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# The TRPP Subfamily and Polycystin-1 Proteins

Mariam Semmo, Michael Köttgen, and Alexis Hofherr

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M. Semmo • M. Köttgen

Renal Division, Department of Medicine, University Medical Centre Freiburg, Hugstetter Straße 55, 79106 Freiburg, Germany

e-mail: [mariam.semmo@uniklinik-freiburg.de](mailto:mariam.semmo@uniklinik-freiburg.de); [michael.koettgen@uniklinik-freiburg.de](mailto:michael.koettgen@uniklinik-freiburg.de)

A. Hofherr (✉)

Renal Division, Department of Medicine, University Medical Centre Freiburg, Hugstetter Straße 55, 79106 Freiburg, Germany

Spemann Graduate School of Biology and Medicine (SGBM), Albert-Ludwigs-University, Freiburg, Germany

Faculty of Biology, Albert-Ludwigs-University, Freiburg, Germany

e-mail: [alexis.hofherr@uniklinik-freiburg.de](mailto:alexis.hofherr@uniklinik-freiburg.de)

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## Abstract

It has been exciting times since the identification of polycystic kidney disease 1 (PKD1) and PKD2 as the genes mutated in autosomal dominant polycystic kidney disease (ADPKD). Biological roles of the encoded proteins polycystin-1 and TRPP2 have been deduced from phenotypes in ADPKD patients, but recent insights from vertebrate and invertebrate model organisms have significantly expanded our understanding of the physiological functions of these proteins. The identification of additional TRPP (TRPP3 and TRPP5) and polycystin-1-like proteins (PKD1L1, PKD1L2, PKD1L3, and PKDREJ) has added yet another layer of complexity to these fascinating cellular signalling units. TRPP proteins assemble with polycystin-1 family members to form receptor–channel complexes. These protein modules have important biological roles ranging from tubular morphogenesis to determination of left–right asymmetry. The founding members of the polycystin family, TRPP2 and polycystin-1, are a prime example of how studying human disease genes can provide insights into fundamental biological mechanisms using a so-called “reverse translational” approach (from bedside to bench). Here, we discuss the current literature on TRPP ion channels and polycystin-1 family proteins including expression, structure, physical interactions, physiology, and lessons from animal model systems and human disease.

## Keywords

TRPP cation channels • Polycystin-1 proteins • Polycystic kidney disease • Cilia • Polycystin physiology

## 1 Introduction

The founding member of the TRP polycystin ion channel family, TRPP2, was discovered as a gene product mutated in autosomal dominant polycystic kidney disease (ADPKD) (Mochizuki et al. 1996). The TRPP subfamily may be the most ancient among the TRP channels, as members of this subfamily extend from yeast to mammals (Palmer et al. 2005; Venkatachalam and Montell 2007). TRPP proteins assemble with polycystin-1 family members to form receptor–channel complexes. These protein modules have important biological roles ranging from tubular morphogenesis to determination of left–right asymmetry. TRPP channels have evolutionarily conserved functions in primary cilia where they are thought to translate extracellular cues into cellular signalling events.

**Table 1** TRPP channel nomenclature

Gene	Protein	TRP
<i>Polycystic kidney disease 2 (PKD2)</i>	Polycystin-2 (PC2)	TRPP2
<i>PKD2-like 1 (PKD2L1)</i>	Polycystin L	TRPP3
<i>PKD2L2</i>	PKD2L2	TRPP5

**Table 2** Polycystin-1 family nomenclature

Gene	Protein
<i>Polycystic kidney disease 1 (PKD1)</i>	Polycystin-1 (PC1)
<i>PKD1-like 1 (PKD1L1)</i>	PKD1L1
<i>PKD1L2</i>	PKD1L2
<i>PKD1L3</i>	PKD1L3
<i>PKD and sperm receptor for egg jelly homolog-like (PKDREJ)</i>	PKDREJ

This review summarises the current literature on TRPP channels and polycystin-1 family members. Since not all aspects can be covered in this review, the reader is referred to a number of excellent reviews on TRPP channels and polycystin-1 family proteins (Tables 1 and 2) (Somlo 1999; Somlo and Ehrlich 2001; Delmas et al. 2004a; Anyatonwu and Ehrlich 2004; Delmas 2004, 2005; Cantiello 2004; Nilius et al. 2005; Witzgall 2005; Köttgen and Walz 2005; Giamarchi et al. 2006; Köttgen 2007; Harris and Torres 2009; Zhou 2009; Woudenberg-Vrenken et al. 2009; Tsiokas 2009; Hofherr and Köttgen 2011; Hofherr 2012).

## 2 TRPP Family Genes

The TRPP (polycystin) subfamily of transient receptor potential (TRP) channels displays a rather limited sequence homology to classical TRP genes (Venkatachalam and Montell 2007). The three human genes encoding for the TRPP protein family are: 1) *polycystic kidney disease 2 (PKD2)*; 2) *PKD2-like 1 (PKD2L1)*; and 3) *PKD2-like 2 (PKD2L2)*. *PKD2* was identified by linkage analysis in ADPKD patients (Mochizuki et al. 1996; Kimberling et al. 1988; Peters and Sandkuijl 1992). Subsequently, the two *PKD2-like* genes were established by homology-based cloning (Nomura et al. 1998; Wu et al. 1998a; Veldhuisen et al. 1999).

Interestingly, TRPP family genes are conserved in vertebrates, invertebrates and yeast, e.g. *pkd2* in *Danio rerio*, *amo* in *Drosophila melanogaster*, *Pkd-2* in *Caenorhabditis elegans*, *suPC2* in sea urchin and *pkd2* in *Schizosaccharomyces pombe* (Palmer et al. 2005; Barr and Sternberg 1999; Watnick et al. 2003; Gao et al. 2003; Neill et al. 2004; Sun et al. 2004). This ancient evolutionary origin has given rise to the hypothesis that TRPP ion channels might comprise the most archetypical TRP subfamily (Venkatachalam and Montell 2007).

*PKD2* (GeneID 5,311) is located on chromosome 4q21–4q23 in positive orientation (Mochizuki et al. 1996). The gene is 70,110 base pairs (bp) long and comprises 15 exons (Hayashi et al. 1997). One mRNA transcript has been

established (NM\_000297). The TRPP2 protein consists of 968 amino acids (109,561 Da) (NP\_000288).

*PKD2L1* (GeneID 9,033) is located on chromosome 10q24 in negative orientation (Nomura et al. 1998; Wu et al. 1998a). The gene is 42,341 bp long and comprises 16 exons (Guo et al. 2000a, b). One mRNA transcript has been established (NM\_016112), which is translated into TRPP3 (805 amino acids; 91,851 Da) (NP\_057196).

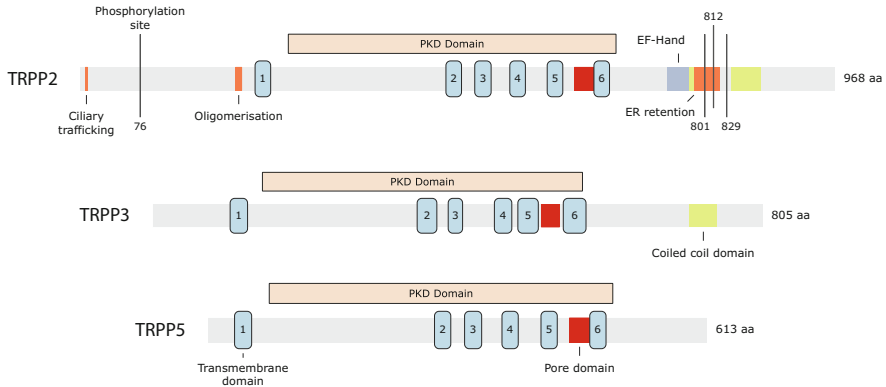
*PKD2L2* (GeneID 27,039) is located on chromosome 5q31 in positive orientation (Veldhuisen et al. 1999). The gene is 51,032 bp long and comprises 14 exons. One mRNA transcript has been established (NM\_014386), which is translated into TRPP5 (613 amino acids; 72,365 Da) (NP\_055201).

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### 3 Expression of TRPP Ion Channels

The TRPP family genes are expressed ubiquitously in vertebrates. Large-scale transcriptome analysis detected TRPP mRNA in almost every human and mouse tissue (Su et al. 2004; Wu et al. 2009). The targeted examination of TRPP expression has confirmed and extended these results: *PKD2* and *PKD2L1* transcripts are indeed found in many foetal and adult tissues, including the heart, brain, lung, testis, ovary and kidney (Mochizuki et al. 1996; Nomura et al. 1998; Veldhuisen et al. 1999; Basora et al. 2002; Volk et al. 2003; Murakami et al. 2005; Ishimaru et al. 2006; Huang et al. 2006; Orts-Del'immagine et al. 2012). In contrast, *PKD2L2* transcription appears to be mostly restricted to the testis (Veldhuisen et al. 1999; Guo et al. 2000b; Taft et al. 2002; Chen et al. 2008). Several TRPP splice variants have been described but their functional consequences remain elusive (Mochizuki et al. 1996; Nomura et al. 1998; Veldhuisen et al. 1999; Guo et al. 2000b).

Spatiotemporal control of *PKD2* expression seems to be partially executed on a post-transcriptional level. Micro-RNAs modify gene expression by reducing protein translation through mRNA degradation or translational repression (He and Hannon 2004). The short non-coding microRNA group 17 (miR-17) and the RNA-binding protein bicaudal C (BICC1) apparently antagonise each other to fine-tune TRPP2 translation (Sun et al. 2010; Tran et al. 2010; Patel et al. 2013). miR-17 has been described to repress the expression of *PKD2* post-transcriptionally (Sun et al. 2010; Tran et al. 2010; Patel et al. 2013). Kidney-specific transgenic over-expression of miR-17 produces kidney cysts in mice, while inactivation of miR-17 retards cyst growth in the heterologous mouse PKD model *Kif3a*<sup>-/-</sup> (Patel et al. 2013). BICC1, on the other hand, promotes *PKD2* mRNA stability and translation efficiency while antagonising the repressive activity of miR-17 (Tran et al. 2010). *Bicc1*<sup>-/-</sup> animals develop a renal cyst phenotype reminiscent of PKD (Tran et al. 2010). However, future experiments will have to address whether the observed miR-17 and *Bicc1*<sup>-/-</sup> cyst phenotypes are exclusively linked to decreased TRPP2 protein levels, because miR-17 targets a plethora of genes some of which are known cyst genes (Tran et al. 2010; Cloonan et al. 2008).



**Fig. 1** The TRPP ion channel family

In *C. elegans* and *D. melanogaster*, *PKD2* expression is highly restricted to ciliated cells, predominantly male-specific sensory neurons and spermatozoa, respectively (Barr and Sternberg 1999; Watnick et al. 2003; Gao et al. 2003; Yang et al. 2011; Köttgen et al. 2011). A temporal control of *pkd2* expression has been proposed in the fission yeast, *S. pombe*, where *pkd2* mRNA levels increase following damage to the cell wall (Palmer et al. 2005).

It is intriguing to speculate that the expansion of TRPP gene expression (and therefore most likely TRPP protein function) is evolutionary coupled to the increase in ciliated cell types. There are very few ciliated cells expressing TRPP genes in invertebrates and almost ubiquitous ciliation and TRPP expression in humans.

## 4 The TRPP Proteins

The nomenclature of TRPP ion channels has been somewhat inconsistent. Initial publications grouped both ADPKD proteins into the polycystin family. The founding member of the TRPP subfamily, polycystin-2, was later classified as TRPP2. The designation TRPP1 has caused some confusion, as it has been used for both polycystin-1 and polycystin-2. We strongly advocate the following TRP nomenclature: 1) *bona fide* TRPP ion channels and 2) receptor-like polycystin-1 family proteins (Tables 1 and 2). Because of ambiguity TRPP1 and TRPP4 should not be used.

TRPP2, TRPP3 and TRPP5 are the three  $\text{Ca}^{2+}$ -permeable non-selective cation TRPP ion channel proteins (Fig. 1) (Clapham 2003; Nilius and Owsianik 2011). They share a high degree of amino acid sequence identity and similarity. ClustalW sequence alignment of TRPP3 and TRPP2 shows 48 % identity and 70 % sequence similarity (Larkin et al. 2007). TRPP5 is only slightly more distant from TRPP2 with 45 % identity and 68 % similarity (Larkin et al. 2007).

Unfortunately, to date no high-resolution crystal structure is available for any full-length TRP channel (Li et al. 2011). Current TRPP protein models are therefore

based on less accurate experimental methods and predictions. Studies on the architecture of TRP channels in general yielded strong evidence that these channels function as tetramers (Jahnel et al. 2001; Kedei et al. 2001; Moiseenkova-Bell et al. 2008). Monomeric TRP channel subunits are integral membrane proteins with six predicted transmembrane helices (S1–S6), framing a pore-forming loop between S5 and S6 and cytosolic amino- and carboxy-termini of varying sizes (Venkatachalam and Montell 2007; Clapham 2003; Nilius and Owsianik 2011; Li et al. 2011). The prominent feature of TRPP ion channels is a large extracellular loop between S1 and S2, consisting of 245 amino acids in TRPP2, 224 in TRPP3 and 225 in TRPP5. While the transmembrane helices are highly conserved in the TRPP family, major deletions have occurred in the protein termini. Basically, TRPP3 is missing approximately 100 amino acids of the TRPP2 amino-terminus and TRPP5 has lost both sections of the TRPP2 amino- and carboxy-terminus. TRPP sequence divergence in mammals, e.g. amino acid substitution, is mainly observed in the loop regions between the transmembrane helices (Ye et al. 2009).

TRPP2 has six predicted transmembrane domains and their orientation has recently been validated by transient expression of truncated TRPP2 mutants and selective membrane permeabilisation (Hoffmeister et al. 2011a). In line with expectations, both the amino- and carboxy-terminus have been found to protrude into the cytoplasm (Hoffmeister et al. 2011a). The carboxy-terminal region of TRPP2 has attracted particular research interest. It comprises several sequence elements required for proper TRPP2 function, including a  $\text{Ca}^{2+}$ -binding EF hand (TRPP2<sup>754–781</sup>), two coiled-coil domains (CC1: TRPP2<sup>769–796</sup>/CC2: TRPP2<sup>835–873</sup>), an endoplasmic reticulum retention motif (TRPP2<sup>787–820</sup>) and an acidic amino acid cluster (TRPP2<sup>810–821</sup>) (Fig. 1) (Cai et al. 1999; Hanaoka et al. 2000; Köttgen et al. 2005; Ćelić et al. 2008, 2012; Yu et al. 2009; Petri et al. 2010; Giamarchi et al. 2010). The EF hand has been implicated in ion channel gating and the acidic cluster in protein trafficking, whereas the two coiled-coil domains have been demonstrated to be required for homo- and heteromerisation of TRPP2 subunits (Köttgen et al. 2005; Ćelić et al. 2008, 2012; Yu et al. 2009; Petri et al. 2010; Giamarchi et al. 2010). Structural analysis of recombinant TRPP2 carboxy-terminal fragments and specific amino acid substitutions in full-length TRPP2 have yielded some insight into the molecular mechanisms controlling TRPP2 channel assembly. The formation of functional ion channel homomers or alternatively heteromers seems to be a controlled multistep process which is initiated by the assembly of TRPP2 homomers (Yu et al. 2009; Giamarchi et al. 2010; Feng et al. 2008, 2011). An amino-terminal oligomerisation domain (TRPP2<sup>199–207</sup>), a cysteine<sup>632</sup>-dependent disulphide bond and CC2 apparently stabilise TRPP2 homomers, which are the basis for CC1-mediated interactions to form active ion channels (Yu et al. 2009; Giamarchi et al. 2010; Feng et al. 2008, 2011; Qian et al. 1997; Tsiokas et al. 1997). However, some controversies concerning the sequence of events and the respective TRPP2 multimerisation state remain unsettled (Yu et al. 2009; Giamarchi et al. 2010; Kobori et al. 2009; Molland et al. 2010). Similar data have been reported for TRPP3 (Molland et al. 2010, 2012; Yu et al. 2012). The crystal structure of TRPP3<sup>561–805</sup> fragments is stabilised by trimerisation (Molland

et al. 1824; Yu et al. 2012). Taken together, these data raise the question whether TRPP proteins form trimers or tetramers, like other TRP ion channels. It is rather difficult to extrapolate from the data provided by the crystal structure of TRPP carboxy-terminal fragments to the full-length ion channel configuration. Further data are required to clarify this issue.

In eukaryotic cells, an additional level of information content is added to protein structures by co- and post-translational modifications. Most frequent are glycosylation and phosphorylation, which are essential for protein processing and function (Tarrant and Cole 2009; Moremen et al. 2012). TRPP2 has been demonstrated to be glycosylated, but a detailed mapping and characterisation of implicated amino acid residues is lacking (Cai et al. 1999; Newby et al. 2002). A large number of phosphorylation sites in TRPP2 have been predicted and identified (Cai et al. 2004; Olsen et al. 2006; Streets et al. 2006, 2010, 2013; Hoffert et al. 2006; Molina et al. 2007; Zanivan et al. 2008; Huttlin et al. 2010; Hsu et al. 2011; Plotnikova et al. 2011). Serine<sup>76</sup>, serine<sup>801</sup>, serine<sup>812</sup> and serine<sup>829</sup> have been studied in more detail (Köttgen et al. 2005; Cai et al. 2004; Streets et al. 2006, 2010, 2013; Plotnikova et al. 2011; Li et al. 2005a; Fu et al. 2008). Glycogen synthase kinase 3 (GSK3) was shown to phosphorylate serine<sup>76</sup>, thereby promoting redistribution of plasma membrane TRPP2 to intracellular compartments (Streets et al. 2006). Phosphorylation of serine<sup>801</sup> appears to be protein kinase D-dependent and increased by epidermal growth factor stimulation (Streets et al. 2010). Phosphorylation of serine<sup>812</sup> by casein kinase 2 (CK2) contributes to the regulation of TRPP2 trafficking and ion channel activity (Köttgen et al. 2005; Cai et al. 2004; Fu et al. 2008). Serine<sup>829</sup> is phosphorylated by either aurora A or protein kinase A (PKA) and has been reported to modulate ion channel function (Plotnikova et al. 2011; Streets et al. 2013). It is important to note, however, that the functional importance of these TRPP2 modifications is still difficult to evaluate as over-expressed TRPP2 is trapped in the endoplasmic reticulum, impeding the electrophysiological analysis at the plasma membrane (also see Sect. 6).

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## 5 TRPP Interacting Proteins

TRPP ion channels are embedded in a complex network of protein–protein interactions. After translation, their localisation, function and activity are shaped by a multitude of associated proteins (<http://trpchannel.org/families/TRPP>) (Tables 3 and 4). Like many TRP proteins, TRPP subunits assemble into functional ion channel homomers, but have also been found to form heteromeric complexes. Their intimate relationship with polycystin-1 family proteins adds yet another layer of complexity to these fascinating proteins. TRPP ion channels and polycystin-1 family proteins constitute versatile receptor–channel modules that use Ca<sup>2+</sup> as second messenger (Fig. 2). They have been implicated in many signalling cascades, including establishment of body asymmetry and coordination of three-dimensional tissue organisation (Hofherr and Köttgen 2011; Hofherr 2012).

**Table 3** TRPP2 protein interactions

Protein	Putative function	References
Adenylyl cyclase 5/6 (AC5/6)	A-kinase anchoring protein complex	Choi et al. (2011)
$\alpha$ -Actinin	Ion channel modulation/actin binding	Li et al. (2005c)
CD2AP	Actin binding	Lehtonen et al. (2000)
Collectrin	Ciliary trafficking	Zhang et al. (2007)
EGFR	Ion channel modulation	Ma et al. (2005)
eIF2 $\alpha$	Regulation of cell proliferation	Liang et al. (2008a)
Filamin A	Ion channel modulation	Sharif-Naeini et al. (2009), Wang et al. (2012)
Filamin B	Ion channel modulation	Wang et al. (2012)
Filamin C	Ion channel modulation	Wang et al. (2012)
FIP2	Protein transport	Li et al. (2008)
FPC (PKHD1)	Ciliogenesis	Kim et al. (2008)
GSK3	Protein transport	Streets et al. (2006)
HAX1	Actin binding	Gallagher et al. (2000)
HERP	Protein degradation	Liang et al. (2008b)
Id2	Regulation of cell proliferation	Li et al. (2005a)
IP3R	Ion channel modulation	Li et al. (2005b)
KIF3A	Tubulin binding	Li et al. (2006)
KIF3B	Tubulin binding/ion channel modulation	Wu et al. (2006)
Kim-1	Development of interstitial fibrosis	Kuehn et al. (2002)
mDia1	Protein transport	Rundle et al. (2004)
NPHP1	Regulation of apoptosis	Wodarczyk et al. (2010)
NPHP9	Protein transport	Sohara et al. (2008)
p97	Protein degradation	Liang et al. (2008b)
PACS-1	Protein transport	Köttgen et al. (2005)
PACS-2	Protein transport	Köttgen et al. (2005)
PATJ	Cell polarity/tight junctions	Duning et al. (2010)
Pericentrin (PCTN)	Assembly of primary cilia	Jurczyk et al. (2004)
PERK	Regulation of cell proliferation	Liang et al. (2008a)
PIGEA-14	Protein transport	Hidaka et al. (2004)
PKD1L1	TRPP signalling module	Field et al. (2011), Kamura et al. (2011)
PKDREJ	TRPP signalling module	Sutton et al. (2006)
PLC $\gamma$ 2	Ion channel modulation	Ma et al. (2005)
Polycystin-1 (PKD1)	TRPP signalling module	Qian et al. (1997), Tsiokas et al. (1997)
PRKCSH	Protein processing	Gao et al. (2010)
RP2	Ion channel modulation	Hurd et al. (2010)
RyR2	Intracellular Ca <sup>2+</sup> release	Anyatonwu et al. (2007)
SEC10	Ciliary localisation	Fogelgren et al. (2011)
Syntaxin-5 (Stx5)	Ion channel modulation	Geng et al. (2008)

(continued)



**Table 3** (continued)

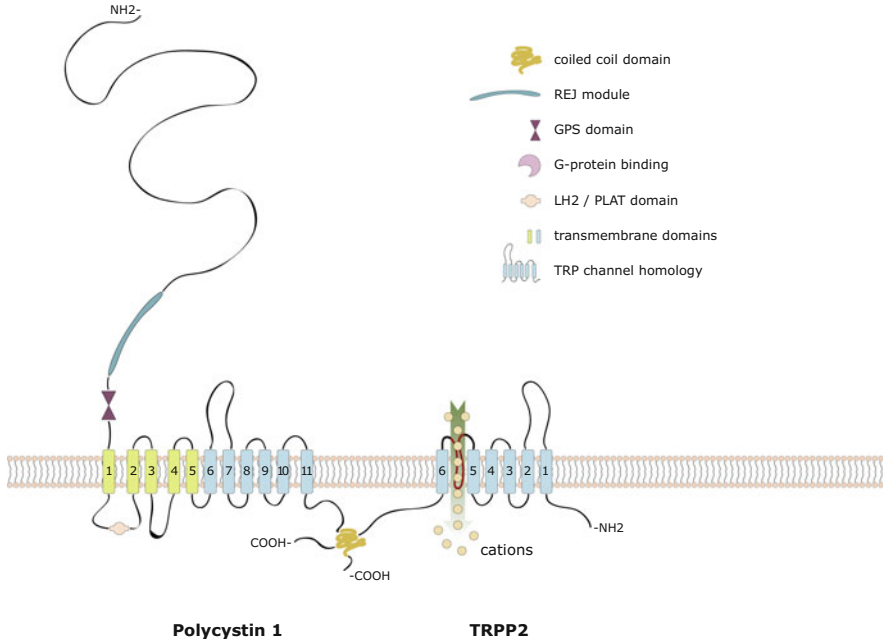
Protein	Putative function	References
TAZ	Protein degradation	Tian et al. (2007)
Troponin-1	Ion channel modulation	Li et al. (2003d)
Tropomyosin-1	Actin binding	Li et al. (2003b)
TRPC1	TRP ion channel	Tsiokas et al. (1999)
TRPC3	TRP ion channel	Miyagi et al. (2009)
TRPC4	TRP ion channel	Du et al. (2008)
TRPC5	TRP ion channel	Sutton et al. (2006)
TRPC7	TRP ion channel	Miyagi et al. (2009)
TRPP2	TRP ion channel	Tsiokas et al. (1997)
TRPV4	TRP ion channel	Köttgen et al. (2008)

**Table 4** TRPP3 protein interactions

Protein	Putative function	References
$\alpha$ -Actinin	Ion channel modulation/actin binding	Li et al. (2007)
PKD1L3	TRPP signalling module	Ishimaru et al. (2006), Lopezjimenez et al. (2006)
PKDREJ	TRPP signalling module	Sutton et al. (2006)
Polycystin-1 (PKD1)	TRPP signalling module	Murakami et al. (2005), Bui-Xuan et al. (2006)
RACK1	Ion channel modulation	Yang et al. (2012)
Troponin-1	Ion channel modulation	Li et al. (2003c)
TRPC1	TRP ion channel	Sutton et al. (2006)
TRPC5	TRP ion channel	Sutton et al. (2006)

## 5.1 The TRPP–Polycystin-1 Signalling Module

*PKD1* was the first ADPKD gene to be identified by linkage analysis (Reeders et al. 1985; European Polycystic Kidney Disease Consortium 1994; International Polycystic Kidney Disease Consortium 1995). Mutations in either *PKD1* or *PKD2* cause virtually indistinguishable disease manifestations in humans (Longo and Harrison 2012). *PKD1* is the founding member of the polycystin-1 family, which consists of five large membrane-bound receptor proteins: *PKD1*, *PKD1-like 1* (*PKD1L1*), *PKD1-like 2* (*PKD1L2*), *PKD1-like 3* (*PKD1L3*) and *PKD and sperm receptor for egg jelly homolog-like* (*PKDREJ*) (Reeders et al. 1985; European Polycystic Kidney Disease Consortium 1994; International Polycystic Kidney Disease Consortium 1995; Yuasa et al. 2002; Li et al. 2003a; Sutton et al. 2006). Their signature feature is the tripartite combination of a G-protein-coupled receptor proteolytic site (GPS), the receptor for egg jelly (REJ) domain and the lipoxxygenase homology/polycystin, lipoxxygenase, atoxin (LH2/PLAT) domain that is separated from the previous two by a transmembrane helix (Qian and Noben-Trauth 2005).



**Fig. 2** The TRPP2/polycystin-1 receptor–channel complex

*PKDI* (GeneID 5,310) is located on chromosome 16q13.3 in negative orientation. The gene is 47,189 bp long and comprises 92 exons (Reeders et al. 1985; European Polycystic Kidney Disease Consortium 1994; International Polycystic Kidney Disease Consortium 1995). Two mRNA transcripts have been established (NM\_001009944, NM\_000296), which are translated into polycystin-1 isoform 1 and polycystin-1 isoform 2 (4,303 and 4,292 amino acids; 462,529 and 461,365 Da, respectively) (NP\_001009944, NP\_000287). In addition, six *PKDI* pseudo-genes (*PKDIP1–PKDIP6*) have been identified in 16q13.11–16q13.13 (GeneIDs: 339,044/283,955/339,039/353,512/348,156/353,511).

*PKD1L1* (GeneID 168,507) is located on chromosome 7q12.3 in negative orientation (Yuasa et al. 2002). The gene is 173,748 bp long and comprises 57 exons. One mRNA transcript has been established (NM\_138295), which is translated into PKD1L1 (NP\_612152), a 315,305 Da protein comprising 2,849 amino acids.

*PKD1L2* (GeneID 114,780) is located on chromosome 16q23.2 in negative orientation. The gene is 119,492 bp long and comprises 61 exons (Li et al. 2003a). Two mRNA transcripts have been established (NM\_052892, NM\_001076780), which are translated into PKD1L2 isoform A and C (2,459 and 991 amino acids; 272,384 and 107,813 Da, respectively) (NP\_443124, NP\_001070248).

*PKD1L3* (GeneID 342,372) is located on chromosome 16q22.3 in negative orientation (Li et al. 2003a). The gene is 70,984 bp long and comprises 30 exons.

One mRNA transcript has been established (XM\_001133467), which is translated into PKD1L3 (XP\_001133467), a 195,894 Da protein (1,731 amino acids).

*PKDREJ* (GeneID 10,343) is located on chromosome 22q13.31 in negative orientation. The single exon gene is 7,660 bp long (Sutton et al. 2006). One mRNA transcript has been established (NM\_006071). The PKDREJ protein consists of 2,253 amino acids (255,449 Da) (NP\_006062).

The interaction of TRPP2 and polycystin-1 has been extensively studied at all levels of complexity (Fig. 2). Loss of either one of these proteins causes severe life-threatening cystic kidney disease (Mochizuki et al. 1996; Reeders et al. 1985; European Polycystic Kidney Disease Consortium 1994; International Polycystic Kidney Disease Consortium 1995). Together they are a prerequisite for the coordination of three-dimensional renal tubular organisation. The TRPP2–PKD1L1 signalling module on the other hand is required for the embryonic establishment of a left–right axis, i.e. the asymmetric arrangement of unpaired organs (also see Sect. 7) (Hofherr 2012; Field et al. 2011; Kamura et al. 2011).

TRPP5 and PKDREJ are abundantly expressed in the male germline, but no physical interaction has been observed (Veldhuisen et al. 1999; Sutton et al. 2006; Hughes et al. 1999).

## 5.2 TRP–TRPP Heteromers

TRPP2 can interact with several TRP channels, including TRPC1, TRPC3, TRPC4, TRPC5, TRPC7 and TRPV4 (Kobori et al. 2009; Sutton et al. 2006; Tsiokas et al. 1999; Köttgen et al. 2008; Du et al. 2008; Miyagi et al. 2009; Stewart et al. 2010). The respective ion channel function seems to be modulated via the TRP subunit composition, adapting the functional properties of TRPP2 to tissue-specific roles including mechano- and chemosensation (Köttgen et al. 2008).

## 5.3 TRPP and the Cellular Cytoskeleton

The dynamic coordination of cellular structures is a major function of the cytoskeleton. It is composed of three main components: 1) actin filaments; 2) intermediate filaments; and 3) microtubules (Wickstead and Gull 2011). Actin filaments provide the cell's scaffold. TRPP2 was shown to be attached to actin by direct and indirect means, e.g. by tropomyosin-1 and  $\alpha$ -actinin or CD2AP and HAX1, respectively (Li et al. 2003b, c, 2005a; Lehtonen et al. 2000; Gallagher et al. 2000). To guide proper cytoskeletal development, actin filaments can be cross-linked to bundles by filamin proteins (Zhou et al. 2010; Ohta et al. 2006). Filamin A and TRPP2 were reported to regulate pressure sensing in mouse vascular smooth muscle cells, i.e. fine-tuning stretch-activated channels to adapt the vascular myogenic response (Sharif-Naeini et al. 2009). Microtubules, on the other hand, make up the internal structure of cilia and provide platforms for intracellular transport (Rosenbaum and Witman 2002). TRPP2 was shown to bind and co-localise with two motor proteins

required for intra-flagellar transport in primary cilia, KIF3A and KIF3B (Li et al. 2006; Wu et al. 2006). At microtubule-organising centres, TRPP2 interactions with pericentrin and mammalian diaphanous 1 protein (mDia1) apparently modulate the intracellular  $\text{Ca}^{2+}$  homeostasis (Jurczyk et al. 2004; Rundle et al. 2004).

## 5.4 TRPP Protein Trafficking

The cellular distribution of TRPP2 is determined by the subsequent interaction with various trafficking proteins. Endoplasmic reticulum, plasma membrane and primary cilia are the most prominent TRPP2 compartments (Witzgall 2005; Cai et al. 1999; Koulen et al. 2002; Pazour et al. 2002; Yoder et al. 2002).

The two proteins implicated in autosomal dominant polycystic liver disease (ADPLD), Sec63p and glucosidase 2 subunit  $\beta$ , function as part of the endoplasmic reticulum translocation, folding and quality control machinery (Drenth et al. 2003; Davila et al. 2004). Their physiological interaction with polycystin-1 and TRPP2 is necessary for module processing. Impairment of either ADPLD gene causes insufficient functional expression of the polycystin-1–TRPP2 receptor–channel complex resulting in cystic disease (Fedeles et al. 2011).

Post-endoplasmic reticulum sorting of TRPP2 seems to be controlled by an intricate interplay of intrinsic TRPP2 amino acid trafficking motifs and their ligands. Multiple motifs have been described including an endoplasmic reticulum retention motif (TRPP2<sup>787–820</sup>), an acidic cluster comprising the serine<sup>812</sup> phosphorylation site (TRPP2<sup>810–821</sup>), and an amino-terminal ciliary import signal, RVxP (R, arginine; V, valine; x, any amino acid; P, proline) (TRPP2<sup>6–9</sup>) (Cai et al. 1999; Hanaoka et al. 2000; Köttgen et al. 2005; Geng et al. 2006). Phosphorylation of serine<sup>812</sup> in TRPP2 by casein kinase 2 (CK2) regulates the binding of phosphofurin acidic cluster sorting protein 1 (PACS-1) or PACS-2 and routes TRPP2 to the endoplasmic reticulum, Golgi complex or plasma membrane compartments (Köttgen et al. 2005). In addition, PIGEA-14 promotes the endoplasmic reticulum to *trans*-Golgi complex transport of TRPP2 by way of a carboxy-terminal interaction (Hidaka et al. 2004). Interestingly, germline inactivation of PIGEA-14 causes defective airway kinocilia (Voronina et al. 2009). Ciliary sorting of TRPP2 was proposed to be dependent on Rab8a expression (Hoffmeister et al. 2011b). Interestingly, the latter study showed that TRPP2 takes different routes to the somatic and ciliary plasma membrane. The transport of TRPP2 to the ciliary and to the somatic plasma membrane compartments originates in a COPII-dependent fashion at the endoplasmic reticulum. TRPP2 reaches the *cis*-Golgi complex in either case, but trafficking to the somatic plasma membrane goes through the Golgi complex, whereas transport vesicles to the cilium leave the Golgi complex at the *cis* compartment (Hoffmeister et al. 2011b).

## 5.5 TRPP and A-Kinase Anchoring Protein (AKAP) Complex

Dysregulation of cyclic adenosine monophosphate (cAMP) signalling has been implicated in the pathogenesis of cystic kidney diseases, i.e. promoting fluid secretion and cell proliferation (Hanaoka and Guggino 2000; Belibi et al. 2004; Torres et al. 2012). The molecular mechanisms leading to increased cAMP production in cyst epithelia are still incompletely understood. Recently, it has been shown that TRPP2 and phosphodiesterase 4C are components of a ciliary A-kinase anchoring protein (AKAP) complex that is disrupted in cystic kidney diseases (Choi et al. 2011). AKAP complexes organise cellular signal transduction by compartmentalising second messenger-regulated enzymes (Wong and Scott 2004; Dessauer 2009). In AKAP complexes, TRPP2 was reported to bind adenylyl cyclase 5/6 (AC5/6), a  $\text{Ca}^{2+}$ -inhibitible enzyme, in primary cilia (Choi et al. 2011). It has therefore been suggested that loss of TRPP2 inhibitory activity may cause increased AC5/6-mediated cAMP production (Choi et al. 2011).

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## 6 Biophysical Description of the Channel Function, Permeation and Gating

TRPP ion channels have been shown to function as  $\text{Ca}^{2+}$ -permeable non-selective cation channels.

### 6.1 TRPP3

TRPP3 was the first member of the TRPP family to be identified as a cation channel (Chen et al. 1999). Expression of TRPP3 in *Xenopus laevis* oocytes gave rise to constitutively active,  $\text{Ca}^{2+}$ -permeable non-selective cation channels with a high single-channel conductance of 137 pS. High intracellular  $\text{Ca}^{2+}$  increased channel activity, whereas low extracellular pH decreased conductance (Chen et al. 1999; Shimizu et al. 2009). More recently, TRPP3 activity was found to be voltage dependent and increased upon cell swelling and by alkalisation (Shimizu et al. 2009, 2011). There have been conflicting results as to whether TRPP3 channel function requires co-expression of PKD1L3 and whether this complex is an acid-sensing channel complex required for sour taste transduction (Yu et al. 2012; Chen et al. 1999; Shimizu et al. 2009; Chaudhari and Roper 2010).

### 6.2 TRPP5

Limited information is available concerning TRPP5 channel function. No spontaneous channel activity has been observed upon over-expression of TRPP5 in HEK293 cells. In outside-out patches, however, these cells exhibited a channel with a single 25 pS conductance state (Sutton et al. 2006).

### 6.3 TRPP2

After cloning of *PKD2* in 1996 and description of its channel-like topology (Mochizuki et al. 1996), it took four more years until the first report of the channel function was published (Hanaoka et al. 2000). The reason for the difficulty in measuring TRPP2 channel function at the plasma membrane was explained by the identification of a carboxy-terminal retention motif (TRPP2<sup>787–820</sup>) causing exclusive endoplasmic reticulum localisation of over-expressed TRPP2 (Cai et al. 1999). Carboxy-terminal truncations of TRPP2 deleting the retention motif traffic to the plasma membrane; channel activity has been reported for these truncation mutants (Chen et al. 2001). The cellular localisation and site of action of full-length TRPP2 has been discussed controversially: some groups favour the endoplasmic reticulum as the physiological site of action of TRPP2, others the plasma membrane (Cantiello 2004; Witzgall 2005; Hanaoka et al. 2000; Köttgen et al. 2005; Koulen et al. 2002). The first report on TRPP2 channel function provided evidence that polycystin-1 and TRPP2 interact to form a functional heteromeric complex (Hanaoka et al. 2000). This study reported that TRPP2 alone did not form functional channels, but co-expression of polycystin-1 and TRPP2 promoted the translocation of TRPP2 to the plasma membrane and produced Ca<sup>2+</sup>-permeable non-selective cation currents (Hanaoka et al. 2000). This finding was later confirmed in neurons where over-expressed polycystin-1 and TRPP2 formed a functional receptor–channel complex (Delmas et al. 2004b).

The functional reconstitution of the polycystin-1/TRPP2 complex in heterologous expression systems could be very useful to screen for ligands and specific inhibitors and to study activation mechanisms as well as regulation of the receptor–channel complex. Considering the fact that functional reconstitution of the polycystin-1/TRPP2 complex in over-expression systems might help to address several fundamental questions in the field, surprisingly little has been published in this area since 2004.

After initial studies reporting TRPP2 whole-cell currents, several single-channel studies characterised the channel properties in more detail (Vassilev et al. 2001; González-Perrett et al. 2001, 2002). The specific biophysical properties and the channel function of TRPP2 are reviewed elsewhere (Delmas et al. 2004a; Cantiello 2004). In brief, TRPP2 has been reported to display a single-channel conductance of 100–200 pS and a spontaneous open probability ranging from 0.2 to 0.4. TRPP2 displays non-selective cation channel activity, with slight preference for divalent cations (Vassilev et al. 2001; González-Perrett et al. 2001; Luo et al. 2003). The properties of endoplasmic reticulum resident TRPP2 were studied at single-channel resolution using reconstitution of microsomes in lipid bilayers (Koulen et al. 2002). These studies confirmed that microsomal TRPP2 functions as a Ca<sup>2+</sup>-permeable non-selective cation channel, but also showed some biophysical properties that differed from those reported for TRPP2 in other studies (Koulen et al. 2002). One interesting aspect of these studies is the regulation of TRPP2 by Ca<sup>2+</sup> via a carboxy-terminal EF hand in the channel protein (Koulen et al. 2002). The EF-hand Ca<sup>2+</sup>-binding motifs of TRPP2 and TRPP3 may be involved in the observed intracellular

$\text{Ca}^{2+}$ -dependent activation of the channel (Koulen et al. 2002; Chen et al. 1999). This is supported by the observation that TRPP2<sup>742X</sup>, a naturally occurring pathogenic mutant lacking the EF hand, does not display  $\text{Ca}^{2+}$  activation (Chen et al. 2001). Furthermore phosphorylation of serine<sup>812</sup> of TRPP2 regulates the  $\text{Ca}^{2+}$ -dependent activation of the channel (Cai et al. 2004). Several recent studies investigated the structural and functional properties of the helix-loop-helix structural EF-hand motif in TRPP2 in more detail (Ćelić et al. 2008, 2012; Petri et al. 2010). Structural analysis demonstrated discrete conformational transitions and oligomerisation state changes upon the addition of  $\text{Ca}^{2+}$  to recombinant TRPP2 fragments (TRPP2<sup>720–797</sup> [EF hand] and TRPP2<sup>704–968</sup> [TRPP2 carboxy-terminus]), and the authors propose that the EF hand is required for channel gating (Ćelić et al. 2012).

In summary, the channel function of TRPP channels (in particular TRPP2) has been studied quite extensively but important questions remain. In the case of TRPP2, this is mostly due to the fact that functional reconstitution of this channel at the plasma membrane has proven to be difficult. There has been a report of TRPP2 channel activity at the ciliary membrane, but these recordings are technically challenging (Raychowdhury et al. 2005). The identification of factors that allow the robust reconstitution of the TRPP2 channel complex at the plasma membrane in over-expression systems would undoubtedly help to advance the electrophysiological analysis of this important disease-associated ion channel. The identification of physiological activation mechanisms, regulatory factors and specific inhibitors of TRPP2 will be critical to study channel function under more physiological conditions, i.e. in the native tissue.

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## 7 Physiological Functions of TRPP Channels in Native Cells, Organs, and Organ Systems

The physiological importance of TRPP channels and polycystin-1 family proteins becomes evident in light of severe phenotypes observed upon loss of function in humans and model organisms. The founding members of the polycystin family, TRPP2 and polycystin-1, are a prime example of how studying human disease genes can provide insights into fundamental biological mechanisms using a so-called “reverse translational” approach (from bedside to bench). In fact, studying polycystic kidney disease genes has provided considerable insights into processes like tubular morphogenesis, left–right patterning and signalling through primary cilia.

Homozygous null alleles of *PKD1* or *PKD2* are embryonic lethal in mice and men (also see Sect. 8) (Lu et al. 1997; Wu et al. 1998b, 2000; Paterson et al. 2002; Piontek et al. 2004, 2007; Pennekamp et al. 2002; Garcia-Gonzalez et al. 2010). Loss of function of either gene causes cyst formation in the kidneys, liver and pancreas. Thus, one physiological function of these proteins must be in regulating tubular morphogenesis and maintenance of tubular structures. Both genes have a role in vascular integrity, since loss of function causes cardiovascular phenotypes ranging from cardiac valve defects to aneurysms and abnormal vascular

permeability in knockout mice (Garcia-Gonzalez et al. 2010; Kim et al. 2000; Boulter et al. 2001). The embryonic lethality in PKD knockout mice appears to be caused by vascular defects in the placenta (Garcia-Gonzalez et al. 2010). In addition, TRPP2 is essential for the establishment of left–right asymmetry in vertebrates, as loss of TRPP2 function results in heterotaxy, i.e. the abnormal left–right distribution of visceral organs, in zebrafish and mice (Pennekamp et al. 2002; Bisgrove et al. 2005; Schottenfeld et al. 2007). Extensive efforts have been devoted to investigate the molecular and cellular mechanisms, which are the basis for these physiological functions. It is assumed that polycystins function as signalling proteins, but there is no consensus yet about the precise role of the polycystins in cellular signal transduction (Köttgen 2007; Torres and Harris 2009). Importantly, neither the activation mechanisms nor the downstream components of the enigmatic polycystin signalling pathway are known. One intriguing concept that has emerged from studying polycystin function is the importance of primary cilia in cellular signal transduction and organ development (Hildebrandt and Otto 2005).

## 7.1 The Ciliary Connection

The primary cilium, once considered an evolutionary relic without apparent function, has recently stepped into the spotlight, as a flood of data indicates that cilia have crucial roles in vertebrate development and human genetic diseases (Hildebrandt et al. 2011; Goetz and Anderson 2010). Research on polycystic kidney disease genes has significantly spurred this Cinderella-like transformation. Cilia are antenna-like structure emanating from the surface of virtually every cell in mammals. Cilia contain an axoneme of nine microtubule doublets surrounded by a ciliary membrane. There is mounting evidence that cilia function as a nexus for signalling pathways, translating extracellular cues into cellular signal transduction events (Goetz and Anderson 2010). Orthologues of polycystin-1 and TRPP2 were first localised on ciliated endings of sensory neurons in *C. elegans* and later in cilia of mammalian cells (Barr and Sternberg 1999; Pazour et al. 2002; Yoder et al. 2002). Meanwhile, a plethora of proteins involved in cystic kidney disease have been detected in primary cilia. Furthermore, genetic ablation of cilia in animal models leads to cyst formation (Hildebrandt et al. 2011; Yoder et al. 1996; Pazour et al. 2000; Lin et al. 2003). It is now generally accepted that cilia play an important role in polycystin function, but the precise mechanisms of polycystins in ciliary signalling remain unresolved. In addition to primary cilia, TRPP2 has been proposed to function in other cellular compartments including the lateral membrane of epithelial cells and the endoplasmic reticulum (Köttgen 2007; Koulen et al. 2002; Scheffers et al. 2002; Li et al. 2005b; Wegierski et al. 2009; Sammels et al. 2010; Mekahli et al. 2012). Despite the apparent importance of primary cilia, other compartment-specific functions of polycystins may also contribute to the diverse roles of these proteins in different organs.



## 7.2 Activation Mechanisms

The activation mechanism of the polycystin-1/TRPP2 receptor–channel complex is an important open question in the field. Cilia have been shown to function as mechanosensors (Praetorius and Spring 2005). Bending of cilia by tubular fluid triggers cytosolic  $\text{Ca}^{2+}$  signals (Praetorius and Spring 2001). Polycystin-1 and TRPP2 are required for flow-induced  $\text{Ca}^{2+}$  signals in renal tubular epithelial cells (Nauli et al. 2003; Boehlke et al. 2010). This finding suggested that the mechanical activation of the polycystin complex could be the critical signal regulating tubular morphogenesis, and it has been proposed that the loss of flow-mediated  $\text{Ca}^{2+}$  signalling causes cyst formation (Nauli et al. 2003; Nauli and Zhou 2004). While the hypothesis that mechanical signals in the tubule lumen convey spatial information to polarised epithelial cells is intriguing, there is also evidence suggesting that flow-mediated  $\text{Ca}^{2+}$  signalling may not be required for the regulation of tubular geometry (Köttgen et al. 2008; Kotsis et al. 2013). An alternative hypothesis for the activation mechanism of the polycystin complex may involve yet-to-be identified ligands. To date, there is some indirect evidence supporting such a hypothesis (Barr and Sternberg 1999; Köttgen et al. 2011; Delmas et al. 2004b). Unfortunately, the identification of ligands for orphan receptors is notoriously challenging. But the prospect to deorphanise the polycystin-1/TRPP2 receptor–channel complex holds great promise to gain a better understanding of polycystin signalling and may, in our view, justify concerted efforts to screen for ligands using biochemical, physiological and genetic approaches.

Another interesting hypothesis concerning putative activation mechanisms of polycystins comes from the fact that polycystin-1 bears striking similarities to the so-called adhesion class G-protein-coupled receptors (adhesion GPCRs) (Qian et al. 2002; Wei et al. 2007; Langenhan et al. 2013). The adhesion GPCRs are a unique protein family with more than 30 members, which are involved in multiple signalling pathways. A common feature of these receptors is a GPCR autoproteolysis-inducing (GAIN) domain and cleavage of the extracellular amino-terminus at a G-protein-receptor-coupled proteolytic site (GPS) (Langenhan et al. 2013). It has been shown that the cleaved amino-terminal fragment can bind to the membrane-anchored carboxy-terminal fragment of adhesion GPCRs, where it could act as an endogenous ligand or play a role in binding ligands (Langenhan et al. 2013). Polycystin-1 has a GAIN domain and it was shown that the huge extracellular amino-terminus of polycystin-1 is cleaved autoproteolytically at the GPS motif (Qian et al. 2002; Wei et al. 2007). The cleaved amino-terminus remains tethered to the membrane-bound carboxy-terminal rest of the protein in a covalent manner (Qian et al. 2002). In addition, it was shown that knock-in mice with a non-cleavable GPS site in polycystin-1 are viable but show a rapid onset of cystic kidney disease developing mainly from the distal parts of the nephron (Yu et al. 2007). Further investigation revealed that two endogenous forms of polycystin-1 coexist in wild-type mice: a small amount of uncleaved full-length PC-1 and cleaved polycystin-1, which is more abundant. These studies provide compelling evidence that cleavage is not essential for embryonic development but

required for maintenance of the integrity of the distal nephron segments (Yu et al. 2007). In summary, it is intriguing to speculate that the amino-terminal cleavage product of polycystin-1 could play a ligand-like or a ligand-binding role in the activation and regulation of the polycystin-1/TRPP2 channel complex akin to models proposed for adhesion GPCRs (Langenhan et al. 2013).

### 7.3 Left–Right Asymmetry

Another interesting connection between cilia and polycystins came from the surprising observation that TRPP2 is required for left–right axis determination in vertebrates (Pennekamp et al. 2002). Loss of TRPP2 has been shown to cause heterotaxy in mice and zebrafish, as well as in three patients with ADPKD (Pennekamp et al. 2002; Bisgrove et al. 2005; Schottenfeld et al. 2007; Bataille et al. 2011). The asymmetric placement of internal organs in vertebrates is established by the action of cilia in a pit-like structure called the embryonic node (McGrath et al. 2003; Hirokawa et al. 2006). Rotating cilia generate unidirectional fluid flow across the node from left to right. TRPP2 is required to sense the fluid flow in immotile cilia of perinodal crown cells (Yoshihara et al. 2012). It is not known whether this process involves chemo- or mechanosensation, or both (Norris and Grimes 2012). Interestingly, loss of *PKD1*, which gives rise to similar phenotypes like *PKD2* in most organs, does not cause heterotaxy. Thus, TRPP2 acts independently of polycystin-1 in the establishment of left–right asymmetry. Recently, it was shown that TRPP2 forms a complex with PKD1L1 in the node to form a sensory protein complex required for left–right patterning (Field et al. 2011; Kamura et al. 2011; Vogel et al. 2010). This finding provides compelling evidence that polycystin-1 and TRPP family members can form distinct signalling modules that are adapted to tissue-specific functions (Hofherr 2012).

### 7.4 The Modular Concept

There is mounting evidence that TRPP channel subunits can form functional homomeric and heteromeric signalling modules, thereby expanding the diversity of organ-specific functions of these ion channels (also see Sect. 5). As mentioned above, there is strong biochemical and genetic data supporting a role for receptor–channel complexes comprised of different combinations of polycystin-1 family members with TRPP channel subunits. Besides the heavily studied complex of the founding members polycystin-1 and TRPP2 in polycystic kidney disease and the function of the PKD1L1/TRPP2 complex in left–right asymmetry, there is now also data suggesting that a heteromeric complex composed of PKD1L3 and TRPP3 might form an acid-activated complex involved in sour taste (Ishimaru et al. 2006; Huang et al. 2006; Lopezjimenez et al. 2006). Several research groups reported the circumscribed co-expression of PKD1L3 and TRPP3 in a specific subset of mouse taste receptor cells (Ishimaru et al. 2006; Huang et al. 2006; Lopezjimenez

et al. 2006). These cells were found in taste buds and were reported to be distinct from the taste receptor cells mediating sweet, umami and bitter taste. Genetic ablation of the PKD1L3- and TRPP3-expressing cells in mice by targeted expression of attenuated diphtheria toxin leads to a complete loss of taste response to sour taste (Huang et al. 2006). The absence of an entire subpopulation of taste cells, however, does not necessarily establish the role of any given protein expressed by the missing cells. Support for the hypothesis that TRPP3 in association with PKD1L3 might form a candidate sour taste receptor came from heterologous over-expression systems. In heterologous expression systems TRPP3 appears to physically interact with PKD1L3 (Murakami et al. 2005; Ishimaru et al. 2006; Huang et al. 2006). HEK293T cells over-expressing PKD1L3 together with TRPP3 generated an inward current upon acid stimulation (Ishimaru et al. 2006). Yet, this channel is sensitive to extracellular pH rather than a drop in cytoplasmic pH, which is known to be the proximate stimulus for sour taste (Lyll et al. 2001; Huang et al. 2008). In addition, mice lacking PKD1L3 remain capable of detecting acid taste stimuli and *Pkd211*<sup>-/-</sup> mice show only a partial reduction in sour taste transduction (Nelson et al. 2010; Horio et al. 2011). Since the PKD1L3/TRPP3 complex does not appear to be required for sour taste transduction, the search for the elusive sour taste receptor will continue.

The modular concept is not limited to TRPP channels and polycystin-1 family members. For example, it has been shown that TRPP2 interacts with other TRP channels like TRPC1 and TRPV4. TRPP2 and TRPV4 form a polymodal sensory channel complex that is involved in ciliary mechano- and thermosensation (Köttgen et al. 2008). A thermosensory role of TRPP channels appears to be evolutionarily conserved as TRPP channels have been shown to mediate cold sensation in *D. melanogaster* (Gallio et al. 2011).

In summary, TRPP channels and polycystin-1-like proteins have important physiological functions linking channel activity to fundamental developmental and sensory processes. We are beginning to understand some of the cellular mechanisms that explain the dramatic phenotypes observed upon loss of function of these proteins. Future studies will have to identify the molecular mechanisms translating channel activity into specific cellular signal transduction pathways controlling organ shape and patterning in vivo.

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## 8 Lessons from Knockouts

The molecular analysis of TRPP2 and polycystin-1 is only the latest step of a long ADPKD research history. There has been an extensive collection of human loss of function data in ADPKD patients well before the molecular identity of the two ADPKD genes was known. However, because of the complex genetic situation in humans, animal model systems have been invaluable to elucidate the physiological function of TRPP and polycystin-1 family proteins. This is because ADPKD patients are heterozygous for the inherited PKD mutation in most of their cells

with only very few cells that are homozygous due to somatic mutations (also see Sect. 9).

A number of constitutive and conditional mouse knockout models for *PKD1* and *PKD2* have been created (Wilson 2008). They faithfully recapitulate central aspects of the human phenotype (Lu et al. 1997; Wu et al. 1998b; Piontek et al. 2004, 2007; Pennekamp et al. 2002; Garcia-Gonzalez et al. 2010; Kim et al. 2000; Boulter et al. 2001). Constitutive *Pkd1*<sup>-/-</sup> and *Pkd2*<sup>-/-</sup> mice develop cystic kidneys, oedema as well as haemorrhage and typically die in utero ~15.5 days post-coitum (Lu et al. 1997; Wu et al. 1998b, 2000; Paterson et al. 2002; Pennekamp et al. 2002; Garcia-Gonzalez et al. 2010). Like in ADPKD patients, renal cysts originate from focal dilatations along all nephron segments, including occasional glomerular cysts (Wu et al. 1998b, 2000; Pennekamp et al. 2002; Baert 1978). Heterozygous PKD animals survive to adulthood; only *Pkd1*<sup>+/-</sup> mice progressively develop scattered cystic disease at the age of 4–19 months, but the phenotype of heterozygous animals is rather mild and does not recapitulate the human disease (Boulter et al. 2001; Lu et al. 1999). Animals heterozygous for both *Pkd1* and *Pkd2* show a harsh progression of disease (Wu et al. 2002).

Tissue-specific and temporal conditional ablation of PKD genes was instrumental in uncovering additional functions of TRPP2 and polycystin-1 usually masked by embryonic lethality. Homozygous loss of *PKD* genes in mice paved the way to additional unexpected *PKD*-dependent phenotypes. One of these phenotypes was the impaired left–right asymmetry with randomisation of unilateral organ placement in *Pkd2* and *Pkd111* mutant mice, but not in *Pkd1*<sup>-/-</sup> (also see Sect. 7) (Field et al. 2011; Kamura et al. 2011; Pennekamp et al. 2002). In addition, vascular fragility with haemorrhage and skeletal malformations were reported in *Pkd1* and *Pkd2* mutant mice (Kim et al. 2000; Boulter et al. 2001; Garcia-Gonzalez et al. 2010; Khonsari et al. 2013).

The time course of ADPKD in mice was elegantly probed using an inducible *Pkd1* gene inactivation model (Piontek et al. 2004, 2007). *Pkd1* deletion before day 13 post-coitum caused rapid progressive cyst formation in mice (Piontek et al. 2007), whereas *Pkd1* inactivation after day 14 resulted in only mild PKD (Piontek et al. 2007). This notable embryonic switch in kidney development was corroborated by data from *Kif3a* and *Ifi88* mice, which present a similar response to timed gene ablation (Davenport et al. 2007).

*Pkd211*<sup>-/-</sup> mice have no obvious phenotype, but show a 25–45 % reduced response to sour stimuli compared to wild-type (Horio et al. 2011). The suggested signalling module partner in sour tasting *Pkd113*, however, presents no taste phenotype upon gene inactivation (Nelson et al. 2010; Horio et al. 2011).

To date no *Pkd212*<sup>-/-</sup> mouse phenotype has been published.

The evolutionary conservation of TRPP proteins facilitated the study of these proteins in *Chlamydomonas reinhardtii*, *D. melanogaster* and *C. elegans* (Barr and Sternberg 1999; Watnick et al. 2003; Gao et al. 2003; Köttgen et al. 2011; Hu and Barr 2005; Huang et al. 2007). In *D. melanogaster*, TRPP2 is a male-specific protein exclusively expressed at the distal tip of spermatozoa. It is required for male fertility, more precisely for the directed movement of spermatozoa in the

female reproductive tract (Köttgen et al. 2011). *Amo*<sup>-/-</sup> (*Pkd2*<sup>-/-</sup>) flies produce normal amounts of motile spermatozoa but are still infertile (Watnick et al. 2003; Gao et al. 2003; Köttgen et al. 2011). The TRPP homologues (*Brivido 1–3*) have been shown to be important for thermosensation in *D. melanogaster* (Gallio et al. 2011). *Brivido* mutant flies display a significant deficit in their avoidance to cold temperatures (Gallio et al. 2011). *Pkd2*<sup>+/-</sup> mice exhibit impaired responses to warm temperatures, supporting an evolutionarily conserved role for TRPP channels in thermosensation (Köttgen et al. 2008). The *C. elegans* homologues of *PKD1* and *PKD2*, *Lov-1* and *Pkd-2*, are expressed in ciliated neuronal cells (Barr and Sternberg 1999; Hu and Barr 2005). The proteins are required for successful male mating behaviour (Barr and Sternberg 1999; Hu and Barr 2005). Studies of TRPP channels in invertebrate model organisms have added interesting functional insights. The restricted expression pattern of invertebrate TRPP channels in ciliated neurons and sperm has the advantage that null mutants are not lethal. This can be exploited to discover components in the TRPP signalling pathways using unbiased forward genetic screens.

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## 9 Hereditary and Acquired Disease

Mutations in *PKD1* or *PKD2* cause ADPKD (#173900 and #613095 in Online Mendelian Inheritance of Man, <http://www.ncbi.nlm.nih.gov/omim/>) (Mochizuki et al. 1996; Reeders et al. 1985; European Polycystic Kidney Disease Consortium 1994; International Polycystic Kidney Disease Consortium 1995; Paterson and Pei 1998; Paul et al. 2014). ADPKD is the most common potentially lethal single-gene disorder in humans affecting one in 400–1,000 live births (U.S. Renal Data System 2012). The hallmark of ADPKD is the age-dependent massive enlargement of both kidneys, which is characterised by the formation of fluid-filled cysts. The defective three-dimensional tissue organisation in ADPKD begins in utero and is slowly progressive. Ultimately, approximately 50 % of affected individuals will develop end-stage renal disease (ESRD) by the sixth decade of life (Gabow et al. 1990; Hateboer et al. 1999; King et al. 2000; Fick-Brosnahan et al. 2002). In 2010, 26,993 United States citizens were suffering from kidney failure due to ADPKD; the incidence of ADPKD ESRD was 12,755 in the period of 2006–2010 (U.S. Renal Data System 2012). With no treatment options other than dialysis and kidney transplant, ESRD remains a severe illness with poor life expectancy. The five-year probability of survival among 2004 incident PKD ESRD patients was 38.8 % (Renal Data System 2011).

In general, ADPKD is slowly progressive. But the clinical course of the disease may be highly variable, ranging from neonatal death to adequate renal function into old age (Longo and Harrison 2012; Bergmann et al. 2008). The underlying sequence alterations in *PKD1* and *PKD2* are rather heterogeneous. Hundreds of unique mutations have been associated with ADPKD, but very limited information is available on genotype-phenotype correlation (The ADPKD Mutation Database, <http://pkdb.mayo.edu>) (Rossetti et al. 2002; Magistroni et al. 2003; Audrézet

et al. 2012). The significant inter- and intra-familial phenotypic variability points to the involvement of genetic and environmental modifiers to the ADPKD phenotype (Persu et al. 2004). Genetic determinants, including the level of polycystin-1 and TRPP2 together with the penetrance of pathogenic alleles, might modify the disorder's slow progression over the course of decades (Fedele et al. 2011; Rossetti et al. 2002). Environmental factors can influence the short-term progression of renal pathology, e.g. ADPKD cyst enlargement is significantly accelerated by acute kidney injury events (Takakura et al. 2009; Bastos et al. 2009; Prasad et al. 2009).

Although the clinical manifestations overlap completely between PKD1 and PKD2, there is a significant locus effect on renal pathology. On a population scale, *PKD1* mutations cause earlier PKD with ESRD occurring at 54.3 years versus 74 years in PKD2 (Hateboer et al. 1999; Torra et al. 1996). In PKD2, gender correlates with phenotypic penetrance: men experience a faster worsening symptomatology than women, with ESRD at 68.1 years and 76 years, respectively (Hateboer et al. 1999; Magistroni et al. 2003). Whether a similar gender correlation holds true for PKD1 remains to be validated (Rossetti et al. 2002; Gabow et al. 1992; Harris et al. 2006).

Approximately 1,000,000 nephrons form a human kidney (Boron and Boulpaep 2009). Still, an ADPKD patient will develop only about a thousand cysts which will eventually disintegrate the kidney in a process associated with a decline in glomerular filtration and ESRD (Grantham 2008). The small quantity of overall cysts in relation to nephrons emphasises that only very few renal tubules undergo cystic transformation. This focal nature of ADPKD is consistent with a “two-hit” model, indicating that each cyst arises as a consequence of a distinct somatic mutation event (“second hit”) on the background of an inherited germline mutation (“first hit”) (Reeders 1992; Pei 2001). The acquired homozygous inactivation of *PKD1* or *PKD2* is a necessary pathogenic step leading to clonal expansion of cysts (Qian et al. 1996; Watnick et al. 1998; Menezes and Germino 2009). Thus, despite the dominant mode of inheritance, ADPKD is likely recessive at the cellular level. The “second hit” instant of time is of particular importance to cyst growth, i.e. inactivation of *Pkd1* before postnatal day 13 provokes severely cystic kidneys within 3 weeks in mice, whereas inactivation at day 14 or later results in cysts only after 5 months (Piontek et al. 2007). Thus, it is likely that the kidney's developmental stage defines the pathologic consequences of *PKD1* deletion.

Genotypes homozygous and compound heterozygous for *PKD1* or *PKD2* have been reported to be embryonic lethal with PKD, cardiac failure and gross oedema (Wu et al. 2000; Paterson et al. 2002; Pennekamp et al. 2002; Boulter et al. 2001; Lu et al. 2001; Muto et al. 2002). Individuals heterozygous for both *PKD1* and *PKD2* mutations survive to adulthood but show an accelerated progression of disease (Wu et al. 2002; Pei et al. 2001).

Renal cysts are the most prominent manifestations of ADPKD, but a wide spectrum of mostly non life-threatening abnormalities accompany the disorder. Pain is a recurrent symptom in adult patients, often caused by cyst haemorrhage, cyst infection or kidney stones (Bajwa et al. 2001, 2004). Gross and microscopic haematuria are prevalent (Grantham et al. 2006). A major contributor to the decline

in kidney function together with cardiovascular morbidity and mortality is arterial hypertension (Kelleher et al. 2004). Hepatic cysts are the primary extra-renal lesion (Bae et al. 2006). Cysts may also develop in the arachnoid membrane, pancreas and seminal tract (Danaci et al. 1998; Wjickicks et al. 2000). Cardiac and vascular manifestations include an increased incidence of valvular heart disease, coronary artery and intracranial aneurysms as well as chronic subdural haematoma (Wjickicks et al. 2000; Hossack et al. 1988; Schievink et al. 1995; Hadimeri et al. 1998; Lumiaho et al. 2001; Leung and Fan 2005).

In summary, ADPKD is a systemic disorder that represents a therapeutic challenge for clinicians across multiple disciplines. It is hoped that a better understanding of the pathogenic mechanisms will provide the basis for rational therapies of this devastating disease.

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### Conclusions

It has been exciting times since the identification of *PKD1* and *PKD2* as the genes mutated in ADPKD. Biological roles of the encoded proteins polycystin-1 and TRPP2 have been deduced from phenotypes in ADPKD patients, but recent insights from vertebrate and invertebrate model organisms have significantly expanded our understanding of the physiological functions of these proteins. The discovery of the central role of primary cilia and the modular assembly of TRPP channels and polycystin-1 family members are a strong foundation for future discoveries. The identification of upstream and downstream components in the enigmatic polycystin signalling pathway is one of the next important milestones. Clearly, we still have quite some work to do before we understand the molecular mechanisms of these proteins in biological processes like tubular morphogenesis and organ patterning.

**Acknowledgments** Since the initial description of TRPP proteins, the accelerated pace of scientific discovery has produced an impressive body of knowledge. The authors apologise to those whose work could not be cited due to space limitations. Funding was awarded by the Deutsche Forschungsgemeinschaft (DFG KFO 201), by the Excellence Initiative of the German Federal and State Governments (GSC-4, Spemann Graduate School) and by the Alfried Krupp von Bohlen und Halbach Foundation.

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