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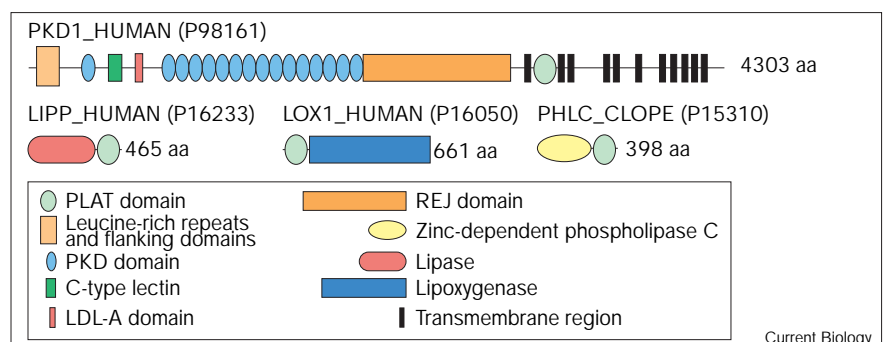
## The PLAT domain: a new piece in the PKD1 puzzle

### Alex Bateman\* and Richard Sandford†

Autosomal dominant polycystic kidney disease (ADPKD) has a prevalence of 1 in 800 of the world's population and accounts for 10% of individuals who require renal replacement therapy, either dialysis or transplantation. Renal cyst

formation occurs as part of a 'two-hit' process in which inactivation of both alleles of ADPKD genes leads to abnormalities of cell proliferation, apoptosis and differentiation [1]. Of ADPKD cases, 85% are due to mutations in the *PKD1* gene, which encodes a 4,302 amino acid protein, polycystin-1 (PKD1), of unknown function. Comparison of the PKD1 sequence with homologous sequences from mouse and *Fugu* predicts polycystin-1 to have a large extracellular region of 3,000 amino acid residues, a region containing 11 putative transmembrane segments and a short intracellular tail [2]. A well-defined extracellular domain structure is apparent; the presence of amino-terminal leucine-rich repeats, a C-type-lectin domain and multiple PKD repeats suggests a role in cell-cell or cell-matrix interactions (Figure 1) [3]. So far, no extracellular ligands of polycystin-1 have been identified. Of the intracellular regions of PKD1, functional properties have been defined only for the short 198 amino acid carboxy-terminal region, which contains a predicted coiled-coil domain. These include a direct interaction with the carboxyl terminus of the protein encoded by *PKD2*, polycystin-2 [4], activation of

Figure 1



Schematic diagram of the domain organisation of PLAT domain proteins. Information and alignments for each of the domains can be found in the Pfam database [14,15] using the following identifiers or accession numbers: leucine-rich repeats,

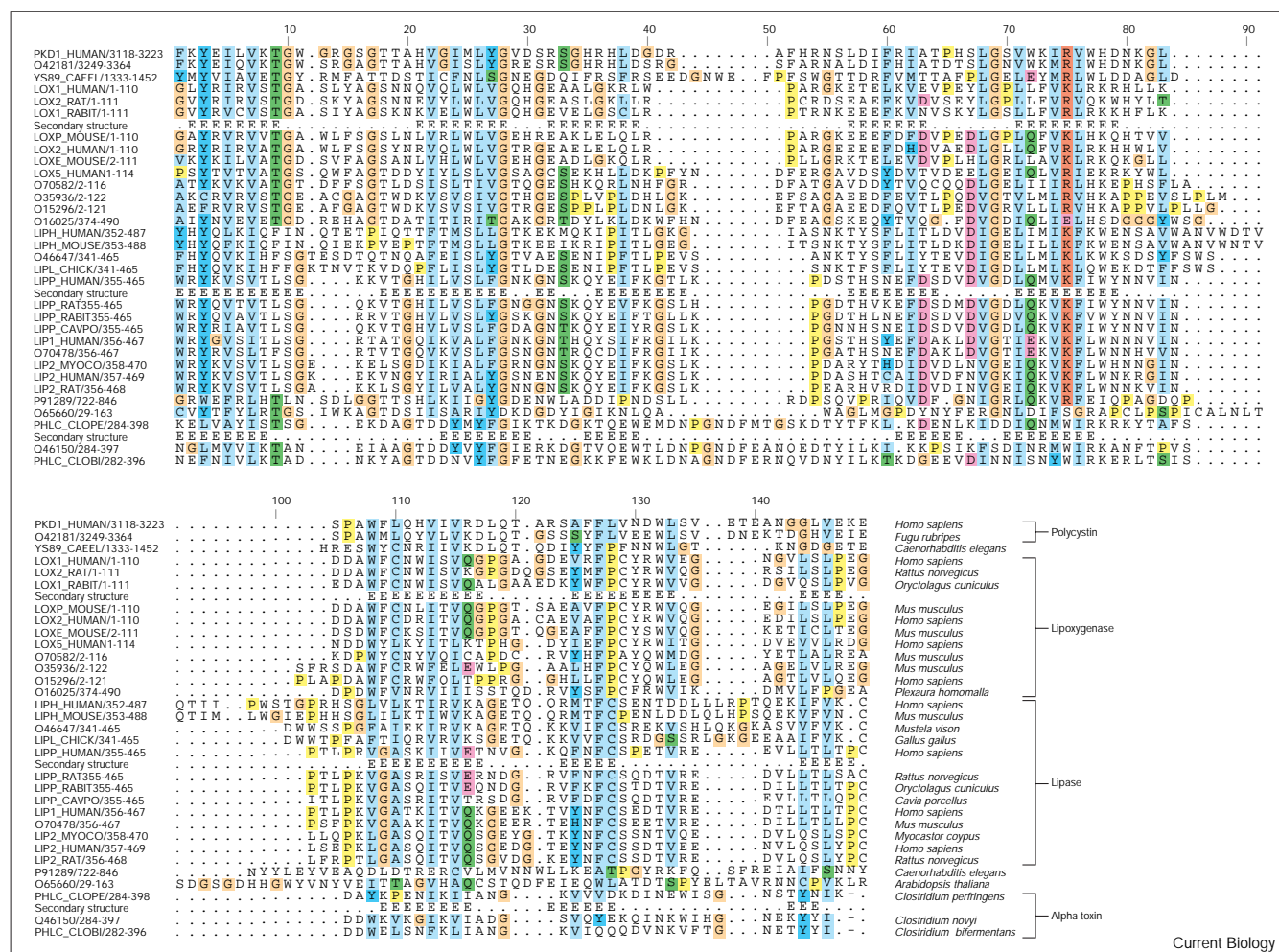
PF00560; C-type lectin, PF00059; LDL-A, PF00057; PKD domains, PF00801; PLAT domain, PF01477; lipoxigenase, PF00305;  $Zn^{2+}$ -dependent phospholipase C, PF00882; lipase, PF00151. Abbreviation: aa, amino acids.

transcription factor AP-1 [5] and activation of heterotrimeric G proteins [6]. The last of these occurs via a motif present in one of polycystin-1's most highly conserved regions. Polycystin-1 may therefore act as a cell-surface receptor or form part of a large membrane-associated complex that is capable of signaling by several different pathways to control cell proliferation and differentiation. To further aid the understanding of this enigmatic protein, we have surveyed all the intracellular regions for potential domains that may suggest novel functions and identify further avenues for experiment.

The current model of polycystin-1 topology suggests that there are four intracellular regions that are large enough to contain a discrete protein domain. These regions are between transmembrane (TM) helices TM1 and TM2 (residues 3,096–3,280), TM3 and TM4 (residues 3,344–3,558), TM5 and TM6 (residues 3,603–3,668) and the carboxy-terminal region after TM11 (residues 4,105–4,302). The high sequence conservation seen in these regions between the human and *Fugu* polycystin-1 suggest that they are functionally important. We have used each of these regions as a query for the sequence comparison program PSI-BLAST, using an

expectation-value (*E*-value) threshold of 0.001 [7]. For each of the four intracellular regions, PSI-BLAST returned the known PKD1 orthologues from human, mouse and *Fugu*. Only one region returned significant matches with PSI-BLAST. The first intracellular region between TM1 and TM2, which represents the most strongly conserved sequence region of PKD1 between human and *Fugu* [2], was found to match to 67 other sequences in SWISS-PROT version 37 and TrEMBL version 9 [8]. These sequences include mammalian lipoxygenases, triacylglycerol lipase and lipoprotein lipase. The common feature found in

Figure 2



A multiple sequence alignment of PLAT domains. The colouring scheme is that used in ClustalX. The secondary structures for the known structures are shown below the sequences; E denotes  $\beta$ -strand.

all these alignments was topological and sequence similarity to a  $\beta$ -sandwich domain. We call this new protein domain the PLAT domain (after polycystin-1, lipoxygenase and alpha toxin). The copy of the PLAT domain found in polycystin-1 therefore identifies an important new region of the protein.

The three-dimensional structure of the PLAT domain is known for human pancreatic lipase [9], rabbit 15-lipoxygenase [10] and alpha toxin from *Clostridium perfringens* [11]. The domain is a  $\beta$ -sandwich composed of two sheets of four strands each. The sequence relationship of the alpha toxin to polycystin-1 can be demonstrated by using the sequence of the PLAT domain from the known structure as a query for PSI-BLAST. The search essentially converges to the same family, including the polycystin-1 PLAT domain. Soybean lipoxygenase L-1 [12] contains a domain structurally related to the PLAT domains. It is more distant in sequence to the rest of the family; PSI-BLAST is able to find relationships to the rest of the family for only a few sequences. Although structural similarities were noticed between these structures, it was not suggested that they share a common ancestor [11].

The most highly conserved regions in the alignment of known PLAT domains (Figure 2) coincide with the  $\beta$ -strands. Most of the highly conserved residues are buried residues. An exception to this is a surface lysine or arginine that occurs on the surface of the fifth  $\beta$ -strand of all the eukaryotic PLAT domains. In pancreatic lipase, the lysine in this position forms a salt bridge with the procolipase protein. The conservation of a charged surface residue may indicate the location of a conserved ligand-binding site within the PLAT domain.

The importance of PLAT domains is underlined by mutations that lead to human disease. Mutations in lipoprotein lipase lead to chylomicronaemia and mutations

in triacylglycerol lipase lead to hepatic lipase deficiency [13]. In pancreatic lipase the PLAT domain is involved in binding to the procolipase protein. This interaction is required to bring the enzymatic active site of the lipase into close contact with its lipid substrate. In 15-lipoxygenase, a protein composed of an amino-terminal  $\beta$ -sandwich (PLAT) and a carboxy-terminal catalytic domain, the PLAT domain may function to localise the enzyme near its membrane or lipoprotein sequestered substrates, by analogy to the lipase-procolipase protein-protein interaction. It is also possible that the PLAT domain of 5-lipoxygenase, another member of the mammalian lipoxygenase family, mediates an interaction with the 5-lipoxygenase activating protein (FLAP), an integral membrane protein. For alpha toxin and plant lipoxygenases, it has been suggested that the PLAT domain interacts directly with the membrane in a  $\text{Ca}^{2+}$  dependent manner. Although a  $\text{Ca}^{2+}$ -binding region has been predicted for alpha toxin from crystallographic data and similarity to eukaryotic calcium-binding C2 domains [11], the conserved residues that form this region are not present in the PLAT domains identified in polycystin-1 or pancreatic lipase. PLAT domains may therefore be involved in protein-protein and protein-lipid interactions. The presence of the PLAT domain in the first cytoplasmic loop of polycystin-1 suggests that this region is important in mediating interactions with other membrane protein(s) involved in polycystin-1 function.

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# A latrophilin/CL-1-like GPS domain in polycystin-1

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## The WSC domain

A PSI-BLAST [S1,S2] search of the region of PKD1 lying between the leucine-rich repeat flanking regions and the first PKD domain of PKD1 (amino acid residues 181–272) using an expect value (*E*-value) inclusion threshold of *E* < 0.01 revealed significant similarity to two regions of *Trichoderma harzianum* β-1,3-exoglucanase [S3] (*E* = 1 × 10<sup>-5</sup> and 6 × 10<sup>-3</sup>) by iteration 1, and nine additional proteins (Figure S1) by convergence after five iterations. Independent evidence for these domain homologues and those discussed below was provided by generalised profile analysis [S4], in which the significance was better than *p* < 0.01 in all cases.

We term these homologues WSC domains, after *S. cerevisiae* WSC1 (cell-wall integrity and stress-response component 1; also called Slg1 and Hcs77), WSC2, WSC3 and WSC4 proteins, which each contain a single such domain [S5]. *S. cerevisiae* WSC1–3 proteins are localised to the plasma membrane and function upstream of the PKC1–MPK1 pathway [S5–S7]. The WSC domains in these proteins are predicted to be extracellular and are

amino-terminal to serine- and threonine-rich regions, a single predicted transmembrane sequence and divergent carboxy-terminal cytoplasmic sequences. The functions of these WSC domains are unknown but the WSC1–3 proteins are suggested to act as sensors of environmental stress [S5–S7], and WSC4 (also called Yhc8p) is implicated in protein translocation to the endoplasmic reticulum [S8].

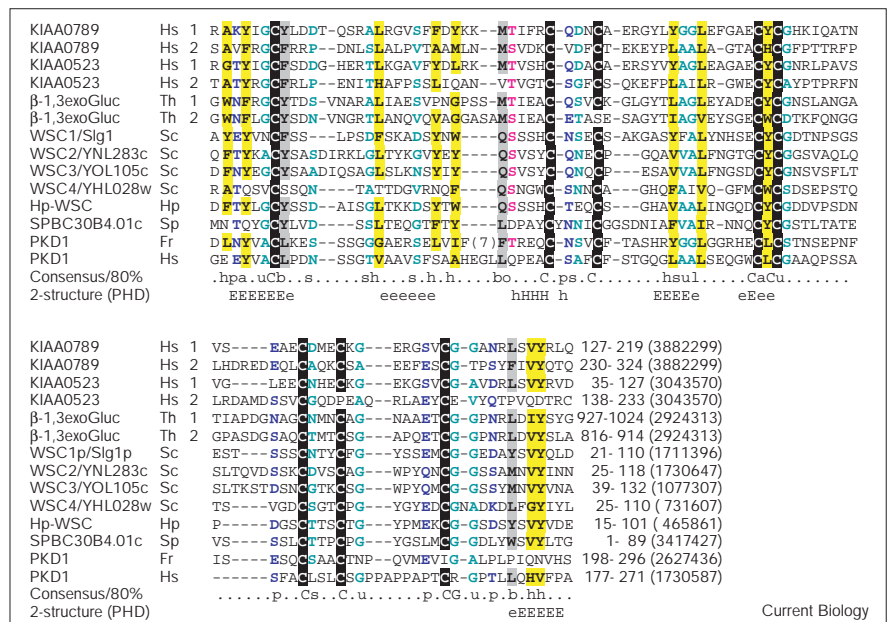
Tandem WSC domains are also found in a hypothetical human protein (KIAA0523) that appears to be a member of a novel sulphotransferase subfamily, and in the *T. harzianum* β-1,3-exoglucanase [S3]. The latter occurrences indicate that the PKD1 WSC domain, and its homologues in general, might possess a carbohydrate-binding role. This would complement the predicted protein-, lipoprotein- and carbohydrate-binding functions conferred by the PKD, LDLα and C-type lectin domains of PKD1.

## The LH2 domain

The cytoplasmic region between the first and second transmembrane regions of PKD1 was found to contain a β-barrel domain, homologous to a non-catalytic domain of

Figure S1

Multiple sequence alignments of WSC domains. Amino acid residues are coloured according to a 80% consensus (calculated using the program Consensus [S13]: + indicates positively charged residues (H, K and R, green); – indicates negatively charged residues (D and E, green); a indicates aromatic residues (F, H, W and Y, highlighted in yellow); b indicates big residues (E, F, I, K, L, M, Q, R, W and Y, grey or yellow); c indicates charged residues (D, E, H, K and R, green); h indicates hydrophobic residues (A, C, F, H, I, L, M, V, W and Y, highlighted in yellow); l indicates aliphatic residues (I, L and V, highlighted in yellow); o indicates alcohol residues (S and T, pink), p indicates polar residues (D, E, H, K, N, Q, R, S and T, dark blue); s indicates small residues (A, C, S, T, D, N, V, G and P, light blue); u indicates tiny residues (A, G and S, light blue). Residues that are predicted to form disulphide bridges are shown as white-on-black. Predicted [S14] secondary structures are indicated below the alignment (e/E, extended or β-strand structure; h/H, helix); lowercase letters represent predictions that have expected accuracies of > 72% and uppercase letters represent predictions that have expected accuracies of > 82%. Residue numbers and GenBank identifiers are shown



following the alignment. Abbreviations: Fr, *Fugu rubripes*; Hp, *Hansenula polymorpha*; Hs, *Homo sapiens*; Sc, *Saccharomyces*

*cerevisiae*; Sp, *Schizosaccharomyces pombe*; Th, *Trichoderma harzianum*; β-1,3exoGluc, β-1,3 exoglucanase.

Figure S2

LOX1	Oc	GYYRVCVSTG--ASIVAGSKN--KVELWLVGQH-----GEVELGSCRPT--RNKEEEKVNVSRY			
LOX1	Gm	HRIKGTIVLMPKNELEVPDGS(11)SVSLQLISATKADAHGKGVKQDTFLGGIN(8)GESAPNHEFDWGS			
LIP2	Rn	WRKVSVITLS--GAKKLSG-----YELVALYGN-----NGSKQDYEIKGSLK--PEARHVRDIDVDIN			
PKD1	Hs	FRYELIVKFG--WGRGSGTTA-----HVGIMLYGVDS-----RSGHRHLDGDRAPH--RNSLDIPLIATPHS			
PKDREJ	Hs	LCYLVITIFFG--SRWGSSTRA--NVFVLRGTVSTSDVHCLSHPHFTILY-----RGSINTELLTTKSD			
PKD	Fr	FRYELIVKFG--WSRGAGTTA-----HVGISLYGRES-----RSGHRHLDGDRGSPA--RNALDIPLIATDTS			
ZK945.9	Ce	YMYVIAVERG--YRMEATDTS-----TICFNLSGNEGQD--IFRSPRSEEDGNMFPFSS--WGTTRDREVMTTAFD			
Consensus/80%		h.Ybl.V.hu.....bhsss.s...p1.L.L.G.....p.cbs..b.....s.p.b.bsss.s			
2° structure		EEEEEEEE EEEEEEE EEEEEEE EEEEEEE EEEEEEE			
LOX1	Oc	LGSLLFVRLRKKHFLK--EDANFCNNTSVALCAAEDKVFPCYRNVVD-----GVQSLPVG	2-	112	(126397)
LOX1	Gm	MGIPGAFYKKNY----QVEFLKSLTLEA--SNQTIREFVCGNWNKLYKSVRIIFAN	6-	146	(126398)
LIP2	Rn	VSEIKQKKEFNNA----APFLGASQITVQSG--VDKKEYNKCSPTVRED-----VLQSLPVC	340-	446	(4139580)
PKD1	Hs	LGSVKKIRVHHDNKGSL--SPANFLQEVIVRDL--QTARSAFPLVNDWLSVE--TEANGGLVEK	3118-	3232	(1730587)
PKDREJ	Hs	LGDHHSIRVWHNNEGR--SPSWYLSRIKVENL--FSRHILWFCQKWLVDV--TTLDRTFHT	1230-	1346	(4336954)
PKD	Fr	LGNVKKIRVHHDNKGSL--SPAWMLQYVLVVDL--QTGSSSYPLVEEWLVDV--NEKTDGHEI	3249-	3363	(2627436)
ZK945.9	Ce	LGELEVMRLWLDAGLDHRESKRYCNRIIVKDL--QTQDIYYFPFNMLGPK--NGDGETERLAR	1333-	1456	(1176908)
Consensus/80%		lqpl..h+lb.p.....psasbhp.l.Vbsl..s.p.hbF.sppWl.sc.....p.hh..			
2° structure		EEEEEEEE EEEEEEE EEEEEEE EEEEEEE EEEEE			

Current Biology

Multiple alignment of LH2 domains, coloured according to the consensus scheme of Figure S1. Predicted [S14] secondary structures are indicated below the alignment (e/E, extended or  $\beta$ -strand structure; h/H, helix); lowercase letters represent predictions that have expected accuracies of > 72% and uppercase letters represent predictions that have expected accuracies of > 82%. Residue numbers and GenBank identifiers are shown following the alignment. Abbreviations: Ce, *Caenorhabditis elegans*; Fr, *Fugu rubripes*; Gm, *Glycine max* (soybean); Hs, *Homo sapiens*; Mm, *Mus musculus*; Oc, *Oryctolagus cuniculus* (rabbit); Rn, *Rattus norvegicus*; LOX1, arachidonate 15-lipoxygenase; LIP2, pancreatic lipase-related protein 2.

lipoxygenases [S9]. A PSI-BLAST search [S1,S2] using PKD1 residues 3,096–3,280 as query revealed significant similarity ( $E < 10^{-6}$ ) by iteration 1 to the amino-terminal domain of mammalian arachidonate 5-lipoxygenases (Figure S2). This domain has an eight-stranded  $\beta$ -barrel fold [S9] and is highly similar in structure to the carboxy-terminal domains of mammalian lipases [S10,S11] and the amino-terminal domains of plant 15-lipoxygenases [S12] (Figure S2). We term these domains lipoxygenase homology 2 (LH2) domains. The current model for the function of LH2 domains is that they facilitate binding of lipase and lipoxygenase substrates to the enzymes' active sites [S9]. Thus the presence of this domain in the first cytoplasmic loop of PKD1 suggests a role in lipid-mediated modulation of PKD1 function.

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