



# Phosphoinositides: Regulators of Nervous System Function in Health and Disease

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Phosphoinositides, the seven phosphorylated derivatives of phosphatidylinositol have emerged as regulators of key sub-cellular processes such as membrane transport, cytoskeletal function and plasma membrane signaling in eukaryotic cells. All of these processes are also present in the cells that constitute the nervous system of animals and in this setting too, these are likely to tune key aspects of cell biology in relation to the unique structure and function of neurons. Phosphoinositides metabolism and function are mediated by enzymes and proteins that are conserved in evolution, and analysis of knockouts of these in animal models implicate this signaling system in neural function. Most recently, with the advent of human genome analysis, mutations in genes encoding components of the phosphoinositide signaling pathway have been implicated in human diseases although the cell biological basis of disease phenotypes in many cases remains unclear. In this review we evaluate existing evidence for the involvement of phosphoinositide signaling in human nervous system diseases and discuss ways of enhancing our understanding of the role of this pathway in the human nervous system's function in health and disease.

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## HISTORICAL PERSPECTIVE

Phosphoinositides are low abundance cellular membrane lipids generated by phosphorylation on the inositol headgroup of phosphatidylinositol. Historically, studies on brain tissue played an important part in the discovery of these molecules. Biochemical fractionation studies by Jordi Folch-Pi on brain extracts lead to the discovery of a mixture (which he named diphosphoinositide) that contained mainly what we now know to be phosphatidylinositol (PI), phosphatidylinositol 4 phosphate (PI4P) and phosphatidylinositol 4,5 bisphosphate [PI(4,5)P<sub>2</sub>] (Folch and Wolleey, 1942; Folch, 1949a,b). The signaling functions of phosphoinositides originated from observations by Hokin and Hokin (1955) that stimulation of pancreatic slices led to the incorporation of phosphate in lipids. It was also reported that stimulation of brain tissue led to the incorporation of phosphate into phosphatidic acid and phosphoinositides (Dawson, 1954a,b); the Hokins' also discovered that stimulation of nervous system tissue (brain slices or dorsal root ganglion) with acetylcholine, resulted in a similar incorporation of phosphate into lipid fractions (Hokin et al., 1960). Subsequently, it became

apparent that in cells, the activity of a phosphoinositide phospholipase C (Rhee and Choi, 1992) results in the hydrolysis of phosphoinositides leading to generation the products, soluble inositol 1,4,5 triphosphate (IP<sub>3</sub>) and diacyl glycerol (DAG) that act as second messengers (Berridge and Irvine, 1984). In the subsequent years, numerous studies have demonstrated the ability of phosphoinositides to regulate key cellular functions through non-PLC mediated mechanisms in a range of cell types. These include actin dynamics, vesicular transport and nuclear function which have all been extensively reviewed (Divecha et al., 1993; Martin, 1998; Simonsen et al., 2001; Haucke, 2005; Di Paolo and De Camilli, 2006; Wu et al., 2014; Posor et al., 2015). Although phosphoinositides are present in every cell type in eukaryota, given the long-established observation that inositol lipids are enriched in the brain, these lipids are likely to support key cellular functions in the human brain and alterations in these could lead to diseases of the nervous system. In this review, we provide a review of the major known functions of phosphoinositides in controlling neural cell function and human disease.

## OVERVIEW OF PHOSPHOINOSITIDE SIGNALING

The *myo*-inositol head group of the lipid phosphatidylinositol (PI) (Figure 1A) can be selectively phosphorylated at positions 3, 4 and 5 to generate seven unique species. These include three monophosphates -phosphatidylinositol 3 phosphate (PI3P), phosphatidylinositol 4 phosphate (PI4P) and phosphatidylinositol 5 phosphate (PI5P); three bisphosphates-phosphatidylinositol 4,5 bisphosphate [PI(4,5)P<sub>2</sub>], phosphatidylinositol 3,5 bisphosphate [PI(3,5)P<sub>2</sub>] and phosphatidylinositol 3,4 bisphosphate [PI(3,4)P<sub>2</sub>] and a single triphosphate-phosphatidylinositol 3,4,5 triphosphate [PI(3,4,5)P<sub>3</sub>] (Figure 1B). Biochemical studies across multiple cell types have revealed that phosphatidylinositol and the seven phosphoinositides are present in defined proportions (Figures 1C,D) and in many cases their cellular levels change in a precise and reversible manner during the response to specific cellular changes or environmental stimuli; these observations underscore their definition as important mediators of information transfer in cells. From a cell biological perspective, it is important to bear in mind that being lipids, phosphoinositides are not freely diffusible in the aqueous cytoplasm; therefore they are spatially restricted to the membrane at which they are produced and can move between intracellular compartments either by vesicular transport or through the action of lipid transport proteins (Cockcroft and Raghu, 2018). As a result of these constraints, each of the phosphoinositides has a distinct spatial pattern of distribution among organelles; most phosphoinositides are primarily enriched at one or two organelle membranes although minor pools of each lipid may also be found at other organelle membranes (Figure 2A) [reviewed in Di Paolo and De Camilli (2006), Balla (2013)]. In this review, we focus on the cellular functions of phosphoinositides in the nervous system. A comprehensive description of the cellular

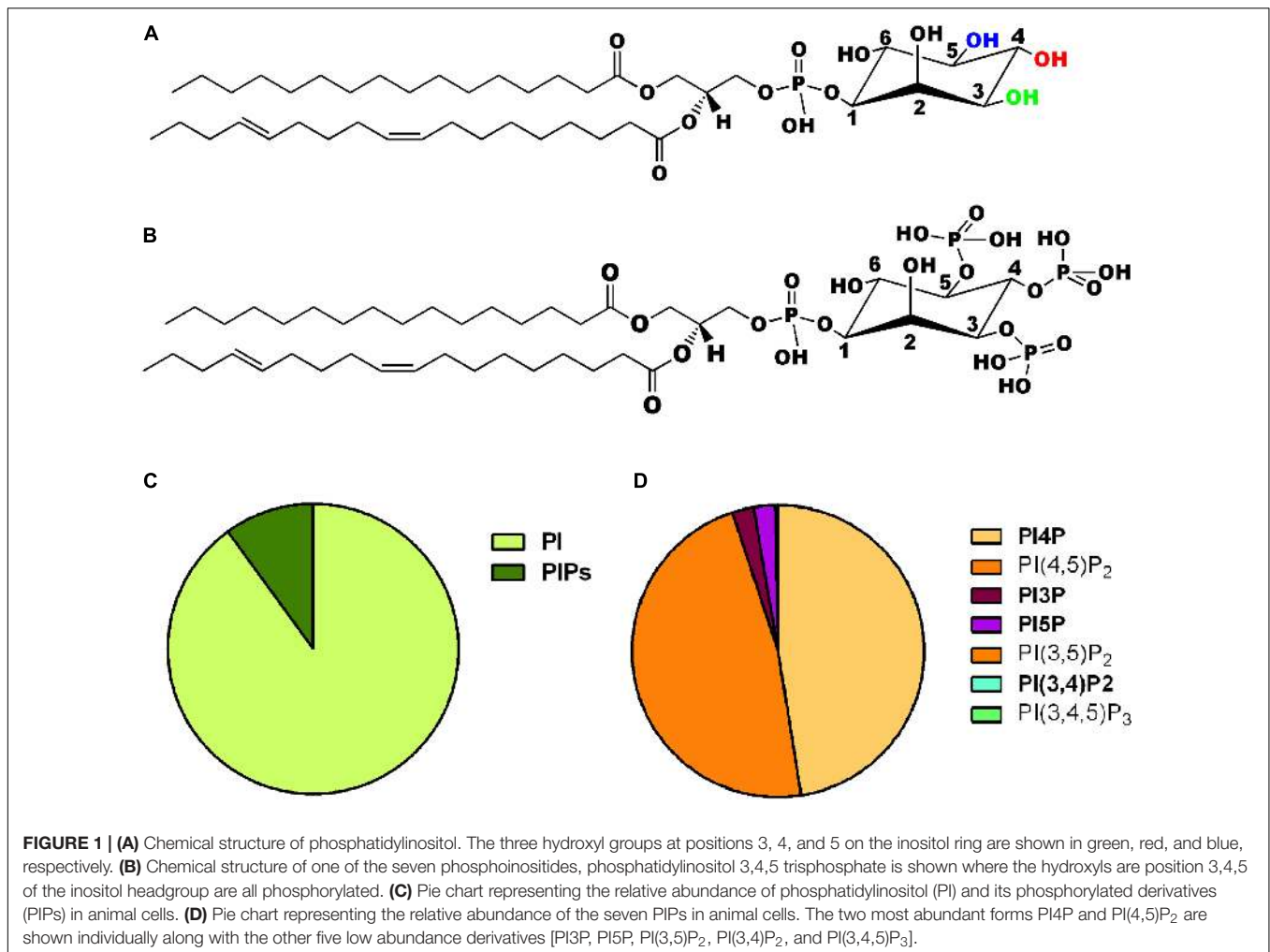
functions of these lipids has been published elsewhere and readers are referred to here for a detailed description of specific topics (Balla, 2013).

## CONTROL OF CELLULAR PHOSPHOINOSITIDE LEVELS

Within cells, phosphoinositides are generated through the selective addition or removal of phosphate groups from the *myo*-inositol headgroup. In general, the addition of phosphates is performed by an evolutionarily conserved group of enzymes called the phosphoinositide kinases. These enzymes are selective in two respects (i) They are specific for the substrate molecule on which they will act: for example a lipid kinase may act only on PI5P but not PI4P (ii) They are specific for the OH group on the *myo*-inositol ring at which they will add the phosphate group: for example an enzyme that will only add a phosphate at position 4 but not position 5. A large and evolutionarily conserved family of kinases has been described that show selectivity based on the above criteria (Table 1, Supplementary Table 1, and Figure 2B). The properties of these enzymes and the huge body of experimental analysis of these have been covered in an excellent and detailed review (Sasaki et al., 2009). Most enzymes of this family are conserved across all of eukaryota although some are seen only in metazoan genomes (e.g., Class I PI3K, PIP4K). In addition to the phosphoinositide kinases, lipid phosphatases that are able to selectively remove a phosphate group from the *myo*-inositol headgroup have been described. These enzymes also show substrate specificity and defined catalytic activity just like the phosphoinositide kinases (Table 1, Supplementary Figure 1, and Figure 2B) and (Sasaki et al., 2009) and are evolutionarily well conserved.

Phospholipases are enzymes which belong to the class hydrolases, i.e., those that use a molecule of water to degrade substrates; they catalyze the breakdown of phospholipids into fatty acids and other constituent molecules (Dennis, 2015). They are named based on the position they hydrolyze on the backbone of phospholipids. Phospholipases are known to be involved in phospholipid turnover, membrane remodeling and neurotransmitter release in brain. Under pathological conditions they result in altered membrane permeability, ion homeostasis and accumulation of lipid peroxidases. The phospholipase of most relevance to phosphoinositide signaling is phospholipase C (EC 3.1.4.11) that is able to hydrolyze PI(4,5)P<sub>2</sub> to generate inositol 1,4,5 triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG) (Rhee, 2001). The expression of phospholipase C genes varies across different brain compartments and tissues as detailed in this review. The phospholipases genes are well conserved across evolution (Table 1).

The phospholipid transfer proteins (LTPs) are molecules that facilitate the transfer of phospholipids between the membranes of sub-cellular compartments thus contributing to lipid homeostasis of cellular organelles. There are many classes of lipid transfer proteins; in the context of phosphoinositide signaling, the most important are the phosphatidylinositol transfer protein family that supports the transfer of PI from its site of



synthesis, the endoplasmic reticulum, to the plasma membrane (Hsuan and Cockcroft, 2001). More recently additional classes of proteins such as the OSH/OSBP family have been discovered that appear to be required for PI4P transfer between organelle membranes (Cockcroft and Raghu, 2018). These lipid transfer proteins are distributed across a range of organisms (Table 1). Collectively the molecules described above are core components in the regulation of phosphoinositide signaling in eukaryotic cells (Balakrishnan et al., 2015) including those in the brain. The metabolism of each phosphoinositide and its cellular functions with respect to neurons are presented below.

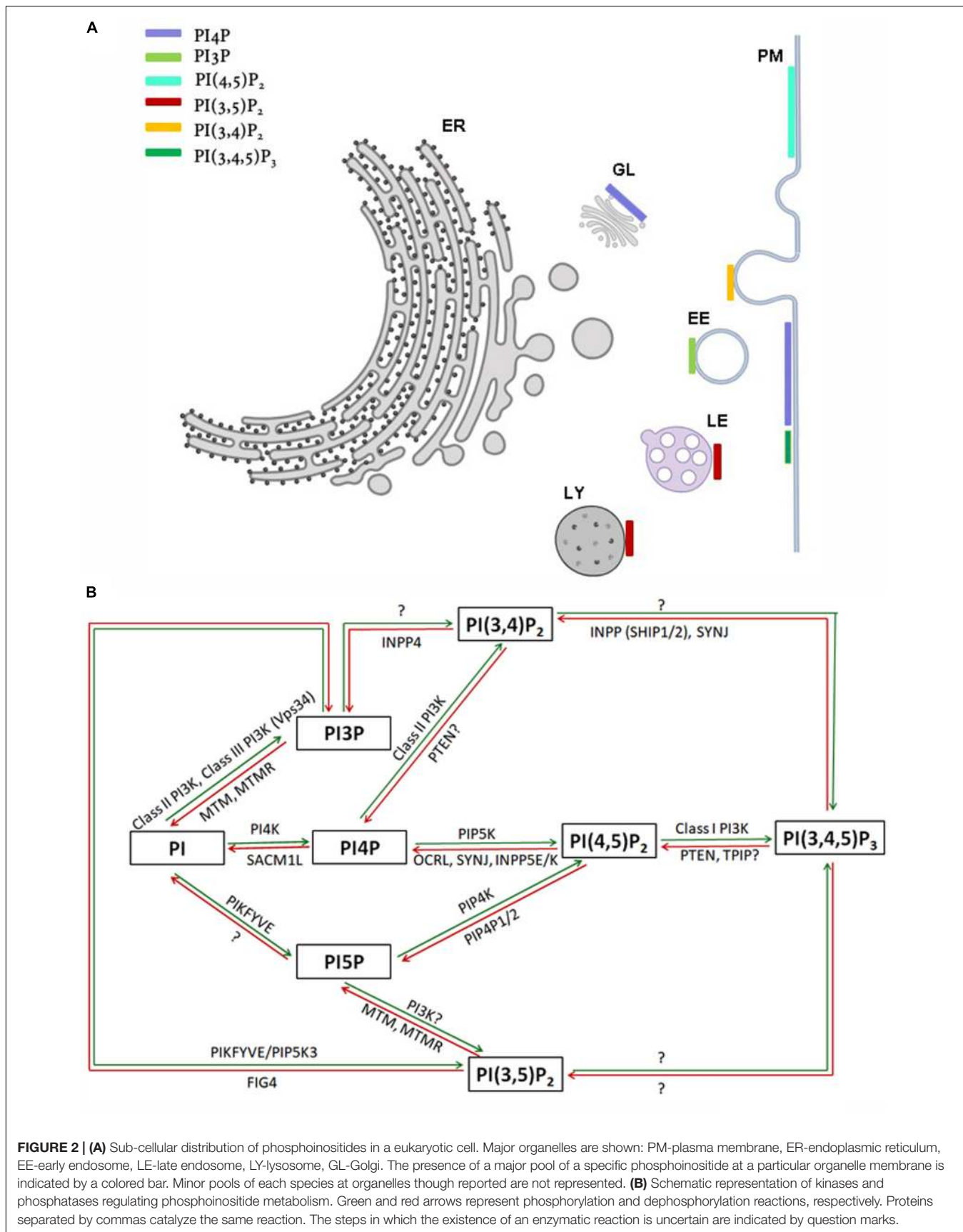
## CELLULAR FUNCTIONS OF PHOSPHOINOSITIDES IN THE NERVOUS SYSTEM

### PI3P

PI3P can be produced from PI by Class III PI3K (Vps34) in endosomes (Schu et al., 1993) or by class II phosphatidylinositol 3-phosphate kinase (PI3K) at the plasma membrane

(Vanhaesebroeck et al., 2010). In addition, PI3P can be generated by dephosphorylation of PI(3,4)P<sub>2</sub> by INPP4a (Sasaki et al., 2010) or PI(3,5)P<sub>2</sub> by FIG4 (Chow et al., 2007). PI3P is mainly found localized at early endosomes and is involved in endosomal trafficking (Gaidarov et al., 2001) but is also generated at the autophagosomal membrane thus regulating autophagy (Noda et al., 2010).

With respect to neural cell function, PI3P may be particularly important in regulating the levels of cell surface receptors for neurotransmitters, or for the control of autophagy which is believed to be a key ongoing process in neurons that is relevant to neurodegeneration (Menzies et al., 2017). In hippocampal neurons of mice, PI3P was found to be localized at dendrites, axons and partially at synapses (Wang et al., 2011). The early endosomal pool of PI3P is involved in the post synaptic clustering of GABA receptors, thus regulating the strength of inhibitory post synapses in cultured hippocampal neurons (Papadopoulos et al., 2017). Depletion of Vps34, the key enzyme in PI3P generation, in selected brain regions results in neuronal degeneration and reactive gliosis that appear to be associated with defects in the endosomal system but not changes in autophagy (Zhou et al., 2010; Wang et al., 2011).



**TABLE 1** | Phosphoinositide kinase and phosphatase orthologs in *Drosophila melanogaster* and *Caenorhabditis elegans*.

	<i>H. sapiens</i>	<i>D. melanogaster</i>	<i>C. elegans</i>
<b>Kinases</b>			
	<i>PIK3C/CB/CD/CG</i>	PI3K92E/CG4141	PI3K/age-1
	<i>PIK3C2A/2B/2G</i>	PI3K68D/CG11621	PI3K/piki-1/NP_510529.1
	<i>PIK3C3</i>	PIK359F/vps34/CG5373/	PI3KC3/NP_001020954.1
	<i>PI4K2/2B</i>	PI4KIIA/CG2929	CELE_ZC8.6/NP_508849
	<i>PI4KA/PI4KA</i>	PI4KIIIA/CG10260	CELE_Y75B8A.24/NP_499596.2
	<i>PI4CB/PI4KB</i>	fwd/CG7004	–
	<i>PIP5K1A/1B/1C</i>	PIP5K59B/CG3682	ppk-1/NP_491576.2
	<i>PIP5K3/PIKFYVE</i>	Fab1/CG6355	–
	<i>PIP4K2A/2B/2C</i>	dpip4K/CG17471	ppk-2/NP_497500.1
<b>Phosphatases</b>			
<i>PI3-phosphatases</i>			
	<i>PTEN/TPTE2</i>	dPTEN/CG5671	hypothetical protein T07A9.6
	<i>MTM1/MTMR1/MTMR2</i>	dmtm/CG9115	MTMR1/NP_491531.2
	<i>MTMR3/MTMR4</i>	CG3632	MTMR3/NP_001022794.2
	<i>MTMR5/SBF1</i>	SBF/CG6939	MTMR5/NP_508888.2
	<i>MTMR6/MTMR7/MTMR8</i>	CG3530	MTMR6/NP_001022602.1
	<i>MTMR14</i>	–	–
<i>PI4-phosphatases</i>			
	<i>INPP4A/4B</i>	CG42271	INPP4/AAM97343.1
	<i>TMEM55A/55B</i>	CG6707	PI(4,5)P <sub>2</sub> 4-phosphatase/NP_497624.3
	<i>SACM1L/SAC1</i>	sac1/CG9128	SAC1/NP_492518.2
<i>PI5-phosphatases</i>			
	<i>SYNJ1/2</i>	synj/CG6562	synaptojanin/NP_001023265.1
	<i>OCRL</i>	ocr1/CG3573	Inositol Polyphosphate-5-Phosphatase/NP_001255510.1
	<i>INPP5B</i>	–	–
	<i>INPP5J</i>	CG6805	–
	<i>SKIP/INPP5K</i>	CG9784	–
	<i>INPP5D/SHIP1</i>	–	–
	<i>INPPL1/SHIP2</i>	–	–
	<i>INPP5E</i>	INPP5E/CG10426	–
	<i>INPP5F/SAC2</i>	CG7956	CELE_W09C5.7/NP_001252206.1
	<i>FIG4</i>	Fig4/CG17840	CELE_C34B7.2/NP_492266.2
<b>Other components</b>			
	<i>PTPMT1</i>	ptpmt1/CG10371	CELE_F28C6.8/NP_001254162.1
<i>Phospholipases</i>			
	<i>PLCB1/2/3</i>	PLC/CG4574	–
	<i>PLCB4</i>	norpA/CG3620	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase/NP_001300035.1
	<i>PLCG1/G2</i>	Small wing/CG4200	Plc-3/NP_96205.2
	<i>PLCD1/3/4</i>	–	PI-PLC/NP_501213.1
	<i>PLCZ1</i>	–	–
	<i>PLCE1</i>	–	PLCE1/NP_001129926.1
<i>PI transfer proteins</i>			
	<i>PITPNA/NB</i>	Vibrator/CG5269	CELE_Y54F10AR.1/NP_497582.3
	<i>PITPNM1/NM2/NM3</i>	rdgB/CG11111	PITP/NP_497726.2
	<i>PITPNC1</i>	RdgB-beta/CG17818	–

The orthologs of human phosphoinositide signaling genes (kinases, phosphatases, phospholipases and lipid transfer proteins) in *D. melanogaster* and *C. elegans* have been reported. The orthologs have been obtained by the reciprocal blast approach, literature survey for reported orthologs or experimental evidence of a specific activity. The flybase gene IDs have been reported for *D. melanogaster* genes and NCBI gene IDs have been reported for *C. elegans* genes. (–) represents genes for which no orthologs are found in either genomes.

Depletion of Vps34 in Schwann cells, the glia of the peripheral nervous system results in defective myelination associated with altered endo-lysosomal system and autophagy (Logan et al., 2017). Finally, PI3P has been found to be selectively deficient in the brains of human patients with Alzheimer's disease (Morel et al., 2013) and mouse models of Alzheimer's

disease with associated defects in endosomal-lysosomal network [reviewed in Nixon (2017)].

## PI4P

PI4P is found in at least two major subcellular locations in cells, the Golgi complex and the plasma membrane. PI4P at



Golgi coordinates several functions including vesicle trafficking, membrane biogenesis and lipid homeostasis (D'Angelo et al., 2008). At the Golgi apparatus, PI4P recruits proteins that bind this lipid and mediate its functions at this location thus regulating processes such as sphingolipid biosynthesis (Kawano et al., 2006) and cargo sorting. At the plasma membrane, PI4P is required for maintaining PI(4,5)P<sub>2</sub> levels during receptor activated PLC signaling; PI4P can directly regulate the function of plasma membrane proteins such as KCNQ2/3 channels (Dickson et al., 2014) and smoothen the receptor for hedgehog signaling (Jiang et al., 2016). PI4P also binds to clathrin adaptors such as epsin R (Hirst et al., 2003) and AP-1 (Wang et al., 2003) thus regulating endosome trafficking. PI4P is generated by the phosphatidylinositol 4-kinase (PI4K) family of enzymes (Balla and Balla, 2006). At the plasma membrane PI4P is produced by the PI4KIII $\alpha$  class of enzymes and regulates PLC dependent functions (Nakatsu et al., 2012; Balakrishnan et al., 2018). By contrast PI4P at the Golgi is generated by the PI4KIII $\beta$  family (Godi et al., 1999; Walch-Solimena and Novick, 1999). PI4P can also be produced by dephosphorylation of PI(4,5)P<sub>2</sub> by 5' lipid phosphatases such as oculocerebrorenal syndrome of Lowe (OCRL) and Synaptojanin. These enzymes are likely to be particularly important in the context of neural cell function (*see below*). PI4P can also be degraded by the lipid phosphatase SACM1L (Sac1 in yeast), an ER resident enzyme that at plasma membrane endoplasmic reticulum contact sites (Stefan et al., 2011; Zewe et al., 2018).

In the nervous system, very little information is available on the direct effect of perturbations in PI4P levels, and more on the enzymes regulating it. The presence of PI4K2 $\alpha$  at high concentration in synaptic vesicles indicates a direct or indirect role of PI4P in neuronal function, as a precursor of PI(4,5)P<sub>2</sub> (Guo et al., 2003), which in turn has been identified to be crucial for clathrin mediated endocytosis (Wenk et al., 2001). *Pi4k2a* mutant adult mice lacking kinase activity exhibit progressive neurological disorders, including substantial degeneration of spinal axons (Simons et al., 2009). In *Drosophila* models, depletion of a protein complex that includes PI4KIII $\alpha$  that generates PI4P at the plasma membrane has been shown to affect the neuronal accumulation A $\beta$ <sub>42</sub> oligomers (Zhang X. et al., 2017).

## PI5P

PI5P is the most recently discovered phosphoinositide (<10% of total cellular phosphatidylinositol monophosphates) (Rameh et al., 1997). Biochemical fractionation studies indicate that PI5P is distributed across multiple cellular compartments including the plasma membrane, nucleus, endo-lysosomal system and the Golgi (Sarkes and Rameh, 2010). A number of studies have suggested a role for PI5P in regulating chromatin function and transcriptional regulation in the nucleus [reviewed in Fiume et al. (2015)]. Ectopic expression of the *Shigella* phosphatase IpgD, that generates PI5P is known to cause endosomal sorting defects of the epidermal growth factor receptor (EGFR) (Ramel et al., 2011) and PI5P binding proteins have been identified in early endosomal fractions (Boal et al., 2015). *In vitro*, PI5P is known to stimulate myotubularin (Schaletzky et al., 2003), proteins that play an

important role in early endosomal sorting (Naughtin et al., 2010). Collectively these observations suggest that PI5P might regulate endosomal trafficking, but the mechanism remains unclear. The mechanism by which PI5P is generated remains unresolved. It has been argued that the enzyme PIKFYVE/Fab1 might synthesize PI5P from PI (Shisheva et al., 2015). An alternative model is that PI5P can be generated by the lipid phosphatase activity of the myotubularin family of enzymes acting on PI(3,5)P<sub>2</sub> to generate PI5P in yeast (Walker et al., 2001) or mammalian cells (Vaccari et al., 2011). PI5P concentration can also be regulated by the phospholipid kinase phosphatidylinositol 5 phosphate 4-kinase (PIP4K) that is able to convert PI5P into PI(4,5)P<sub>2</sub> (Gupta et al., 2013) and reviewed in Kolay et al. (2016).

There is limited information available on the role of PI5P in neurons. *In vitro* knock down or pharmacological inhibition of the PIP4K isoform PIP4K2C is reported to reduce mutant huntingtin protein aggregates by increasing basal autophagy, suggesting that the kinase could be a potential target for treatment of the progressive neurodegenerative Huntington's disease (Al-Ramahi et al., 2017). *Drosophila* mutants with elevated PI5P levels have been reported to have defects in the early endosomal compartment of neurons (Kamalesh et al., 2017). It has also recently been reported that depletion of PIP4K2C results in defects in the recycling of Notch to the cell surface (Zheng and Conner, 2018); since Notch is a key regulator of neurogenesis, these findings may imply a role for PI5P, the substrate of PIP4K2C in brain development. Collectively these observations suggest a role for PI5P in regulating membrane transport in neural cells that remains to be fully understood.

## PI(4,5)P<sub>2</sub>

PI(4,5)P<sub>2</sub> is mainly localized at the plasma membrane of cells although other minor pools of this lipid have been described on the membranes of internal organelles such as endosomes and lysosomes (van den Bout and Divecha, 2009). In this location it controls a number of cellular processes. Historically the oldest known function of PI(4,5)P<sub>2</sub> is to serve as the substrate for receptor activated phospholipase C which generates inositol 1,4,5 trisphosphate (IP<sub>3</sub>) and diacylglycerol (DAG) which themselves serve as second messengers. However, it is now apparent that a major function of PI(4,5)P<sub>2</sub> is to interact with and modulate the activity of numerous proteins that regulate key sub-cellular processes such as vesicular transport (endocytosis and exocytosis), cytoskeletal reorganization and the regulation of ion channel and transporter activity [reviewed in Kolay et al. (2016)]. PI(4,5)P<sub>2</sub> is mainly produced by the phosphorylation of PI4P by phosphatidylinositol 4-phosphate 5-kinase (PIP5K) (Funakoshi et al., 2011). In humans, three PIP5K isozymes are expressed namely PIP5K $\alpha$ ,  $\beta$ , and  $\gamma$  (Funakoshi et al., 2011). A minor pool of PI(4,5)P<sub>2</sub> is also synthesized by phosphatidylinositol 5-phosphate 4-kinase (PIP4K) using PI5P (Rameh et al., 1997) and PTEN using PIP<sub>3</sub> as substrates (Rahdar et al., 2009). PI(4,5)P<sub>2</sub> is consumed by the activity of PLC, Class I PI3K that converts it into PI(3,4,5)P<sub>3</sub> and also by the activities of the 5' phosphatases synaptojanin (SYNJ) and OCRL.

PI(4,5)P<sub>2</sub> has a number of critical functions in the nervous system. Many receptors for neurotransmitters in the brain use

G-protein coupled, PLC mediated hydrolysis of PI(4,5)P<sub>2</sub> as a key step in signal transduction [reviewed in Dickson and Hille (2019)] and numerous ion channels in the nervous system require PI(4,5)P<sub>2</sub> for their normal function [reviewed in Hille et al. (2015)]. In addition, PI(4,5)P<sub>2</sub> regulates multiple steps of the synaptic vesicle cycle. The lipid kinase PIP5K $\gamma$  is enriched at nerve terminals and plays a key role in regulating PI(4,5)P<sub>2</sub> levels (Wenk et al., 2001); PIP5K $\gamma$ <sup>-/-</sup> mice show decreased PI(4,5)P<sub>2</sub> in the brain and defects in synaptic transmission (Di Paolo et al., 2004). Dephosphorylation of PI(4,5)P<sub>2</sub> is also important for the recycling synaptic vesicles that are endocytosed at the presynaptic terminal. The PI(4,5)P<sub>2</sub> 5-phosphatase SYNJ1 plays a key role in the uncoating of clathrin-coated synaptic vesicles (Mani et al., 2007). Increased PI(4,5)P<sub>2</sub> levels and clustering of clathrin-coated vesicles at nerve endings were observed in the neurons of SYNJ1-deficient mice (Cremona et al., 1999), and the internalization of postsynaptic AMPA receptor, involved in fast excitatory synaptic transmission, was inhibited in cultured *Synj1* knockout mouse hippocampal neurons (Gong and De Camilli, 2008). A role for PI(4,5)P<sub>2</sub> has also been proposed for regulating cytoskeletal function in neurons; the kinesin motor Unc104 can bind PI(4,5)P<sub>2</sub> (Klopfenstein et al., 2002) and this binding plays a key role in kinesin based transport in neurons (Klopfenstein and Vale, 2004; Kumar et al., 2010). Since PI(4,5)P<sub>2</sub> performs multiple functions in neurons, an interesting question arises on how these are controlled independently. Recent studies have proposed a role for functional pools of PI(4,5)P<sub>2</sub> generated in neurons by specific lipid kinases [(Chakrabarti et al., 2015) and reviewed in Kolay et al. (2016)].

### PI(3,5)P<sub>2</sub>

PI(3,5)P<sub>2</sub> is a lipid that is primarily found on late endosomes and lysosomal membranes. Its levels rise in response to changes in extracellular stimuli including osmotic stress in yeast or stimulation with growth factors and phagocytosis in mammalian cells [reviewed in Hasegawa et al. (2017)]. A number of studies implicate PI(3,5)P<sub>2</sub> in late endosomal dynamics and it has also been proposed to regulate the function of TPC ion channels on the lysosomal membrane (Jha et al., 2014). Tsuruta et al. (2009), Seebohm et al. (2012). PI(3,5)P<sub>2</sub> is produced in cells by the activity of a PI3P-5 kinase (Fab1 in yeast and PIKFYVE in mammals). PI(3,5)P<sub>2</sub> can be dephosphorylated *in vitro* by the activity of the phosphatase FIG4 to generate PI3P; members of the MTMR family have also been proposed to regulate PI(3,5)P<sub>2</sub> levels although the relevance of these mechanisms *in vivo* remains unclear [reviewed in Hasegawa et al. (2017)].

In neurons decreased levels of PI(3,5)P<sub>2</sub> directly affect NMDA-induced voltage-gated Ca<sup>2+</sup> channel internalization which causes neuronal excitotoxicity (Tsuruta et al., 2009) and in the hippocampus neurons of new-born rats, defects in postsynaptic GluA1 receptor turnover are seen when PI(3,5)P<sub>2</sub> levels are altered (Seebohm et al., 2012). PI(3,5)P<sub>2</sub> levels have also been shown to increase during homeostatic downscaling, where neurons reduce their postsynaptic strength to prevent chronic neuronal hyperactivity (McCartney et al., 2014). A number of studies have shown a role for PI(3,5)P<sub>2</sub> in regulating lysosomal function and autophagy in the nervous system. Analysis of

spontaneous mouse mutants of *Fig4* and *Vac14*, members of the PIKFYVE-FIG4 enzyme complex, has shown that although these proteins are widely expressed across the body, the nervous system that is particularly susceptible to the loss of these enzymes, presumably through altered PI(3,5)P<sub>2</sub> levels. These effects include neuronal degeneration, myelination defects and accumulation of inclusions in astrocytes [reviewed in Lenk and Meisler (2014)]. These findings have led to a mechanistic explanation for a number of human neurological syndromes in which proteins involved in PI(3,5)P<sub>2</sub> metabolism are affected (see below).

### PI(3,4)P<sub>2</sub>

PI(3,4)P<sub>2</sub> is a lipid that is primarily found at the plasma membrane and the early endosomal system. The function of this lipid is unclear but it has been proposed to regulate early endosomal dynamics and also alter the gain of the Class I PI3kinase signaling pathway (Zhang S. et al., 2017). The best characterized route of PI(3,4)P<sub>2</sub> synthesis is the dephosphorylation of PI(3,4,5)P<sub>3</sub> by 5' phosphatases [reviewed in Hawkins and Stephens (2016)] although it has also been proposed to be generated in the early endosomal system during clathrin mediated endocytosis by Class II PI3K activity on PI4P (Posor et al., 2013; He et al., 2017). The myotubularin family of lipid phosphatases may control the levels of this lipid by degrading it to PI4P.

The available literature points to the role of PI(3,4)P<sub>2</sub> in neurite initiation and dendrite morphogenesis (Zhang S. et al., 2017) by promoting actin aggregation at the site of initiation, leading to the cytoskeletal reorganization for forming the cylindrical neurite. PI(3,4)P<sub>2</sub> was also shown to be present in the postmitotic multipolar neurons derived from radial glia. The actin remodeling protein lamellipodin binds to PI(3,4)P<sub>2</sub> and recruits Ena/vasodilator-stimulated phosphoprotein (VASP) to positively regulate the number of primary processes in the multipolar cells (Yoshinaga et al., 2012).

### PI(3,4,5)P<sub>3</sub>

PI(3,4,5)P<sub>3</sub> is a very low abundance lipid found at the plasma membrane of cells following activation of plasma membrane receptors (Ming et al., 1999; Henle et al., 2011; Arendt et al., 2014). The principal mechanism of synthesis is the activity of Class I PI3K enzymes that phosphorylate PI(4,5)P<sub>2</sub> to generate PI(3,4,5)P<sub>3</sub>. PI(3,4,5)P<sub>3</sub> can be degraded by the activity of 3' phosphatases such as PTEN or by the action of 5' phosphatases such as SHIP.

As in all other tissues and cell types, the levels of PI(3,4,5)P<sub>3</sub> play a key role in growth through its ability to control cell division and size through activation of a number of intracellular signaling pathways (Engelman et al., 2006). PI(3,4,5)P<sub>3</sub> has been found enriched in the growth cones of developing neurites (Ménager et al., 2004), and has been implicated in the control of numerous processes in both developing and mature neurons. These include remodeling of the actin cytoskeleton during neurite outgrowth and dendrite morphogenesis (Ming et al., 1999; Henle et al., 2011). Synthesis and availability of PI(3,4,5)P<sub>3</sub> is also required for maintaining AMPA-type glutamate receptors at synaptic membrane, and this

in turn regulates synaptic function in hippocampal neurons (Arendt et al., 2014). PTEN, that regulates PI(3,4,5)P<sub>3</sub> levels is expressed and plays an important role during neuronal morphogenesis and differentiation (Lachyankar et al., 2000; van Diepen and Eickholt, 2008). Knockout of PTEN and resulting elevated PI(3,4,5)P<sub>3</sub> level leads to an increase in the diameter of parallel fiber axons of granule cells, an increase in oligodendrocyte differentiation and *de novo* myelination of normally unmyelinated parallel fibers (Goebbels et al., 2017). Inhibition of PTEN by bisperoxovanadium has also shown to promote oligodendrocyte proliferation and myelination of dorsal root ganglion neurons (De Paula et al., 2014). At the same time, PTEN loss does not show an improvement in remyelination following brain injury (Harrington et al., 2010).

## EFFECTORS OF PHOSPHOINOSITIDE SIGNALING

The oldest known function of phosphoinositides is the regulation of calcium signaling. This process is triggered by the metabolic conversion of PI(4,5)P<sub>2</sub> into IP<sub>3</sub> and DAG by phospholipase C leading the activation of intracellular calcium release channels and plasma membrane calcium influx channels (Berridge and Irvine, 1989). However, we now know that phosphoinositides function through multiple mechanisms including their ability to bind to cellular proteins and regulate their activity. Given their negative charge, phosphoinositides may bind to proteins by interacting with single or clusters of positively charged residues (as in the case of KiR channels) (Hansen, 2015) or via well-defined protein domains (e.g., PH, PX, FYVE domains) [reviewed in Hammond and Balla (2015)]. A specific domain may be found in the context of multiple proteins that bind a specific phosphoinositide (for example identification of an FYVE domain may be an indication of a protein that binds PI3P and the context for its cellular function). More recently an unbiased quantitative mass spectrometry analysis has described a large set of more than 400 proteins that bind phosphoinositides (Jungmichel et al., 2014) and are likely to be key mediators of the effects of phosphoinositides in cells.

The well-characterized phosphoinositide-binding domains in effector proteins are the PH (pleckstrin homology), PX (phox homology), FYVE (Fab1, YOTB, Vac1 and EEA1), ENTH (epsin amino-terminal homology) and FERM (Four-point-one, ezrin, radixin and moesin) domains (Balla, 2005). Through their interactions with specific phosphoinositides, these effector proteins are recruited onto membrane surfaces and participate in various cellular processes (Di Paolo and De Camilli, 2006).

## EXPRESSION OF PHOSPHOINOSITIDE SIGNALING GENES IN THE HUMAN NERVOUS SYSTEM

Gene expression in human tissues and cell types is differentially regulated depending on the developmental stage, tissue type, cell type and in some cases is altered in specific disease conditions.

In addition to core genetic mechanisms, gene expression is also controlled epigenetically. Post-transcriptional processes can change the levels of transcripts and control of translation and protein stability can also affect the levels of proteins in the nervous system. The spatial and temporal pattern of gene expression can often give an insight into the potential function of a gene. Several studies have documented patterns of gene expression in human cells and tissues and an analysis of data on expression in brain regions, cell types and temporal patterns from such studies can provide an insight into the function of specific genes in the nervous system.

Several large-scale studies have documented gene expression in the human nervous system. Gene expression studies in the brain are mostly done from post-mortem samples. Studies have shown that death results in significant expression change in only 10% of genes with varied functional categorization, thus justifying the use of post-mortem brain samples for expression analysis (Franz et al., 2005). Such studies have included (i) the analysis of gene expression in specific cell types of the nervous system<sup>1</sup>, (ii) expression in distinct regions of the normal human brain and also a profile of the expression of each gene as a function of time starting with fetal development through to adult human brains and subsequently in the ageing brain<sup>2</sup> and (iii) gene expression analysis in the diseased brain<sup>3</sup>. Likewise the Human Protein Atlas provides information on the sub-cellular localization and expression of more than 50% of human protein coding genes in major human tissues and organs (Bae et al., 2015). We have mined such databases for information on the expression of genes encoding components of the phosphoinositide signaling system in the human nervous system. The expression of genes in all these datasets is represented as TPM (Transcripts Per Million base pairs) values which is normalized for the dataset under study and cannot be compared across different datasets. These TPM values have been used to plot the heat maps and tables discussed below. The expression of genes in brain regions, cell types and their temporal expression profile is provided with a view to identifying those with potentially important roles in the structure and function of the nervous system.

## Spatial Expression Pattern of Phosphoinositide Signaling Genes in the Nervous System

Approximately 80–90% of protein-coding genes are expressed in some part of the brain during development and adult human life, though there are a large number of genes with a specific expression and alternate splicing patterns (Bae et al., 2015). Human specific expression (as compared to other primates) when noted is usually associated with enrichment in the neocortex and hippocampus. The expression values (TPM values) of 214 genes (phosphoinositide signaling genes listed in **Table 1**) in different brain regions was extracted from the GTEx database (see footnote 2) (Lonsdale et al., 2013). The expression of each gene was normalized to its expression in whole blood

<sup>1</sup><http://www.brainrnaseq.org>

<sup>2</sup><https://gtexportal.org/home/>

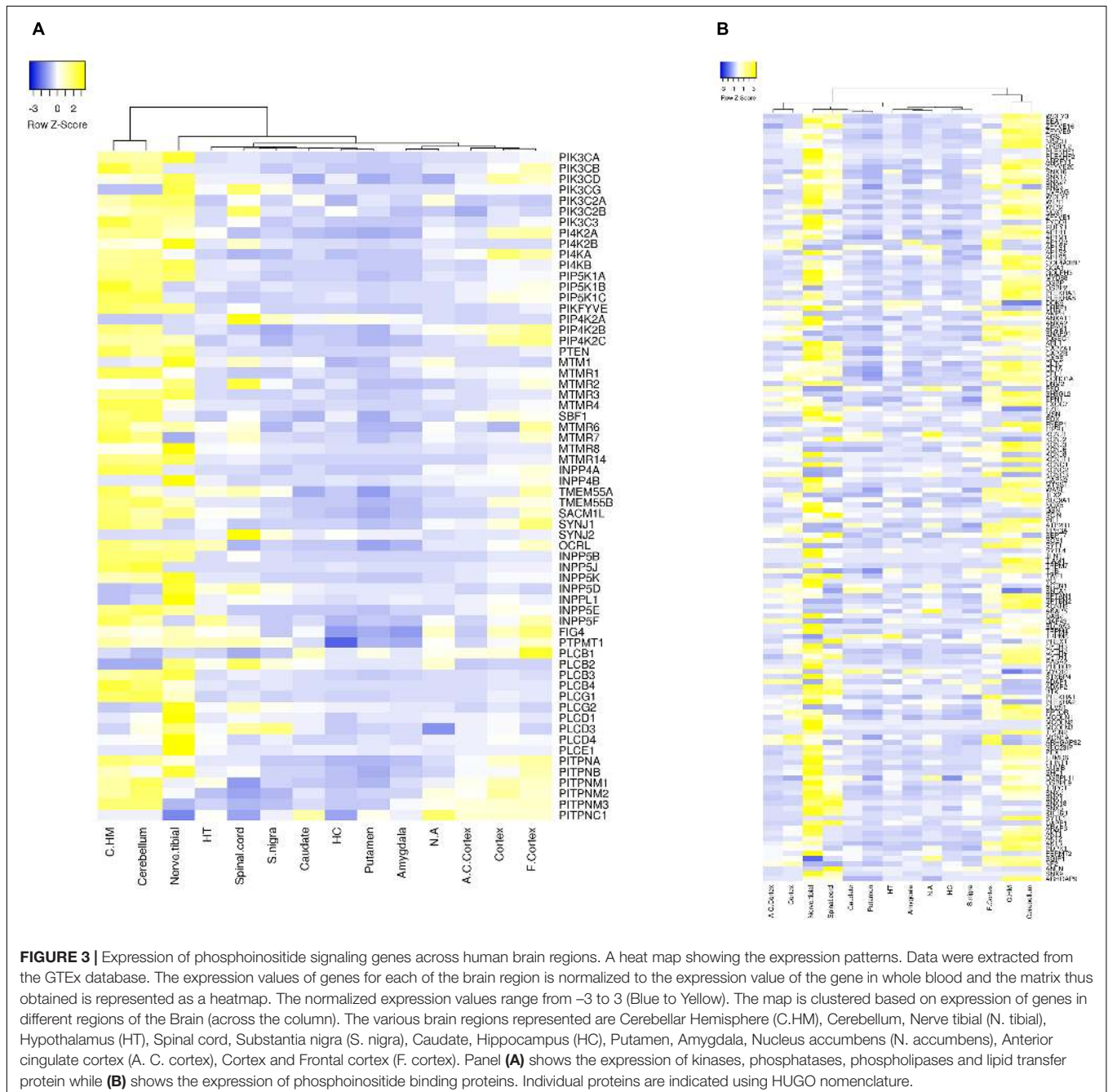
<sup>3</sup><https://www.libd.org/brain-cloud/>

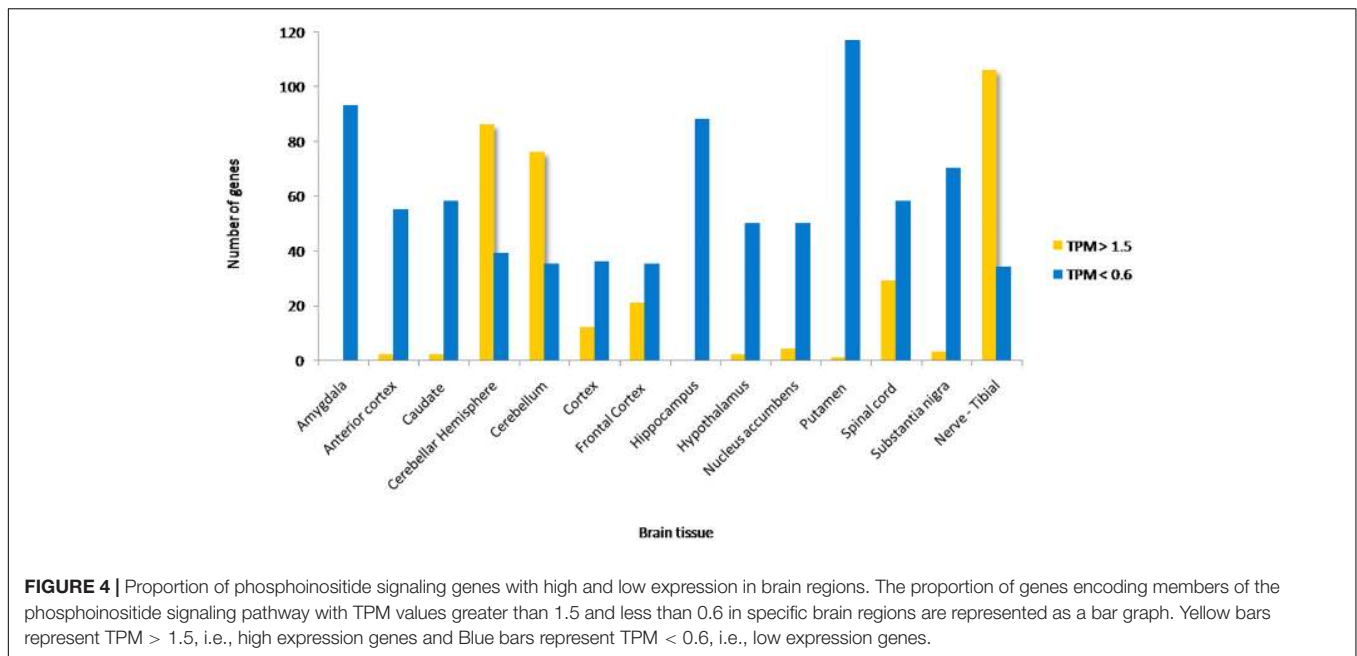


( $TPM_{\text{brain}}/TPM_{\text{whole\_blood}}$ ) and is represented in the form of a heatmap that has been clustered across different regions of the brain (along the columns of the heatmap) (Figures 3A,B). This analysis reveals that most genes enriched in the nervous system are usually expressed in the cerebral cortex, cerebellum and tibial nerve. We then calculated the number of phosphoinositide signaling genes with  $TPM_{\text{brain}}/TPM_{\text{whole\_blood}} > 1.5$  or  $TPM_{\text{brain}}/TPM_{\text{whole\_blood}} < 0.6$  in each brain region in order to identify genes that are either highly expressed or minimally expressed in specific regions of the brain (Figure 4). This analysis revealed that the maximum number of genes with high

$TPM_{\text{brain}}/TPM_{\text{whole\_blood}}$  values were observed in peripheral nerves (represented by the tibial nerve), the cerebral and cerebellar hemispheres. In most of the other brain regions, the phosphoinositide signaling genes seem to be expressed at very low levels, with basal ganglia, hippocampus and amygdala having slightly higher numbers of such genes.

Of all the highly enriched genes in the brain, the 10 genes that have highest TPM values across various brain regions were noted. Of these, seven genes are highly expressed in at least 10 of the 15 major regions of the brain. These genes include *GAP43*, *KCNQ2*, *SNAP91*, *DOK 5*, *SH3GL2*



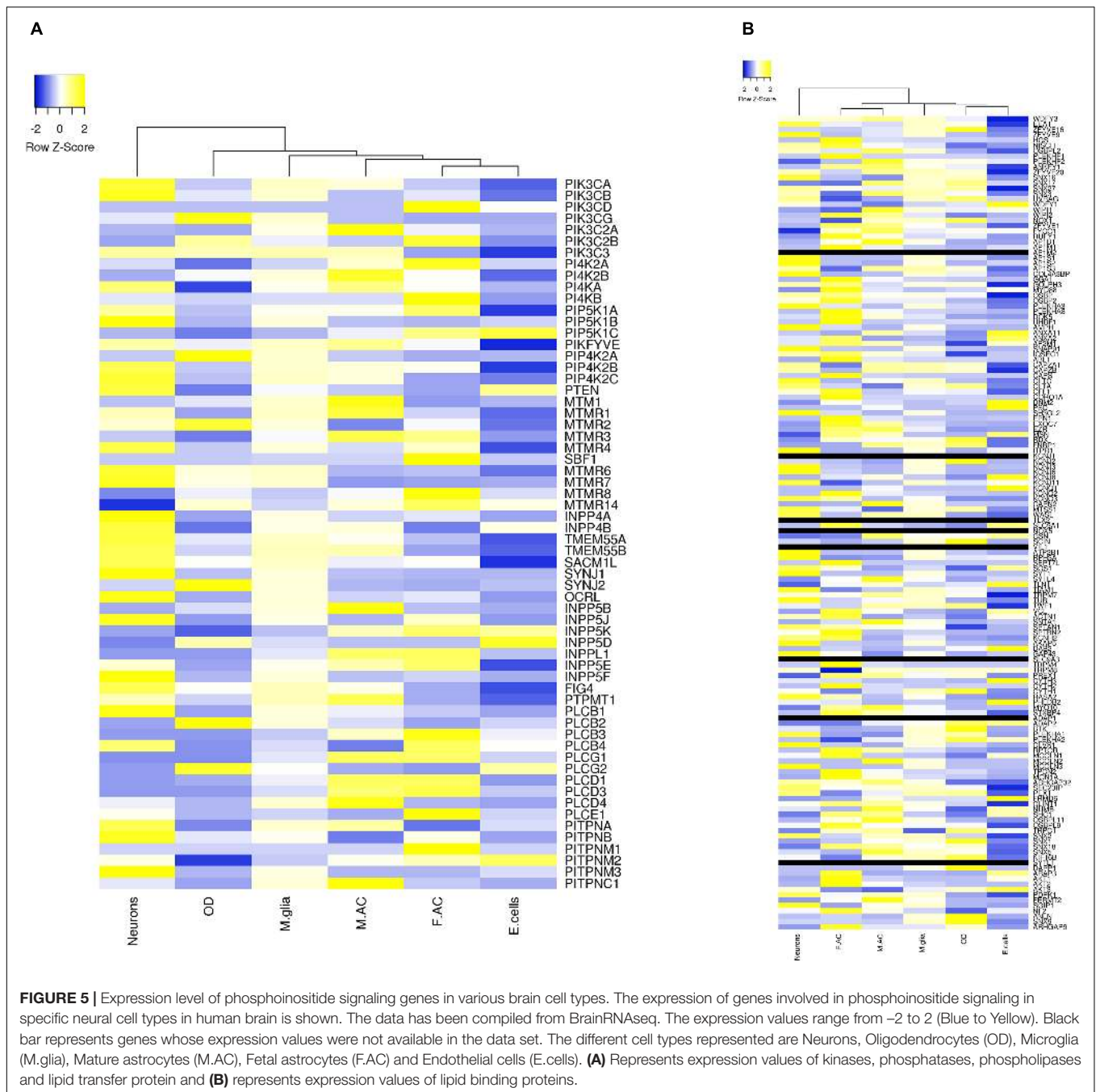


and *SYT1*. *GAP43* a growth-associated protein that is highly expressed during neuronal growth and axonal regeneration (Holahan, 2017); *KCNQ2* a potassium channel which plays a key role in neuronal excitability (Jentsch, 2000); *SNAP91*, Synaptosome Associated Protein 91 a regulator of clathrin dependent endocytosis (Hill et al., 2001); *DOK5* which interacts with phosphorylated receptor tyrosine kinases, activates MAP kinase signaling and is essential for neurite outgrowth (Grimm et al., 2001); *SH3GL2* (SH3 Domain Containing GRB2 Like 2/, Endophilin A1) a known regulator of synaptic vesicle endocytosis (Vehlow et al., 2013) and *SYT1* (synaptotagmin 1) a regulator of neurotransmitter release at the synapse (18). There were also a number of highly expressed genes code for phosphoinositide binding proteins unique to the tibial nerve, i.e., not expressed in other parts of the nervous system (*FERMT2*, *FRMD6*, *SLC9A3*, *PLCE1*, *TRPC1*, *KCNJ8*, and *MCOLN3*) and may indicate a significant role for these in the function of peripheral nerves. It is interesting to note that most genes that show such enrichment patterns are phosphoinositide binding proteins or effectors, whereas genes encoding phosphoinositide metabolizing enzymes (kinases, phosphatases, lipases and transport proteins) appear to not show enrichment in a specific brain region, These findings are consistent with a broad role for phosphoinositide signaling in the nervous system with downstream effects being mediated in specific regions by proteins with more restricted expression patterns. While the data sets generated in such large scale gene expression analyses can be influenced by many factors, these data suggest the choices of tissue types for analyses as well as the potential nervous system compartments in which this signaling pathway could play a particularly important functional role in the context of normal physiology as well as diseases of the nervous system.

## Expression of Phosphoinositide Signaling Genes in Neural Cell Types

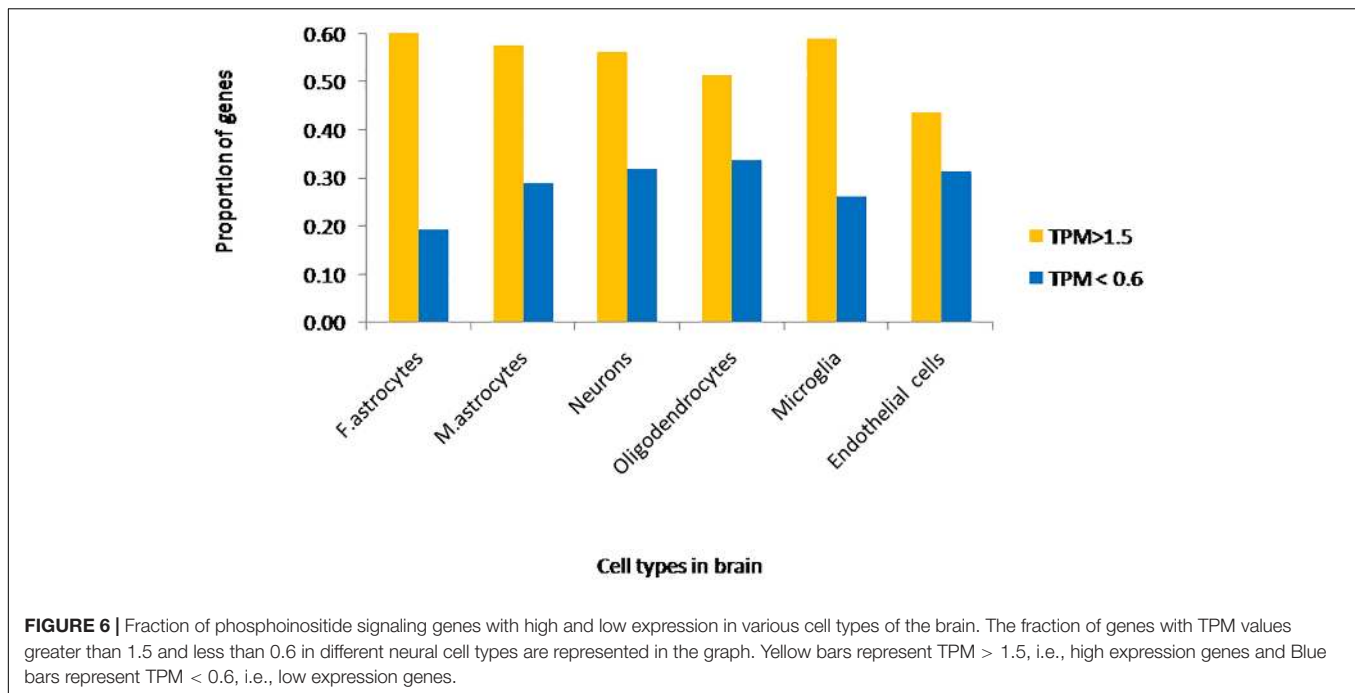
Every region of the nervous system includes multiple cell types including neurons, glial cells (astrocytes, microglia, oligodendrocytes) and endothelial cells of the vasculature. Transcriptomes of all these cell types have been generated and are available at <http://www.brainrnaseq.org>. More than 2000 genes seem to be differentially enriched in specific cell types (Zhang et al., 2016). Single cell transcriptome analysis shows that neurons express a higher number of genes as compared to other cell types and microglia and endothelial cells express fewest genes (Darmanis et al., 2015). Neuronal cells can be further grouped into seven sub-populations with differential gene expression patterns and gene-expression in distinct cell types has also shown to vary with age and under neuropathological conditions (Hagenauer et al., 2018).

We extracted expression values (TPM values) for phosphoinositide signaling genes from Brain RNA-Seq data for various cell-types. The cell type specific expression values for 214 genes have been represented as a heatmap that has been clustered across different cell types in the brain (column-wise clustering in the heatmap) (Figures 5A,B). The probable connection between differential expression of genes and the disease condition has been discussed at the end of this section. The fraction of genes with TPM > 1.5 and TPM < 0.6 in each cell-type is presented (Figure 6). This analysis suggests that among all cell types, fetal astrocytes express the largest number of highly expressed genes (TPM > 1.5) and are also the cell type that show the smallest number of downregulated genes (TPM < 0.6). Among the various cell types, endothelial cells express the fewest number of differentially expressed phosphoinositide signaling genes. The top ten



highly expressed genes for each cell-type were identified and compared for expression in multiple cell types. Of these AKT3, a serine/threonine protein kinase is highly expressed in all six cell types; AKT3, a mediator of growth factor signaling is implicated in a variety of biological processes such as cell proliferation, differentiation, apoptosis, tumorigenesis and glucose uptake. AKT3 is important for brain development and autophagy in neural cells (Howell et al., 2017; Soutar et al., 2018). Cofilin 1 (CFL1) is highly expressed in four of the cell-types (Fetal astrocytes, oligodendrocytes, microglia and endothelial cells). This protein is involved in polymerization

and depolymerization of F-actin and G-actin in a pH dependent manner (Kanellos and Frame, 2016). CFL1 is required for neural tube morphogenesis and neural crest cell migration (Gehler et al., 2004). Clathrin heavy chain (CLTC) is also expressed in four of the cell types (neurons, oligodendrocytes, microglia and mature astrocytes). Clathrin is a major protein present in the cytoplasm that plays a role in vesicular transport and has been associated with neurological disorders (Nahorski et al., 2015). Spectrin alpha (SPTAN1), an essential cytoskeletal protein is expressed in the astrocytes, neurons and endothelial cells in the brain, and mutations in this gene is known to



result in epileptic encephalopathy (Tohyama et al., 2015). Interestingly, among the most highly expressed genes, *SNAP91*, *PLCB1*, *SYNJ1* and *APIS2* are all specific to neurons. Such expression patterns highlight the most useful cell type for the analysis of the cellular function of a specific gene. They could also suggest the cellular basis of a brain disorder when mutations are found in a given gene in human patients with brain disorders.

### Temporal Expression of Phosphoinositide Signaling Pathway Genes in the Brain

The BrainCloud application (see footnote 3) was used to obtain the expression (TPM values) of phosphoinositide signaling genes in the brain cortex of individuals with no neuropathological diagnosis during development (from fetal development to 80 years of age) (Colantuoni et al., 2011). Expression values were arranged as a function of increasing order of age and binned at every 5 years. As observed for all genes in the study (Colantuoni et al., 2011), significant changes in the expression of phosphoinositide signaling genes is seen immediately after birth, at adolescence and then at 70 years of age. Most enzymes in the phosphoinositide signaling cascade show limited temporal variation in expression. However, 20% of phosphoinositide metabolizing enzymes show deviations with expression values ranging from (0 to +1.5 or 0 to -1.5). A similar analysis on small set of genes has shown stable transcriptional networks and gene colocalization control PI metabolism in brain cortex during development (Rapoport et al., 2015). Thus, expression levels of such enzymes could be used as an indication of their potential role in the context of human disease.

### Gene Expression Data and Disease Relevance

Specific patterning of gene expression across different tissues and cell types in the brain is a feature observed in the expression data. Such expression patterns can be correlated well to some of the disease conditions of the brain as mentioned below. This data on expression could also be used to connect genes involved in PI signaling and their function in nervous system for a disease condition under study.

#### Phosphoinositide Kinases

Mutations in the genes *PIK3CA* and *PI4KA* that encode phosphoinositide kinases are associated with polymicrogyria and cortical dysplasia, disorders that result in altered cerebral cortex morphology and cellular composition (Mirzaa et al., 2012; Pagnamenta et al., 2015). Expression data shows that *PIK3CA* and *PI4KA* are highly expressed in the cerebral hemisphere compared to other brain regions and also enriched in the neurons as compared to other cell types in the brain. The high expression of these genes in the cerebral cortex tissue and a clear cortical development phenotype resulting from mutations in these genes underscores the potential value of using gene expression data to link gene function to disease phenotype in human brain disorders. A similar example is the *PIK3C3* gene that shows high expression in neurons; loss of this gene is associated with neuronal apoptosis and neurodegeneration in a mouse knockout model (Zhou et al., 2010). Loss of *PI4K2A* results in a progressive neurological motor disorder associated cerebellar and spinal cord degeneration (Simons et al., 2009) and this is well correlated with high expression of this gene in the cerebellum and cerebral cortex. Loss of *PIKFYVE* is associated with abnormal brain morphology and decreased brain weight (Zolov et al., 2012).



This gene is highly expressed in mature astrocytes as compared to other cell types. Astrocytes are known to provide metabolic support to neurons and maintain brain morphology (Jha and Morrison, 2018) thus correlating the expression of this gene with phenotypes resulting from its depletion.

### Phosphoinositide Phosphatases

Expression data shows that the *MTMR2* gene is upregulated in oligodendrocytes (cells required for myelination of axons in the CNS) and this is well-correlated with the finding that mutations in this gene can result in Charcot-Marie-tooth disease, type 4B1 (due to demyelination of the axons in the brain) (Bolino et al., 2000). Parkinson's disease involves the slow degeneration of neurons in the substantia nigra area of the midbrain. The *INPP5F* gene that is linked by GWAS studies to Parkinson's disease condition is differentially expressed in neurons (Nalls et al., 2014). Similarly the *PLCB1* gene, implicated in Alzheimer's disease involving nerve cell damage and atrophy in the pre-frontal cortex seems to be enriched in this region (Bakkour et al., 2013). Overall these examples illustrate the value of expression data in trying to link human brain disease phenotypes with specific genes by studying their expression pattern in the brain.

## PHOSPHOINOSITIDE SIGNALING AND DISEASES OF THE HUMAN NERVOUS SYSTEM

Conceptually, disorders of the nervous system may arise from defects in processes that impact the development of the brain, the maintenance of normal function in developed brain cells and those that result in an inability to maintain the normal structure and function of the nervous system leading to neurodegenerative disease. There may of course be some overlap between these categories since it is now postulated that adult neurodegenerative diseases may arise from defects in brain development (Kovacs et al., 2014). Brain disorders can result from mutations in a single gene [Online Mendelian Inheritance in Man (OMIM)<sup>4</sup>] or DNA sequence variants in genes can alter the severity and clinical spectrum of a disorder. Defects in phosphoinositide signaling implicated in nervous system disorders of both these categories are discussed below. We include a brief description on the key clinical features of each disease; comprehensive descriptions on each neurological disorder can be found in Brain's Diseases of the Nervous system (Donaghy, 2011).

### Monogenic Disorders Brain Development Disorders

Dominant or recessive single-gene mutations in proteins regulating phosphoinositide signaling have been implicated in neurodevelopmental disorders. The oldest and most well-known, that impacts neurodevelopment, is the X-linked monogenic disorder OCRL, or Lowe syndrome. Lowes syndrome results from mutations in the *OCRL* gene, that encodes one of the inositol polyphosphate 5-phosphatase enzymes that

dephosphorylates PI(4,5)P<sub>2</sub> to generate PI4P [(Olivos-glander et al., 1995) and reviewed in Mehta et al. (2014)]. The disease affects the central nervous system along with the eyes and kidneys, although the extent to which each organ is affected is variable. With regard to the nervous system, most patients show varying degrees of developmental delay, intellectual disability, hypotonia, absence of deep tendon reflexes and convulsions. Motor development is affected, and many patients show moderate mental retardation. Maladaptive behaviors including stubbornness and temper tantrums have been reported (Kenworthy et al., 1993; Bökenkamp and Ludwig, 2016). PI(4,5)P<sub>2</sub> is known to control a number of key cellular processes in developing neural cells particularly in relation to endocytosis and the control of plasma membrane receptor composition and alterations in these may result in abnormal brain function. However, the basis for nervous system defects remains unknown and the cellular mechanism by which OCRL deficiency results in neural cell dysfunction also remains to be investigated.

Monogenic mutations in members of the Class I PI3K pathway has been found to cause multiple disorders affecting brain development in addition to non-neural consequences. Many of these mutations occur as somatic mosaics and the extent of defects in brain development depend on the stage of embryonic development at which the mutation occurs (Madsen et al., 2018). A comprehensive study on 33 children with pediatric epilepsy identified germline mutations (*PTEN*) or mosaic activating mutations (*PIK3CA* and *AKT3*) in PI3K pathway genes which dramatically manifests as different forms of brain malformations like megalencephaly and cortical dysplasia (Poduri et al., 2012; Jansen et al., 2015). Phosphatase and tensin homolog (*PTEN*) gene codes for a phosphatidylinositol 3,4,5 trisphosphate 3-phosphatase which negatively regulates PI3K/AKT pathway (Sansal and Sellers, 2014). Dominant mutations in *PTEN* are associated with macrocephaly autism syndrome, extreme macrocephaly ranging from >2.5 to 8.0 SD above the mean (Butler et al., 2005; Varga et al., 2009; McBride et al., 2010), poorly developed white matter and reduced cognitive abilities (Frazier et al., 2015). Autosomal mutations in *PIK3CA*, coding for p110 $\alpha$  subunit of Class I phosphatidylinositol 3-kinase (PI3K), results in megalencephaly-capillary malformation-polymicrogyria syndrome which is characterized by brain overgrowth (megalencephaly), capillary malformations, and thick cerebral cortex due to development of excessive, unusually small folds on brain surface (polymicrogyria) (Mirzaa et al., 2012). And finally, mosaic mutation at p.Glu17Lys in pleckstrin homology (PH) domain of *AKT3*, a predominant effector of PI3K signaling, causes an elevation in binding to phosphatidylinositol-3,4-bisphosphate, with patients exhibiting asymmetric cortical dysplasia, while constitutive mutation in other domains showed a range of brain malformations (Poduri et al., 2012; Alcantara et al., 2017). Such overgrowth phenotypes in the brain are likely to arise from the key role that PI(3,4,5)P<sub>3</sub> plays in the control of cell proliferation and cell growth.

Polymicrogyria is also a symptom in disorders resulting from *PIK4CA* (phosphatidylinositol 4-kinase), *FIG4* (phosphoinositide 5-phosphatase) and *AKT3* mutations (Baulac et al., 2014; Pagnamenta et al., 2015), while mutations in the 5-phosphatase

<sup>4</sup><https://www.omim.org>

domain of polyphosphate 5-phosphatase *INPP5E* manifests as the ciliopathy Joubert Syndrome 1 (Bielas et al., 2009) characterized by cerebellar hypoplasia/aplasia (incomplete development of cerebellum), thickened cerebellar peduncles and abnormally large interpeduncular fossa ('molar tooth sign') (Travaglini et al., 2013; Shetty et al., 2017). These observations illustrate the function phosphoinositides in brain development; a key biochemical mechanism is likely to be the role of PI(4,5)P<sub>2</sub> and PI(3,4,5)P<sub>3</sub> in cell division and growth.

## Neurodegeneration

Phosphoinositides play an active role in membrane trafficking and cellular signaling. Since neurons are terminally differentiated cells, they are sensitive to cellular stress and susceptible to cell death. Any perturbation in the tightly regulated levels of phosphoinositides affects intracellular vesicular trafficking, membrane turnover and may result in the accumulation of cellular components that should have been degraded resulting ultimately in neuronal degeneration. Such alterations in phosphoinositide levels in the brain can result from mutations in enzymes that regulate their levels or drugs that inhibit the activity of enzymes involved in PI signaling. Important examples of such mutations are discussed below.

Synaptojanin 1 (SYNJ1), a polyphosphoinositide phosphatase whose Sac1 domain dephosphorylates PI(4,5)P<sub>2</sub> and PI(3,4,5)P<sub>3</sub> (Cremona et al., 1999), is highly concentrated at nerve terminals (McPherson et al., 1996). Two distinct disorders have been associated with mutations in *SYNJ1* gene. Alterations in *SYNJ1* likely alter PI(4,5)P<sub>2</sub> at the synapse, influence the synaptic vesicle cycle and hence contribute to the brain phenotypes described in human patients. Studies by independent groups identified homozygous missense mutation at R258Q of *SYNJ1* in patients with early onset Parkinson disease-20 that affect the phosphatase activity of Sac1 domain (Krebs et al., 2013; Quadri et al., 2013; Olgjati et al., 2014). The patients exhibited tremor and bradykinesia with mild cerebral cortical atrophy. At the same time, mutations resulting in complete loss of *SYNJ1* function have been identified in patients with early infantile epileptic encephalopathy 53, a severe neurodegenerative disorder characterized by epileptic seizures, severe intellectual disability and spastic quadriplegia (Hardies et al., 2016; Al Zaabi et al., 2018). A homozygous truncating mutation in *SYNJ1* identified in a patient with intractable seizures also showed neurofibrillary degeneration and presence of tau protein in substantia nigra region of brain (Dyment et al., 2015). In addition to specific mutations in *SYNJ1*, trisomy at the locus 21q22.11 containing *SYNJ1* gene has been identified in multiple lymphoblastoid cell lines developed from individuals with Down syndrome; these cells show enlarged endosomes as a result of overexpression of *SYNJ1* in these cells (Cossec et al., 2012), indicating a link of *SYNJ1* to Down syndrome. This result was substantiated from previous observations of increased *SYNJ1* expression in brains of patients with Down syndrome (Arai et al., 2002), as well in Ts65Dn mice, a mouse model for Down syndrome exhibiting altered PI(4,5)P<sub>2</sub> levels (Voronov et al., 2008). It is noted that patients with Down syndrome show early onset Alzheimer's disease; this could result from a combination of overexpression

of APP, the precursor of the A $\beta$  peptide and overexpression of *SYNJ1*, which results in decreased levels of PI(4,5)P<sub>2</sub>, altered cellular handling of the A $\beta$  peptide and hence early onset disease. Overall these findings imply that the specific phenotype in the patient may be impacted by the type of mutation in a given gene and its effect on the activity of the enzyme it encodes as well as interactions with other genetic changes in the patient's genome leading to altered disease phenotype.

FIG4 is another Sac domain-containing phosphoinositide 5'-phosphatase that dephosphorylates PI(3,5)P<sub>2</sub> to PI3P. 'Pale tremor mouse' that carries a mutation in the *Fig4* gene shows enlarged late-endosomes/lysosomes with severe neurodegeneration of dorsal root ganglion cells and large myelinated axons. The mice exhibit severe tremor and impaired motor coordination resembling Charcot-Marie-Tooth disorder in humans (Chow et al., 2007) and has been widely used as a model to study neurodegenerative disorders associated with *FIG4* mutations. Compound-heterozygous loss-of-function mutation and I41T/R183X missense mutation have been identified in the autosomal recessive Charcot-Marie-Tooth type 4J (CMT4J) syndrome (Chow et al., 2007) with patients exhibiting progressive, asymmetric motor neuron degeneration, severe demyelination and axonal loss (Zhang et al., 2008; Nicholson et al., 2011). Individuals carrying one *FIG4* null allele or missense mutation in one allele, and a normal allele, exhibit one form of autosomal dominant amyotrophic lateral sclerosis (Chow et al., 2009), with less severe symptoms to CMT4J. In contrast, null mutations in *FIG4* resulting in complete loss of function is the cause of Yunis-Varon syndrome, which is characterized by severe neurological impairment affecting central nervous system with enlarged vacuoles in neurons, muscle and cartilage, in addition to skeletal abnormalities (Campeau et al., 2013; Nakajima et al., 2013). Around 30 individuals have thus far been identified with this syndrome (Campeau et al., 2013). PI3P is a lipid that controls endosomal trafficking and autophagy. Thus, phenotypes resulting from *FIG4* and *MTMR* mutations likely affect the brain through alterations in membrane turnover in neural cells.

Charcot-Marie-Tooth type 4B is a group of autosomal recessive demyelinating neuropathic disorders that are typically characterized by irregular thickness of myelin sheaths due to abnormal outfolding (Othmane et al., 1999). Mutations in myotubularin related protein 2 (*MTMR2*), which dephosphorylates PI3P and PI(3,5)P<sub>2</sub> and the catalytically inactive pseudophosphatase *MTMR13/SBF2* (SET binding factor 2) genes are responsible for CMT4B1 and CMT4B2, respectively (Bolino et al., 2000; Azzedine et al., 2003). Even though *MTMR13* is catalytically inactive, it has been suggested that the protein associates with *MTMR2* to form a membrane-associated complex to regulate phosphoinositide levels (Robinson and Dixon, 2005). Since Both *FIG2* and *MTMR2* regulate the PI(3,5)P<sub>2</sub> pool in the cells; the myelin sheath folding abnormalities could be due to the vesicle trafficking defects in neurons or Schwann cells as a result of PI(3,5)P<sub>2</sub> dysregulation.

Mutations in other phosphoinositide signaling genes have been implicated in less severe forms of neuropathy and intellectual disability. In addition to the developmental disorder Joubert Syndrome, mutations in 5'-phosphatase inositol

polyphosphate 5-phosphatase E (*INPP5E*) causes moderate mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM) syndrome (Hampshire et al., 2006). Similarly, mutations in 5'-phosphatase inositol polyphosphate 5-phosphatase K (*INPP5K*) result in the autosomal recessive MDCCAIID (Muscular Dystrophy, Congenital, Cataracts And Intellectual Disability) disorder, where the patients suffer from mild intellectual disability in addition to the main symptoms of muscular dystrophy and early-onset cataract (Osborn et al., 2017; Wiessner et al., 2017). **Table 2** lists nervous system disorders associated with mutations in phosphoinositide signaling genes. Since a monogenic disease cannot be studied experimentally in humans, several mouse strains with specific gene knockouts have been generated. Mouse knockouts of genes involved in phosphoinositide pathway with their phenotypes collated from Mouse Genome Informatics database<sup>5</sup> are summarized in **Supplementary Table 1**.

## Phosphoinositide Signaling in Bipolar Disorder

Bipolar disorder (BD) is a psychiatric illness characterized by disruptive mood swings resulting in alterations between mania and depression (Simon, 2003; Tighe et al., 2011). Studies in the early 1990s showed elevated levels of phosphatidylinositol-4, 5-bisphosphate (PIP<sub>2</sub>) in platelets from BD patients compared to controls (Soares and Mallinger, 1995) and that Protein kinase C (PKC) activity is enhanced in BD patients. These observations are consistent with a hyperactive PI cycle (Friedman et al., 1993) in BD patients. Although it was John Cade who first had treated manic depression with Lithium bromide (Cade, 1949) an understanding of the therapeutic action of lithium (Li<sup>+</sup>) came from the studies of Allison and Stewart who discovered that Li<sup>+</sup> decreases the concentration of *myo*-inositol in the cerebral cortex of rats (Berridge et al., 1982, 1989) and that the decrease in *myo*-inositol concentration upon Li<sup>+</sup> treatment is accompanied by an increase in the concentration of inositol monophosphate suggesting that Li<sup>+</sup> might inhibit the enzyme inositol monophosphatase (IMPase) (Berridge et al., 1982; Harwood, 2005). Elevation of the intracellular inositol monophosphate level upon Li<sup>+</sup> treatment was also observed in the salivary glands in insects (Berridge et al., 1982). IMPase dephosphorylates inositol 1-monophosphate to generate free *myo*-inositol and thereby replenish intracellular *myo*-inositol pool (Ohnishi et al., 2007; Agam et al., 2009). *Myo*-inositol is a precursor of phosphatidylinositol and when condensed with CDP-diacylglycerol by the enzyme phosphatidylinositol synthase generates phosphatidylinositol. Thus, IMPase could be integral to the maintenance of the phosphoinositide pools in mammalian cells. Such observations led Berridge to propose the “inositol depletion hypothesis” which suggests that Li<sup>+</sup> prevents the recycling of *myo*-inositol by inhibiting the enzyme IMPase thereby preventing re-synthesis of phosphatidylinositol and phosphatidylinositol-4, 5-bisphosphate (PIP<sub>2</sub>) synthesis (Berridge et al., 1989). Purified IMPase was subsequently shown to be inhibited by Li<sup>+</sup> (Hallcher and Sherman, 1980) via a

non-competitive mechanism. Li<sup>+</sup> binds to the enzyme-substrate complex, displacing Mg<sup>2+</sup> from the active site thereby preventing the hydrolysis of the phosphate from inositol monophosphate (Harwood, 2005). However, decisive evidence that inositol depletion and alteration in PIP<sub>2</sub> levels underlie the therapeutic action of Li<sup>+</sup> in BD patients remains to be established and it has also recently been proposed that elevated inositol monophosphate levels may underlie the mechanism of action of Li<sup>+</sup> (Saiardi and Mudge, 2018). Although a recent elegant biochemical analysis has once again established the ability of Li<sup>+</sup> to regulate phosphatidylinositol turnover in neurons, the mechanism by which it does so and the relevance to therapeutic effects in BD remains a topic of active investigation (Mertens et al., 2015). Apart from IMPase, Li<sup>+</sup> has multiple additional targets including the inositol transporter SMIT1, cyclooxygenase (COX), beta-arrestin 2 (βArr2) and glycogen synthase kinase 3 (GSK-3) (Freland and Beaulieu, 2012). The relative importance of these additional targets and their relation to PI turnover in the brain remains to be investigated.

## Phosphoinositide Signaling Gene Loci Linked to Neurological Disorders

Identification of genetic variants associated with specific complex phenotypes for the brain have been made possible through the use of genome-wide association studies (GWAS) (Ripke et al., 2014; Ikeda et al., 2018). This approach does away with the bias of candidate gene approach where genes to be analyzed are selected based on pre-existing knowledge regarding their biological relevance. GWAS have generated huge amount of information spanning the entire genome to identify single nucleotide polymorphisms (SNPs) and other genomic variants associated with brain disorders. A catalog of such variants is curated and maintained by NHGRI-EBI<sup>6</sup> (MacArthur et al., 2017) and can be mined to identify variants associated with genes involved in phosphoinositide signaling.

Genes encoding a number of phosphoinositide kinases and phosphoinositide binding proteins have been linked in GWAS studies with brain disorders. For example, variants in the kinase *PIK3C2A*, and the PI binding proteins *UHRF1* (PI5P), *SNAP91* and *CAPN2* [PI(4,5)P<sub>2</sub>], *RPTOR* [PI(3,5)P<sub>2</sub>], *AKT3* [PI(3,4)P<sub>2</sub> and PI(3,4,5)P<sub>3</sub>] have been linked to schizophrenia patients (Goes et al., 2015) and another study identified *PIK3C2A* linked to schizophrenia and bipolar disorder (Ruderfer et al., 2014). In other studies, associations have been proposed between *PIK4CA* and *PIP4K2A* (previously named PIP5K2A) and schizophrenia (Schwab et al., 2006; Jungerius et al., 2008; Thiselton et al., 2009). Association studies have also suggested a link between PIP4K2A and a protective effect in tardive dyskinesia, which occurs as a complication of long-term anti-psychotic treatment (Fedorenko et al., 2015), while the diplotype ATTGCT/ATTGCT in *PIP4K2A* results in poor antipsychotic response in schizophrenia patients (Kaur et al., 2014). Another GWAS study has associated a *PI4K2B* SNP with cannabis dependence (Sherva et al., 2016), which in turn is associated with increased risk of schizophrenia (Vaucher et al., 2017), while *PI4K2B* has also been identified as a candidate

<sup>5</sup><http://www.informatics.jax.org>

<sup>6</sup><http://www.ebi.ac.uk/gwas>

**TABLE 2 |** Monogenic disorders due to mutations in phosphoinositide signaling genes.

Gene name	Ensembl ID	Chromosome location	Gene/locus MIM number	Phenotype	Phenotype MIM number	Inheritance
<b>Brain growth and development</b>						
<i>PIK4CA/PI4KA</i>	ENSG00000241973.6	22q11.21	600286	Polymicrogyria, perisylvian, with cerebellar hypoplasia and arthrogryposis	616531	Autosomal recessive
<i>PIK3CA</i>	ENSG00000121879.3	3q26.32	171834	Megalencephaly-capillary malformation-polymicrogyria syndrome, somatic	602501	
<i>PTEN</i>	ENSG00000171862.5	10q23.31	601728	Macrocephaly/autism syndrome	605309	Autosomal dominant
<i>OCRL</i>	ENSG00000122126.11	Xq26.1	300535	Lowe syndrome	309000	X-linked recessive
<i>INPP5E</i>	ENSG00000148384.11	9q34.3	613037	Joubert syndrome 1	213300	Autosomal recessive
<i>FIG4</i>	ENSG00000112367.6	6q21	609390	Polymicrogyria, bilateral temporooccipital	612691	Autosomal recessive
<i>WDFY3</i>	ENSG00000163625.11	4q21.23	617485	Microcephaly 18, primary, autosomal dominant	617520	Autosomal dominant
<i>AKT3</i>	ENSG00000117020.12	1q43-q44	611223	Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2	615937	Autosomal dominant
(1) <i>NF2</i>	ENSG00000186575.13	22q12.2	607379	Meningioma, NF2-related, somatic	607174	Autosomal dominant
(2) <i>NF2</i>	ENSG00000186575.13	22q12.2	607379	Neurofibromatosis, type 2	101000	Autosomal dominant
(3) <i>NF2</i>	ENSG00000186575.13	22q12.2	607379	Schwannomatosis, somatic	162091	
<b>Neurodegeneration</b>						
<i>SYNJ1</i>	ENSG00000159082.13	21q22.11	604297	Parkinson disease 20, early-onset	615530	Autosomal recessive
(1) <i>FIG4</i>	ENSG00000112367.6	6q21	609390	Yunis-Varon syndrome	216340	Autosomal recessive
(2) <i>FIG4</i>	ENSG00000112367.6	6q21	609390	Amyotrophic lateral sclerosis 11	612577	Autosomal dominant
<i>ANXA11</i>	ENSG00000122359.13	10q22.3	602572	Amyotrophic lateral sclerosis 23	617839	Autosomal dominant
(1) <i>ITPR1</i>	ENSG00000150995.13	3p26.1	147265	Gillespie syndrome	206700	Autosomal dominant/recessive
(2) <i>ITPR1</i>	ENSG00000150995.13	3p26.1	147265	Spinocerebellar ataxia 15	606658	Autosomal dominant
(3) <i>ITPR1</i>	ENSG00000150995.13	3p26.1	147265	Spinocerebellar ataxia 29, congenital non-progressive	117360	Autosomal dominant
(1) <i>SPTBN2</i>	ENSG00000173898.7	11q13.2	604985	Spinocerebellar ataxia 5	600224	Autosomal dominant
(2) <i>SPTBN2</i>	ENSG00000173898.7	11q13.2	604985	Spinocerebellar ataxia, autosomal recessive 14	615386	Autosomal recessive
<b>Peripheral neuropathy</b>						
<i>MTMR2</i>	ENSG00000087053.14	11q21	603557	Charcot-Marie-Tooth disease, type 4B1	601382	Autosomal recessive
<i>MTMR13/SBF2</i>	ENSG00000133812	11p15.4	607697	Charcot-Marie-Tooth disease, type 4B2	604563	Autosomal recessive
<i>MTMR5/SBF1</i>	ENSG00000100241.16	22q13.33	603560	Charcot-Marie-Tooth disease, type 4B3	615284	Autosomal recessive
<i>FIG4</i>	ENSG00000112367.6	6q21	609390	Charcot-Marie-Tooth disease, type 4J	611228	Autosomal recessive
<i>DNM2</i>	ENSG00000079805.12	19p13.2	602378	Charcot-Marie-Tooth disease, axonal type 2M	606482	Autosomal dominant
<i>DNM2</i>	ENSG00000079805.12	19p13.2	602378	Charcot-Marie-Tooth disease, dominant intermediate B	606482	Autosomal dominant
<b>Epilepsy/seizure</b>						
(1) <i>KCNQ2</i>	ENSG00000075043.13	20q13.33	602235	Epileptic encephalopathy, early infantile, 7	613720	Autosomal dominant
(2) <i>KCNQ2</i>	ENSG00000075043.13	20q13.33	602235	Seizures, benign neonatal, 1	121200	Autosomal dominant
(3) <i>KCNQ2</i>	ENSG00000075043.13	20q13.33	602235	Myokymia	121200	Autosomal dominant
<i>KCNQ3</i>	ENSG00000184156.11	8q24.22	602232	Seizures, benign neonatal, 2	121201	Autosomal dominant
<i>PLCB1</i>	ENSG00000182621.12	20p12.3	607120	Epileptic encephalopathy, early infantile, 12	613722	Autosomal recessive
<i>SYNJ1</i>	ENSG00000159082.13	21q22.11	604297	Epileptic encephalopathy, early infantile, 53	617389	Autosomal recessive
<b>Mental retardation</b>						
<i>INPP5E</i>	ENSG00000148384.11	9q34.3	613037	Mental retardation, truncal obesity, retinal dystrophy, and micropenis	610156	Autosomal recessive
<i>AP1S2</i>	ENSG00000182287.9	Xp22.2	300629	Pettigrew syndrome/Mental retardation, X-linked syndromic 5	304340	X-linked recessive
<i>COL4A3BP</i>	ENSG00000113163.11	5q13.3	604677	Mental retardation, autosomal dominant 34	616351	Autosomal dominant
<i>CLTC</i>	ENSG00000141367.7	17q23.1	118955	Mental retardation, autosomal dominant 56	617854	
<i>SKIP/INPP5K</i>	ENSG00000132376.15	17p13.3	607875	Muscular dystrophy, congenital, with cataracts and intellectual disability	617404	Autosomal recessive
<i>PIP5K1C</i>	ENSG00000186111.4	19p13.3	606102	Lethal congenital contractural syndrome 3	611369	Autosomal recessive

Table representing monogenic brain disorders reported as loss of function or mutation in genes of the phosphoinositide signaling pathway. The reaction catalyzed by each gene product and its function in brain are also reported.



**TABLE 3 |** GWAS and other association studies linking phosphoinositide signaling genes to brain disorders.

Gene name	PubMed ID	Disease/Trait	Region	Strongest SNP-risk allele	Type of variant
<b>Kinases</b>					
(1) <i>PIK3C2A</i>	26198764	Schizophrenia	11p15.1	rs2008905-T	intron_variant
(2) <i>PIK3C2A</i>	24280982	Schizophrenia or bipolar disorder	11p15.1	rs4356203-?	intron_variant
(3) <i>PIK3C2A</i>	21926974	Schizophrenia	11p15.1	rs4356203-?	intron_variant
<i>PIK3C2G</i>	24086445	Gray matter volume (schizophrenia interaction)	12p12.3	rs11044045-?	intron_variant
<i>PI4K2B</i>	27028160	Cannabis dependence	4p15.2	rs73252553-A	non_coding_transcript_exon_variant
<i>PIP4K2C</i>	18794853	Rheumatoid arthritis	12q13.3	rs1678542-C	intron_variant
<b>Phosphatases</b>					
<b>PI3-phosphatases</b>					
<i>MTMR3</i>	28247064	Cerebrospinal P-tau181p levels	22q12.2	rs411157-T	non_coding_transcript_exon_variant
<i>MTMR4</i>	25644384	Cognitive function	17q22	rs2429369-?	intron_variant
<i>MTMR7</i>	22137330	Creutzfeldt-Jakob disease (variant)	8p22	rs4921542-?	intron_variant
<b>PI4-phosphatases</b>					
<i>INPP4A</i>	23092984	Bipolar disorder with mood-incongruent psychosis	2q11.2	rs12617721-C	intron_variant
<i>INPP4B</i>	24529757	Amyotrophic lateral sclerosis (sporadic)	4q31.21	rs2667100-?	intron_variant
<i>SACM1L/SAC1</i>	22041458	Response to anti-depressant treatment in major depressive disorder	3p21.31	rs2742417-T	5_prime_UTR_variant
<b>PI5-phosphatases</b>					
<i>SYNJ1</i>	26830138	Alzheimer disease and age of onset	21q22.11	rs147991290-T	intron_variant
(1) <i>INPP5B</i>	24529757	Amyotrophic lateral sclerosis (sporadic)		kgp15327256-?	
(2) <i>INPP5B</i>	24390342	Rheumatoid arthritis	1p34.3	rs28411352-T	3_prime_UTR_variant
<i>INPP5D/SHIP1</i>	24162737	Alzheimer's disease (late onset)	2q37.1	rs35349669-T	intron_variant
<i>INPP5F/SAC2</i>	25064009	Parkinson's disease	10q26.11	rs117896735-A	intron_variant
<b>Phospholipases</b>					
<b>Phospholipase C</b>					
(1) <i>PLCB1</i>	24564958	Social communication problems	20p12.3	rs3761168-A	intron_variant
(2) <i>PLCB1</i>	20125193	Cognitive performance	20p12.3	rs6118083-?	intron_variant
(3) <i>PLCB1</i>	19734545	Cognitive performance	20p12.3	rs6056209-?	intron_variant
(4) <i>PLCB1</i>	26079190	Suicide ideation score in major depressive disorder	20p12.3	rs6055685-A	intron_variant
(5) <i>PLCB1</i>	27846195	Response to paliperidone in schizophrenia (Multivariate)	20p12.3	rs6055808-?	intron_variant
(1) <i>PLCB2</i>	21926974	Schizophrenia	15q15.1	rs1869901-?	intron_variant
2) <i>PLCB2</i>	25056061	Schizophrenia	15q15.1	rs56205728-A	intron_variant
<b>PI transfer proteins</b>					
(1) <i>PITPNM2</i>	23974872	Schizophrenia	12q24.31	rs11532322-A	intron_variant
(2) <i>PITPNM2</i>	25056061	Schizophrenia	12q24.31	rs2851447-G	intron_variant
(3) <i>PITPNM2</i>	28540026	Autism spectrum disorder or schizophrenia	12q24.31	rs2851447-?	intron_variant
<b>PI binding proteins</b>					
<b>PI3P</b>					
(1) <i>WDFY3</i>	26252872	Cerebral amyloid deposition (PET imaging)	4q21.23	rs76117213-G	intron_variant
(2) <i>WDFY3</i>	26252872	Cerebral amyloid deposition (PET imaging)	4q21.23	rs13152543-A	intergenic_variant
(1) <i>NISCH</i>	23974872	Schizophrenia	3p21.1	rs4687552-T	non_coding_transcript_exon_variant
(2) <i>NISCH</i>	25056061	Schizophrenia	3p21.1	rs2535627-T	downstream_gene_variant
(3) <i>NISCH</i>	21926972	Bipolar disorder	3p21.1	rs736408-C	intron_variant
(4) <i>NISCH</i>	28540026	Autism spectrum disorder or schizophrenia	3p21.1	rs3617-?	missense_variant
(5) <i>NISCH</i>	28540026	Autism spectrum disorder or schizophrenia	3p21.2	rs353547-?	intron_variant
<i>MTMR4</i>	25644384	Cognitive function	17q22	rs2429369-?	intron_variant
<i>ANKFY1</i>	24039173	Functional impairment in major depressive disorder, bipolar disorder and schizophrenia	17p13.2	rs7221595-?	intron_variant
<b>PI4P</b>					
<i>GGA1</i>	22041458	Response to anti-depressant treatment in major depressive disorder	22q13.1	rs12157904-G	upstream_gene_variant
<i>PLEKHA3</i>	26746183	Rapid functional decline in sporadic amyotrophic lateral sclerosis		chr2:179179368916-C	

(Continued)

TABLE 3 | Continued

Gene name	PubMed ID	Disease/Trait	Region	Strongest SNP-risk allele	Type of variant
<b>PI5P</b>					
<i>UHRF1</i>	26198764	Schizophrenia	19p13.3	rs34232444-T	upstream_gene_variant
<b>PI(4,5)P<sub>2</sub></b>					
<i>AP2M1</i>	22472876	Major depressive disorder	3q27.1	rs1969253-?	intron_variant
(1) <i>SNAP91</i>	28540026	Autism spectrum disorder or schizophrenia	6q14.2	rs7752643-C	intron_variant
(2) <i>SNAP91</i>	26198764	Schizophrenia	6q14.2	rs3798869-G	intron_variant
(3) <i>SNAP91</i>	23092984	Bipolar disorder with mood-incongruent psychosis	6q14.2	rs1171113-C	intron_variant
(1) <i>SH3GL2</i>	19734545	Cognitive performance	9p22.2	rs10810865-?	intergenic_variant
(2) <i>SH3GL2</i>	22451204	Parkinson's disease	9p22.2	rs1536076-?	intron_variant
(3) <i>SH3GL2</i>	27182965	Parkinson's disease	9p22.2	rs2209440-?	intron_variant
(4) <i>SH3GL2</i>	19734545	Cognitive performance	9p22.2	rs4284125-?	intergenic_variant
(5) <i>SH3GL2</i>	27846195	Response to paliperidone in schizophrenia (negative Marder score)	9p22.2	rs141473550-A	intergenic_variant
<i>EPN1</i>	23377640	Major depressive disorder	19q13.42	rs17634917-G	upstream_gene_variant
<i>RDX</i>	24684796	Cognitive function	11q22.3	rs7945071-T	intron_variant
(1) <i>KCNJ2</i>	22648509	Formal thought disorder in schizophrenia	17q24.3	rs1015657-?	intergenic_variant
(2) <i>KCNJ2</i>	26297903	Depressive episodes in bipolar disorder	17q24.3	rs2190547-?	intergenic_variant
<i>KCNJ6</i>	22554406	Electroencephalographic traits in alcoholism	21q22.13	rs2835872-G	intron_variant
<i>KCNJ11</i>	24564958	Social communication problems	11p15.1	rs1557765-C	non_coding_transcript_exon_variant
<i>CAPN2</i>	26198764	Schizophrenia	1q41	rs7539624-A	intron_variant
<i>MTSS1</i>	24684796	Cognitive function	8q24.13	rs2116081-T	intron_variant
<i>GSN</i>	20889312	Bipolar disorder and schizophrenia	9q33.2	rs767770-?	downstream_gene_variant
<i>VIL1</i>	22959728	Amyotrophic lateral sclerosis	2q35	rs7607369-A	upstream_gene_variant
<i>SOS1</i>	26077951	Corticobasal degeneration	2p22.1	rs963731-?	intron_variant
<i>TIAM1</i>	20801718	Amyotrophic lateral sclerosis	21q22.11	rs13048019-T	intron_variant
(1) <i>SPTBN2</i>	28115744	Bipolar disorder	11q13.2	rs10896135-G	intron_variant
(2) <i>SPTBN2</i>	21926972	Bipolar disorder	11q13.2	rs10896135-G	intron_variant
(1) <i>GAP43</i>	28632202	Borderline personality disorder	3q13.31	rs283386-G	intron_variant
(2) <i>GAP43</i>	26989097	Response to cognitive-behavioral therapy in anxiety disorder	3q13.31	rs16823934-?	intergenic_variant
(1) <i>TRPM8</i>	24529757	Amyotrophic lateral sclerosis (sporadic)	2q37.1	rs1987842-?	downstream_gene_variant
(2) <i>TRPM8</i>	27322543	Migraine without aura	2q37.1	rs6724624-?	intergenic_variant
(3) <i>TRPM8</i>	27182965	Migraine	2q37.1	rs1965629-?	upstream_gene_variant
(4) <i>TRPM8</i>	22683712	Migraine	2q37.1	rs10166942-?	upstream_gene_variant
(5) <i>TRPM8</i>	21666692	Migraine	2q37.1	rs10166942-T	upstream_gene_variant
(6) <i>TRPM8</i>	23793025	Migraine	2q37.1	rs6741751-?	intron_variant
(7) <i>TRPM8</i>	27322543	Migraine	2q37.1	rs10166942-?	upstream_gene_variant
<b>PI(3,4,5)P<sub>3</sub></b>					
<i>CYTH1</i>	24047446	Anxiety and major depressive disorder	17q25.3	rs4796827-A	intergenic_variant
<i>PHLDB2</i>	20125193	Cognitive performance	3q13.2	rs4450776-?	intron_variant
<i>MYO10</i>	23377640	Major depressive disorder	5p15.1	rs17651119-C	intron_variant
<b>PI(3,4) P<sub>2</sub></b>					
<i>PLEKHA2</i>	25993607	Neuroticism	8p11.22	rs11782824-A	intron_variant
<b>PI(3,5)P<sub>2</sub></b>					
(1) <i>CLVS1</i>	24529757	Amyotrophic lateral sclerosis (sporadic)	8q12.2	rs7830371-?	intron_variant
(2) <i>CLVS1</i>	23793025	Migraine	8q12.2	rs12681792-?	intron_variant
<i>RPTOR</i>	26198764	Schizophrenia	17q25.3	rs8066384-C	intron_variant
<b>PI binding proteins with degenerate specificity</b>					
<b>PI3P, PI4P, PI5P</b>					
<i>SEC23IP</i>	26545630	Cerebrospinal fluid clusterin levels	10q26.12	rs2456721-?	intron_variant
<i>MTMR3</i>	28247064	Cerebrospinal P-tau181p levels	22q12.2	rs41157-T	non_coding_transcript_exon_variant
<b>PI3P, PI4P</b>					
(1) <i>FRMD6</i>	20171287	Brain structure	14q22.1	rs7140150-?	intron_variant
(2) <i>FRMD6</i>	26252872	Cognitive decline rate in late mild cognitive impairment	14q22.1	rs192549394-G	intron_variant

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TABLE 3 | Continued

Gene name	PubMed ID	Disease/Trait	Region	Strongest SNP-risk allele	Type of variant
<b>PI3P, PI(4,5)P<sub>2</sub></b>					
<i>NUMB</i>	23092984	Bipolar disorder with mood-incongruent psychosis	14q24.3	rs2333194-?	intron_variant
<b>PI(4,5)P<sub>2</sub>, PI(3,4,5)P<sub>3</sub></b>					
<i>SEPT5</i>	26830138	Alzheimer disease and age of onset	22q11.21	rs141503849-T	intergenic_variant
<b>PI(3,4)P<sub>2</sub>, PI(3,4,5)P<sub>3</sub></b>					
<i>DAPP1</i>	20195266	Response to antipsychotic treatment	4q23	rs11735070-?	intergenic_variant
<i>ARAP3</i>	26252872	Cerebral amyloid deposition (PET imaging)	5q31.3	rs57450513-C	regulatory_region_variant
<i>AKT2</i>	26252872	Cerebrospinal T-tau levels	19q13.2	rs76137255-T	intron_variant
(1) <i>AKT3</i>	21441570	Diabetic retinopathy	1q44	rs476141-A	intron_variant
(2) <i>AKT3</i>	21441570	Diabetic retinopathy	1q44	rs10927101-A	intron_variant
(3) <i>AKT3</i>	28346443	Non-glioblastoma glioma	1q44	rs12076373-G	intron_variant
(4) <i>AKT3</i>	23726511	Post-traumatic stress disorder (adjusted for relatedness)	1q44	rs4430311-?	upstream_gene_variant
(5) <i>AKT3</i>	23974872	Schizophrenia	1q44	rs14403-C	3_prime_UTR_variant
(6) <i>AKT3</i>	26198764	Schizophrenia	1q44	rs13376709-C	intron_variant
(7) <i>AKT3</i>	25056061	Schizophrenia	1q43	rs77149735-A	intron_variant
(1) <i>FERMT2</i>	27064256	Glaucoma (primary angle closure)	14q22.1	rs7494379-G	intron_variant
(2) <i>FERMT2</i>	24162737	Alzheimer's disease (late onset)	14q22.1	rs17125944-C	intron_variant
<b>PI3P, PI4P, PI(3,4)P<sub>2</sub>, PI(3,5)P<sub>2</sub>, PI(4,5)P<sub>2</sub></b>					
<i>SGIP1</i>	28641921	Cerebrospinal fluid t-tau:AB1-42 ratio	1p31.3	rs6662771-?	intron_variant
<b>PI(3,4)P<sub>2</sub>, PI(4,5)P<sub>2</sub>, PI(3,5)P<sub>2</sub>, PI(3,4,5)P<sub>3</sub></b>					
(1) <i>SNX9</i>	28632202	Borderline personality disorder	6q25.3	rs6922614-T	intron_variant
(2) <i>SNX9</i>	26830138	Alzheimer disease and age of onset	6q25.3	rs34804891-T	intron_variant
<b>PI(3,4,5)P<sub>3</sub>, PI(3,4)P<sub>2</sub>, PI(4,5)P<sub>2</sub></b>					
<i>TIAM1</i>	20801718	Amyotrophic lateral sclerosis	21q22.11	rs13048019-T	intron_variant

The table reports the diseases linked to genes (phosphoinositide signaling pathway genes) based on GWAS studies. For every gene the disease trait, affected chromosomal region, risk allele and type of variant are reported. The rs ID represents the dbSNP ID for each gene.

gene in schizophrenia on a study on Scottish population cohort (Houlihan et al., 2009).

Mirroring the numerous monogenic disorders that result from mutations in phosphoinositide phosphatases, GWAS studies have linked mutations in the 5-phosphatase gene *SYNJ1* causing PARK20 to Alzheimer's disease (Herold et al., 2016), while another study has directly correlated *SYNJ1* polymorphisms to age of onset in familial Alzheimer's disease (Miranda et al., 2018). In a large study conducted in 74,026 individuals, a new locus was also identified with SNPs in *INPP5D/SHIP1*, the enzyme dephosphorylating PI(3,4,5)P<sub>3</sub> into PI(3,4)P<sub>2</sub>, linking it to Alzheimer's disease (Lambert et al., 2013). SNPs in genes for the 4-phosphatase *INPP4B* and the 5-phosphatase *INPP5B* have been linked to sporadic amyotrophic lateral sclerosis (Xie et al., 2014). An intronic variant was identified in the genetic locus of myotubularin related protein 7 (*MTMR7*), a 3-phosphatase dephosphorylating PI3P and inositol 1,3-bisphosphate and linked to variant Creutzfeldt-Jakob disease susceptibility (Sanchez-Juan et al., 2012).

Although the detection of a disease susceptibility locus is by no means a validated proof implicating a gene in a brain disorder, it can provide a starting point for validation of the mechanistic role of that gene through other forms of genetic analysis. **Table 3** depicts the genetic loci in phosphoinositide signaling genes that are linked to brain disorders in humans.

## CONCLUSION

In the past few years, our understanding of phosphoinositide function in cell biology and physiology has rapidly advanced. Although these are quantitatively minor lipids, their impact on neuronal cell biology and function is clearly widespread. Most of these studies were done in experimentally tractable model organisms with a complex nervous system such as *Drosophila*, *Caenorhabditis elegans* or rodents and indicate a crucial role of phosphoinositides in orchestrating major subcellular pathways. Over the same period, advances in next generation DNA sequencing technology and related techniques in human genetic analysis have thrown up a large number of DNA sequence variants and suggested links between these variants and human diseases (Guerreiro et al., 2014; Splinter et al., 2018; Ganapathy et al., 2019); such observations are also true for genes involved in phosphoinositide signaling and their potential function in the context of diseases of the human nervous system. However, there have been two major challenges in this area of science (i) the ability to observe and measure aspects of the cell biology of human brain cells and to test the significance of the observations experimentally (ii) evaluating the functional significance of genetic variants reported in the context of brain disorders in genes related to phosphoinositide signaling. Recent technological advances

offer the promise of rapid advances and progress in this area. The difficulty in obtaining live biopsy samples of the human brain has been a major deterrent in studying cellular mechanisms underlying neurological disorders. One possible solution to the inability to observe and experimentally manipulate human brain cells has emerged over the last 10 years in the form of induced pluripotent stem (iPS) cell technology. Using this approach one can derive pluripotent stem cells from somatic human tissue through reprogramming (Shi et al., 2017). These reprogrammed stem cells can then be differentiated into neural cell types and used to study neural cell biology and physiology.

To date, several neurological diseases have been modeled based on patient-derived iPS cell technology and subsequent neural differentiation to study cellular mechanisms in disease (Russo et al., 2015; Wen et al., 2016). A recent study by Mertens et al., using iPS cell technology, has revealed mitochondrial abnormalities and neuronal hyper-excitability in young neurons derived from BD patients; this hyperexcitability can be reversed by  $\text{Li}^+$  treatment only in neurons derived from  $\text{Li}^+$  sensitive patients (Mertens et al., 2015). Another recent study on iPS derived neurons from Parkinson's disease patients has revealed defects in the regulation of ER  $\text{Ca}^{2+}$  stores, which can be linked to the  $\text{PI}(4,5)\text{P}_2$  cycle since it actively regulates  $\text{Ca}^{2+}$  homeostasis (Korecka et al., 2019). An iPS model for Lowe Syndrome has also been developed by Barnes et al., that suggests abnormalities in F-actin polymerization, WAVE-1 expression and altered  $\text{PI}(4,5)\text{P}_2$  levels in patient specific iPS derived neurons, giving a further insight about the disease pathology at the cellular level (Barnes et al., 2018).

A second major development in recent times is the development of genome engineering technologies such as  $\text{Zn}^{2+}$  finger nucleases, TALEN and CRISPR/Cas9 that allow DNA sequence changes to be introduced into many human cell types including iPS cells. By adopting this approach, one can experimentally test the contributions of DNA sequence variants

described in patient samples to the development of disease phenotypes, as demonstrated by Barnes et al. (2018). Together, these approaches are likely to accelerate our understanding of the role of phosphoinositide signaling in human disease biology in relation to the nervous system.

## AUTHOR CONTRIBUTIONS

PR conceptualized and wrote the review. AJ, HK, PS, and SS wrote the review. HK and AJ mined public databases and collated gene expression data and disease data.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnmol.2019.00208/full#supplementary-material>

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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