *Dev. Dyn.* **238**, 3035–3042 (2009).
129. Wallingford, J. B. & Mitchell, B. Strange as it may seem: the many links between Wnt signaling, planar cell polarity, and cilia. *Genes Dev.* **25**, 201–213 (2011).
130. Hu, Q. et al. A septin diffusion barrier at the base of the primary cilium maintains ciliary membrane protein distribution. *Science* **329**, 436–439 (2010).
131. Gerondopoulos, A. et al. Planar cell polarity effector proteins inturned and fuzzy form a Rab23 GEF complex. *Curr. Biol.* **29**, 3323–3330.e8 (2019).
132. Boutin, C. et al. A dual role for planar cell polarity genes in ciliated cells. *Proc. Natl Acad. Sci. USA* **111**, E3129–38 (2014).
133. Conduit, P. T., Wainman, A. & Raff, J. W. Centrosome function and assembly in animal cells. *Nat. Rev. Mol. Cell Biol.* **16**, 611–624 (2015).
134. Tissir, F. et al. Lack of cadherins Celsr2 and Celsr3 impairs ependymal ciliogenesis, leading to fatal hydrocephalus. *Nat. Neurosci.* **13**, 700–707 (2010).
135. Watanabe, D. et al. The left-right determinant Inversin is a component of node monocilia and other 9+0 cilia. *Development* **130**, 1725–1734 (2003).
136. Simons, M. et al. Inversin, the gene product mutated in nephronophthisis type II, functions as a molecular switch between Wnt signaling pathways. *Nat. Genet.* **37**, 537–543 (2005).
137. Itoh, K., Jenny, A., Mlodzik, M. & Sokol, S. Y. Centrosomal localization of Diversin and its relevance to Wnt signaling. *J. Cell Sci.* **122**, 3791–3798 (2009).
138. Park, T. J., Mitchell, B. J., Abitua, P. B., Kintner, C. & Wallingford, J. B. Dishevelled controls apical docking and planar polarization of basal bodies in ciliated epithelial cells. *Nat. Genet.* **40**, 871–879 (2008).
139. Cervenka, I. et al. Dishevelled is a NEK2 kinase substrate controlling dynamics of centrosomal linker proteins. *Proc. Natl Acad. Sci. USA* **113**, 9304–9309 (2016).
140. Chu, C. W., Ossipova, O., Ioannou, A. & Sokol, S. Y. Prickle3 synergizes with Wtip to regulate basal body organization and cilia growth. *Sci. Rep.* **6**, 24104 (2016).
141. Dressler, G. R. The cellular basis of kidney development. *Annu. Rev. Cell Dev. Biol.* **22**, 509–529 (2006).
142. Krneta-Stankic, V., DeLay, B. D. & Miller, R. K. Xenopus: leaping forward in kidney organogenesis. *Pediatr. Nephrol.* **32**, 547–555 (2017).
143. Costantini, F. & Kopan, R. Patterning a complex organ: branching morphogenesis and nephron segmentation in kidney development. *Dev. Cell* **18**, 698–712 (2010).
144. Costantini, F. Genetic controls and cellular behaviors in branching morphogenesis of the renal collecting system. *Wiley Interdiscip. Rev. Dev. Biol.* **1**, 693–713 (2012).
145. Shaw, G. & Renfree, M. B. Wolffian duct development. *Sex. Dev.* **8**, 273–280 (2014).
146. Boletta, A. & Germino, G. G. Role of polycystins in renal tubulogenesis. *Trends Cell Biol.* **13**, 484–492 (2003).
147. Rowan, C. J., Sheybani-Deloui, S. & Rosenblum, N. D. Origin and function of the renal stroma in health and disease. *Results Probl. Cell Differ.* **60**, 205–229 (2017).
148. Sequeira-Lopez, M. L. S. & Torban, E. New insights into precursors of renal endothelium. *Kidney Int.* **90**, 244–246 (2016).
149. Hughson, M., Farris, A. B. III, Douglas-Denton, R., Hoy, W. E. & Bertram, J. F. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int.* **63**, 2113–2122 (2003).
150. Baldelomar, E. J., Charlton, J. R., Beeman, S. C. & Bennett, K. M. Measuring rat kidney glomerular number and size in vivo with MRI. *Am. J. Physiol. Ren. Physiol* **314**, F399–F406 (2018).
151. Marcotte, M., Sharma, R. & Bouchard, M. Gene regulatory network of renal primordium development. *Pediatr. Nephrol.* **29**, 637–644 (2014).
152. Nicolaou, N., Renkema, K. Y., Bongers, E. M., Giles, R. H. & Knoers, N. V. Genetic, environmental, and epigenetic factors involved in CAKUT. *Nat. Rev. Nephrol.* **11**, 720–731 (2015).
153. van der Ven, A. T., Vivante, A. & Hildebrandt, F. Novel insights into the pathogenesis of monogenic congenital anomalies of the kidney and urinary tract. *J. Am. Soc. Nephrol.* **29**, 36–50 (2018).
154. Torban, E. et al. Tissue, cellular and sub-cellular localization of the Vangl2 protein during embryonic development: effect of the Lp mutation. *Gene Expr. Patterns* **7**, 346–354 (2007).

155. Yates, L. L. et al. The planar cell polarity gene Vangl2 is required for mammalian kidney-branching morphogenesis and glomerular maturation. *Hum. Mol. Genet.* **19**, 4663–4676 (2010).
156. Viktorinova, I., Konig, T., Schlichting, K. & Dahmann, C. The cadherin Fat2 is required for planar cell polarity in the Drosophila ovary. *Development* **136**, 4123–4132 (2009).
157. Saburi, S., Hester, I., Goodrich, L. & McNeill, H. Functional interactions between Fat family cadherins in tissue morphogenesis and planar polarity. *Development* **139**, 1806–1820 (2012).
158. Rocque, B. L. et al. Deficiency of the planar cell polarity protein vangl2 in podocytes affects glomerular morphogenesis and increases susceptibility to injury. *J. Am. Soc. Nephrol.* **26**, 576–586 (2015).
159. Ciani, L., Patel, A., Allen, N. D. & ffrench-Constant, C. Mice lacking the giant protocadherin mFAT1 exhibit renal slit junction abnormalities and a partially penetrant cyclopia and anophthalmia phenotype. *Mol. Cell Biol.* **23**, 3575–3582 (2003).
160. Bagherie-Lachidan, M. et al. Stromal Fat4 acts non-autonomously with Dchs1/2 to restrict the nephron progenitor pool. *Development* **142**, 2564–2573 (2015).
161. Mao, Y., Francis-West, P. & Irvine, K. D. Fat4/Dchs1 signaling between stromal and cap mesenchyme cells influences nephrogenesis and ureteric bud branching. *Development* **142**, 2574–2585 (2015).
162. Wang, Y., Chang, H., Rattner, A. & Nathans, J. Frizzled receptors in development and disease. *Curr. Top. Dev. Biol.* **117**, 113–139 (2016).
163. Wang, Y., Zhou, C. J. & Liu, Y. Wnt signaling in kidney development and disease. *Prog. Mol. Biol. Transl. Sci.* **153**, 181–207 (2018).
164. Halt, K. & Vainio, S. Coordination of kidney organogenesis by Wnt signaling. *Pediatr. Nephrol.* **29**, 737–744 (2014).
165. Nomachi, A. et al. Receptor tyrosine kinase Ror2 mediates Wnt5a-induced polarized cell migration by activating c-Jun N-terminal kinase via actin-binding protein filamin A. *J. Biol. Chem.* **283**, 27973–27981 (2008).
166. Huang, L. et al. Wnt5a is necessary for normal kidney development in zebrafish and mice. *Nephron Exp. Nephrol.* **128**, 80–88 (2014).
167. Yun, K. et al. Non-canonical Wnt5a/Ror2 signaling regulates kidney morphogenesis by controlling intermediate mesoderm extension. *Hum. Mol. Genet* **23**, 6807–6814 (2014).
168. Majumdar, A., Vainio, S., Kispert, A., McMahon, J. & McMahon, A. P. Wnt11 and Ret/Gdnf pathways cooperate in regulating ureteric branching during metanephric kidney development. *Development* **130**, 3175–3185 (2003).
169. Karner, C. M. et al. Wnt9b signaling regulates planar cell polarity and kidney tubule morphogenesis. *Nat. Genet.* **41**, 793–799 (2009).
170. Yu, J. et al. A Wnt7b-dependent pathway regulates the orientation of epithelial cell division and establishes the cortico-medullary axis of the mammalian kidney. *Development* **136**, 161–171 (2009).
171. Kunimoto, K. et al. Disruption of core planar cell polarity signaling regulates renal tubule morphogenesis but is not cystogenic. *Curr. Biol.* **27**, 3120–3131.e4 (2017).
172. Ye, X., Wang, Y., Rattner, A. & Nathans, J. Genetic mosaic analysis reveals a major role for frizzled 4 and frizzled 8 in controlling ureteric growth in the developing kidney. *Development* **138**, 1161–1172 (2011).
173. Drawbridge, J., Meighan, C. M., Lumpkins, R. & Kite, M. E. Pronephric duct extension in amphibian embryos: migration and other mechanisms. *Dev. Dyn.* **226**, 1–11 (2003).
174. Stewart, K. & Bouchard, M. Coordinated cell behaviours in early urogenital system morphogenesis. *Semin. Cell Dev. Biol.* **36**, 13–20 (2014).
175. Lienkamp, S. S. et al. Vertebrate kidney tubules elongate using a planar cell polarity-dependent, rosette-based mechanism of convergent extension. *Nat. Genet.* **44**, 1382–1387 (2012).
176. Xu, B. et al. Protein tyrosine kinase 7 is essential for tubular morphogenesis of the Wolffian duct. *Dev. Biol.* **412**, 219–233 (2016).
177. Carroll, T. J., Park, J. S., Hayashi, S., Majumdar, A. & McMahon, A. P. Wnt9b plays a central role in the regulation of mesenchymal to epithelial transitions underlying organogenesis of the mammalian urogenital system. *Dev. Cell* **9**, 283–292 (2005).
178. Kispert, A., Vainio, S. & McMahon, A. P. Wnt-4 is a mesenchymal signal for epithelial transformation of metanephric mesenchyme in the developing kidney. *Development* **125**, 4225–4234 (1998).
179. Stark, K., Vainio, S., Vassileva, G. & McMahon, A. P. Epithelial transformation of metanephric mesenchyme in the developing kidney regulated by Wnt-4. *Nature* **372**, 679–683 (1994).
180. Tanigawa, S. et al. Wnt4 induces nephronic tubules in metanephric mesenchyme by a non-canonical mechanism. *Dev. Biol.* **352**, 58–69 (2011).
181. Pietila, I. et al. Wnt5a deficiency leads to anomalies in ureteric tree development, tubular epithelial cell organization and basement membrane integrity pointing to a role in kidney collecting duct patterning. *PLoS ONE* **11**, e0147171 (2016).
182. Qi, X., Okinaka, Y., Nishita, M. & Minami, Y. Essential role of Wnt5a-Ror1/Ror2 signaling in metanephric mesenchyme and ureteric bud formation. *Genes Cell* **21**, 325–334 (2016).
183. Schuchardt, A., D'Agati, V., Larsson-Blomberg, L., Costantini, F. & Pachnis, V. Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase receptor Ret. *Nature* **367**, 380–383 (1994).
184. Chi, X. et al. Ret-dependent cell rearrangements in the Wolffian duct epithelium initiate ureteric bud morphogenesis. *Dev. Cell* **17**, 199–209 (2009).
185. Nishita, M. et al. Role of Wnt5a-Ror2 signaling in morphogenesis of the metanephric mesenchyme during ureteric budding. *Mol. Cell Biol.* **34**, 3096–3105 (2014).
186. Zhang, H. et al. FAT4 fine-tunes kidney development by regulating RET signaling. *Dev. Cell* **48**, 780–792.e4 (2019).
187. Zhao, H. et al. Role of fibroblast growth factor receptors 1 and 2 in the ureteric bud. *Dev. Biol.* **276**, 403–415 (2004).
188. Brzoska, H. L. et al. Planar cell polarity genes Celsr1 and Vangl2 are necessary for kidney growth, differentiation, and rostrocaudal patterning. *Kidney Int.* **90**, 1274–1284 (2016).
189. Kibar, Z. et al. Ltap, a mammalian homolog of Drosophila Strabismus/Van Gogh, is altered in the mouse neural tube mutant Loop-tail. *Nat. Genet.* **28**, 251–255 (2001).
190. Yates, L. L. et al. The PCP genes Celsr1 and Vangl2 are required for normal lung branching morphogenesis. *Hum. Mol. Genet.* **19**, 2251–2267 (2010).
191. Torban, E., Wang, H. J., Groulx, N. & Gros, P. Independent mutations in mouse Vangl2 that cause neural tube defects in looptail mice impair interaction with members of the Dishevelled family. *J. Biol. Chem.* **279**, 52703–52713 (2004).
192. Miller, R. K. et al. Pronephric tubulogenesis requires Daam1-mediated planar cell polarity signaling. *J. Am. Soc. Nephrol.* **22**, 1654–1664 (2011).
193. Warrington, S. J., Strutt, H. & Strutt, D. The Frizzled-dependent planar polarity pathway locally promotes E-cadherin turnover via recruitment of RhoGEF2. *Development* **140**, 1045–1054 (2013).
194. Williams, B. B. et al. VANGL2 regulates membrane trafficking of MMP14 to control cell polarity and migration. *J. Cell Sci.* **125**, 2141–2147 (2012).
195. Coyle, R. C., Latimer, A. & Jessen, J. R. Membrane-type 1 matrix metalloproteinase regulates cell migration during zebrafish gastrulation: evidence for an interaction with non-canonical Wnt signaling. *Exp. Cell Res.* **314**, 2150–2162 (2008).
196. Kopan, R., Chen, S. & Little, M. Nephron progenitor cells: shifting the balance of self-renewal and differentiation. *Curr. Top. Dev. Biol.* **107**, 293–331 (2014).
197. Das, A. et al. Stromal-epithelial crosstalk regulates kidney progenitor cell differentiation. *Nat. Cell Biol.* **15**, 1035–1044 (2013).
198. O'Brien, L. L. et al. Wnt11 directs nephron progenitor polarity and motile behavior ultimately determining nephron endowment. *eLife* **7**, e40392 (2018).
199. Ramalingam, H. et al. Disparate levels of beta-catenin activity determine nephron progenitor cell fate. *Dev. Biol.* **440**, 13–21 (2018).
200. Karner, C. M. et al. Canonical Wnt9b signaling balances progenitor cell expansion and differentiation during kidney development. *Development* **138**, 1247–1257 (2011).
201. Liu, C. et al. Null and hypomorph Prickle1 alleles in mice phenocopy human Robinow syndrome and disrupt signaling downstream of Wnt5a. *Biol. Open* **3**, 861–870 (2014).
202. San Agustin, J. T. et al. Genetic link between renal birth defects and congenital heart disease. *Nat. Commun.* **7**, 11103 (2016).
203. Babayeva, S. et al. Planar cell polarity pathway regulates nephrin endocytosis in developing podocytes. *J. Biol. Chem.* **288**, 24035–24048 (2013).
204. Derish, I. et al. Differential role of planar cell polarity gene Vangl2 in embryonic and adult mammalian kidneys. *PLoS ONE* **15**, e0230586 (2020).
205. Fischer, E. et al. Defective planar cell polarity in polycystic kidney disease. *Nat. Genet.* **38**, 21–23 (2006).
206. Saburi, S. et al. Loss of Fat4 disrupts PCP signaling and oriented cell division and leads to cystic kidney disease. *Nat. Genet.* **40**, 1010–1015 (2008).
207. Matakatsu, H. & Blair, S. S. Separating planar cell polarity and Hippo pathway activities of the protocadherins Fat and Dachsous. *Development* **139**, 1498–1508 (2012).
208. Happe, H. et al. Altered Hippo signalling in polycystic kidney disease. *J. Pathol.* **224**, 133–142 (2011).
209. Cai, J. et al. A RhoA-YAP-c-Myc signaling axis promotes the development of polycystic kidney disease. *Genes Dev.* **32**, 781–793 (2018).
210. Mammoto, T., Jiang, E., Jiang, A. & Mammoto, A. Extracellular matrix structure and tissue stiffness control postnatal lung development through the lipoprotein receptor-related protein 5/Tie2 signaling system. *Am. J. Respir. Cell Mol. Biol.* **49**, 1009–1018 (2013).
211. Sekiguchi, R. & Yamada, K. M. Basement membranes in development and disease. *Curr. Top. Dev. Biol.* **130**, 143–191 (2018).
212. Sutherland, A., Keller, R. & Lesko, A. Convergent extension in mammalian morphogenesis. *Semin. Cell Dev. Biol.* **100**, 199–211 (2020).
213. Collins, I. & Wann, A. K. T. Regulation of the extracellular matrix by ciliary machinery. *Cells* **9**, 278 (2020).
214. Nishio, S. et al. Loss of oriented cell division does not initiate cyst formation. *J. Am. Soc. Nephrol.* **21**, 295–302 (2010).
215. Castelli, M. et al. Polycystin-1 binds Par3/aPKC and controls convergent extension during renal tubular morphogenesis. *Nat. Commun.* **4**, 2658 (2013).
216. Babayeva, S., Zilber, Y. & Torban, E. Planar cell polarity pathway regulates actin rearrangement, cell shape, motility, and nephrin distribution in podocytes. *Am. J. Physiol. Ren. Physiol.* **300**, F549–F560 (2011).
217. Yaoita, E. et al. Role of Fat1 in cell-cell contact formation of podocytes in puromycin aminonucleoside nephrosis and neonatal kidney. *Kidney Int.* **68**, 542–551 (2005).
218. Gee, H. Y. et al. FAT1 mutations cause a glomerulotubular nephropathy. *Nat. Commun.* **7**, 10822 (2016).
219. Montaldo, P. et al. Small renal size in newborns with spina bifida: possible causes. *Clin. Exp. Nephrol.* **18**, 120–123 (2014).
220. Wang, M., Marco, P., Capra, V. & Kibar, Z. Update on the role of the non-canonical wnt/planar cell polarity pathway in neural tube defects. *Cells* **8**, 1198 (2019).
221. Murdoch, J. N. et al. Circletail, a new mouse mutant with severe neural tube defects: chromosomal localization and interaction with the loop-tail mutation. *Genomics* **78**, 55–63 (2001).
222. Person, A. D. et al. WNT5A mutations in patients with autosomal dominant Robinow syndrome. *Dev. Dyn.* **239**, 327–337 (2010).
223. Bunn, K. J. et al. Mutations in DVL1 cause an osteosclerotic form of Robinow syndrome. *Am. J. Hum. Genet.* **96**, 623–630 (2015).
224. White, J. J. et al. DVL3 alleles resulting in a -1 frameshift of the last exon mediate autosomal-dominant robinow syndrome. *Am. J. Hum. Genet.* **98**, 553–561 (2016).
225. Afzal, A. R. et al. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. *Nat. Genet.* **25**, 419–422 (2000).
226. van Bokhoven, H. et al. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal recessive Robinow syndrome. *Nat. Genet.* **25**, 423–426 (2000).
227. Brunetti-Pierri, N. et al. Robinow syndrome: phenotypic variability in a family with a novel intragenic ROR2 mutation. *Am. J. Med. Genet. A* **146A**, 2804–2809 (2008).
228. Mansour, S. et al. Van Maldergem syndrome: further characterisation and evidence for neuronal migration abnormalities and autosomal recessive inheritance. *Eur. J. Hum. Genet.* **20**, 1024–1031 (2012).
229. Lahrouchi, N. et al. Homozygous frameshift mutations in FAT1 cause a syndrome characterized by colobomatous-microphthalmia, ptosis, nephropathy and syndactyly. *Nat. Commun.* **10**, 1180 (2019).

230. Zhang, W. et al. Expanding the genetic architecture and phenotypic spectrum in the skeletal ciliopathies. *Hum. Mutat.* **39**, 152–166 (2018).
231. Otto, E. A. et al. Mutations in INVS encoding inversin cause nephronophthisis type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. *Nat. Genet.* **34**, 413–420 (2003).
232. Heydeck, W. & Liu, A. PCP effector proteins inturned and fuzzy play nonredundant roles in the patterning but not convergent extension of mammalian neural tube. *Dev. Dyn.* **240**, 1938–1948 (2011).
233. van Amerongen, R. & Nusse, R. Towards an integrated view of Wnt signaling in development. *Development* **136**, 3205–3214 (2009).
234. Minegishi, K. et al. A Wnt5 activity asymmetry and intercellular signaling via PCP proteins polarize node cells for left-right symmetry breaking. *Dev. Cell* **40**, 439–452.e4 (2017).
235. Nishimura, T., Honda, H. & Takeichi, M. Planar cell polarity links axes of spatial dynamics in neural-tube closure. *Cell* **149**, 1084–1097 (2012).
236. Marlow, F., Topczewski, J., Sepich, D. & Solnica-Krezel, L. Zebrafish Rho kinase 2 acts downstream of Wnt11 to mediate cell polarity and effective convergence and extension movements. *Curr. Biol.* **12**, 876–884 (2002).
237. Weiser, D. C., Row, R. H. & Kimelman, D. Rho-regulated myosin phosphatase establishes the level of protrusive activity required for cell movements during zebrafish gastrulation. *Development* **136**, 2375–2384 (2009).
238. Butler, M. T. & Wallingford, J. B. Planar cell polarity in development and disease. *Nat. Rev. Mol. Cell Biol.* **18**, 375–388 (2017).
239. Happe, H., de Heer, E. & Peters, D. J. Polycystic kidney disease: the complexity of planar cell polarity and signaling during tissue regeneration and cyst formation. *Biochim. Biophys. Acta* **1812**, 1249–1255 (2011).

Acknowledgements
The authors thank L. Gusella (Icahn School of Medicine at Mount Sinai, New York, NY, USA) for comments on the manuscript before submission. We apologize to those investigators whose studies we could not cite due to the constraints for space. The authors' work was supported by grants from the Kidney Foundation of Canada KFOC1719 and the Canadian Institute of Health Research (MOP130315 and PJT-169082) to E.T. and National Institutes of Health grants (GM122492, HD092990, DE027665 and NS100759) to S.Y.S.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors declare no competing interests.

Peer review information
Nature Reviews Nephrology thanks R. Miller, M. Simons and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41581-021-00395-6.

RELATED LINKS
Genitourinary Development Molecular Anatomy Project (GUDMAP): www.gudmap.org