*Journal of Inherited Metabolic Disease*

WILEY

JIMD SSIEM

REVIEW OPEN ACCESS

# Phosphoinositide Metabolism: Biochemistry, Physiology and Genetic Disorders

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**Received:** 23 December 2024 | **Revised:** 3 February 2025 | **Accepted:** 4 February 2025

**Communicating Editor:** Carlos R. Ferreira

**Funding:** The authors received no specific funding for this work.

**Keywords:** cellular trafficking | inborn error of metabolism | inherited metabolic disease | phosphatidylinositol | phosphoinositide | polyphosphoinositide

## ABSTRACT

Phosphatidylinositol, a glycerophospholipid with a *myo*-inositol head group, can form seven different phosphoinositides (PItds) by phosphorylation at inositol carbons 3, 4 and/or 5. Over 50 kinases and phosphatases participate in PItd metabolism, creating an interconnected PItd network that allows for precise temporal and spatial regulation of PItd levels. We review paradigms of PItd action, including (1) the establishment of subcellular organelle identity by the acquisition of specific PItd signatures, permitting regulation of key processes of cell biology including trafficking (exocytosis, clathrin-dependent and -independent endocytosis, formation and function of membrane contact sites, cytoskeletal remodeling), (2) signaling through phospholipase C cleavage of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate and DAG, and (3) roles of PItds in molecular transport at membrane contact sites. To date, variants in 34 genes of PItd metabolism account for at least 41 distinguishable monogenic conditions. Clinical presentations of these disorders produce a broad and often multisystemic spectrum of effects. The nervous system is often involved, and muscular, immunological, skeletal, renal, ophthalmologic and dermatologic features occur in several conditions. Some syndromes involving PItd metabolism can be distinguished clinically, but most diagnoses currently result from broad molecular diagnostic testing performed for the patient's presenting clinical complaint. Genetic disorders of PItd metabolism are a broad, expanding and challenging category of inborn errors. Challenges include improved documentation of the clinical spectra, development of broad biochemical diagnostic methods for these conditions and better understanding of the PItd networks in different cells and subcellular compartments necessary for the development of disease-specific therapies.

**Abbreviations:** CCV, clathrin-coated vesicle; CDP-DAG, CDP-diacylglycerol; CDS, CDP-diacylglycerol synthase; DAG, diacylglycerol; ER, endoplasmic reticulum; FA, fatty acid; GDPIM, genetic disorder of phosphoinositide metabolism; GPCR, G-protein coupled receptor; GPI, glycosylphosphatidylinositol; $IP_3$, inositol 1,4,5-trisphosphate; LTP, lipid transfer protein; MCS, membrane contact site; PHTS, *PTEN*-hamartoma tumor syndrome; PI, phosphatidylinositol; $PI(3,4,5)P_3$, phosphatidylinositol 3,4,5-trisphosphate; $PI(3,4)P_2$, phosphatidylinositol 3,4-bisphosphate; $PI(3,5)P_2$, phosphatidylinositol 3,5-bisphosphate; PI3P, phosphatidylinositol 3-phosphate; $PI(4,5)P_2$, phosphatidylinositol 4,5-bisphosphate; PI4P, phosphatidylinositol 4-phosphate; PI5P, phosphatidylinositol 5-phosphate; PIS, phosphatidylinositol synthase; PItd(s), phosphoinositide(s); PITP, phosphatidylinositol transfer protein; $PLA_2$, phospholipase $A_2$; PLC, phospholipase C; PROS, *PIK3CA*-related overgrowth spectrum.

## 1 | Introduction

Phosphatidylinositol (PI) and its phosphorylated derivatives (phosphoinositides [PItds]) are essential for the function of all eukaryotic cells [1]. Despite the wealth of basic research into PItd biology and the identification of over 41 PItd-related inborn errors, this field is little known to most metabolic physicians, and the bridge between PItd physiology and clinical manifestation is often incompletely understood. In this review, we briefly summarize PItd metabolism and its roles in cell physiology, membrane biology and vesicular trafficking. Then we describe the known genetic disorders of PItd metabolism, henceforth abbreviated GDPIMs.

## 2 | Phosphoinositide Metabolism

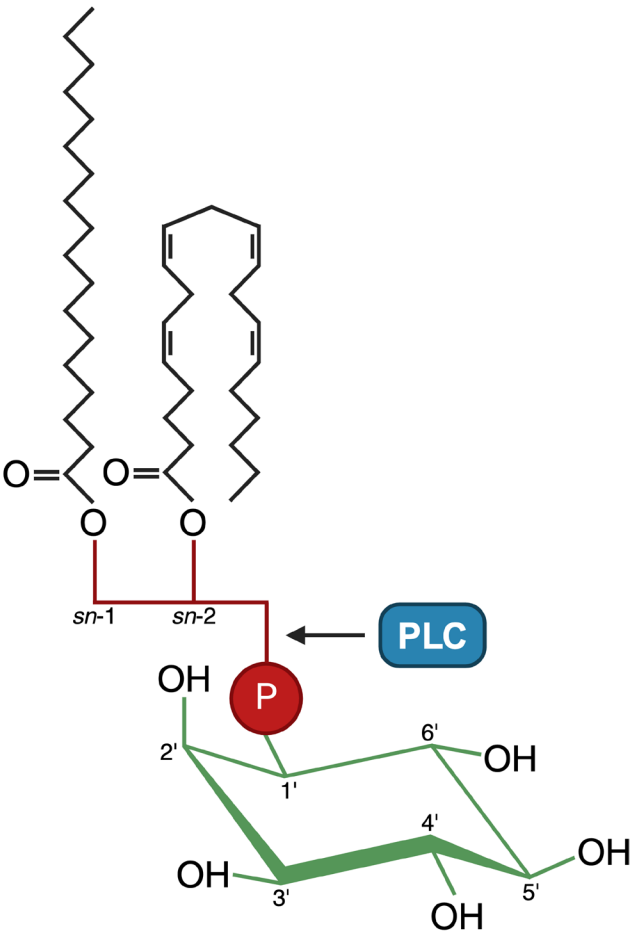
PI plays multiple roles in biology (Box 1). PItds were first identified for their role in cell signaling and have since been recognized to control important steps of membrane and vesicular trafficking through the recruitment of different effector proteins [2]. PI is synthesized in the endoplasmic reticulum (ER) in two steps: CDP-diacylglycerol synthase (CDS) converts phosphatidic acid and CTP into CDP-diacylglycerol (CDP-DAG), then phosphatidylinositol synthase (PIS) converts CDP-DAG and inositol into PI [3, 4]. PI then is transported from the ER to other organelles or to the plasma membrane by vesicular transport or by lipid transfer proteins (LTPs) such as PI transfer proteins (PITP) found at membrane contact sites [2, 5, 6]. Two main models of PITP function are described: a transport model, in which PITP directly transfers PItd from the ER to the receiving membrane; and a presentation model, in which PITP presents the PItd to kinases for phosphorylation. This last model may explain how some kinases that are inhibited under most experimental conditions can phosphorylate substrates presented in this fashion, allowing for refined control of PItd signaling [5].

Phosphorylation of PI into PItd occurs mostly after PI transport from the ER to the cytosolic surface of the plasma membrane or other organelles. Multiple kinases and phosphatases act to phosphorylate and dephosphorylate, respectively, the inositol ring [3, 10, 11]. The phosphatidic acid moiety of PI binds at the D1 position of the inositol ring (Box 1), and phosphorylation can occur at the D3, D4 and/or D5 positions. There are seven possible species of PItd (Figure 1): phosphatidylinositol 3-phosphate (PI3P), phosphatidylinositol 4-phosphate (PI4P), phosphatidylinositol 5-phosphate (PI5P), phosphatidylinositol 3,4-bisphosphate ($PI(3,4)P_2$), phosphatidylinositol 3,5-bisphosphate ($PI(3,5)P_2$), phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) and phosphatidylinositol 3,4,5-trisphosphate ($PI(3,4,5)P_3$) [2, 4]. Each PItd can undergo multiple phosphorylation or dephosphorylation events and be converted to any other PItd (Figure 1), making their cellular levels highly interdependent [2, 10]. Activity of phospholipase C (PLC), a part of many transduction pathways, releases the second messengers inositol 1,4,5-trisphosphate ($IP_3$) and DAG, which can eventually be recycled into PI (Figure 2) [2, 3].

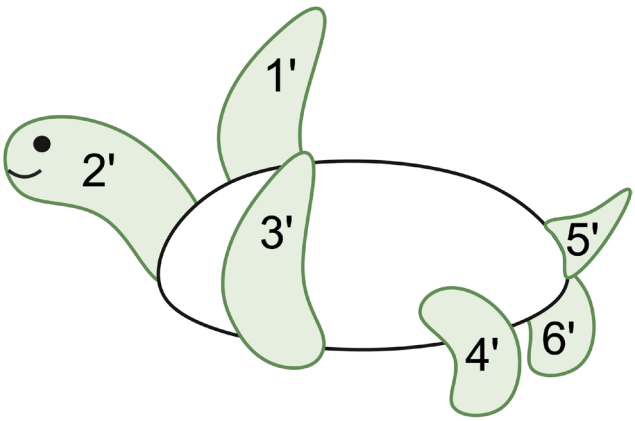
**BOX 1** | Inositol and phosphoinositides (PItds).

Inositol is a six-carbon molecule synthesized from glucose-6-phosphate by isomerization to inositol-3-phosphate by inositol synthase, Ino1 (*MIPS1*). Dephosphorylation produces free inositol [7]. In humans, most inositol comes from endogenous synthesis (~4 g/day), especially in the kidney; about 1 g/day comes from the diet [7]. Inositol is also produced from the degradation of phosphoinositides (PItds).

*Myoinositol and other variants of inositol.* Each carbon atom of inositol has one hydroxyl group (Box Figure A) and one hydrogen group, oriented in the opposite direction to the hydroxyl with respect to the plane of the molecule (not shown). Chemical variants of inositol are defined by the positions of each hydroxyl group relative to the plane of the molecule. The most prevalent form in biology is *myo*-inositol (shown), which is the only form discussed further in this article and will henceforth be designated as "inositol." Figure B is a mnemonic to recall the positions of the hydroxyl groups in myoinositol. Bernard Agranoff likened this molecule to a swimming turtle [8], with head, forelimbs and tail raised (i.e., carbons 1, 2, 3 and 5), but hindlimbs (i.e., carbons 4 and 6) pointing downward.



**BOX 1** | Continued




*Structure of phosphatidylinositol*. Box Figure A schematically shows a PI molecule. The phosphate (red circle), glycerol (red lines) and esterified fatty acids (FAs, black) are shown in relation to inositol (green).

*Fatty acid composition of PI*. In cells, the FAs of PI are embedded in the cytoplasmic leaflet of cellular membranes. The FAs are esterified to the first and second carbon atoms of a glycerol molecule, together forming the diacylglycerol (DAG) moiety of the PI molecule. The first glycerol carbon is usually esterified to a saturated fatty acid (FA), typically stearic acid (C18:0, octadecanoic acid); the second carbon, to a polyunsaturated FA such as arachidonic acid (C20:4, i.e., 20 carbon atoms and 4 unsaturated bonds, at positions 5–6, 8–9, 11–12 and 14–15, i.e., 5Z,8Z,11Z,14Z-eicosatetraenoic acid). Using magnetic resonance spectroscopy, the total number of carbon atoms and the number of double bonds in the fatty acid molecules can be determined, but the two FAs cannot be differentiated individually by most instruments. Hence, for example, a common DAG species that has one 18:0 and one 20:4 FA will be designated as "C38:4," reflecting the sums of carbon atoms and of double bonds of the two FA molecules.

*Phosphoinositides*. In PI, carbon 1 of inositol is ester-bound to the phosphate of the phosphatidic acid moiety. Hydroxyl groups 3, 4 and 5 (i.e., the left limbs and tail of the turtle) project from the cytoplasmic surfaces of membranes. Each of these positions can be phosphorylated, in any combination, for a total of seven different PI species. Inositol is thus the most diverse head group among cellular phospholipids. Figure A also shows the site of action of phospholipase C (PLC). Cleavage of $PI(4,5)P_2$ by phospholipase C (PLC, shown) produces two biologically important products, free inositol 1,4,5-phosphate ($IP_3$) and a membrane-bound diacylglycerol (DAG). This important reaction of cell signaling is discussed later.

*Other functions of inositol*. Physiologically, free inositol is an endogenous osmol [7]. Another important function not further detailed in this article is the use of membrane PI to anchor the synthesis of polysaccharide chains for N-linked protein glycosylation (GPI anchors) [9].

Together, PI and PItds represent 10–15 mol% of the total phospholipid content in an average cell [4, 14]. PI alone accounts for about 90–95 mol% of this pool [15]. PI4P and $PI(4,5)P_2$ are the most abundant PItds, each representing about 2–5 mol% of the total. The other PItd species are rarer, with PI3P representing 0.2 to 0.5 mol% of the total, $PI(3,4)P_2$ less than 0.1 mol%, $PI(3,4,5)P_3$ less than 0.05 mol%, $PI(3,5)P_2$ 0.05 to 0.1 mol%, and PI5P 0.01 mol% of the total PI plus PItd content [4, 6, 16, 17]. More important than their overall abundance, the concentrations of specific PItds in localized membrane regions can regulate important cell processes [10]. Table 1 summarizes PItd levels and intracellular localization and provides some examples of their function. Although PI synthesized in the ER is required for PItd synthesis, it can be found in high levels only in some membranes, such as the Golgi, peroxisomes, and outer mitochondrial membrane. Other membranes, such as the plasma membrane, are relatively depleted of PI despite maintaining substantial amounts of PItd. This suggests a dependence on sustained transport of PI from the ER for maintenance of PItd concentration in membranes [18].

The expression of PItd in organelles is tightly regulated and results in local enrichment of specific PItd species at precise sites of intracellular and plasma membranes (Figure 3) [2, 25], a key factor in defining organelle identity. Some properties of PItds make them particularly effective for this function: as other phospholipids, they can quickly diffuse laterally in membranes (but are not as easily transported between membranes), and can rapidly be converted from one to another [25]. As vesicular trafficking proceeds, recruitment of PI kinases and phosphatases allows for changes in PItd composition, activating different effector proteins necessary for that phase of trafficking. For example, at fusion, membrane PItds direct the recruitment and the retention of effector proteins [2], both in the carrier vesicle and in the acceptor membrane. After fusion, shifts in PItd levels, due to dilution of the transported PItds in the acceptor membrane and to the action of different phosphatases and kinases in the new compartment, create a different environment [25]. This dynamic interconversion of PItds allows for conservation of organelle identity despite a high flux of membrane traffic [2].

The regulation of PItd localization depends upon many factors [10], including the availability of a precursor PItd and the action of adaptor proteins to recruit the necessary PI kinases and phosphatases to the right cellular location [26]. Membrane curvature and fatty acid composition can also affect PItd kinases and phosphatases [27]. Conversely, effector proteins may affect PItd metabolism: some $PI(4,5)P_2$ effector proteins recruit specific kinases that enhance $PI(4,5)P_2$ synthesis, allowing for further activation of effectors and creating a local amplification loop [28].

The fatty acids (FAs) of PItds can influence function. The most prevalent FA composition of PItds is a stearic acid (18:0) in the *sn*-1 position and an arachidonic acid (20:4) in the *sn*-2 position (1-stearoyl-2-arachidonyl-PI), representing 40% to 85% of PI, depending on cell type. *De novo* synthesized PI shows a diverse pool of acyl chains, suggesting that enrichment for certain FAs is required and likely occurs by remodeling through the Lands cycle of FA cleavage and ligation. The cycle is mediated by several acyltransferases, including *MBOAT7* (LPIAT; lysophospholipid acyltransferase), *LCLAT1* (ALCAT1: lysocardiolipin acyltransferase) and also phospholipases $A_1$ and $A_2$ [3]. Nevertheless, specific acyl chains are required in some instances, such as saturated acyl chain

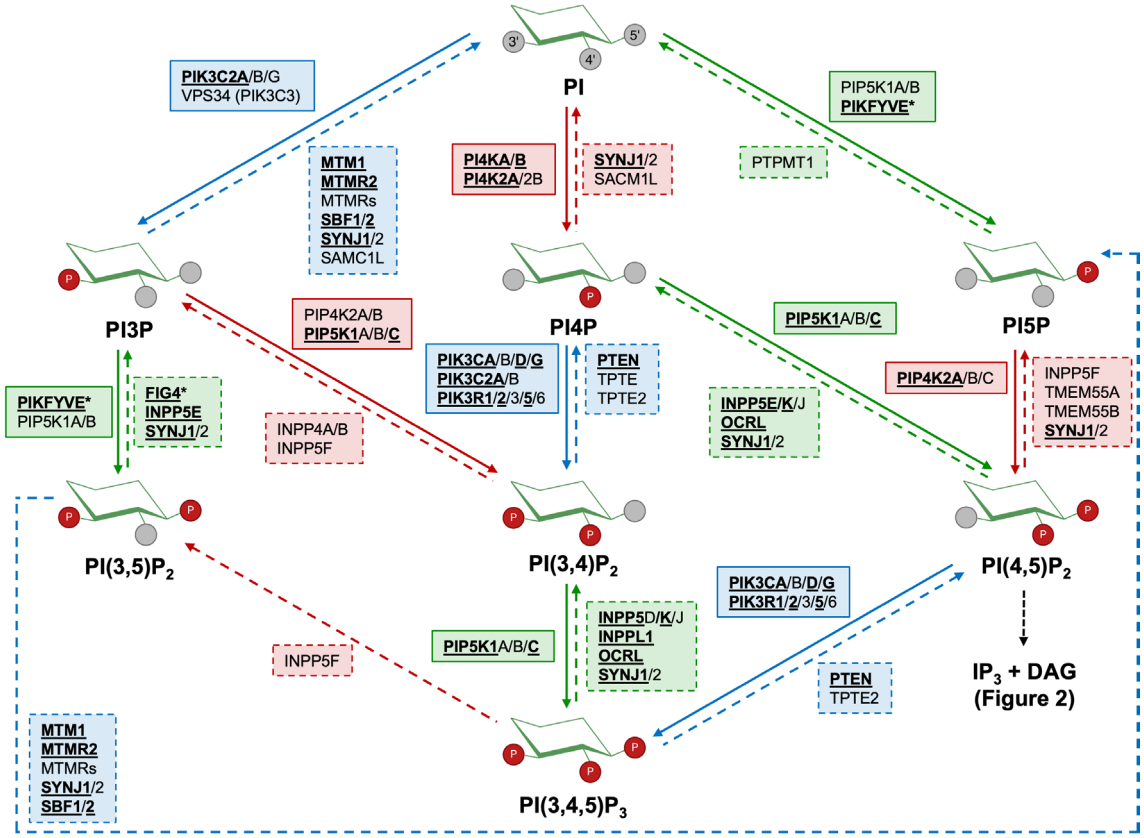



**FIGURE 1** | Phosphoinositide metabolism. Reactions and enzymes of the PI-PItd network [12, 13]. At many steps, different enzymes can catalyze the same generic reaction, but this overview does not consider the differing organelle expression patterns of the individual enzymes. Asterisks indicate interaction with VAC14, a protein that complexes with both PIKFyve and FIG4. Another accessory protein, HYCC1, a regulator of PI4P synthesis required to localize PI4K at the plasma membrane, is not illustrated.

$PI(4,5)P_2$ for activation of the $K_{ir}2.1$ channel, and the preference of seipin for PI3P with unsaturated acyl chains [29]. The cleavage and liberation of FA from PI/PItds can influence cell function. One example is the regulation of leukotriene biosynthesis by pools of free arachidonic acid that can derive from cleavage of PI or PItd [30].

Most of the steps of the network linking the seven different PItds can be catalyzed by more than one kinase or phosphatase (Figure 1) [10, 11]. What is the function of this high degree of redundancy? One suggestion is that it may provide a built-in compensation for defects in the pathway. However, the finding that many GDPIMs arise from single enzyme modifications in this pathway suggests that compensation is partial at best. In another model, the action of individual kinases and phosphatases may be necessary only in specific subcellular locations or under specific conditions (e.g., cell type, physiological state). Several factors may influence this phenomenon: organelle-specific targeting; cell-specific or developmental window-specific expression or regulation; and/or repressed expression of functionally redundant enzymes [10, 31].

## 3 | Roles of Phosphoinositides

PItds function by binding and retaining cytosolic proteins or cytosolic domains of membrane proteins in a time- and location-specific manner [6], generally through electrostatic interactions with the negatively charged phosphorylated PItd head group. Over 400 such PItd-binding proteins were identified in one proteomic study [32]. Motifs that interact with PItd include Pleckstrin homology (PH), FYVE, or Phos homology (PX) domains [4, 25]. In addition, certain clusters of polybasic amino acids serve as non-canonical PItd-binding sites [25]. In general, binding between PItd and an effector protein is of low affinity. Affinity increases in the presence of additional factors, including other proteins and lipids. This phenomenon, by which the combination of different but nearly simultaneous signals greatly increases the chance of a biological response, is termed coincidence detection; it allows for both compartment specificity and rapid modulation of the response [2, 6, 25]. For example, sorting nexins bind to PItd through a PX domain and also contain a BAR domain allowing for sensing of membrane curvature [6]. The combination of both PItd binding and the correct membrane curvature suffices to activate sorting nexin 9, an essential step of exo-endocytic budding and fusion [6]. Similarly, the presence of hydrophobic residues in the protein may allow for partial entry of the protein into the membrane, which may further stabilize the structure [25].

Some PItd-binding proteins function by competitive inhibition, making PItd unavailable to the effector proteins. For example, although $PI(4,5)P_2$ is relatively abundant in the plasma membrane, proteins such as MARCKS, GAP43 and CAP23 sequester as much as two thirds of the total $PI(4,5)P_2$ pool. Small changes in total $PI(4,5)P_2$ levels may substantially change

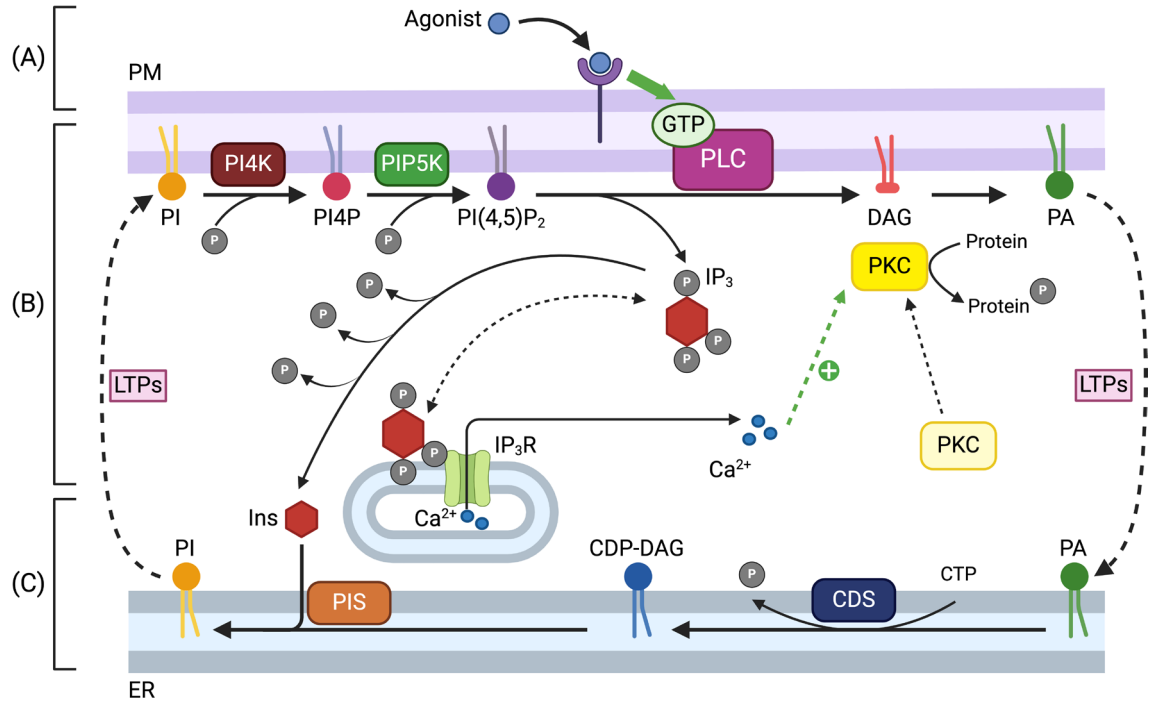



**FIGURE 2** | PI—PI(4,5)$P_2$ cycle. The PI—PI(4,5)$P_2$ cycle is a paradigm of cell signaling [2, 3]. (A) *Activation of phospholipase C (PLC).* Typically, an extracellular signaling molecule stimulates a G-protein-coupled transmembrane receptor. Receptor activation leads to GTP binding, which activates membrane PLC. (B) *Signaling.* The plasma membrane contains locally synthesized PI(4,5)$P_2$. PLC-mediated cleavage of PI(4,5)$P_2$ generates diacylglycerol (DAG) and inositol 1,4,5-trisphosphate ($IP_3$) moieties, both of which are biologically active. The DAG remains membrane-bound and enhances the localization of protein kinase C (PKC) to the plasma membrane, activating PKC. $IP_3$ is released into the cytoplasm and can bind receptors ($IP_3$Rs) on smooth ER, which are calcium channels. $IP_3$ binding stimulates calcium release to the cytoplasm. Calcium has multiple actions, including synergistic further activation of DAG-bound PKC. PKC can phosphorylate a set of effector proteins. (C) *Inactivation and recycling.* $IP_3$ is inactivated by dephosphorylation, producing inositol. DAG is inactivated to PA. These molecular remains can be used in the ER for resynthesis of PI, then transported to the Golgi by lipid transport proteins (LTPs), where re-phosphorylation can occur. Abbreviations: CDP, cytidine diphosphate; CTP, cytidine triphosphate; PA, phosphatidic acid.

the levels of free PI(4,5)$P_2$, its availability and physiologic effects [28].

PItds participate in many physiological reactions. An exhaustive catalogue is beyond the scope of this article. However, some examples are presented to illustrate general paradigms by which PItds influence cell physiology and transport.

### 3.1 | Phosphoinositides in Cell Signaling

PItds regulate signal transduction and cytoplasmic calcium levels. Cleavage of PI(4,5)$P_2$ by phospholipase C (PLC) releases inositol 1,4,5-trisphosphate ($IP_3$), a soluble second messenger that stimulates intracellular calcium release from the ER. Breakdown of PItds by phospholipase $A_2$ ($PLA_2$) similarly releases signaling metabolites (a FA, typically arachidonate, and *sn*-2 lyso-PItd) [25]. Different PItds affect signal transduction differently. For instance, phosphorylation of PI(4,5)$P_2$ to PI(3,4,5)$P_3$ enhances growth factor signaling, whereas dephosphorylation of PI(4,5)$P_2$ by PI 5-phosphatases inhibits this by decreasing PI(4,5)$P_2$ availability [25]. Similarly, in insulin signaling, transient increases of PItds, including PI(3,4,5)$P_3$, activate Akt, increasing glucose uptake through GLUT4 trafficking and, in liver and muscle, reducing gluconeogenesis and increasing glycogen and lipid synthesis [26].

Exocytic roles of PItds (discussed later) also impact insulin release and GLUT4 trafficking [26]. PItds can regulate G-protein coupled receptor signaling (GPCR), affecting the association of GPCRs with G proteins, kinases and other proteins, and activating downstream proteins [29].

Phosphoinositides can also act through allosteric activation of different membrane proteins, including channels and transporters. For example, for some potassium channels (e.g., $K_{ir}2.1$), PI(4,5)$P_2$ binding at the interface between the cytosolic and transmembrane domains enhances the opening of the channel [6]. Some ion channels interact with multiple PItds; others interact with only one. This specificity may be useful in suppressing the activity of ion channels during their synthesis in the ER and trafficking to their final target membrane, where channel activity could be toxic, with activation occurring only in the target membrane that contains the PItd profile required for activation [33].

### 3.2 | Phosphoinositides in Inter-Organellar Trafficking

Vesicular trafficking is intimately linked to PItds, which are central to various steps of endocytosis and exocytosis, from

**TABLE 1** | Phosphoinositide abundance, localization, and primary functions.

| Phosphoinositide | Fraction of PI + PItds (mol%) | Localization | Examples of functions |
|---|---|---|---|
| PI | 90–95 | ER<br>*Also present in Golgi* | PItd precursor |
| PI3P | 0.2–0.5 | Early endosomes<br>*Possibly ER, Golgi* | Autophagy, early endosome and phagosome maturation, endosome fusion/trafficking, retrograde transport |
| PI4P | 2–5 | *Trans*-Golgi, endosomes<br>*Also present in plasma membrane* | Vesicle budding and clathrin adaptor recruitment, maintenance of Golgi structure |
| PI5P | 0.01 | Debated<br>*Highest in plasma membrane, enriched in ER, Golgi, early endosomes, present in nuclear envelope* | Apoptosis, stress signaling, potential nuclear functions |
| $PI(3,4)P_2$ | < 0.1 | Plasma membrane, endosomes | Cell migration/adhesion/invasion, endocytosis |
| $PI(3,5)P_2$ | 0.05–0.1 | Late endosomes, lysosomes | Cargo sorting in late endosomes or internal vesicle of multivesicular bodies |
| $PI(4,5)P_2$ | 2–5 | Plasma membrane<br>*Small amounts in Golgi, endolysosomal system* | Exocytosis, autophagy, clathrin-dependent endocytosis, cytoskeletal organization, regulation of multiple proteins/receptors |
| $PI(3,4,5)P_3$ | < 0.05 | Plasma membrane<br>*Also in some endocytic compartments* | Cell growth and survival, apoptosis, transcription/translation, adhesion, cell polarity/movement/chemotaxis |

*Note:* Adapted from Dickson et al. [16] and additional sources [5, 6, 15, 17–20]. Abundance numbers given here are estimates and may vary substantially from one cell type to another.

budding initiation to membrane fusion [2]. For example, the transport of vesicles from the *trans*-Golgi involves the recruitment of GOLPH3 by PI4P, which promotes binding to myosin 18A and F-actin, producing the conditions necessary for transport from the Golgi [34].

Membrane contact sites (MCS) ensure proximity between membranes of two organelles, allowing for lipid, protein and small metabolite exchanges [2, 35]. For example, at ER-Golgi MCSs, the protein OBSP binds both to membrane proteins of the ER and to PI4P in the Golgi. OBSP-mediated cholesterol transport to the Golgi is powered by a cycle of PI4P phosphorylation and dephosphorylation and the concentration gradient that this creates (Figure 4). Once in the ER, PI4P is dephosphorylated by SACM1L and recycled to the Golgi where PI4P is resynthesized. A similar exchange of PI4P and phosphatidylserine occurs through the action of ORP5 and ORP8 at ER-plasma membrane MCSs [35]. PI4P phosphorylation at each membrane is performed by different kinases: in mouse Schwann cells, deletion of PI4KA, which is present at the plasma membrane under normal conditions, resulted in a significant decrease in phosphatidylserine but not phosphatidylethanolamine and sphingomyelin contents [37]. On the other hand, inactivation of PI4KB, which is located in the Golgi, resulted in significant cholesterol, phosphatidylethanolamine and sphingomyelin depletion but without a significant decrease in phosphatidylserine content [38]. Those results are consistent with previous work which demonstrates that the transport of PI4P from the plasma membrane to the ER drives the counter-transport of phosphatidylserine from the ER to the plasma membrane at ER-plasma membrane contact sites [39]. By the same token, those studies [37, 38] conclude that PI4KA and PI4KB contribute differently to myelination of the peripheral nervous system. As for PI3P, interaction of protrudin with PI3P and RAB7 allows for the formation of MCSs between the ER and late endosomes, and recruits kinesin-1, which moves the endosome towards the plasma membrane [35].

Vesicle formation is also assisted by PItds. For example, the activation of epsins and other proteins by $PI(4,5)P_2$ promotes the formation of membrane tubules which can become vesicles. PItds participate in cytoskeletal remodeling (section 3.4) and membrane remodeling, notably through the interaction of $PI(4,5)P_2$ with N-WASP and the Arp2/3 complex [28]. Finally, the interaction of PItds with sorting nexins allows for the regulation of trafficking between different compartments, as with $PI(4,5)P_2$, SNX5 and the targeting of E-cadherin from endosomes to lysosomes for degradation [28].

#### 3.2.1 | Exocytosis

Several steps in exocytosis depend upon PItd metabolism. The exocyst, an eight-subunit complex required for constitutive exocytosis, is regulated by PI4P and Rab11, although the extent of the mechanisms by which PI4P operates is yet to be

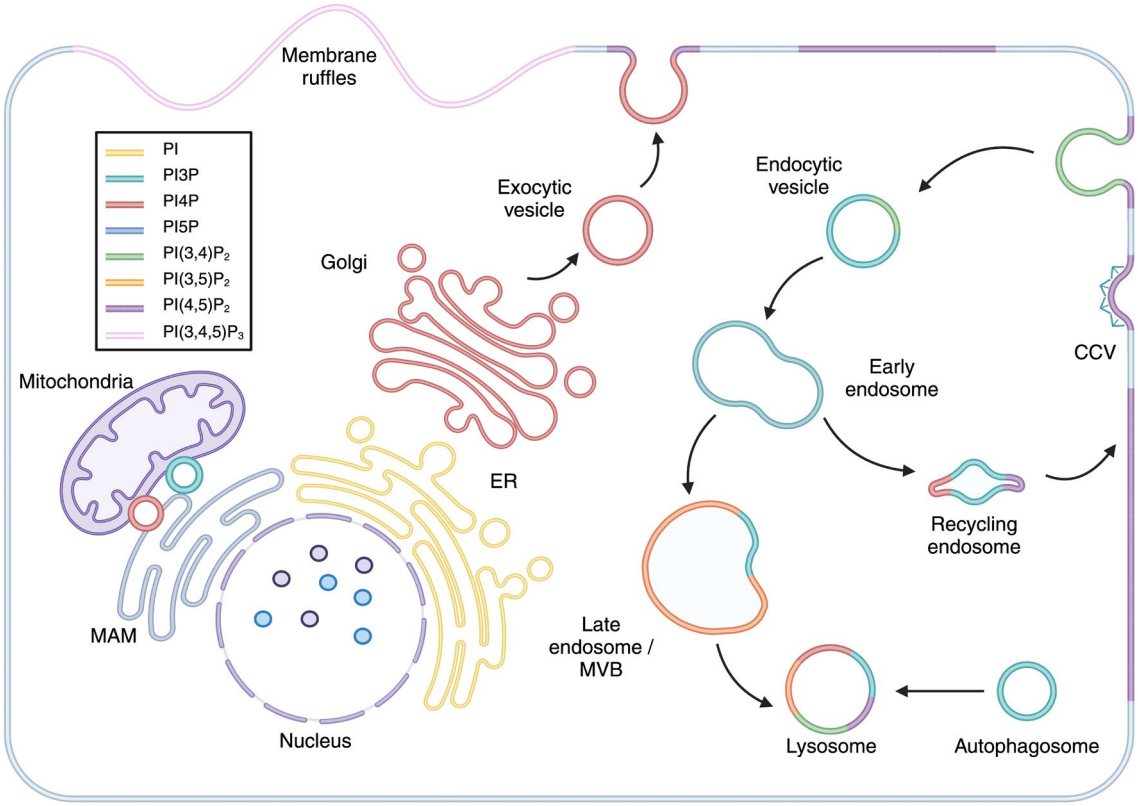



**FIGURE 3** | Intracellular distribution of PI and PItds. This schematic figure depicts only the major PItd domains [2, 21, 22]. In most membranes, the main species is PI, with small amounts of different PItds. PI synthesis mainly occurs in the ER (denoted in yellow). The Golgi is enriched in PI4P. In exocytosis, the production of $PI(4,5)P_2$ at the neck of exocytotic vesicles is shown. Its presence leads to the accumulation of proteins that surround and narrow the neck of the vesicle, which can control the release of vesicular content (e.g., of insulin) [23]. Uptake and transport via clathrin-coated vesicles (CCV) also require $PI(4,5)P_2$ [2]. In endocytosis, PI3P is prominent. Vesicles of the lysosomal system accumulate $PI(3,5)P_2$, shown for multivesicular bodies (MVB) and lysosomes. $PI(3,4,5)P_3$ levels are high at the edge of extended cell processes and membrane ruffles during chemotaxis or the phagocytic cup. Mitochondrial membranes contain some $PI(4,5)P_2$, but the import of PI4P from lysosomes and the Golgi as well as PI3P from endosomes at mitochondria-associated membranes (MAMs) is important in mitophagy [24]. In the nucleus, non-membrane-bound PIP accounts for about half of the total PIP content.

fully characterized. It binds the exocytic vesicles to the plasma membrane by binding with $PI(4,5)P_2$ [2]. For example, in epithelial cells, synthesis of $PI(4,5)P_2$ by PIP5K1γ, recruits the exocyst complex at the plasma membrane, which allows delivery of E-cadherin to adherens junctions, and acts on talin, allowing for the remodeling of the cells' leading edge [28]. Domains of high concentration of $PI(4,5)P_2$ have been identified in neuroendocrine cells at the sites of exocytosis. The mechanisms underlying the formation of these $PI(4,5)P_2$ clusters are incompletely understood, but involve multiple PI kinases and phosphatases, PLC, and other factors [40]. Exocytosis and membrane fusion require $PI(4,5)P_2$-mediated recruitment of multiple effector proteins regulating SNARE function, including CAPS, Munc13 and synaptotagmin-1. Syntaxin-1, a protein that clusters in the presence of moderate levels of $PI(4,5)P_2$, is felt to have roles in vesicle docking and fusion, allowing for a favorable membrane curvature [40].

### 3.2.2 | Endocytosis

The endosomal system is particularly enriched in PI3P, which is required for many functions, from endosomal fusion to sorting as well as the formation of intraluminal vesicles in multivesicular bodies [21]. Several events of PItd interconversion are required during the endocytic process: conversion from $PI(4,5)P_2$ to $PI(3,4)P_2$ allows for the maturation of clathrin-coated vesicles; conversion of PI3P to $PI(3,5)P_2$ promotes maturation and degradative sorting of the endosomes [41].

Clathrin-coated vesicle (CCV) formation and transport involves multiple PItd kinases and phosphatases including synaptojanin (SYNJ1/2), INPPL1 (SHIP2), PIK3C2A, OCRL and INPP4A [2, 21]. The first steps of CCV formation involve $PI(4,5)P_2$ (Figure 5). $PI(4,5)P_2$ is also critical for the recruitment and activation of other proteins in the initial stages of clathrin coat assembly, including epsins, dynamin, β-arrestin, Numb and Dab2, as well as BAR domain proteins [21, 28]. The increased levels of $PI(4,5)P_2$ permit AP-2 assembly at the membrane, then, clathrin triskeles surround the AP-2 and membrane core. Both clathrin and AP-2 permit the recruitment of various proteins, including PItd kinases and phosphatases. For example, AP-2 recognition of $PI(4,5)P_2$ at the plasma membrane recruits PIP5K1, allowing for a further local increase of the $PI(4,5)P_2$ pool and accelerating the nucleation process. As the CCV grows, the clathrin lattice stabilizes and displaces PIP5K1, reducing $PI(4,5)P_2$ level. Then, PI 5-phosphatases synaptojanin and INPPL1, recruited during CCV maturation,

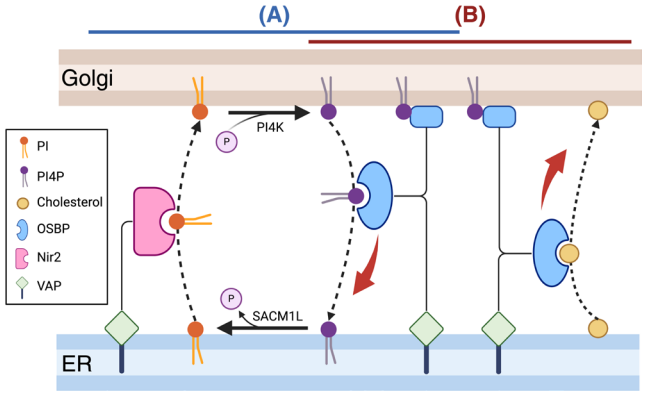



**FIGURE 4** | PItd-mediated lipid transport at membrane contact sites (MCS). A PI-PI4P cycle regulates lipid transport at sites of membrane proximity [2, 36]. (A) PI phosphorylation and dephosphorylation power a cycle of membrane transport. A PI4P gradient is maintained between Golgi and ER, in part by PI transport from the ER to Golgi followed by PI4P synthesis in the Golgi. Lipid transport proteins such as oxysterol binding protein (OSBP) can transport PI4P down the resulting concentration gradient to the ER, where it is dephosphorylated to PI then returned to the Golgi by another transporter. Such LTPs bind to PI4P on the Golgi and VAP on the ER. (B) Cargoes of OSBP. The pathway to the ER with PI4P is described above. Returning to the Golgi, OSBP transports a cholesterol molecule. Phosphatidylserine is transported in an analogous fashion (not shown). Abbreviations: Nir2, N-terminal domain-Interacting Receptor, also known as Phosphatidylinositol Transfer Protein, Membrane-Associated 1 or PITPNM1; SACM1L, Suppressor of Actin mutations 1-like; VAP, Vesical-associated membrane protein (VAMP)-associated protein.

convert PI(4,5)$P_2$ into PI4P, and clathrin recruits PI3KC2α for the conversion of PI4P into PI(3,4)$P_2$ [21]. PI3KC2α is an autoinhibited kinase, but the binding of its PX and C2 domains to PI(4,5)$P_2$ at the plasma membrane unmasks its enzymatic activity, permitting the synthesis of PI(3,4)$P_2$. This PI(3,4)$P_2$ is required for constriction at the neck of the invaginated membrane through the recruitment of proteins SNX8 and SNX19, important intermediates in the process. Fission of the CCV also requires dynamin, which in turn requires PI(4,5)$P_2$ at the neck of invaginated CCVs. Synaptojanin may support dynamin by preferentially hydrolyzing PI(4,5)$P_2$ in highly curved membranes such as the neck of the budding CCVs. In contrast, less PI(4,5)$P_2$ is hydrolyzed adjacent to the neck, facilitating fission [21]. Clathrin uncoating by auxilin relies on PI(3,4)$P_2$ and endocytic proteins. The presence of PI(3,4)$P_2$ may also be the precursor of PI3P in endosomes, possibly through the activity of INPP4A and INPP4B [21, 43]. Thus, a single subcellular structure is sequentially dependent on different PItds that recruit the proteins necessary to complete the phases of this critical form of membrane trafficking.

Clathrin-independent endocytosis also relies on PItds, although in less documented fashions than for CCVs. PI(4,5)$P_2$ accumulates at the rim of caveolae, plasma membrane invaginations produced by caveolins. PI(3,4,5)$P_3$ occurs at sites of internalization of the interleukin-2 receptor. PI(4,5)$P_2$ and possibly PI(3,4)$P_2$ are implicated in the CLIC pathway responsible for endocytosis of glycosylphosphatidylinositol anchor proteins from the plasma membrane [21]. Macropinocytosis, allowing for uptake of nutrients and other molecules into cells, involves several PI kinases and phosphatases including PIP5K1α/γ, PI3Ks, INPP5D (SHIP1), INPPL1 (SHIP2), INPP4A/B, MTMR6 and PLC, similar to those involved in phagosome formation described below [2, 44].

Several steps of phagosome formation involve PItds. Rapid transitory increases of PI(4,5)$P_2$ are seen during particle binding and extension of the pseudopods that bind and engulf the endocytic target. PItds interact with Rho GTPases to form filamentous actin networks that provide structure to the pseudopods. Also in phagocytosis, PI(4,5)$P_2$ influences receptor mobility, activation of integrins, membrane trafficking and ion channel activity, each at specific times and locations [44]. Roles for PI(3,4,5)$P_3$ are suggested in pseudopod progression, phagosome sealing and actin breakdown, and for PI3P in phagosome maturation, including the targeting of internalized contents for degradation and the acquisition of bactericidal properties [44]. Intracellular pathogens can hijack PItd metabolism to facilitate their own cellular adhesion and entry [44, 45].

### 3.3 | Phosphoinositides, Lysosomes and Autophagy

An important function of PItds in lysosomes involves changes related to nutrient conditions. PI3P and PI(3,5)$P_2$ are involved in the regulation of lysosomal activity [2], influencing lysosome position, autophagic lysosome formation and nutrient signaling. Other PItds implicated include PI4P and PI(4,5)$P_2$, and possibly PI5P [2, 46]. In nutrient-rich conditions, insulin and other growth factors activate PI 3-kinases class I, generating PI(3,4,5)$P_3$, itself an activator of Akt. Hydrolysis of PI(3,4,5)$P_3$ to PI(3,4)$P_2$ by INPPL1 (SHIP2) further contributes to Akt activation [2]. Akt itself indirectly activates mTORC1, favoring anabolism. Similarly, after amino acid loading, activation of PIK3C3 synthesizes PI3P in the lysosomal membrane, providing anchoring sites for protrudin and FYCO1 and moving lysosomes towards the plasma membrane, where they fuse with cargo-carrying vesicles [47]. Activation of mTORC1 in this context is maintained through the recruitment of phospholipase $D_1$, which cleaves the PI head group and produces phosphatidic acid in the lysosomal membrane. The presence of phosphatidic acid causes dissociation of DEPTOR, an inhibitory subunit of mTORC1. Conversely, in nutrient-deprived conditions, recruitment of PI3KC2β from the cytosol generates PI(3,4)$P_2$, repressing mTORC activity and promoting perinuclear lysosomal clustering [43].

Autophagy is initiated by the autophagy-related (ATG) proteins at sites of PI3P enrichment on the ER called omegasomes. Local PI3P production is achieved by PIK3C3, itself activated by the ULK1 complex, and possibly by PI3KC2α [2, 48]. PI3P promotes the recruitment of several proteins including DFCP1, WIPI1 and ATG16L1, allowing assembly of the phagophore. During stress (e.g., starvation, energy deficiency), PI5P can replace PI3P in recruiting similar proteins [48]. As the process advances, PI3P degradation is required, which occurs through interactions with MTMR proteins [2]. In order to achieve fusion with the lysosome, the presence of PI4P is required; its production is initiated by PI4K2α, trafficked from

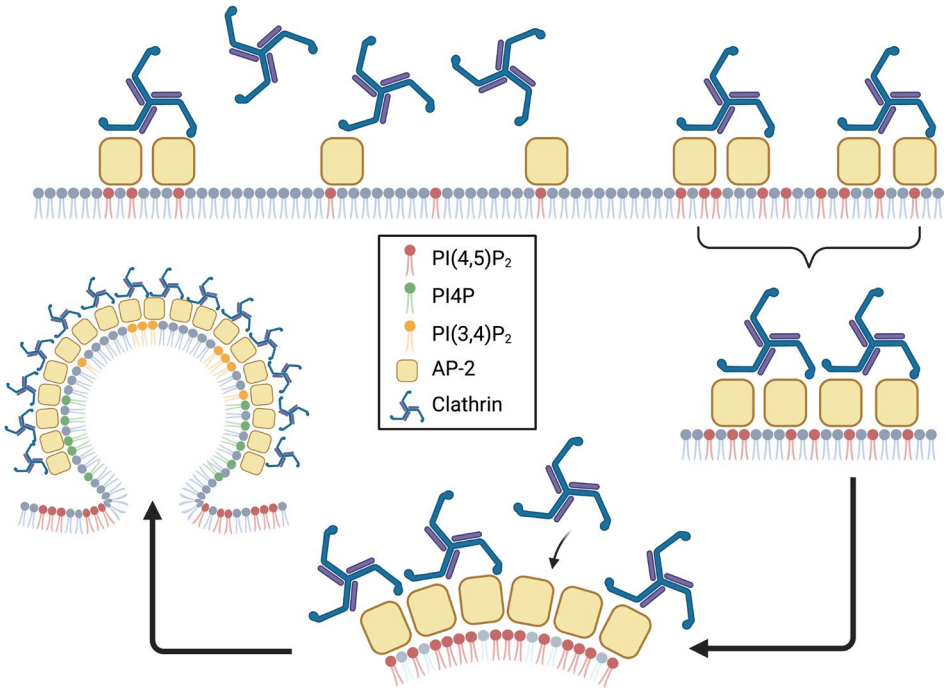



**FIGURE 5** | Clathrin-coated vesicle formation and PItd. PItds direct much of cellular membrane traffic. This example illustrates $PI(4,5)P_2$ levels and their role in the early phase of development of clathrin-coated vesicles (CCVs). The synthesis of $PI(4,5)P_2$ molecules (red) in the cytoplasmic leaflet of the plasma membrane confers a low affinity for AP2 monomers. $PI(4,5)P_2$ binding is brief and weak. The membrane concentration of $PI(4,5)P_2$ is critical because binding to a second $PI(4,5)P_2$ molecule retains AP2 for longer in this position. Above a certain level of $PI(4,5)P_2$, the process proceeds rapidly. Clathrin binding to two AP2 molecules further stabilizes this structure. AP2-clathrin units may coalesce with similar units. An increasingly robust clathrin-AP2 network forms, imposing curvature upon the membrane and creating a clathrin-coated vesicle. The crucial initial steps occur within seconds [42]. Compared with the morphologically spectacular accumulation of structural proteins, membrane $PI(4,5)P_2$ levels are easy to overlook, but they provide the critical trigger for the entire process. As the CCV matures, the transition to other PItds such as PI4P and $PI(3,4)P_2$ will direct the separation of the CCV from the plasma membrane and vesicle uncoating [21]. This and other membrane pathways controlled by PItd levels are reviewed elsewhere [2]. Abbreviation: AP2, adaptor protein molecule 2.

the Golgi with GABARAP proteins [48]. $PI(3,5)P_2$ is also reported to enhance autophagosome–lysosome fusion and lysosomal acidification [48, 49].

### 3.4 | Phosphoinositides and Cytoskeleton Remodeling

PItd action upon the cytoskeleton, particularly the actin framework that determines cell morphology, mobility, division and polarity, is a recurrent theme mentioned later in the brain, muscle, immune and renal sections. $PI(4,5)P_2$, for example, participates in actin polymerization, frees G-actin by permitting its dissociation from actin monomer-profilin complexes, and enhances the function of adaptor proteins between the plasma membrane and the cytoskeleton, important for cell-matrix and cell–cell adhesion [25]. $PI(4,5)P_2$ and $PI(3,4,5)P_3$ are critical players. Interactions between $PI(4,5)P_2$ and proteins such as ezrin, moesin, radixin (ERM) and myosins contribute to cell shape maintenance by binding to the actin cytoskeleton [50]. In migrating cells, the accumulation of $PI(4,5)P_2$ at the leading edge allows for microtubule capture and influences cytoskeleton regulators such as talin, Rho family small GTPases, IQGAP, gelsolin, and Src tyrosine kinase [28]. $PI(3,4,5)P_3$ also functions at the leading edge of migrating cells, as in peripheral ruffles [25, 50]. Some evidence also suggests a role for PI4P in actin remodeling [37].

Cell division is influenced by PItd kinases and phosphatases. These processes include mitotic cell rounding, spindle orientation, cell elongation, cortical stability, symmetry of the furrow, furrow ingression, bridge stability, abscission and mid-body remnant clearance [51]. The presence of $PI(4,5)P_2$ allows for the recruitment of proteins binding to the cytoskeleton and force generator complexes, playing a role in spindle orientation, cell shape and bridge stability. Hydrolysis of $PI(4,5)P_2$ and production of PI3P both have central roles in cytokinesis [51].

PItds play many roles in primary cilia. Different PItds are found at specific parts of the cilium; for example, $PI(4,5)P_2$ and $PI(3,4,5)P_3$ at the base and PI4P along the length of the cilium [35]. PI4P is present at the centrosome prior to ciliogenesis, and PI3P in the pericentriolar recycling endocytic compartments. PItd kinases and phosphatases INPP5B/E, OCRL, INPPL1 (SHIP2) and PTEN contribute to the stability and disassembly of cilia [35].

### 3.5 | Phosphoinositides and Mitochondria

Both PI and $PI(4,5)P_2$ are in mitochondrial inner and outer membranes, as well as several enzymes of PItd metabolism, including PI4K2α/β and synaptojanin 2 [24, 52, 53]. Disruption of mitoaggregates prior to mitophagy is partly driven by $PI(4,5)P_2$,

**TABLE 2** | Disorders of phosphoinositide metabolism.

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *FIG4* | Phosphatidylinositol 3,5-bisphosphate 5-phosphatase | AR | Yunis-Varón syndrome | Skeletal dysplasia with severe neurologic involvement. Skeletal findings: cleidocranial dysplasia with calvarial dysostosis, hypoplastic/absent clavicles, pelvic dysplasia with hip dislocations, digital abnormalities (often absent or hypoplastic 1st fingers and toes). Neurologically, developmental delay, swallowing difficulties, microcephaly (~50%) and CNS abnormalities (e.g., frontal lobe, cerebellum, basal ganglia) and possible cardiac involvement, including congenital heart defects. Dysmorphic features. Sparse hair. *Note*: Families with intermediate phenotypes between Yunis-Varón syndrome and CMT4J (below) are known, some with leuko-encephalopathy [59] and/or parkinsonism [60] | [59–62] |
| *FIG4* | Phosphatidylinositol 3,5-bisphosphate 5-phosphatase | AR | Charcot–Marie–Tooth disease type 4J | Sensory and motor polyneuropathy with weakness, sensory deficits, areflexia and gait difficulties. Age of onset and severity is variable, from childhood to adulthood. Loss of ambulation in more severe cases. Some individuals reported with parkinsonism or phenotypes intermediary between CMT4J and Yunis-Varón syndrome. | [63–65] |
| *FIG4* | Phosphatidylinositol 3,5-bisphosphate 5-phosphatase | AR | Familial epilepsy with polymicrogyria | Described in a single family (6 affected individuals) with temporo-occipital polymicrogyria, epilepsy and psychiatric manifestations (psychosis, aggressiveness). One patient also had neuropathy. | [66, 67] |
| *FIG4* | Phosphatidylinositol 3,5-bisphosphate 5-phosphatase | AD | Amyotrophic lateral sclerosis type 11 | Some variants in *FIG4* have been found to be a risk factor with incomplete penetrance for amyotrophic lateral sclerosis (ALS) or primary lateral sclerosis, identified at low frequency in large cohorts of ALS. | [68, 69] |
| *HYCC1* | Hyccin PI4KA lipid kinase complex subunit 1 (FAM126A) | AR | Hypomyelinating leukodystrophy and congenital cataract | Progressive pyramidal and cerebellar involvement. Initially normal development progressing to severe spastic paraplegia; loss of walking in late childhood/adolescence. Diffuse hypomyelination on brain MRI. Cataracts, typically congenital but may appear later. Mild to moderate ID and cognitive dysfunction is frequent. Seizures in ~1/3. Polyneuropathy described later in course. | [70–72] |
| *INPP5E* | Inositol polyphosphate-5-phosphatase E | AR | Joubert syndrome (and related disorders) | First identified in a family with MORM syndrome (mental retardation, truncal obesity, retinal dystrophy and micropenis). Later associated with Joubert syndrome: ID, oculomotor apraxia, “molar tooth” sign on brain MRI. Ocular findings frequent (retinopathy, coloboma). Possible non-syndromic retinal degeneration. | [73–76] |

(Continues)

**TABLE 2** | (Continued)

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *INPP5K* | Inositol polyphosphate-5-phosphatase K or skeletal muscle and kidney-enriched inositol 5-phosphatase (SKIP) | AR | Congenital muscular dystrophy with cataracts and intellectual disability | Described in a few families with muscle weakness, variable ID, short stature, often early-onset cataracts. Spasticity, microcephaly and seizures reported in some affected individuals. | [77–79] |
| *INPPL1* | Inositol polyphosphate phosphatase like 1 or SRC homology 2 domain-containing inositol phosphatase 2 (SHIP2) | AR | Opsismodysplasia | Delayed bone maturation, micromelia with short hands and feet, platyspondyly, metaphyseal cupping, dysmorphic features (hypertelorism, high forehead, short nose, large fontanelle) with relative macrocephaly. Respiratory insufficiency and renal phosphate wasting are frequent. Some present mild motor delays. | [80, 81] |
| *ITPR1* | Inositol-1,4,5-trisphosphate receptor type 1 | AD, AR | Gillespie syndrome | Neonatal non-progressive cerebellar ataxia, aniridia, variable ID, progressive cerebellar atrophy on brain MRI. Described with *de novo* monoallelic variants in the $IP_3$-binding domain or biallelic truncating variants. | [82–84] |
| *ITPR1* | Inositol-1,4,5-trisphosphate receptor type 1 | AD | Spinocerebellar ataxia type 15 (SCA15) | Adult-onset slowly progressive cerebellar ataxia with cerebellar atrophy. Variants typically large deletions of *ITPR1*, often encompassing *SUMF1*. Recently, some missense variants have also been associated with SCA15. | [82, 85, 86] |
| *ITPR1* | Inositol-1,4,5-trisphosphate receptor type 1 | AD | Spinocerebellar ataxia type 29 (SCA29) | Typically, infantile-onset non-progressive ataxia, developmental delay, variable cognitive impairment and cerebellar hypoplasia/atrophy. Ophthalmoplegia, ptosis and movement disorders (e.g., dystonia, chorea) are reported. | [87–89] |
| *ITPR1* | Inositol-1,4,5-trisphosphate receptor type 1 | AD | Pontocerebellar hypoplasia with ataxia | Described in one individual with pontocerebellar hypoplasia, developmental delay and non-progressive ataxia. Associated with *de novo* variant in transmembrane domain. | [82] |
| *ITPR2* | Inositol-1,4,5-trisphosphate receptor type 2 | AR | Generalized isolated anhidrosis | Reported in one family with 5 affected members. Heat intolerance, anhidrosis, but normal numbers and morphology of sweat glands. | [90] |
| *MTM1* | Myotubularin 1, Phosphatidylinositol 3-phosphatase | XL | X-linked centronuclear myopathy | Presents in newborn males. Profound, diffuse weakness, ptosis and ophthalmoparesis, respiratory failure and feeding difficulties. Most patients require ventilatory, feeding and ambulatory support. Extra-muscular signs, e.g., learning difficulties, are reported. Most females are asymptomatic, but a few develop muscle involvement, from mild to neonatal severe. | [91–96] |

(Continues)

**TABLE 2** | (Continued)

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *MTMR2* | Myotubularin-related protein 2, Phosphatidylinositol 3-phosphatase | AR | Charcot–Marie-Tooth (CMT) disease type 4B1 | Demyelinating neuropathy with upper and lower limb weakness and facial weakness (~60%), presentation infancy to late childhood. Vocal cord palsy and respiratory difficulties (~1/3). Pes planus is frequent. Nonsense variants associated with more severe disease than missense/C-terminal truncating variants. | [97–99] |
| *OCRL* | Phosphatidylinositol 4,5-bisphosphate 5-phosphatase | XL | Oculocerebrorenal syndrome of Lowe | Renal disease: initially low-molecular weight proteinuria and albuminuria, evolving into Fanconi syndrome (most individuals have aminoaciduria, calcium/phosphate wasting, and more rarely potassium wasting and glycosuria). Nephrocalcinosis (~45%). Neonatal cataracts in nearly all, plus growth retardation, developmental delay and behavioral abnormalities. In adulthood, risk of arthropathy and end-stage kidney disease. | [100–102] |
| *OCRL* | Phosphatidylinositol 4,5-bisphosphate 5-phosphatase | XL | Dent disease type 2 | Lowe syndrome-like condition but milder. Low molecular weight proteinuria, hypercalciuria, growth retardation. Aminoaciduria, phosphate wasting and glycosuria are rare. Cataracts (~7%). Developmental delay (~1/4). *Note:* Atypical forms with digenic inheritance described (*CLCN5* [103]; *INPP5B* [104]). | [101, 103–106] |
| *PI4KA* | Phosphatidylinositol 4-kinase α | AR | *PI4KA*-related disorder | Disorder of variable severity with neurologic abnormalities: ID, epilepsy, spastic paraplegia & ataxia. Brain MRI: possible hypomyelination, white matter atrophy, thin/dysplastic corpus callosum, cerebellar hypoplasia/atrophy. Severely affected cases reported (polymicrogyria, arthrogryposis). Multiple intestinal atresias, inflammatory bowel disease, and immunodeficiency reported in patient subgroups. Milder presentations (spastic paraplegia, cervical cord atrophy, normal cognition) reported in a few. | [107–112] |
| *PI4KB* | Phosphatidylinositol 4-kinase β | AD | *PI4KB*-related deafness | Identified in one family and 5 other individuals with nonsyndromic sensorineural hearing loss and inner ear malformations, including cochlear dysplasia and enlarged vestibular aqueduct. | [113] |
| *PI4K2A* | Phosphatidylinositol 4-kinase type 2 α | AR | PI4K-associated neurodevelopmental disorder | Described in 5 individuals from 4 families with severe neurodevelopmental delay with structural CNS abnormalities (corpus callosum dysgenesis/hypoplasia, white matter volume loss, vermis hypoplasia), akathisia, epilepsy. Subtle dysmorphic features were reported, including a progeroid appearance with cutis laxa in one case [114] | [114–116] |

(Continues)

**TABLE 2** | (Continued)

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *PIK3C2A* | Phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 α | AR | Oculoskeletodental syndrome | Seven individuals (4 families) with short stature, coarse facial features, skeletal and dental abnormalities (including scoliosis), congenital cataracts, and developmental delay; some also presented strokes, hearing loss, nephrocalcinosis or proteinuria. Mild elevation of urine glycosaminoglycans has been reported. | [117, 118] |
| *PIK3CA* | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α | Som | *PIK3CA*-related disorders | Group of disorders with segmental overgrowth, vascular malformations and other lesions. Can cause neurologic (ventriculomegaly, seizures, developmental delay) and vascular (coagulopathy, thromboembolism) complications, infections, pain and functional impairment. Non-specific genitourinary abnormalities reported. *Refer to Box 2 for details.* | [119–125] |
| *PIK3CD* | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ | AD | Activated PI3Kδ syndrome (APDS) 1 | Recurrent infections, most notably sinopulmonary (especially encapsulated organisms: *H. influenzae*, *S. pneumoniae*), and viral infections (herpesviruses: EBV, CMV, VZV, HPV). Also: non-neoplastic lymphoproliferation (lymphadenopathies, splenomegaly, hepatomegaly), autoimmune predisposition (hematologic, including immune thrombocytopenic purpura and autoimmune hemolytic anemia), risk of lymphoma. APDS1 presents more often with bronchiectasis, cytopenias and splenomegaly than PIK3R1-related APDS2 (below). | [126–129] |
| *PIK3CD* | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ | AR | PI3Kδ deficiency syndrome | Few patients described. Severe humoral immunodeficiency, recurrent infections, autoimmune disorders (inflammatory bowel disease, thrombocytopenia, hepatitis, JIA). | [130, 131] |
| *PIK3CG* | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit ɣ | AR | Immunodeficiency 97 with autoinflammation | Described in 2 unrelated people: immunodeficiency, autoimmunity, colitis, pneumonitis, cytopenias. Macrophage activation in one without fulfilling criteria for hemophagocytic lymphohistiocytosis. | [132, 133] |
| *PIK3R1* | Phosphoinositide-3-kinase regulatory subunit 1 | AD | Activated PI3Kδ syndrome (APDS) 2 | As in PIK3CD-related APDS1 (above), but higher risk of dysmorphic features, failure to thrive, developmental delay & lymphoma than APDS1. | [127–129, 134] |
| *PIK3R1* | Phosphoinositide-3-kinase regulatory subunit 1 | AD | SHORT syndrome | SHORT (Short stature, Hyperextensibility of joints and/or inguinal hernia, Ocular depression, Rieger abnormality and Teething delay). Only ~50% have ≥4 features. Dysmorphia: progeroid appearance frequent, with partial lipodystrophy & insulin resistance, diabetes typically from late childhood/early adulthood. | [135–137] |

(Continues)

**TABLE 2** | (Continued)

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *PIK3R1* | Phosphoinositide-3-kinase regulatory subunit 1 | AR | Agammaglobulinemia | In 2 families with agammaglobulinemia and cytopenias (B-cell lymphopenia, neutropenia, thrombocytopenia). Colitis in one individual. All variants have been in exon 7. | [138, 139] |
| *PIK3R2* | Phosphoinositide-3-kinase regulatory subunit 2 | AD | *PIK3R2*-associated megalencephaly and polymicrogyria | Severe megalencephaly, bilateral perisylvian polymicrogyria (often slightly asymmetric), epilepsy and ID (mild - moderate). Mosaicism possible, with milder signs (isolated megalencephaly; perisylvian polymicrogyria without megalencephaly). Frequent cause of polymicrogyria in one cohort [140]. | [140–142] |
| *PIK3R5* | Phosphoinositide-3-kinase regulatory subunit 5 | AR | Ataxia with oculomotor apraxia 3 | Four individuals from one family: ataxia, cerebellar atrophy, dysarthria, axonal sensory polyneuropathy and oculomotor apraxia presenting between ages 12–18. | [143] |
| *PIKFYVE* | Phosphatidylinositol-3-phosphate 5-kinase, type III | AD | Fleck corneal dystrophy | Corneal stroma with small white flecks/hyperreflective dots, due to dilated keratocytes with intracytoplasmic vesicles with complex lipids/glycosaminoglycans. | [144, 145] |
| *PIKFYVE* | Phosphatidylinositol-3-phosphate 5-kinase, type III | AD | Congenital cataracts | Described in one extended family and one other individual with non-syndromic congenital cataracts. | [146, 147] |
| *PIP5K1C* | Phosphatidylinositol-4-phosphate 5-kinase type 1 ɣ | AR | Lethal congenital contractural syndrome 3 | Seven affected infants from 2 families. Severe joint contractures, muscle wasting (especially in lower limbs). Neonatal death from respiratory insufficiency. | [148, 149] |
| *PIP5K1C* | Phosphatidylinositol-4-phosphate 5-kinase type 1 ɣ | AD | *PIP5K1C*-gain of function neurodevelopmental disorder | Moderate to severe ID (most cannot walk; non-verbal), epilepsy, acquired microcephaly, visual abnormalities (strabismus, cerebral visual impairment, optic atrophy). On MRI: abnormalities of the lateral ventricles and white matter. Skeletal abnormalities: craniosynostosis, talipes equinovarus and scoliosis. Gain-of-function dominant *de novo* variants in *PIP5K1C*. | [150] |
| *PLCB1* | Phospholipase C $\beta_1$ | AR | Developmental and epileptic encephalopathy 12 | Epileptic encephalopathy reported in a few families, presenting with seizures in infancy (spasms, focal seizures, febrile status epilepticus) and developmental delay with regression or stagnation. Swallowing difficulties are reported. | [151, 152] |
| *PLCB3* | Phospholipase C $\beta_3$ | AR | Spondylometaphyseal dysplasia with corneal dystrophy | Two individuals from one family: spondylometaphyseal dysplasia, short limbs, narrow thorax, abnormal iliac bones, vertebral beaking. Other manifestations include dysmorphia, corneal opacities, developmental delay, and chronic lung disease requiring oxygen supplementation. | [153] |

(Continues)

**TABLE 2** | (Continued)

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *PLCB4* | Phospholipase C $\beta_4$ | AD, AR | Auriculocondylar syndrome 2 | Predicted monoallelic dominant-negative variants (type 2A) or, more rarely, biallelic variants (type 2B) in *PLCB4*. Variable mandibular and condylar hypoplasia/dysplasia and temporomandibular joint abnormalities, "question mark" ears and microstomia, prominent cheeks. In some: sleep apnea, feeding and speech difficulties and developmental delay. | [154–156] |
| *PLCD1* | Phospholipase C $\delta_1$ | AD, AR | Hereditary leukonychia | i.e., partial to complete whitening of the nails, with koilonychia in a few families. | [157, 158] |
| *PLCD1* | Phospholipase C $\delta_1$ | AD | Hereditary trichilemmal cysts or pilomatricomas | Benign tumors of the hair follicles, as trichilemmal cysts [159] or pilomatricomas [160]. | [159, 160] |
| *PLCE1* | Phospholipase C $\varepsilon_1$ | AR | Steroid-resistant nephrotic syndrome | Nephrotic syndrome. Average onset ~4 years. Progression to kidney failure. In most cases, focal segmental glomerulosclerosis or diffuse mesangial sclerosis. | [161, 162] |
| *PLCG2* | Phospholipase C $\gamma_2$ | AD | *PLCG2*-associated antibody deficiency and immune dysregulation (PLAID) | Broad spectrum including recurrent sinopulmonary infections, humoral immune deficiency, atopy and autoinflammation. Often classified clinically as PLAID (with large in-frame deletions) or APLAID (autoinflammatory PLAID, with gain-of function variants). Cold-induced urticaria typically seen in PLAID phenotype. Haploinsufficiency is associated with predisposition to herpesvirus and NK defects, whereas gain-of-function is associated with granulomas. | [163, 164] |
| *PLCH1* | Phospholipase C $\eta_1$ | AR | PLCH1-associated holoprosencephaly | In 2 families (4 affected children). Holoprosencephaly, some with congenital heart defects. Associated with nonsense variants in *PLCH1*. | [165] |
| *PTEN* | Phosphatase and tensin homolog; phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase | AD | PTEN-hamartoma tumor syndrome | Tumor predisposition syndrome with a highly variable presentation, even intrafamilial. Mosaic forms are frequent (10%–40% of *de novo PTEN* variants). Patients with disseminated mosaicism may be clinically indistinguishable from those with dominantly-inherited forms. *Refer to Box 3 for details*. | [166–173] |
| *SBF1* | SET-binding factor 1 or Myotubularin-related protein 5 (MTMR5), a PI 3-phosphatase MTMR2 binding protein | AR | Charcot–Marie-Tooth (CMT) disease type 4B3 | Reported in some families with axonal motor polyneuropathy with cranial nerve involvement, microcephaly, ID. Brain MRI may show a "fork and bracket" sign ($T_2$ hyperintensity in pons and mesencephalon from cranial nerve VI and VII degeneration). Also, isolated demyelinating sensory-motor neuropathy in 3 patients [174]. | [99, 174, 175] |

(Continues)

**TABLE 2** | (Continued)

| Gene | Protein name and function | Inh | IMD name | Clinical features | Ref. |
|---|---|---|---|---|---|
| *SBF2* | SET binding factor 2 or Myotubularin-related protein 13 (MTMR13), a PI 3-phosphatase MTMR2 binding protein | AR | Charcot–Marie-Tooth (CMT) disease type 4B2 | Demyelinating neuropathy, limb weakness, foot deformities, vocal cord palsy (~40%), onset from infancy to early adulthood. Facial weakness is less frequent than in CMT4B1; glaucoma in ~1/3. | [99, 176, 177] |
| *SYNJ1* | Synaptojanin 1, polyphosphoinositide phosphatase | AR | Developmental and epileptic encephalopathy 53 | Severe progressive neurologic disorder, refractory seizures (often neonatal), severe developmental delay/ID, spastic tetraplegia, often need tube feeding; cortical blindness in some. | [178–180] |
| *SYNJ1* | Synaptojanin 1, polyphosphoinositide phosphatase | AR | Early-onset Parkinson disease 20 | Movement disorder: parkinsonism, dystonia, dysarthria, dysphagia, postural instability. In some, supranuclear vertical gaze palsy or cognitive impairment. Onset mostly third decade, but some earlier. Seizures are frequent, often appearing before movement disorder. Variable response to levodopa. | [180, 181] |
| *VAC14* | VAC14. In multiprotein complex with PIKFYVE and FIG4. | AR | Yunis-Varón-like syndrome | Described in a single child with Yunis-Varón syndrome-like phenotype: dysmorphic features, sparse hair, skeletal dysplasia (handlebar clavicles, flared iliac wings, acetabular dysplasia, intervertebral disc calcifications, multiple bone hypoplasias in hand/feet including 1st fingers/toes), osteopenia with multiple fractures, progressive neurologic signs (basal ganglia cysts, leukodystrophy, axonal polyneuropathy, hydrocephalus). | [182] |
| *VAC14* | VAC14. In multiprotein complex with PIKFYVE and FIG4. | AR | Childhood-onset striatonigral degeneration | Progressive complex neurologic disorder with dystonia, dysarthria, gait abnormalities, hypersalivation, hearing loss and ataxia in some. Brain MRI may show hyperintensity of the striatum and iron deposition in the substantia nigra and pallidum. | [183, 184] |

Abbreviations: AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; APDS, activated PI3Kδ syndrome; AR, autosomal recessive; ID, intellectual disability; Inh, inheritance pattern; JIA, juvenile idiopathic arthritis; Ref, references; SCA, spinocerebellar ataxia; Som, somatic variants; XL, X-linked.

which promotes actin polymerization [54]. WIPI2, a PI3P effector, and valosin-containing protein (VCP) were shown to be recruited to damaged mitochondria, allowing for ubiquitination and targeting to the proteasome [55]. As in lysosomes, PItds can drive mitochondrial fission in response to nutrition. Under fed conditions, PI3P on early endosomes promotes mitochondrial fission through its binding with RRBP1 and kinectin 1 [56]. The final stages of mitochondrial fission require PI4P, produced both by lysosomes and the Golgi, the transport of which to mitochondria is facilitated by mitochondria-associated membranes [24]. Conversely, under nutrient-poor conditions, dephosphorylation of PI3P by MTM1 represses fission [24].

### 3.6 | Phosphoinositides in the Nucleus

In contrast to other organelles, in which PItds are membrane-bound, as much as 40% of PItds in the nucleus are solubilized in nucleoplasmic speckles [28, 57]. In these structures, several proteins hide the PItd acyl chains within a hydrophobic core. This positions the phosphorylated head groups to the surface for intranuclear signaling [57]. PI(4,5)$P_2$ negatively interacts with histone $H_1$, decreasing chromatin condensation and increasing gene expression. PI(4,5)$P_2$ can modulate factors that impact chromatin remodeling, messenger RNA export and processing and DNA repair [28, 58]. Also, PI5P has been shown to interact with PHD finger-containing proteins, which are involved in reading, writing and erasing of the histone code [58].

## 4 | Genetic Disorders of Phosphoinositide Metabolism

PItds play multiple roles in all cell types (Figures 2–5). Their levels are controlled precisely in time and space by the action of over 50 phosphatases and kinases (Figure 1). As expected from this complexity, increasing numbers of genetic disorders of phosphoinositide metabolism (GDPIMs) are described, and they produce a broad spectrum of clinical manifestations. Known monogenic conditions associated with GDPIM are listed in Table 2.

### 4.1 | Neurologic Manifestations

Most GDPIMs have some neurological involvement, which may reflect the many roles of PItds in the central and peripheral nervous systems. Neurotransmission is partly regulated by PItds. For example, PI3P enhances the clustering of GABA receptors on post-synaptic membranes, low PI(3,5)$P_2$ levels increase the internalization of NMDA-mediated calcium channels and PI(3,4,5)$P_3$ helps to maintain AMPA-type glutamate receptors at the synaptic membrane [185, 186]. PI(4,5)$P_2$ regulates synaptic neurotransmitter release similar to its role in exocytosis [28, 40]; PItds also participate in the recycling of synaptic vesicle membranes [21]. Certain neurotransmitters activate PLC pathways, notably in the regulation of endocannabinoid neuronal excitability [186]. Cortical development is influenced by PItds, notably by actin cytoskeleton remodeling, for example, PI(3,4)$P_2$ in neurite initiation, PI(3,4,5)$P_3$ in growth cones of developing neurites, and both PI(3,4)$P_2$ and PI(3,4,5)$P_3$ in dendrite morphogenesis [185, 186].

Developmental delay or intellectual disability occurs in numerous GDPIMs. For example, intellectual disability or autism spectrum disorders are observed in some *PTEN*-hamartoma tumor syndrome (PHTS) patients [166, 167] and developmental regression is described in *PLCB*-related encephalopathy [151, 152]. Other signs in addition to developmental abnormalities occur in nearly all of these disorders.

Epilepsy occurs in several PItd-related disorders, including variants in *PLCB1* [151, 152] and *SYNJ1* [178, 179], and with *PIP5K1C* gain of function [150]. Cortical malformations may relate to the seizures in *PIK3R2*-associated megalencephaly and polymicrogyria syndrome [141, 142], with biallelic *PI4KA* [107–109] or *PI4K2A* [115, 116] variants, and *PIK3CA*-related disorders [119, 120].

White matter abnormalities are also described in GDPIMs, including leukodystrophy in *PI4KA*-related disorders [108–110] and periventricular white matter lesions in oculoskeletodental syndrome, which may relate to the role of PIK3C2A in angiogenesis and vascular response [117].

Movement disorders occur in several PItd-related conditions. Ataxia is prevalent with *ITPR1* variants, with onsets in newborns (e.g., Gillespie syndrome, with aniridia and intellectual disability), children (spinocerebellar ataxia type 29) or adults (spinocerebellar ataxia type 15) [82]. Biallelic *PIK3R5* variants are associated with ataxia with oculomotor apraxia [143]; perhaps related to high PIK3R5 expression in the fetal cerebellum [31]. A fraction of Joubert syndrome, a ciliopathy with abnormalities of the vermis, is caused by variants in *INPP5E*, which affects cilial biology (see section 3.4) [73, 74]. Dystonia, dysarthria and parkinsonism occur in early-onset Parkinson disease associated with *SYNJ1* variants [180, 181] and childhood-onset striatonigral degeneration, with biallelic *VAC14* variants [183, 184].

Four forms of Charcot–Marie–Tooth (CMT) neuropathy are described in GDPIMs, linked to different genes: *MTMR2* (CMT4B1) [97, 98], *SBF2* (CMT4B2) [176, 177], *SBF1* (CMT4B3) [174] and *FIG4* (CMT4J) [63]. These can present from infancy through adulthood, with CMT4B1 tending to present earlier (average 2.8 years, range 0–13) than CMT4B2 (average 6.7 years, range 1–20) [99]. Facial weakness and vocal cord paralysis can occur, particularly in CMT4B1 [99]. MTMR2, SBF2 and FIG4 are involved in PI(3,5)$P_2$ metabolism, suggesting an importance for this PItd in peripheral nerves [31].

### 4.2 | Muscular Manifestations

Some disorders of PItd metabolism primarily show muscle involvement. The most frequent of these is X-linked centronuclear myopathy, caused by variants in myotubularin 1 (*MTM1*), a PI 3-phosphatase [91–93]. Affected males typically present with severe neonatal muscle weakness requiring ventilatory and feeding support. Mortality is estimated at 10% per year, mostly from respiratory failure. Among survivors, about half can maintain a sitting position and about 13% achieve standing or walking [94]. Most heterozygous females are asymptomatic, but some have mild myopathy or even neonatal presentations as severe as those of their male counterparts [95]. Deficiency of MTM1 increases

dynamin 2 (*DMN2*) [96], which participates in clathrin-mediated endocytosis and interacts with the actin cytoskeleton. Primary variants in *DMN2* are themselves associated with centronuclear myopathy [187].

Two very rare GDPIMs with muscular manifestations include congenital muscular dystrophy with cataracts and intellectual disability (biallelic *INPP5K* variants [77]) and lethal congenital contractural syndrome 3 (biallelic *PIP5K1C* variants [148]).

### 4.3 | Skeletal Manifestations

Some GDPIMs have overt skeletal dysplasia. Yunis-Varón syndrome is a skeletal dysplasia with severe neurologic involvement, caused by variants in *FIG4*, encoding a PI 5-phosphatase that can convert $PI(3,5)P_2$ into PI3P [61]. This condition presents with cleidocranial dysplasia (wide fontanelles, absent or hypoplastic clavicles), absent or hypoplastic thumbs and first toes, pelvic dysplasia, absent sternal ossification centers and fractures. FIG4 complexes with the kinase PIKfyve and the scaffolding protein VAC14; interestingly, in one Yunis-Varón patient with normal *FIG4* analysis, variants in *VAC14* were found [182]. The complex localizes to the endosomal and lysosomal compartments, and large vacuoles compatible with enlarged lysosomes are identified by histopathology; vacuolization occurs in primary osteoblasts cultured from *Fig4*-deficient mice. Together, these data suggest involvement of FIG4 in membranous and endochondral ossification, as well as skeletal maintenance [61].

Another skeletal dysplasia, opsismodysplasia, is associated with biallelic variants in *INPPL1*, also known as *SHIP2*, which encodes a $PI(3,4,5)P_3$ 5-phosphatase. Patients have micromelia, and radiographs show delayed ossification, platyspondyly, metaphyseal cupping and squared metacarpals [80, 81]. Interaction of INPPL1 with Akt signaling as well as potential roles in cell polarity and FGF signaling is proposed to underlie the skeletal manifestations of this disorder [188]. INPPL1 is ubiquitous but enriched in mesenchymal precursors of chondrocytes and osteoblasts [31].

Skeletal abnormalities also occur in oculoskeletodental syndrome (caused by *PIK3C2A* variants) [118], spondylometaphyseal dysplasia with corneal dystrophy (*PLCB3*) [153], and auriculocondylar syndrome 2 (*PLCB4*) [154]. The last two suggest a role for phospholipase C activity in bone. Skeletal manifestations also occur in overgrowth syndromes discussed in section 4.5.

### 4.4 | Immunologic Manifestations

PItds are deeply implicated in innate and adaptive immunity, regulating phagocytosis (section 3.2.2), autophagy (section 3.3) and actin remodeling (section 3.4) which determines cell movement [44]. PItds regulate neutrophil survival [189], and in B cells, they mediate development, survival and activation by antigens [19]. Recently, biallelic *PI4KA* variants have been shown to disrupt B cell metabolism, inducing mitochondrial dysfunction as well as deranged cytoskeleton organization [190]. PI 3-kinases are important, regulating chemoattraction [191]; neutrophil/macrophage activation [19]; receptor-driven granule secretion [19]; pro-inflammatory cytokine production [192]; T cell development, differentiation, proliferation and survival [19]. Conversely, PItd metabolism can be hijacked by intracellular bacteria [44]: increased $PI(3,4,5)P_3$ and low $PI(4,5)P_2$ remodel actin, promoting bacterial entry by micropinocytosis [45], and bacterial suppression of PI3P production reduces lysosomal fusion and bacterial destruction [45].

Some GDPIMs have primarily immune phenotypes. Activated PI3Kδ syndromes 1 and 2 (APSD1/2) are caused by monoallelic variants in *PIK3CD* [126] and *PIK3R1* [134], respectively. *PIK3CD* encodes the catalytic subunit of PI3Kδ, and *PIK3R1*, the regulatory subunit of PI3Kδ. Both APSDs are characterized by recurrent sinopulmonary and viral infections (particularly herpesviruses) and autoimmune disorders (most often hematologic), lymphadenopathy and hepatosplenomegaly. However, APDS1 typically presents with bronchiectasis, cytopenia and splenomegaly, whereas APDS2 has higher risks of lymphoma, developmental delay, failure to thrive and dysmorphism [127]. PIK3CD, PIK3CG and PIK3R1 are associated with other recessive immune phenotypes: biallelic variants in *PIK3CD* have been associated with PI3Kδ deficiency syndrome (immunodeficiency, autoimmune disorder predisposition) in a few individuals [130, 131]; PIK3CG deficiency was described in two individuals with immune deficiency and autoimmunity [132, 133]; and biallelic *PIK3R1* variants have been found in two families with agammaglobulinemia and cytopenia [138, 139].

*PLCG2*-associated antibody deficiency and immune dysregulation (PLAID) presents with cold urticaria, humoral immune deficiency and autoimmunity. A related phenotype, APLAID (i.e., autoinflammation plus PLAID), reportedly has prominent interstitial lung disease, enterocolitis and autoinflammation, but without cold urticaria. PLAID was first described with large in-frame deletions encompassing the autoinhibitory domain of PLCɣ2, with signaling defects at normal temperature but activated signaling in the cold, APLAID was associated with gain-of-function variants [163, 164]. Recent research reveals other mechanisms, including hypermorphic, gain-of-function, dominant negative variants and haploinsufficiency [164].

Outside of the neurologic manifestations discussed earlier, autosomal recessive PI4KA-related disorder is associated with combined immunodeficiency, inflammatory bowel disease and, in severe cases, with multiple intestinal atresias [108–111].

### 4.5 | Overgrowth & Tumors

PItds have many links to tumorigenesis. $PI(3,4,5)P_3$ has been termed an "oncogenic" PItd, since its increase in tumors promotes proliferation and inhibits apoptosis [31]. Increases in $PI(3,4,5)P_3$, notably from gain-of-function variants in the PI 3-kinase PIK3CA, or from loss-of-function variants in the PI 3-phosphatase PTEN, have been reported in numerous solid tumors [193, 194]. Many cancers have altered PI 3-kinase function, and PI3K increases protein synthesis and cell cycle progression in response to growth signaling [195], notably via the PI3K/AKT/mTOR signaling pathway, which enhances cell survival, cell motility, cell cycle progression, genomic

**BOX 2** | PIK3CA-related disorders.

*Introduction*: This group of conditions is caused by somatic variants in the PI kinase, *PIK3CA*, associated with segmental overgrowth, vascular malformations, and cutaneous abnormalities. Several disorders with a wide array of clinical presentations have been described, depending on tissue mosaicism. As such, molecular confirmation of the diagnosis most often relies on sequencing of a biopsy of an affected tissue. Diagnoses associated with *PIK3CA* variants include *PIK3CA*-related overgrowth spectrum (PROS), *PIK3CA*-related vascular malformations, and *PIK3CA*-related nonvascular lesions [119–125].

*PIK3CA-related overgrowth spectrum (PROS)*: Different diagnostic entities have been grouped under the name PROS, including:

- Macrodactyly: overgrowth limited to one or several fingers or toes
- Facial/fibroadipose infiltrating lipomatosis
- Lipomatosis of nerve
- Muscular hemihypertrophy
- Klippel-Trénaunay syndrome: cutaneous vascular malformation, limb overgrowth, typically isolated to a lower extremity with extension to the lower trunk
- Fibroadipose overgrowth (FAO)/hemihyperplasia with multiple lipomatosis (HHML)
- Fibroadipose vascular anomaly
- CLOVES syndrome: Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis/Skeletal and Spinal anomalies
- CLAPO: Capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry, and Partial/generalized Overgrowth
- Megalencephaly—Capillary malformation—Polymicrogyria syndrome (MCAP)
- Dysplastic megalencephaly/hemimegalencephaly
- Diffuse capillary malformation with overgrowth

*Diagnostic criteria*. Diagnostic criteria are summarized below. For greater detail, readers should consult the original publication (Keppler-Noreuil et al.) [119]:

- Presence of somatic *PIK3CA* variant
- Onset before early childhood
- Overgrowth sporadic and mosaic (patchy, irregular)
- Either (1) or (2)
  1. Two or more of, typically progressive features:
     - Overgrowth (adipose, muscle, nerve, skeletal)
     - Vascular malformation (capillary, venous, arteriovenous, lymphatic)
     - Epidermal nevus
  2. One of:
     - Large isolated lymphatic malformation
     - Isolated macrodactyly
     - Overgrown splayed feet/hands
     - Overgrown limbs
     - Truncal adipose overgrowth
     - Hemimegalencephaly
     - Dysplastic megalencephaly
     - Focal cortical dysplasia
     - Epidermal nevus
     - Seborrheic keratoses
     - Benign lichenoid keratoses

stability, angiogenesis and inflammatory response [31]. PI 4-kinases have been shown to have a tumor suppressor role, and PI 5-phosphatases can function either as tumor suppressors or enhancers in different cancers [20, 58]. Dysregulation of PI 4-kinases has been linked with abnormal levels of reactive oxygen species, p53 stress signaling, and conditions promoting metastasis such as decreased E-cadherin expression [58]. Roles of PItds in histone code reading may also play a role in the expression of tumor suppressor genes [58]. GOLPH3, a PI4P effector, has roles in the Golgi DNA damage response, cell migration and growth factor signaling, all of which enable carcinogenesis [34].

Whereas cancer is defined as an "uncontrolled proliferation of transformed cells subject to evolution by natural selection" [196], overgrowth is more loosely defined as the presence of

**BOX 3** | PTEN-hamartoma tumor syndrome.

*Introduction*: Conditions related to PTEN, a PItd phosphatase, include PTEN-hamartoma tumor syndrome (PHTS), which groups multiple diagnostic entities with autosomal dominant transmission, including Cowden syndrome [168], Bannayan-Riley-Ruvalcaba syndrome [169], Lhermitte-Duclos disease (cerebellar dysplasia and gangliocytoma of the cerebellum) [170], Proteus-like syndrome [171], and macrocephaly—intellectual disability—autism syndrome [172].

*Diagnostic features*: The features are summarized as follows. For the classification of individual patients, readers are advised to consult the complete revised diagnostic criteria for PHTS (Pilarski et al. [166]):

*In an individual*:

1. ≥3 major criteria of which at least 1 must be macrocephaly, Lhermitte-Duclos or GI hamartomas
2. ≥2 major criteria and ≥3 minor criteria

*In a member of a family in which another individual meets the revised criteria or has a PTEN variant*:

1. ≥2 major criteria
2. 1 major criterion and 2 minor criteria
3. ≥3 minor criteria

*Major criteria*

- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- ≥3 gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplastic polyps)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97th percentile, ♀ ≥58 cm, ♂ ≥60 cm)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (≥3 trichilemmomas with ≥1 biopsy proven OR ≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules OR ≥3 mucocutaneous neuromas) OR oral papillomas (≥3 OR biopsy proven OR diagnosed by dermatologist)

*Minor criteria*

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthosis
- ≥3 lipomas
- Intellectual disability
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary, follicular variant of papillary)
- Thyroid structural lesions (adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

a generalized or localized excessive growth as compared to age-matched controls or other body areas [197, 198]. Cancer predisposition and segmental overgrowth are described in two well-characterized disorders of PItd metabolism related respectively to *PIK3CA* and to *PTEN* (see Boxes 2 and 3 for diagnostic criteria). Of note, alpelisib, a PI3K inhibitor, recently approved for the treatment of *PIK3CA*-related overgrowth syndrome (PROS), has produced reduction of hemihypertrophy and vascular tumors, and improvement of congestive heart failure and scoliosis [199, 200].

### 4.6 | Renal Manifestations

PItds affect renal filtration, reabsorption and cell polarization. Cell polarization, with the formation of distinct apical and basolateral membranes, depends partly on the synthesis of $PI(4,5)P_2$ from $PI(3,4,5)P_3$ at the apical membrane, recruiting annexin 2 and allowing for actin polymerization, whereas the basolateral membrane remains rich in $PI(3,4,5)P_3$ [10]. Evidence suggests that PItds also participate in podocyte physiology, notably in the formation of the podocyte slit diaphragm, dependent on the

actin cytoskeleton. PItd-dependent clathrin-mediated endocytosis (section 3.2.2) is important for endocytotic resorption of proteins in the tubule [10].

The oculocerebrorenal syndrome of Lowe, caused by variants in the X-linked *OCRL* gene, causes a multisystemic phenotype including neonatal cataracts, developmental delay, growth retardation, and chronic kidney disease [100–102]. Renal dysfunction in Lowe syndrome is characterized by low-molecular weight proteinuria that further evolves into a partial to complete Fanconi syndrome, with aminoaciduria and calcium and phosphate wasting in most patients and glycosuria and/or potassium wasting in a smaller fraction [101, 102]. OCRL is an important regulator of clathrin-mediated endocytosis in the kidney; OCRL deficiency causes accumulation of $PI(4,5)P_2$ in endosomal membranes, actin accumulation, abnormal trafficking, mis-sorting of membrane receptors such as megalin, mannose-6-phosphate receptors and epidermal growth factor receptor [10, 51] and abnormal autophagy [10].

Childhood onset steroid-resistant nephrotic syndrome with focal segmental glomerulosclerosis and diffuse mesangial sclerosis can result from biallelic variants in *PLCE1*, encoding phospholipase $C\varepsilon_1$ [161, 162].

### 4.7 | Ophthalmologic Manifestations

PItds function in phototransduction and cone photoreceptor survival [201], but retinal changes are infrequent in GDPIMs. A major exception is *INPP5E*-related Joubert syndrome with retinal dystrophy [73, 74]. Cataracts occur in Lowe syndrome (*OCRL*) [101, 102], oculoskeletodental syndrome (*PIK3C2A*) [117, 118], congenital muscular dystrophy with cataracts and intellectual disability (*INPP5K*) [77], and in a form of dominantly inherited congenital cataracts (*PIKFYVE*) [146, 147]. Variants in *PIKFYVE* are associated with Fleck corneal dystrophy, characterized by hyperreflective white flecks in the corneal stroma, due to vesicles containing lipids and glycosaminoglycans [144, 145]. Corneal opacities are also observed with the spondylometaphyseal dysplasia caused by biallelic variants in *PLCB3* [153]. Other various eye features reported in GDPIMs include Rieger anomaly in SHORT syndrome (*PIK3R1*) [135–137], optic atrophy, strabismus and cerebral visual impairment in *PIP5K1C* gain-of-function [150], and aniridia in Gillespie syndrome [82].

### 4.8 | Cutaneous Manifestations

Typically, dermatologic signs occur in GDPIMs as one aspect of a multisystemic syndrome. Vascular or lymphatic malformations and overgrowth occur with variants in *PIK3CA* and *PTEN* (Boxes 2 and 3). Somatic *PIK3CA* variants can cause lichenoid and seborrheic keratoses and epidermal nevi [119]. *PTEN*-related dermatological signs are hyperkeratosis, lipomas, mucocutaneous neuromas and macular pigmentation of the glans penis [166]. Cold-induced urticaria is a useful diagnostic feature of *PLCG2*-associated PLAID syndrome [163]. Syndromic cutis laxa occurred in one patient with *PI4K2A* variants [114].

Isolated skin findings occur with *PLCD1* variants [157, 158] and include leukonychia (white finger- and toenails), koilonychia (nail shape showing central depression and lateral elevation) and benign tumors of hair follicles (trichilemmal cysts [159], pilomatricomas [160]). Autosomal recessive isolated anhidrosis with histologically normal sweat glands has been associated with *ITPR2* variants [90].

## 5 | Conclusion

Inborn errors of phosphoinositide metabolism (GDPIMs) are a challenging and expanding sector of biochemical genetics (Table 2). Most affect multiple organs but lack signs that are familiar signals for metabolic specialists, such as systemic decompensations. Their unique clinical spectra derive from the basic properties of PItd metabolism: PItds comprise a small fraction of total membrane lipids but changes in their levels, which can occur rapidly at highly focused points within cells, can trigger profound changes in cell biology and structure that manifest clinically.

GDPIMs raise many clinical, diagnostic and therapeutic considerations. Clinically, most have neurologic involvement of diverse types (developmental delay, cortical dysplasia, cerebellar anomalies, white matter abnormalities, movement disorders and/or neuropathy). Muscular, immunologic, ophthalmologic, renal, skeletal, dermatologic phenotypes, plus tumor predisposition and growth abnormalities, are observed repeatedly among the known GDPIMs. The clinical features of patients with a given GDPIM often show a broad spectrum. At the time that patients present, specific GDPIMs can sometimes be suspected if several clinical signs correspond to those of a known GDPIM syndrome (Table 2). Conversely, GDPIMs cannot be eliminated strictly on clinical grounds, especially because of the broad clinical spectra of known GDPIMs and the fact that the clinical phenotypes related to many steps in PItd biology are as yet unknown. Better description of clinical spectra and natural history is clearly a priority; new syndromic associations will likely emerge and will help to standardize diagnosis and treatment, as illustrated by *PIK3CA* and *PTEN*.

Most laboratory diagnoses of GDPIMs come from broad-based molecular testing. At the time of writing, no clinically established biochemical test provides reliable diagnosis for groups of GDPIMs. Such a test would be particularly important for patients with molecular variants of undetermined significance. A major challenge is that PItd levels in intracellular membranes have little or no effect upon known circulating or excreted metabolites, suggesting that biochemical diagnoses may require a cell-based system. The quantitation of total cell PItd is possible (e.g., HPLC, mass spectrometry), but it is challenging to apply this to specific intracellular membranes [6, 202]. Microscopy-based methods allow dynamic studies of PItd localization but have their own challenges, including the non-specificity of probes that may detect multiple PItds [6, 202]. The redundancy among the enzymes of the PItd network adds to the challenge of developing reliable specific clinical biochemical diagnoses [6, 202].

Most GDPIMs have no specific treatment. This observation provides one of the strongest rationales for the study of GDPIMs as a group, since in the interconnected PItd network, modification of

one component might alter the levels of others. Increasing knowledge of the properties of this network will be useful for research into all GDPIMs. The recent success of the PI 3-kinase inhibitor alpelisib for the treatment of *PIK3CA*-related overgrowth provides a glimmer of hope for other inborn errors of PItd metabolism.

### Author Contributions

Francis Rossignol: Concept and design, drafting and critical revision of the manuscript. Foudil Lamari: Concept and design, critical revision of the manuscript. Grant A. Mitchell: Concept and design, critical revision of the manuscript.


### Acknowledgments

Dedicated to Jean-Marie Saudubray for his inspiring vision, support and teaching in the field of human metabolic medicine. Figures were created with BioRender.com. This research was supported in part by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health.


### Ethics Statement

All authors complied with the ethical guidelines according to the requirements of the JIMD.

### Conflicts of Interest

The authors declare no conflicts of interest.

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