Review article

Dual-specificity phosphatases in mental and neurological disorders

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A R T I C L E   I N F O

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A B S T R A C T

The dual-specificity phosphatase (DUSP) family includes a heterogeneous group of protein phosphatases that dephosphorylate both phospho-tyrosine and phospho-serine/phospho-threonine residues within a single substrate. These protein phosphatases have many substrates and modulate diverse neural functions, such as neurogenesis, differentiation, and apoptosis. DUSP genes have furthermore been associated with mental disorders such as depression and neurological disorders such as Alzheimer’s disease. Herein, we review the current literature on the DUSP family of genes concerning mental and neurological disorders. This review i) outlines the structure and general functions of DUSP genes, and ii) overviews the literature on DUSP genes concerning mental and neurological disorders, including model systems, while furthermore providing perspectives for future research.

1. Introduction

Mental and neurological disorders are becoming highly prevalent, and in turn, exerting significant socioeconomic and personal burdens (Wittchen et al., 2011). For instance, mental disorders are often associated with a reduced quality of life and also reduced maximal life expectancy (Chesney et al., 2014), possibly due to the early onset of these disorders, the impact on social interactions and their frequent occurrence as a comorbidity with other physiological health issues, i.e., cardiovascular, metabolic and immune-related disorders (Wykes et al., 2015).

Recent progress in the study of mental and neurological disorders has allowed for a better understanding of critical underlying determinants, as well as associated molecular and cellular mechanisms. The etiology of mental and neurological disorders is associated with an interplay between genetic predisposition and epigenetic mechanisms that are influenced by environmental exposures throughout life (Klengel and Binder, 2015; Nestler et al., 2016). Developments in the fields of psychiatric genetics and epigenetics have enabled the first wave of genome-wide analyses on groups of people diagnosed with specific mental and neurological disorders compared to control populations. These analyses have provided critical initial insights, suggesting the involvement of distinct genes and biological processes in the onset and course of mental and neurological disorders. That being said, increasing evidence from a range of genetic and epigenetic studies have identified associations between several genes in the dual-specificity phosphatases (DUSP) family and a variety of mental and neurological disorders (Duric et al., 2010; Perez-Sen et al., 2019).

Abbreviations: AD, Alzheimer’s disease; ADF, actin-depolymerizing factor; ASDs, autism spectrum disorders; ATM, ataxia-telangiectasia mutated; Aβ, amyloid-beta; APP, amyloid precursor protein; CDC14, cell division cycle 14 phosphatases; CUS, chronic unpredictable stress; DG, dentate gyrus; DUSPs, dual-specificity phosphatases; ECS, electroconvulsive seizure; ERK, extracellular signal-regulated kinase; HD, Huntington’s disease; JNK, c-Jun amino-terminal kinase; LBs, lafora bodies; LD, lafora disease; LTP, long-term potentiation; MAPK, MAP kinases; MKPs, mitogen-activated protein kinase phosphatases; PD, Parkinson’s disease; PI3K, phosphatidylinositol 3-kinase; PRL, phosphatases of regenerating liver; PTEN, phosphatase and tensin homologs deleted on chromosome 10; PTP, protein tyrosine phosphatase; PTSD, posttraumatic stress disorder; SNO, S-nitrosylation of PTEN; 6-OHDA, 6-hydroxydopamine.

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These groups of phosphatases are characterized by the removal of a phosphorus group from both phospho-tyrosine and phospho-serine/phospho-threonine residues within a single substrate, leading to conformational changes in proteins, a process that can be reversed by kinase phosphorylation. Additionally, these protein phosphatases have a variety of substrates and as such can modulate diverse cellular functions, such as neurogenesis, neuronal differentiation, and apoptosis via three main signaling pathways, including MAP kinase pathways (Patterson et al., 2009), Phosphatidylinositol 3-kinase (PI3K)/AKT (Carracedo and Pandolfi, 2008), and BDNF/ p75NTR pathways (Finelli et al., 2013; Perez-Sen et al., 2019).

While a range of studies on DUSP genes has linked these genes to cancer (Bermudez et al., 2010; Low and Zhang, 2016) and disorders of the immune system (Lang et al., 2006), accumulating evidence for links between DUSP genes and mental disorders, such as depression and bipolar disorder, as well as neurological disorders such as Alzheimer’s disease, is increasingly documented (Rios et al., 2014).

Herein, we aim to summarize, converge, and critically review the current literature on the DUSP family of genes implicated in mental and neurological disorders.

2. Structure, expression, and function of DUSP family members

DUSPs’ primary mode of action is the dephosphorylation of tyrosine and/or serine/threonine residues and the resulting activity regulation of their substrates. The physiological outcomes of DUSPs’ functions thus hinge on their substrate specificity and phosphatase activity, however, the substrates for DUSPs are not precisely defined. The archetypical DUSP, DUSP1/MKP1, was initially discovered to regulate the activities of MAP kinases by dephosphorylating the TXY motif in the kinase domain. However, although DUSPs were discovered more than a decade ago, on Wittchen et al. in 2011 in the past few years have their various functions begun to be described. DUSPs can be categorized based on the presence or absence of a MAP kinase-interacting domain into typical DUSPs and atypical DUSPs, respectively. A subset of DUSPs contains an N-terminal region composed of two CDC25 homology 2 (CH2) domains and an intervening cluster of basic amino acids known as the MAP kinase-binding (MKB) motif. All DUSP proteins contain a common phosphatase domain which consists of conserved Asp, Cys, and Arg residues forming the catalytic site (Huang and Tan, 2012).

The subcategorization of DUSPs into subgroups is supported by the phylogenetic tree of DUSP sequences similarities with consideration of substrate preferences (Huang and Tan, 2012). Based on this, the DUSP family members can be categorized into the following subgroups: 1) slingshot homolog (SSH) family of phosphatases, 2) phosphatases of regenerating liver (PRL) family, 3) cell division cycle 14 (CDC14) phosphatases, 4) phosphatase and tensin homologs deleted on chromosome 10 (PTEN), 5) myotubularins, 6) mitogen-activated protein kinase phosphatases (MKPs) and 7) atypical DUSPs (Patterson et al., 2009). DUSP family members and synonyms can be found in Table 1 of the Supplementary materials, while atypical DUSPs are presented in Supplementary Table 2.

In the following paragraphs, we will review the current knowledge about the structure, tissue expression and function of the DUSP family members. A summary of DUSP Protein or RNA expression in animal and human brain can be found in Table 1, while their expression in non-brain tissues is shown in Supplementary Table 3. The function of DUSP proteins is summarized in Table 2.

### 2.1. Slingshot homolog (SSH) family of phosphatases

#### 2.1.1. Structure and homologues

Slingshot homolog (SSH), encoded by the SSH gene, was initially recognized as a coflin phosphatase in genetic studies performed in Drosophila (Jung et al., 2007). Cofilin is an actin-depolymerizing factor (ADF) that is abundant in human and other mammalian brains (Minamide et al., 2000). In mammals, three SSH homologs have been

| Isoforms | Expression | Protein/ RNA | Species | Ref. |
|----------|------------|--------------|---------|------|
| SSH1 | Frontal cortex, cerebellum | Protein | Human | (Barone et al., 2014; Zafar et al., 2017) |
| | Primary cortical neurons | | Mice | (Barone et al., 2014) |
| | Dorsal root ganglion neurons | | Chick | (Endo et al., 2003) |
| SSH2 | Brain, thalamus, hippocampus | mRNA | Mice | (Kousaka et al., 2008) |
| SSH3 | Hippocampus, temporal gyrus, frontal gyrus | mRNA | Human | (Wang and Wang, 2020) |
| | Prefrontal cortex, hypothalamus | | | (van Heerd et al., 2009) |
| | Amygdala | | | (McCullough et al., 2018) |
| PRL1 | Cerebellum | mRNA | Human | (Dumaual et al., 2006) |
| | Neuronal lineages in the embryo. | | Zebrash | (Lin et al., 2013) |
| PRL2 | Cerebellum, cerebral cortex | mRNA | Human | (Dumaual et al., 2006) |
| | Neuronal lineages in an embryo. | | Zebrash | (Lin et al., 2013) |
| CDC14A | Cortical slices | mRNA | Human | (Seboll et al., 2012) |
| | Cerebral cortex | | | (www.protein atlas.org) |
| hCDC14B1par | Adult and fetal brain | mRNA | Human | (Rosso et al., 2008) |
| hCDC14B1 | Hippocampus, prefrontal cortex, amygdala, hypothalamus | mRNA | Human | (Rosso et al., 2008) |
| hCDC14B2 | Hippocampus, prefrontal cortex, amygdala, hypothalamus | mRNA | Human | (Rosso et al., 2008) |
| hCDC14B3 | Hippocampus, prefrontal cortex, amygdala, hypothalamus | mRNA | Human | (Rosso et al., 2008) |
| hCDC14C | Adult brain and embryonic forebrain, including the dorsal telencephalon | mRNA | Human | (Rosso et al., 2008) |
| PTENs | Protein | Human | (www.protein atlas.org) |
| | Cerebral cortex, cerebellum, hippocampus | | | |
| | Anterior olfactory nucleus, cerebral cortex, amygdala | | | |
| | midbrain, pons. | | | |

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identified so far and denoted as SSH-1, SSH-2, and SSH-3 (Jung et al., 2007).

The sequence alignment of the three SSH phosphatases shows more than 80% sequence similarity (Jung et al., 2007). For instance, SSH proteins from human, mouse, and Drosophila possess three highly conserved domains, A, B, and P (a phosphatase domain) in the N-terminal region (Ohta et al., 2003). Amino acid sequences of the P domain of the SSH family are distantly related to those of a family of MKPs and share a Dual Specific Phosphatase (DSP) active site (HCxxGxxR) conserved within both DSP and protein tyrosine phosphatases (PTP) (Barford et al., 1998; Niwa et al., 2002). The short serine-rich sequence motif (S domain) is conserved only in SSH-1 and SSH-2 in mouse and human but not in SSH-3 of the mouse, human, or Drosophila SSH protein (Fig. 1A) (Ohta et al., 2003).

### 2.1.2. Expression and function

At the cellular level, human SSH (hSSH)-1 is primarily expressed in the plasma membrane, cytosol, and nucleoplasm, while hSSH-2 and hSSH-3 reside in the cytoplasm (the Human Protein Atlas (www...
**Table 2**

*DUSP* genes in normal and pathological brain function.

| Isoforms | Function in Normal Brain | Function in Pathological Brain |
|----------|--------------------------|-------------------------------|
| **SSH1** | SSH1 along with Cofilin1 promoted dynamic changes in the cytoskeleton needed for axon engagement like growth cone collapse and neurite outgrowth, and myelination in Schwann cells in rat (Ulsieh et al., 2006; Sparrow et al., 2012). SSH1 increases growth cone motility and extension, and the growth cone becomes slender and branchy in chick (Gasloe et al., 2003). | SSH1 reduced and remained inactive as Cofilin1 in the frontal cortex of sporadic AD in human (Barone et al., 2014). |
| **SSH3** | SSH3 mRNA is differentially regulated gene in hippocampus tissue, temporal gyrus tissue, frontal gyrus tissue and whole blood in patients diagnosed with AD (Wang and Wang, 2020). SSH3 mRNA has been found to be downregulated in central amygdala Drd2-expressing population following foot shock fear conditioning compared to controls in mice (McCullough et al., 2018). SSH3 mRNA is over expressed in prefrontal cortex, and hypothalamus in mice subjected to maternal separation for 3 h per day and lasted for 14 days (van Heerden et al., 2009). | PRL3 promotes cell proliferation, migration, and invasion in glioblastoma cells in Human (Mu et al., 2018; Wang et al., 2016a). |
| **PRL3** | | |
| **CDC14A** | CDC14A involved in cell cycle regulation of human brain vascular endothelial cells following injury induced by high glucose, free fatty acids, and hypoxia (Su et al., 2015) | Upregulated in response to Amyloid- Oligomers in adult human cortical brain slices (Sebollela et al., 2012). |
| **CDC14B** | Regulates RNA polymerase II and represses cell cycle transcription in primary mouse embryonic fibroblasts (Guillamot et al., 2011). | Involved in glioblastoma growth in human (Galeano et al., 2013). |
| **PTENs** | PTEN moved to nucleus and promoted neuron survival in mice (Goh et al., 2014). PTEN and β-catenin signaling regulates normal brain growth trajectory by controlling cell number, and imbalance in this relationship can result in abnormal brain growth in mice (Chen et al., 2015). | PTEN single nucleotide polymorphisms associated with increased risk of depression in a Chinese cohort (Liu et al., 2016). PTEN protein levels are higher in postmortem lysates of the ventral prefrontal cortex from suicide victims diagnosed with depression when compared to non-depressed healthy controls (Barge et al., 2011). |
| **MKP1 (DUSP1)** | MKP1 controls axon branching induced by BDNF signaling via mediating JNK deactivation in mice (Jeanneau et al., 2010) MKP-1 functions in light-dependent and time-of-day-dependent manners in the mouse central clock structure-the suprachiasmatic nucleus (Doi et al., 2007) | Depression mice model showed increased hippocampal MKP1 expression, which can be normalized by antidepressant, while mice lacking MKP1 are resilient to stress (Djuric et al., 2010) MKP1 mRNA increased in the DG and CA1 of human diagnosed with depression (Duric et al., 2010). Increased MKP-1 expression levels could be the cause of the high resistance to conventional chemotherapy in human glioblastoma multiforme in human (Yu et al., 2012) DUSP1 protein levels increased in the hippocampus (Jiao et al., 2011) and the ventrolateral orbital cortex (Zhao et al., 2017) of stressed rats when compared to controls. |
| **MKP2 (DUSP4)** | MKP2 promotes neuroplasticity and memory, and its deletion impairs synaptic plasticity and hippocampal-dependent memory in mice (Abdul Rahman et al., 2016) | MKP2 were significantly decreased in cerebellar vermis from schizophrenic patients compared to control subjects (Koyyseva et al., 1999). MKP2 was increased in BAs 8, 9, 10, and hippocampus, without any change in the cerebellum of depressed suicide subjects compared with control subjects (Dwivedi et al., 2001). |
| **MKP3 (DUSP6)** | DHA-enriched fish-oil induced MKP3 that enhance GFAP in developing rat brain astrocytes (Tripathi et al., 2017). | DUSP6 mRNA was differentially expressed in post-mortem tissue ventromedial PFC of patients with depressive disorder in a sex-specific manner (Labonte et al., 2017). |
| **Hvrh3 (DUSP5)** | Regulate the signaling of pressure-dependent myogenic cerebral arterial constriction in rat (Wickramasekera et al., 2013). | DUSP5 served as transcriptional target of tumor suppressor p53 in glioblastoma in human (Ueda et al., 2003). |
Table 2 (continued)

| Isoforms | Function in Normal Brain | Function in Pathological Brain |
|----------|--------------------------|-------------------------------|
| MKP-X (DUSP7) | The expression of DUSP7 was mediated by ERK1/2 activity both in resting and LPS-stimulated microglia in rat (Ham et al., 2015) | DUSP7 mRNA expression was reduced in the whole brain after chronic amphetamine injections in mice (Sokolov et al., 2003). |
| Hvh5 (DUSP8) | Abundant in human and mice brain and inactivate mitogen-activated protein kinase (Martell et al., 1995a). | Hvh5 mRNA was induced in the nucleus accumbens, caudate putamen, frontal cortex, and hippocampus by i.p. Injection of cocaine and fluoxetine in rat (Thiriet et al., 1998). |
| MK-STYX (STYX-L1) | MK-STYX induced neurite extensions through the Rho signaling pathway and forms synapse in PC-12 cells. MK-STYX altered their morphology in primary hippocampal neurons in rat (Banks et al., 2017; Flowers et al., 2014) | MK-STYX missense mutation was identified in intellectual disability, accompanied by seizures and behavioral problems in human (Isrie et al., 2015) |
| MTMR2 | MTMR2 contributes to the maintenance of excitatory synapses by inhibiting excessive endosome formation and destructive endosomal traffic to lysosomes in rat (Lee et al., 2010). | Loss of MTMR2 in Schwann cells causes CMT4B1 neuropathy, which is characterized by a dysmyelinating neuropathy with myelin outfoldings in mice (Rodin et al., 2005). |
| MTMR4 | MTMR4 was differentially expressed between grade II-III gliomas and (grade IV) glioblastomas in human (Bourgonje et al., 2016). | MTMR4 was differentially expressed between grade II-III gliomas and (grade IV) glioblastomas in human (Bourgonje et al., 2016). |
| MTMR5 (SBF1) | MTMR5 suppress neurite growth in hippocampal neurons in rat. Overexpression of MTMR5 reduce hippocampal neurite outgrowth (Buchser et al., 2010). | SBF1 mutations may cause a syndromic form of autosomal recessive axonal neuropathy (AR-CMT2) in addition to CMT4B3 in Human (Manole et al., 2017). |
| MTMR7 | MTMR7 interacted with the neurofilament light chain protein, NF-L, in both Schwann cells and neurons in rat and human (Previtali et al., 2003). | An intronic variant was identified in the genetic locus of MTMR7 linked to variant Creutzfeldt-Jakob disease susceptibility in human (Sanchez-Juan et al., 2012). |
| MTMR8 | MTMR8 was differentially expressed in 65 % of the glioblastoma multiforme patient sample (Waugh, 2016). | MTMR10 was affected via 15q13.3 microdeletion and displayed strong phenotypes related to autism-like behavior (Forsingdal et al., 2016; Kogan et al., 2015) and autism like behavior in mice (Valbonesi et al., 2015). |
| MTMR10 | MTMR10 was affected via 15q13.3 deletion and was present in ADHD patients (Valbonesi et al., 2015). | MTMR11 was frameshift mutated in children with epileptic encephalopathies (Veeramah et al., 2013). |
| MTMR11 | MTMR11 was frameshift mutated in children with epileptic encephalopathies (Veeramah et al., 2013). | Mtmr13−/− mice show both the initial dysmyelination and later degenerative pathology of CMT4B2 (Ng et al., 2013; Robinson et al., 2008). Mutation in the MTMR13 gene associated with a classical Charcot-Marie-Tooth 4B2 phenotype in human (Chen et al., 2014; Negri et al., 2014). |
| MTMR13 | The phosphatase activity of laforin is dispensable to rescue Epm2a−/− mice from Lafora disease (Gayarre et al., 2014). | The phophatase activity of laforin is dispensable to rescue Epm2a−/− mice from Lafora disease (Gayarre et al., 2014). |
| Laforin (EPM2A) | EPM2A gene was expressed lower to control cells in fibroblasts from Lafora disease in human (Garcia-Gimeno et al., 2018). | EPM2A gene has 11 kinds of mutations in the patients of Lafora disease in human (Gomez-Garre et al., 2000). |
| DUSP11 | DUSP11 mRNA was downregulated in the model of nicotine-induced seizures in mice (Kedmi and Orr-Urtreger, 2007). | DUSP11 mRNA was downregulated in the model of nicotine-induced seizures in mice (Kedmi and Orr-Urtreger, 2007). |
| DUSP13A | DUSP13A interacts with the N-terminal domain of Apoptosis signal-regulating kinase 1 in an oxidative stress-independent manner in brain neuroblastoma. The knock-down of DUSP13A decreased the phosphorylation and activation of apoptosis signal-regulating kinase 1 (Park et al., 2010). | DUSP13A interacts with the N-terminal domain of Apoptosis signal-regulating kinase 1 in an oxidative stress-independent manner in brain neuroblastoma. The knock-down of DUSP13A decreased the phosphorylation and activation of apoptosis signal-regulating kinase 1 (Park et al., 2010). |
| DUSP14 | DUSP14 was a direct negative-feedback mechanism of 3, 4-methylenedioxyxymethamphetamine (MDMA)- induced ERK signaling in the striatum of mice (Marie-Claire et al., 2008). DUSP14 was a gene target limiting axon growth and regeneration downstream of Krüppel-like transcription factor 9 | DUSP14 mRNA was upregulated in the frontal cortex in response to Environmental chronic mild stress in mice (Tordera et al., 2011). |

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The balance between SSH and LIM domain kinase 1 is responsible for actin polymerization, which leads to a reduction in the protraction of neurites and inhibits the formation of this complex. This inhibition then drives the ADF/cofilin complex. At the tissue level, hSSH-1 proteins were expressed in healthy elderly persons (Barone et al., 2014; Zafar et al., 2017) as well as in human keratinocytes (Kligys et al., 2007).

SSH phosphatases modulate actin separation and reunion by regulating the ADF/cofilin complex in vivo (Niiwa et al., 2002). SSH phosphatases remove a phosphorus group from ADF/cofilin to activate this protein. In contrast, activated LIM domain kinase 1, a negative regulator of actin-polymerization dynamics, adds a phosphorus group to ADF/cofilin and thereby determines the WPD loop (conserved in the PTP family) residues for the transfer of a phosphate group (Fig. 1B) (Rios et al., 2013). CAAX proteins are involved in global gene expression in rat (Muth et al., 2016).

2.2.1. Structure and homologues

Within this subgroup, three proteins subtypes, PRL-1, PRL-2, and PRL-3, have been identified based on their amino acid sequences (Campbell and Zhang, 2014), which share greater than 50 % homology and memory processes (Yuen et al., 2010).

The variant rs950302 of cytosolic gene DUSP27 associate with heroin addiction vulnerability in African Americans (Nielsen et al., 2010). DUSP23 inhibition via NSC-87877 function in neuroblastoma, resulting in decreased tumor growth and increased p53 and p38 activity in mice (Shi et al., 2015). DUSP26 expression and JNK activation were enhanced in the hippocampus of AD patients (Jung et al., 2016). The SNP (rs3746599) of DUSP15 was significantly associated with autism in human (Tian et al., 2017).

2.2.2. Expression and function

While the cellular functions of this family remain yet to be uncovered, what we currently know is that PRLs are oncogenes (Wei et al., 2018). Within this subgroup, three proteins subtypes, PRL-1, PRL-2, and PRL-3, have been identified based on their amino acid sequences (Campbell and Zhang, 2014), which share greater than 50 % homology in humans (Rios et al., 2013).

PRLs carry the CAAX motif and are the only CAAX proteins in the DUSP family (Rios et al., 2013). CAAX proteins are involved in global cellular functions, such as proliferation and differentiation. A polybasic region localizes next to the CAAX box and mediates membrane or nuclear localization of PRLs. The catalytic or protein phosphatase (PTP) domain is responsible for enzymatic activity, requiring the P-loop residues and the WPD loop (conserved in the PTP family) residues for the transfer of a phosphate group (Fig. 1B) (Rios et al., 2013).

Table 2

| Isoforms | Function in Normal Brain | Function in Pathological Brain |
|----------|--------------------------|--------------------------------|
| DUSP14 | Decreased in HD mice and can be enriched after pridopidine treatment in mice (Geva et al., 2016). | |
| DUSP19 | The mRNA levels of DUSP19 were increased in the dentate gyrus from depression postmortem tissue (Duric et al., 2010). | |
| DUSP22 | The promoter hypermethylation of the DUSP22 gene was identified in the hippocampus from controls and AD patients. DUSP22 inhibits PKA activity and thereby determines tau phosphorylation status and CREB signaling (Sanchez-Mut et al., 2014). | |
| DUSP23 | The mRNA expression of the gene DUSP23 was significantly lower in patients that have died from the disease compared with neuroblastoma patients with no evidence of disease (Caren et al., 2011). | |
| DUSP26 | The mRNA levels of DUSP26 were differentially expressed between grade II-III gliomas and (grade IV) glioblastomas in human (Bourgonje et al., 2016). | |
| DUSP27 | The variant rs3746599 of cytosolic gene DUSP27 associate with heroin addiction vulnerability in African Americans (Nielsen et al., 2010). | |

Note: AD: Alzheimer's disease; HD: Huntingdon’s disease; CMT4: Charcot-Marie-Tooth Neuropathy Type 4.

proteinatlas.org). At the tissue level, hSSH-1 proteins were expressed in the frontal cortex and cerebellum of human post-mortem brain tissues of healthy elderly persons (Barone et al., 2014; Zafar et al., 2017) as well as in human keratinocytes (Kligys et al., 2007).

SSH phosphatases modulate actin separation and reunion by regulating the ADF/cofilin complex in vivo (Niiwa et al., 2002). SSH phosphatases remove a phosphorus group from ADF/cofilin to activate this complex (Endo et al., 2007, 2003; Kim et al., 2009; Wang et al., 2005). In turn, the activated ADF/cofilin complex depolymerizes and dismantles actin filaments in order to drive the protraction of growth cones and neurite extensions, as observed in rat hippocampal neurons. In contrast, activated LIM domain kinase 1, a negative regulator of actin-polymerization dynamics, adds a phosphorus group to ADF/cofilin and thereby determines the WPD loop (conserved in the PTP family) residues for the transfer of a phosphate group (Fig. 1B) (Rios et al., 2013).
nucleus, whereas at the tissue level, subtypes of human PRLs (hPRLs) differ depending on the type and severity of the tumor in question. hPRL-1 and hPRL-2 mRNA expression patterns are widespread in healthy adult human tissues. hPRL-2 is expressed at higher levels in the brain than hPRL-1, especially in the granular layer of the cerebellum (Dumaul et al., 2006). hPRL-3 mRNA is expressed in both skeletal muscle and the heart during development (Matter et al., 2001). When compared to other mammalian tissue, such as mouse tissue, similarities do exist. For instance, mouse PRL (mPRL)-1 is 100% identical to hPRL-1 in the number of amino acid subunits (Zeng et al., 1998). mPRL-2 mRNA is expressed in skeletal muscle, and mPRL-3 is expressed in both skeletal muscle and heart tissue (Zeng et al., 1998).

PRLs promote cell proliferation, migration, invasion, tumor growth, and metastasis via multiple signaling pathways, including extracellular signal-regulated kinase (ERK) 1/2 pathways (Luo et al., 2009; Peng et al., 2009), the mechanistic target of the rapamycin (Ye et al., 2015), and the phosphatidylinositol 3-kinase (PI3K)/Akt pathways (Zhang et al., 2018). It has been observed that PRL-1 and PRL-2 induce cell invasion and motility through the activation of ERK 1/2. Moreover, PRL-3 stimulates both cell proliferation and epithelial-mesenchymal transition, a crucial developmental process, by acting upstream of PI3K. Interestingly, ERK1/2 and PI3K are common signaling pathways in cell proliferation, migration, invasion, tumor growth, and metastasis (Rios et al., 2013).

2.3. Cell division cycle 14 (CDC14) phosphatases

2.3.1. Structure and homologues

CDC14 phosphatases, encoded by the CDC14 gene, are the subgroup that is mainly involved in cell cycle regulation (Clifford et al., 2008; Trautmann and Collum, 2002). CDC14 comprises three isoforms, CDC14A, CDC14B, and CDC14C (Bremmer et al., 2012). The isoform CDC14B encodes four splice variants, including CDC14Bpar, CDC14B1, CDC14B2, and CDC14B3 (Rosso et al., 2008). Interestingly, the isoform CDC14C (also known as CDC14Bretro) is produced by the CDC14B splice variant CDC14Bpar, by gene retroduplication, a process which occurred in hominoids (Mocciaro and Schiebel, 2010; Rosso et al., 2008).

CDC14A contains a core domain and a nuclear export signal, which is responsible for the translocation of CDC14A from the nucleus to the cytoplasm. The core domain contains two structurally similar domains, A and B (Gray et al., 2003). The protein structure of human hCDC14A shares 65% compatibility with hCDC14B except for the nuclear targeting sequence (N-terminal 44 amino acids) that is responsible for localizing CDC14B to the nucleolus throughout interphase during cell division (Gray et al., 2003). CDC14C structure is similar to hCDC14B except for the C-terminus (Fig. 1C) (Rosso et al., 2008).

2.3.2. Expression and function

At the cellular level, CDC14A localizes to the centrosomes of cells during interphase (Mailand et al., 2002). CDC14B1 is expressed in the nucleoli and CDC14B2 in nuclear speckles localized within the nucleus, as demonstrated in COS7-cells. Moreover, CDC14B3 and CDC14Bpar exhibit co-localization with microtubules in COS7-cells (Rosso et al., 2008). It has been also demonstrated that CDC14C co-localizes with a marker of the endoplasmic reticulum in COS7 cells, human HeLa, or LN229 cell lines (Rosso et al., 2008).

At the tissue level, hCDC14A and hCDC14B are both found in the cerebral cortex, lymph nodes, liver, colon, kidneys, and testis (www.proteinatlas.org). While hCDC14Bpar mRNA is predominantly expressed in the adult and fetal brain, hCDC14B1, hCDC14B2, and...
hCDC14B3 mRNAs are expressed in the adult brain, including the hippocampus, prefrontal cortex, amygdala, and hypothalamus (Rosso et al., 2008). hCDC14C mRNA is found in the adult brain and embryonic forebrain, including the dorsal telencephalon (Rosso et al., 2008).

The CDC14 family is conserved within eukaryotes and plays a role in the inactivation of mitotic cyclin-dependent kinase via dephosphorylation. While activation of cyclin-dependent kinase drives cells into mitosis, their inactivation promotes mitotic exit and cytokinesis. Furthermore, CDC14 regulates a variety of other cellular events, such as DNA recombination, telomere segregation, mitotic spindle dynamics, and cytokinesis (Bremmer et al., 2012; Stegmeier and Amon, 2004).

2.4. Phosphatase and tensin homologs deleted on chromosome 10 (PTENs) family

2.4.1. Structure and homologues

The PTEN gene codes for the PTEN protein, a protein in which tumor-suppression functions due to its phosphatase activity (Govender and Chetty, 2012; Knafo and Esteban, 2017). PTEN carries two isoforms: a CUG initiated isoform designated PTENx, and an AUG initiated isoform referred to as PTENi with a smaller molecular weight than PTENx (Li et al., 2017). The N-terminal domain of PTEN contains the catalytic N-terminal PI3P-binding domain and PTP domain. The C-terminal domain consists of the following subdomains: C2, C-tail, and the PDZ, with the active catalytic site being HCrexGxxR (Fig. 1D) (Hopkins et al., 2014; Worby and Dixon, 2014). PTEN’s phosphatase domain carries a similar structure to protein phosphatases but with a more significant active site allowing it to bind other substrates such as phosphoinositide (PI). Additionally, PTEN’s C2 domain has been shown to bind phospholipid micelles in vitro and thus aid in the steering and anchoring of PTEN to the cellular membrane (Lee et al., 1999). Together this interplay between both domains carries implications for the suppression and stimulation of tumor cell growth.

2.4.2. Expression and function

At the cellular level, PTENx is expressed in the cytoplasm and the mitochondrial inner membrane, while PTENi is in the nucleolus (Li et al., 2017, 2014). In neurons, PTEN dynamically localized to specialized subcellular compartments, such as the neuronal growth cone or dendritic spines, as well as the nucleus (Kreis et al., 2014; LaSarge et al., 2016).

At the tissue level, PTEN protein and mRNA expression have been observed in the human pancreas (Ebert et al., 2000) and in the human brain, including the cerebral cortex, cerebellum, and hippocampus (www.proteinatlas.org). PTEN exhibits differential distribution in the rat brain, with the highest levels found in the anterior olfactory nucleus, cerebral cortex, amygdaloid nucleus, hippocampus, Purkinje cells, and several nuclei in the basal ganglia, thalamus, midbrain, and pons (Cai et al., 2009).

PTEN regulates cellular proliferation, survival, energy metabolism, cellular architecture, and motility (Worby and Dixon, 2014). During development, PTEN modulates cell proliferation and neuronal growth by dephosphorylating PIP3 and antagonizing PI3K signaling. PI3K signaling mediates responses to different cellular stimuli, including hormones and growth factors (Bermudez Brito et al., 2015; Leslie and Downes, 2002; Ye et al., 2012). On the other hand, the inhibition of PTEN causes axonal regeneration and neural repair (Ghate et al., 2015). PTEN plays a fundamental role in the maintenance of chromosomal stability through physical interactions with centromeres and controls DNA repair (Shen et al., 2007).

2.5. Myotubularins

2.5.1. Structure and homologues

Myotubularins can be found in almost all eukaryotes, ranging from yeast to mammals. In humans, 14 clearly defined myotubulin-related paralogs have been described, with MTM1 being the first recognized myotubulin. Subsequently, 13 myotubulin-related proteins, labeled MTMR1 to MTMR13, were identified (Raess et al., 2017).

All myotubularins share the PH-GRAM (Pleckstrin Homology - Glucosyltransferase, Rab-like GTPase Activator, and Myotubularins) domain and catalytically active or inactive phosphatase domains. Additionally, myotubularins can also carry other functional domains, including the PDZ binding site, the PH (Pleckstrin homology) and FYVE (Fab1-YOTB-Vac1-EEA1) domains, and the DENN (Differentially Expressed in Normal and Neoplastic cells) domain. Except for MTMR10, all myotubularins are composed of a coiled-coil domain (Fig. 1E) (Begley and Dixon, 2005; Raess et al., 2017).

2.5.2. Expression and function

At the cellular level, myotubularins do not show any nuclear expression but are primarily localized in the cytoplasm as a richly-formed network. Additionally, myotubularins have also been shown to localize to Rac1-inducible plasma membrane ruffles. This localization to Rac1-induced ruffles seems to be associated with a highly conserved myotubulin domain referred to as RID (Laporte et al., 2002).

At the tissue level, myotubulin mRNA expression has been documented for various human organs, including the spinal cord and substantia nigra (SN) of the central nervous system, skin, lungs, and vagina (Raess et al., 2017). At the protein level, myotubularins are expressed in the brain, including the cerebral cortex, hippocampus, and cerebellum, as well as non-brain tissues like lungs, muscles, endocrine tissue, bone marrow, immune system, liver, gallbladder, and pancreas (www.proteinatlas.org).

Myotubularins are involved in several cellular processes, including autophagy, apoptosis, the actin cytoskeleton, and intermediate filaments dynamic and PI metabolism. Active myotubulin can remove phosphate on carbon number 3 of PtdIns3P or PtdIns(3,5)P2, and turn it into PtdIns or PtdIns5P, respectively (Hnia et al., 2012). Additionally, they are also involved in myelin formation in neurons. For instance, MTMR2 is present in the nucleus and cytoplasmic compartments of Schwann cells and motor neurons but not in the nucleus of sensory neurons. Moreover, MTMR2 interacts with the neurofilament light chain protein NF-L in both Schwann cells and neurons (Previtali et al., 2003). Schwann cell/dorsal root ganglion neuron co-cultures from MTMR2 knockout mice exhibit excessive redundant myelin, also known as myelin outflowing, and MTMR2 replacement was shown to rescue this myelin outflowing phenotype (Bolis et al., 2009). Interestingly, the deletion of MTMR2 phospholipid phosphatase in humans causes childhood-onset of an autosomal recessive demyelinating neuropathy, also known as Charcot–Marie–Tooth type 4B1 (Bolino et al., 2000).

2.6. Mitogen-activated protein kinase phosphatases (MKPs)

2.6.1. Structure and homologues

The MKP genes encode phosphatases that dephosphorylate MAP kinase (MAPK) signaling elements in vivo hence deactivating them (Konidoh and Nishida, 2007). In turn, this leads to the modulation of several physiological processes via a conformational change of their substrates.

MKPs are composed of the MAPK-binding (MKB) domain in the N-terminal end and the DSP domain in the C-terminal end. The N-terminal MAPK-binding domain regulates enzymatic specificity through docking interaction with MAPK. The binding of phosphorylated MAPK to the MAPK-binding domain alters the structure of the DUSP domain. This alteration in the conformation of the protein, in addition to the interaction of the catalytic domain with MAPK, increases MKPs’ catalytic activity (Fig. 1F).

2.6.2. Expression and function

MKPs seem to be highly expressed in a variety of tissue types, including the brain, endocrine tissues, lung, digestive tract, liver,
gallbladder, kidneys, male and female reproductive tissues, adipose tissue (www.proteinatlas.org).

The MKP family can bind to substrates from MAPK signaling pathways, including ERK, JNK, and p38 (Caunt and Keyse, 2013; Kondoh and Nishida, 2007). The DSP domain of MKPs inactivates MAPK by docking into phospho-MAPK (Kondoh and Nishida, 2007). MAPK signaling converts extracellular stimuli into a variety of intracellular responses, such as proliferation, differentiation, survival, apoptosis, and migration (Dwivedi et al., 2001; Kim and Choi, 2015; Yuan et al., 2010). MAPK signaling pathways have many predominant kinases, including JNK, ERK, and p38, all of which can be inactivated by different MKPs (Owens and Keyse, 2007).

2.7. Atypical DUSPs

2.7.1. Structure and homologues

Atypical DUSP genes have multiple nomenclatures and remain poorly characterized (Huang and Tan, 2012; Rios et al., 2014). The HUGO (Human Genome Organization) Gene Nomenclature Committee includes 16 atypical DUSPs genes (Cain and Beeser, 2013), Patterson et al., identify 20 members of atypical DUSPs (Patterson et al., 2009), and Huang and Tan 15 atypical DUSP members (Huang and Tan, 2012). Moreover, phylogeny analysis has shown that atypical DUSPs appear not to be derived from a common proximal ancestor (Huang and Tan, 2012; Patterson et al., 2009). Atypical DUSPs encode proteins with a molecular weight of less than 27 kDa (Patterson et al., 2009; Rios et al., 2014). All the members of atypical DUSPs are listed in Supplementary Table 2.

Atypical DUSPs predominantly contain the consensus DSP catalytic domain. Some atypical DUSPs contain a CH2 domain, carbohydrate-binding domain, and an Arginine-rich or Proline-rich region (Fig. 1G) (Patterson et al., 2009).

2.7.2. Expression and function

At the cellular level, the majority of atypical DUSPs are localized in the cytoplasm, with some being in the nucleus, and another subset in the mitochondria and Golgi in various cell types (Patterson et al., 2009).

At the tissue level, the brain expression of atypical DUSPs is presented in Table 1, while their localization in other tissues is described in Supplementary Table 3.

Some atypical DUSPs regulate MAPK, playing a role in cell proliferation and apoptosis. In addition to MAPK protein substrates, several substrates of atypical DUSPs include nucleic acids (such as RNA), and phosphorylated carbohydrates (such as amylopectin and glycogen). Nonetheless, the physiological substrates of many atypical DUSPs remain unknown (Bayón and Alonso, 2010; Patterson et al., 2009).

3. DUSP genes and mental disorders

Accumulating evidence from the current literature on the link between DUSP genes and mental disorders such as depression, bipolar disorder, autism spectrum disorder (ASDs), schizophrenia, post-traumatic stress disorder (PTSD), and substance abuse disorders are described in the following section. The summary of the pathological implication of DUSP family members in mental disorders is presented in Table 2.

3.1. Depression

Depression is characterized by psychological and physiological symptoms, including negative thinking,anhedonia, fatigue, memory impairment, insomnia, extreme weight loss, or weight gain. The World Health Organization (WHO) reported that depression is a leading cause of disability worldwide. The neurobiological mechanisms underlying depression are complex, however, first-line antidepressants are effective in a subset of patients by reversing some of the symptoms of depression (Thornicroft et al., 2017). However, not all individuals benefit from current antidepressants, and genetic factors have been shown to contribute to the risk of treatment-resistant depression (Willner et al., 2013).

3.1.1. PTEN and depression

Genetic studies have demonstrated an association between three distinct PTEN single nucleotide polymorphisms, rs701848, rs2735343, and rs11202590, and increased risk of depression in a Chinese cohort (Liu et al., 2016). Other studies have provided evidence that PTEN protein levels are higher in postmortem lysates of the ventral prefrontal cortex (Brommaud’s area 11) from suicide victims diagnosed with depression when compared to non-depressed healthy controls (Karege et al., 2011). Besides, the enzymatic activity of the kinases P3K and AKT1 were found to be decreased in the ventral prefrontal cortex (Brommaud’s area 11) of suicide victims diagnosed with depression, while their protein levels did not differ. Conversely, PTEN protein levels in the ventral prefrontal cortex were observed to be increased in patients with a depressive disorder. This attenuation of P3K and AKT1 activity in suicide victims with a depressive disorder may be related to elevated levels of PTEN, which in turn may result in insufficient phosphorylation of second lipid messengers PIP3-phosphate, PIP2 and PIP3 (Karege et al., 2011).

P3K and AKT are also involved in mediating depressive-like behavior in mice induced by stress (Deng et al., 2019; Wu et al., 2018), and inhibitors of P3K/ AKT have been shown to prevent antidepressant-like effects (characterized by decreased immobility time) induced by creatine in mice following the stress-inducing tail suspension test (Cunha et al., 2016; Ludka et al., 2016). Together, these results highlight that the phosphorylation of AKT and the downstream effects might be of interest as a potential treatment of depression. Previous work has indicated that deficits in vital cellular processes such as cell survival and neuroplasticity are observed in major depression (Pittenger and Duman, 2008). Therefore, looking into the enzymatic activity of PTEN and P3K and their association with abnormalities in neurotrophic signaling is pertinent (Karege et al., 2011).

3.1.2. DUSP1 and depression

DUSP1 has also been documented to play a role in the pathophysiology of depression in human subjects (Akbarian and Davis, 2010). For instance, DUSP1 mRNA expression was shown to be increased in the hippocampus of depressed patients when compared to healthy controls (Duric et al., 2010). As negative regulators of DUSP1, MAPK and its downstream kinases were decreased in the prefrontal cortical areas and the hippocampus of suicide subjects with depression (Dwivedi et al., 2006, 2003; Dwivedi et al., 2001). Recent evidence from animal studies suggests the involvement of MKPs in depression-like behavior. For instance, in one study, DUSP1 protein levels were observed to be increased in the hippocampus of stressed rats when compared to controls in the resident-intruder paradigm. Kinase substrates of DUSP1, including phosphorylated MEK1/2 and ERK1/2, were decreased in the hippocampus of stressed rats when compared to controls (Jio et al., 2011). In another stress model – the chronic unpredictable stress (CUS) model – the upregulated protein levels of DUSP1 in the hippocampus was rescued by the antidepressant fluoxetine, two weeks after inducing depressive-like behaviors in rodents (Duric et al., 2010). Similarly, the upregulated protein level of DUSP1 in the ventrolateral orbital cortex of rats subjected to chronic unpredictable mild stress was attenuated by expressing mir-101 expression and so was the depressive-like behavior (Zhao et al., 2017). mir-101 is a functional silencing small RNA targeting DUSP1 (Llorens et al., 2013; Zhu et al., 2010) and the amyloid precursor protein (APP) (Vilardo et al., 2010). Moreover, overexpression of DUSP1 in the hippocampus induced anhedonia-like behavior, including a reduced preference for sucrose and increased frequency of failure-to-escape in the active avoidance test (Duric et al., 2010). DUSP1 knockout mice were also resistant to CUS-induced depressive-like behaviors (Duric et al., 2010).
Antidepressant treatments have an impact on the expression of DUSP1 in healthy animal subjects. For example, the administration of fluoxetine reduced DUSP1 mRNA expression in the prefrontal cortex of healthy rats (Kodama et al., 2005). Moreover, electroconvulsive therapy (ECT), a treatment for drug-resistant depression, induced upregulation of DUSP1 mRNA levels in all hippocampal subregions, and the prefrontal cortex of healthy rats (Kodama et al., 2005).

These results together strengthen the association between DUSP1 and depression. Future studies looking into treatments for depression should consider targeting DUSP1 as a therapeutic strategy by, for example, making use of small RNAs, particularly miRNAs, to silence the expression of DUSP1 hence reversing signs and symptoms of depression.

3.1.3. DUSP4 and depression

Analyses of postmortem brain tissue samples indicated increased protein levels of DUSP4 (aliases MKP-2, the ERK1/2 phosphatase) in prefrontal cortical areas and the hippocampus of patients with major depressive disorder following the death by suicide compared to non-psychiatric control subjects. This increase was accompanied by decreased expression of mRNA and protein levels of ERK1 and ERK2, resulting in reduced MAPK activity (Owivedi et al., 2001). Another study showed sex-dependent differential expression of DUSP4 mRNA in the ventral subiculum of patients with depression compared to healthy controls; with differences observed in male but not in female subjects (Labonte et al., 2017).

DUSP4 protein expression remained unchanged in the hippocampus and the frontal cortex of rats subjected to prenatal stress (Budziszewska et al., 2010) and in a male rat model of depression, which was induced by neonatal treatment with clomipramine (Feng et al., 2003). Treatments, including antidepressants and ECT, have led to changes in DUSP4 expression in healthy animals. For instance, ECT treatment in healthy male rats induced increased expression of DUSP4 mRNA in the dentate gyrus (DG) of the hippocampus and the prefrontal cortex (Kodama et al., 2005).

Although these findings suggest DUSP4 changes in both human patients and animals subjected to antidepressant treatments ECS, the available studies do not show DUSP4 change in the stress paradigm in animals, like the prenatal stress and depression model of neonatal treatment with clomipramine. These unchanged results might be due to the limitations of the stress paradigm in animals. Besides, even though studies show DUSP4 level is sex-dependent in human depression studies, no studies show that the DUSP4 level is sex-dependent in animal models of depression, which creates limitations in specifying the involvement of DUSP4 in depression.

3.1.4. DUSP6 and depression

In post-mortem brain tissue, DUSP6 mRNA was shown to be differentially expressed in the ventromedial prefrontal cortex of patients with depressive disorder in a sex-specific manner (Labonte et al., 2017). Besides, the DUSP6 substrates, phospho-ERK1/2, showed elevated protein expression in the prefrontal cortex of female patients with depressive disorder (Labonte et al., 2017). Downregulation of DUSP6 mediated by virus injection in the ventromedial prefrontal cortex of chronic stressed induced depressive-like phenotype in female mice, but not male mice. The overexpression of DUSP6 mediated by a Herpes simplex virus vector rescued the depressive-like behavior in female mice (Labonte et al., 2017). This sex-differential response of the stressed mice suggests that DUSP6 exerts a sex-specific role in the stress response, possibly via an interaction with sex-specific hormones.

Moreover, viral-mediated downregulation of DUSP6 was accompanied by increased phosphorylated ERK1/2 levels in the ventromedial prefrontal cortex of stressed female mice compared to control (Labonte et al., 2017). However, the total ERK1/2 protein levels in the DUSP6-downregulated female stressed mice remain unchanged in the ventromedial prefrontal cortex compared to control. These findings resemble findings observed in post-mortem brain tissue analyses of female patients diagnosed with depression. Females diagnosed with depression showed elevated levels of phospho-ERK1/2 in the prefrontal cortex compared to healthy female controls. Elevated phospho-ERK1/2-reactive cell density mainly localized in layers II/III and layers V/VI of the prefrontal cortex of female patients with depressive disorder (Labonte et al., 2017).

Additionally, ECT and administration of antidepressants are shown to have an impact on DUSP6 expression. For instance, ECT induces the upregulation of DUSP6 mRNA levels in the prefrontal cortex and DUSP6 protein levels in the hippocampus and prefrontal cortex of healthy rats (Kodama et al., 2005). The administration of fluoxetine, however, reduced the mRNA expression of DUSP6 in the prefrontal cortex of healthy rats (Kodama et al., 2005). This discrepancy in results highlights the need to further investigate the involvement of DUSP6 in mood disorders such as depression.

3.1.5. DUSP2, DUSP12, DUSP19, DUSP23, DUSP24 and depression

The subregions of the hippocampus exhibit differential RNA expression of MKPs in post-mortem brain samples of patients diagnosed with depressive disorder. For instance, while DUSP2 and DUSP19 show higher expression in the hippocampal DG than in the CA1, mRNA levels of DUSP12 and DUSP24 are increased in the CA1 region of postmortem brain tissue of patients diagnosed with depression (Duric et al., 2010) as compared to healthy controls. Another study showed differential expression of DUSP19 mRNA in the ventral subiculum and of DUSP23 mRNA in the nucleus accumbens and the Brodman area of male patients with depressive disorder, but not in female patients (Labonte et al., 2017). These results indicate that distinct DUSP genes may be linked with depression differently, including sex-specific effects. Despite these observations, further experimental studies are needed to better understand the involvement of MKPs in depression and eventually target their expression to reverse depressive symptoms.

3.2. Bipolar disorder

Bipolar disorder is characterized by mood instability, with episodes of mania and depression. Bipolar disorder is a complex disorder with high estimated heritability. Despite the accumulating evidence of the etiology of bipolar disorder, the underlying biological mechanisms that give rise to this mood disorder remain elusive (Harrison et al., 2018). Besides underlying genetic factors, environmental risk factors have also been identified as being partly responsible for the onset of bipolar disorder (Rowland and Marwaha, 2018). Bipolar disorder is associated with multiple dysregulations including disturbed brain development, neuroplasticity, and chronobiology, specifically, neurotransmitter, neurotrophic factors, neuroinflammation, autoimmunity, cytokines, stress axis activity, oxidative stress, and mitochondrial dysfunctions (Sigitova et al., 2017).

3.2.1. DUSP2 and bipolar disorder

It has been observed that patients diagnosed with bipolar disorder have increased proportions of monocytes in the blood or cerebrospinal fluid (CSF) compared to controls (Barbosa et al., 2014; Jakobsson et al., 2015). It has also been found that the monocytes of patients with bipolar disorder and the offspring of bipolar parents show aberrant levels in DUSP2 mRNA expression. For instance, patients with bipolar disorder taking medication show elevated blood mRNA levels of DUSP2 compared to healthy controls. DUSP2 carries a strong correlation to the mRNA expression of inflammatory cytokines (Drexhage et al., 2010). DUSP2 mRNA expression has been shown to be significantly higher in monocytes of patients with mood disorder compared to healthy controls (Padmos et al., 2008). Furthermore, lithium carbonate- and antipsychotic-treated patients with bipolar disorder exhibited lower levels of expression of DUSP2 mRNA in monocytes compared to non-lithium- and non-antipsychotic-treated patients with bipolar disorder (Padmos et al., 2008). Thus, DUSP2 may be an attractive target for...
further analyses in patients with bipolar disorder.

3.2.2. DUSP6 and bipolar disorder

There is a positive association between the DUSP6 gene and patients with bipolar disorder (Kim et al., 2012; Lee et al., 2006). A genetic study including 160 patients with a diagnosis of schizophrenia, 132 patients with bipolar disorder, and 336 healthy controls, indicated that the G allele of the T/G polymorphism of the DUSP6 gene was significantly more common in patients with bipolar disorder than controls. However, there was no difference between schizophrenia patients and controls. This contrast suggests a specific association of the DUSP6 gene with bipolar disorder but not with schizophrenia (Lee et al., 2006). However, this association was not observed in male patients with bipolar disorder (Kim et al., 2012), hence suggesting a sex-specific effect.

The lower expression of DUSP6 gene observed in postmortem brain samples of patients with bipolar disorder has been found to show sex-specificity, with a reduced level of mRNA transcripts expression in female but not male patients with bipolar disorder (Struyf et al., 2008). Additionally, in vitro studies demonstrated functional Leu114Val and Ser144Ala polymorphisms in DUSP6 blunted the effects of lithium on ERK1/2 activation by using SH-SY5Y human neuroblastoma cells infected with recombinant adenoviruses (Kim et al., 2012). Other evidence has suggested that DUSP6 may be linked with bipolar disorder, possibly via the involvement of the ERK pathway and circadian rhythm dysregulation (Lee et al., 2006).

Also, DUSP6, a negative regulator of ERK1/2, has been linked to the disruption of the circadian rhythm in cell cultures of fibroblasts derived from patients with bipolar disorder. The knock-down of DUSP6 in these fibroblasts has been shown to reverse lithium-induced increases in amplitude of circadian rhythm. That being said, the inability of lithium to regulate circadian rhythms in bipolar disorder may reflect reduced amplitude of circadian rhythm. That being said, the inability of lithium to regulate circadian rhythms in bipolar disorder may reflect reduced DUSP6 expression (Lee et al., 2006). However, this association was not observed in male patients with bipolar disorder (Kim et al., 2012), hence suggesting a sex-specific effect.

3.3. Autism spectrum disorders (ASD)

Autism spectrum disorder is a developmental disorder characterized primarily by a lack of social reciprocity accompanied by repetitive behavior such as stereotypical or repetitive motor movements. The heritability of ASD is considerably high, and common genetic variants have been shown to play a role in conferring risk to ASD (Grove et al., 2019). Besides, indirect evidence suggests a contribution of environmental factors in interaction with genetic factors in the development of ASD (Chaste and Leboyer, 2012).

3.3.1. PTEN and ASD

PTEN gene mutations have been shown to be risk factors for ASDs associated with macrocephaly (Butler et al., 2005; Buxbaum et al., 2007; Herman et al., 2007). This specific type of ASD associated with macrocephaly is termed PTEN-ASD, typically characterized by reduced levels of PTEN protein expression in conjunction with increased brain size and cognition impairment (Frazier et al., 2015). In the last decades, PTEN mutation frequencies in PTEN-ASD has been reported in ten human studies (Tilot et al., 2015). Moreover, PTEN loss in mice leads to alterations in synapses and cytoarchitecture (Tilot et al., 2015). Ablation of PTEN in neural stem cells in the subgranular zone of the hippocampus of mice leads to increased proliferation and differentiation rate of the stem cells, which later developed into hypertrophied neurons (Amiri et al., 2012). Several mouse models characterized by PTEN deficiency or dysfunction show autism-like behaviors, including social deficit and repetitive behavior (Knafo and Esteban, 2017). One of these models, PTEN<sup>m3m4</sup> animals, exhibits the same disrupted genes as those in human ASD (Tilot et al., 2016), including genes related to myelination such as myelin basic protein. Interestingly, PTEN<sup>m3m4</sup> animals present an enlarged corpus callosum, white matter abnormalities, and impaired learning and memory processes (Frazier et al., 2015).

3.3.2. DUSP15 and ASD

The analysis of peripheral blood from 255 children affected by ASD and 427 healthy controls revealed that DUSP15 could be a susceptibility biomarker for ASD (Tian et al., 2017). Additionally, recurrent identical de novo mutations of DUSP15 were found via exome sequencing using 175 samples from ASD cases and their parents (Neale et al., 2012). Therefore, DUSP15 seems to carry a peculiar role in ASD risk and should be further investigated as a potential biomarker for ASD in children.

3.4. Schizophrenia

Schizophrenia is a debilitating disease affecting various daily functions, including self-care, social aspects, and occupational functions (Mueser and McGurk, 2004; van Os et al., 2010). The symptoms of schizophrenia include hallucination, delusion, bizarre behavior, anhedonia, and concentration problems (Andreasen and Olsen, 1982). Evidence shows that the factors contributing to schizophrenia include genetic factors, early environmental influences, and social factors (e.g., poverty) (Mueser and McGurk, 2004; van Os et al., 2010). Schizophrenia is a complex disease affecting 1–3% of the population. It is also considered among the top ten causes of disability worldwide (Mueser and McGurk, 2004). Dysfunction of dopaminergic neurotransmission and synaptic function seems to contribute to psychotic symptoms and abnormalities of neuronal connectivity, respectively (Owen et al., 2016). Current first-line treatment mainly includes the administration of antipsychotic drugs (such as chlorpromazine and haloperidol) combined with psychotherapy, social support, and rehabilitation (Owen et al., 2016).

3.4.1. DUSP4 and schizophrenia

A post-mortem brain study demonstrated decreased DUSP4 protein levels in the cerebellar vermis of the patient with schizophrenia compared to control (Kyosseva et al., 1999). This is particularly interesting given the increasing evidence showing the involvement of the cerebellum in psychiatric disorders, mainly schizophrenia. As substrates of DUSP4, ERK protein levels also seem to be disrupted in the post-mortem brains of schizophrenia patients. For instance, ERK1 protein expression is reduced in the prefrontal cortex, while ERK2 is elevated in the thalamus (Hirayama-Kurogi et al., 2017).

3.4.2. DUSP22 and schizophrenia

The hypermethylation of the DUSP22 promoter has been reported in a recent study investigating genetic vulnerability to schizophrenia (Boks et al., 2018). The blood and brain tissues of patients exhibited significant hypermethylation at the DUSP22 gene promoter. Furthermore, the DUSP22 gene promoter showed higher DNA methylation levels in the dopamine-exposed schizophrenia patients compared to non-dopamine exposed groups. Thus, dopamine seemed to be a susceptible factor in the onset of schizophrenia. In an in vitro model of dopamine, nutritionally deprived patient-derived fibroblasts showed hypermethylated DUSP22. These results suggest an association between epigenetic changes on the DUSP22 gene and increased susceptibility to the impact of an environmental risk factor on mental disorders (Boks et al., 2018). Although no correlation was found to exist between DNA methylation and gene expression of the DUSP22, these results suggest changes in gene expression regulation of DUSP22, in response to extreme conditions like dopamine, may moderate or mediate risk for schizophrenia. Additionally, the hypermethylation of DUSP22 in the blood and brain of schizophrenia patients that were not exposed to dopamine, also suggests that dysregulations in DUSP22 methylation are associated with underlying mechanisms in the onset and development of schizophrenia. Further research on the involvement of DUSP22 in neuronal development is required to
strengthen this association and better understand the changes that are brought by aberrant DUSP22 methylation.

3.4.3. MTMR2, MTMR9 and schizophrenia

MTMR9 mRNA level was found to be reduced approximately two- fold in peripheral blood lymphocytes from patients with schizophrenia compared to healthy controls (Bowden et al., 2006). Furthermore, MTMR2 mRNA was shown to be lower in the superior temporal cortex of patients diagnosed with schizophrenia as compared to controls without a schizophrenia diagnosis (Schmitt et al., 2012). These results suggest that further research into MTMR9 is required to investigate whether it would eventually be qualified as a biomarker for the diagnosis of schizophrenia.

3.5. Post-traumatic stress disorder (PTSD)

PTSD symptoms include intrusions, avoidance/numbing, hyper- arousal, sensitization to stressors, and negative alterations in cognitions and mood. The cause of the PTSD remains elusive, and various factors have an impact on the pathology of PTSD, including genetic factors, trauma exposure, and interaction between gene and environment (Mehta and Binder, 2012; Yehuda et al., 2015). The global burdens of PTSD in public health are substantial because the symptoms lead to impaired functions in several aspects of one’s life, including health, social, and professional life (Watson, 2019). Given the complexity of the pathology of PTSD, the treatment of PTSD consists of various methods, including pharmacologic approaches (Friedman and Bernardy, 2017; Horn et al., 2016), psychotherapies (Steenkamp et al., 2015), and mindfulness (Lang, 2017).

3.5.1. DUSP22 and PTSD

Differential DNA methylation at the DUSP22 gene is receiving increased attention to psychiatric disorders such as schizophrenia and PTSD. A recent longitudinal study in a Dutch military cohort identified changes in DNA methylation at several differentially methylated positions, including DUSP22 (Rutten et al., 2018). Decreased DNA methylation around the DUSP22 gene was linked to increased PTSD symptoms (Rutten et al., 2018). Although this observation was not replicated in an independent replication study, a thorough understanding of the role of epigenetic changes around the DUSP22 gene in the face of extreme environmental conditions like traumatic stress and famine is required.

3.6. Substance abuse disorders

Substance abuse disorders represent complex behaviors or symptoms involved in compulsive drug-seeking, including impaired control of substance use and social interactions (Volkow et al., 2016). Low affect, behavior self-regulation and interaction with social factors during child development predispose to substance abuse in adolescence (Tarter, 2002). Besides, genetic factors and their interaction with the environment contribute to the etiology of substance abuse and related behaviors (McGuere et al., 1996). The pathophysiology of substance abuse involves repeated perturbation of reward circuits, abnormalities in the prefrontal cortex, and molecular neuro-adaptations (Koob et al., 2008). The treatment usually includes medication in combination with social and psychotherapy (Tenegr and Leebold, 2016).

3.6.1. DUSP5, DUSP6, DUSP27 and heroin abuse

Heroin impairs synaptic plasticity in neural projections extending from the prefrontal cortex to the nucleus accumbens in animals trained to self-administer the drug. In human studies, the variant rs950302 of DUSP27 gene was significantly associated with heroin addiction vulnerability in African Americans (Nielson et al., 2010). This gene encodes a recently identified member of the cytosolic dual-specificity phosphatase family, which may be involved in energy metabolism. DUSP5 and DUSP6 mRNA expression increased by at least 1.4-fold in the medial prefrontal cortex of rats trained to self-administer heroin following 14 d of abstinence and the 90-minute extinction session compared to the saline-treated controls. The importance of drug-seeking behavior and memory of previous drug-taking sessions suggest that such genes may be essential for relapse (Kuntz-Melavage et al., 2009). DUSP5 mRNA expression level was significantly lower (0.67-fold) in the nucleus accumbens following heroin treatment than after saline treatment in mice (Seleman et al., 2014). This study indicated that DUSP5 might be linked to both heroin exposure as well as to drug-seeking behavior.

3.6.2. DUSP1, DUSP6 and methamphetamine abuse

DUSP1 and DUSP6 mRNAs were shown to be increased in the rat striatum, thalamus, cortex, striatum, and hippocampus after single methamphetamine administration (Ujike et al., 2002). Besides, another study found that DUSP1 mRNA and protein levels were increased in a range of rat brain regions, including the cortex, the striatum, and the thalamus, after administration of methamphetamine (Takaki et al., 2001). Elevated levels of DUSP6 mRNA have been observed in the cortex, striatum, and hippocampus of rats after acute methamphetamine administration (Takaki et al., 2001). Together these results suggest the involvement of DUSP genes not only in inferring vulnerability to substance abuse disorders but also in the development and exacerbation of this addictive disorder.

4. DUSP genes and neurological disorders

Accumulating evidence from the current literature on the link between DUSP genes and neurological disorders such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), and epilepsy, is described in the following section. The summary of the pathological implication of DUSP family members in neurological disorders is presented in Table 2.

4.1. Alzheimer’s disease (AD)

AD is characterized by progressive memory loss, impairments in cognition, and neuropsychiatric disturbances such as mood and personality changes, anxiety, and aggression (Scheltens et al., 2016). The prevalence of AD is 10–30 % in individuals over 65 years, with incidence doubling every ten years after 60 (Eratne et al., 2018; Masters et al., 2015). The pathophysiological hallmarks of AD are the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofilibrillary tangles of hyperphosphorylated-tau that lead to neuronal loss due to neurotoxic effects. So far, there is no cure for AD, and the current treatment options have been shown to only slow down its progression (Rafii, 2013).

4.1.1. DUSP1 and AD

The protein level of DUSP1 decreased in the hippocampus and temporal cortex of patients diagnosed with AD compared to aged matched healthy controls (Du et al., 2019). Similarly, DUSP1 protein levels were decreased in the hippocampus of APP/PS1 transgenic AD model mice at the age of 9 months compared to control mice (Du et al., 2019). DUSP1 inhibits the amyloidogenic process through the ERK/MAPK signaling pathway, and DUSP1 reduces Aβ generation and plaque formation and alleviates synaptic and cognitive impairments in APP/PS1 mice (Du et al., 2019). In PC12 cell culture, DUSP1 mitigates Aβ-induced apoptosis, oxidative stress, and neuroinflammation by inhibiting the JNK signaling pathway, thereby playing a neuroprotective role. From the animal and cell culture studies, DUSP1 alleviates amyloid beta-induced neurotoxicity (Gu et al., 2018). The results suggest that DUSP1 impairment facilitates the pathogenesis of AD, whereas the upregulation of DUSP1 plays a neuroprotective role to reduce Alzheimer related phenotypes (Du et al., 2019).
4.1.2. DUSP26 and AD

DUSP26 protein was observed to be elevated in the hippocampal of postmortem brain tissue of patients with AD compared to controls (Jung et al., 2016). In the APP-expressing HEK293/APP695 cell lines, overexpression of DUSP26 increased Aβ42 levels by twofold (Jung et al., 2016). In contrast, the enzymatically inactive mutant of DUSP26 failed to induce Aβ oligomers or APP processing. Thus, DUSP26 has been linked to Aβ generation and APP processing in these cell lines (Jung et al., 2016), thereby suggesting the involvement of DUSP26 in the pathophysiology of AD.

4.1.3. SSH1, SSH3 and AD

SSH1 protein level showed a 45% significant reduction in the frontal cortex of patients diagnosed with AD compared to healthy controls. This reduction was accompanied by unchanged pSSH1 levels, which led to the significant decrease of the pSSH1/SSH1 ratio indicative of the inactivation of SSH1 in human AD (Barone et al., 2014). Besides, SSH3 mRNA was shown to be differentially expressed in the hippocampus, the temporal and frontal cortex, as well as in the whole blood of patients diagnosed with AD in comparison with healthy controls (Wang and Wang, 2020).

SSH phosphatase dephosphorylates cofilin, and the reduced protein expression and inactivation of SSH1 were further accompanied by an increase in cofilin1 phosphorylation/inactivation in human and animal studies (Barone et al., 2014). Hyperphosphorylation of cofilin can result in tau pathology, which can be induced by Aβ oligomers (Kang et al., 2011).

4.1.4. DUSP22 and AD

Analyses of blood/brain samples indicated that methylation of the region in DUSP22 correlated linearly and powerfully with the Braak stages of neuro-pathology, an index of AD progression (Pearson correlation coefficient R = 0.95, P < 0.05) (Sanchez-Mut et al., 2014). In the hippocampus of patients diagnosed with AD, hypermethylation of the DUSP22 promoter and decreased protein expression of DUSP22 as compared to age-matched controls have been reported (Sanchez-Mut et al., 2014). Reductions in DUSP22 levels may lead to increased tau phosphorylation due to weaker inhibitory control of protein kinase A-mediated tau-phosphorylation, at least as suggested by findings in neuronal cell lines (Sanchez-Mut et al., 2014). Besides, it has been found in SK-N-BE(2) cell culture studies that are depleting DUSP22 through small hairpin RNA’s resulted in a higher survival capability than cells with control or healthy and overexpression of DUSP22 (Sanchez-Mut et al., 2014). It would be interesting for future studies on AD pathophysiology to establish the regulatory role of DUSP22 in tau phosphorylation, Aβ accumulation, and neuronal death AD.

4.1.5. PTEN and AD

AD is associated with excessive recruitment of PTEN into synapses, leading to aberrant synaptic depression (Knafo and Esteban, 2017). It has furthermore been observed that layer III of the temporal cortex in patients with AD showed a 15% loss of PTEN immunoreactive neurons compared to controls, while the majority of the layer III temporal cortex were PTEN immunoreactive in control cases (Rickle et al., 2006). PTEN protein levels decreased in the AD temporal cortex compared with matched controls, and PTEN levels have been negatively correlated with the severity of neurofibrillary pathology or senile plaques (Griffin et al., 2005).

It has been observed in AD, that PTEN delocalizes from the nucleus to the cytoplasm and intracellular neurofibrillary tangles in postmortem brain tissues (Sonoda et al., 2010). The nuclear PTEN immunoreactivity reduced in neurons of the CA1, subiculum, and entorhinal cortex of AD cases, while the PTEN immunoreactivity increased in apical dendrites in the CA1 and subiculum in AD cases compared with control (Griffin et al., 2005). However, in the temporal cortex, PTEN protein levels were not significantly different in either nucleus or membrane fractions in AD postmortem brains and controls (Rickle et al., 2006). Instead, the ratio of Ser380 p-PTEN / total PTEN protein reduced in temporal cortical homogenates in AD compared to control (Rickle et al., 2006), which indicated reduced PTEN phosphorylation at residue Ser380 in AD. Decreased PTEN and increased tau phosphorylation were evident in frontal cortex brain slices of AD (Zhang et al., 2006). This suggests that PTEN phosphorylation is involved in AD pathology and that PTEN dynamics in AD brain might be region dependent.

PTEN contributes to AD pathology in animal and cell culture models (Frere and Slutsky, 2016). Overexpression of PTEN induces synaptic depression, similar to Aβ-induced depression in transgenic mice (Knafo et al., 2016). Additionally, the overexpression of the PTEN protein in Chinese hamster ovary cells reduces tau phosphorylation (Kerr et al., 2006). Another study demonstrated that overexpression of PTEN decreases the formation of tau aggregates in COS-7 cells.

In contrast, the phosphatase-null or inactive PTEN increases tau aggregation in rat cortical primary neurons transfected with a mutant form of PTEN (Zhang et al., 2006). The loss of PTEN causes neurodegeneration through the hyperphosphorylation of tau and neurofilaments in mouse cerebellar neurons (Naveem et al., 2007). However, induction of PTEN is accompanied by okadaic acid-induced tau phosphorylation, while the knockdown of PTEN reduced tau hyperphosphorylation in SH-SY5Y neuroblasts cells, and increased cell proliferation and survival. Inhibition of PTEN reduces tau phosphorylation in SH-SY5Y neuroblastoma cells (Chen et al., 2012). Furthermore, inhibition of PTEN via intracerebroventricular delivery of a PTEN inhibitor, VO-OHpic, rescued Aβ42-induced impairment in both basal synaptic transmission and LTP, as well as spatial learning tasks, in APP/PS1 transgenic mouse model of AD (Knafo et al., 2016).

The PDZ-binding domain of PTEN is central to Aβ-induced synaptic toxicity and cognitive dysfunction (Knafo et al., 2016). Deletion of this PDZ-binding domain results in resistance to Aβ toxicity in postsynaptic neurons (Knafo et al., 2016). Overexpression of PTEN reduced tau phosphorylation in Chinese hamster ovary cells (Kerr et al., 2006). Thus, taken together, these findings indicate that PTEN may be centrally involved in moderating or mediating AD’s pathophysiology.

4.2. Parkinson’s disease (PD)

PD is a progressive disease with motor and non-motor symptoms, which consist of slow movements, tremors, rigidity, impaired balance during walking, various disturbances in autonomic functions with orthostatic hypotension, constipation, sleep disturbances, and a spectrum of neuropsychiatric symptoms (Sveinbjornsdottir, 2016). The cause of PD is unknown but is believed to involve both genetic and environmental factors (Kouli et al., 2018). Parkinson’s disease affects 1% of the population above 60 years old and is more frequently prevalent in men than women (Tynsae and Storstein, 2017). The main hallmark of PD are Lewy bodies and the degeneration of dopaminergic neurons in the substantia nigra. However, recent findings suggest that PD’s pathophysiology is heterogeneous. Other protein aggregates like α-synuclein, DJ-1 (Waragai et al., 2010), tau, and β-amyloid also play a role (Parnetti et al., 2013) in the onset and progression of the disease.

4.2.1. PTEN and PD

Protein level of nuclear PTEN has been shown to be significantly increased by 5-6-fold in the substantia nigra of PD brain compared to the age-matched controls. PTEN downstream regulators, PI3K regulatory subunit p85, PIP3, and Akt1/2/3 protein levels decreased by two-fold in nuclear of substantia nigra region of PD brain samples compared to the age-matched controls (Sekar and Taghibiglou, 2018).

Downregulation of PTEN inhibits elevated levels of intracellular reactive oxygen species and neuronal death in rat hippocampal and in human dopaminergic SH-SY5Y neurons caused by neurotoxin 1-methyl-4-phenylpyridinium iodide toxicity which mimic Parkinson’s disease (Zhu et al., 2007). PTEN deletion in adult dopaminergic neurons protects
these neurons from 6-hydroxydopamine (6-OHDA) neurotoxicity and restores striatal dopamine levels in mouse models of PD (Domanskyi et al., 2011).

PTEN has been involved in response to DNA damage repair in PD (Ogino et al., 2016). Specific defects in DNA impact the dopaminergic system and are associated with PD pathology in both cell and animal models (Sepe et al., 2016). Thus, PTEN plays a role in DNA damage in PD.

4.2. DUSP1 and PD

There are currently few studies on DUSP1 in patients with PD. However, one study reported decreased DUSP1 mRNA expression in the dorsolateral prefrontal cortex of idiopathic PD patients (Renton, 2010).

In cell culture studies using neuronal PC12 cells, Serial Analysis of Gene Expression-based study showed that acute (8 h) exposure to 6-OHDA, a dopaminergic neurotoxin commonly used to induce PD-like symptoms in experimental studies (Grotty et al., 2008; Walsh et al., 2011), induced a 35-fold increase of DUSP1 mRNA levels (Iby et al., 2005). Moreover, DUSP1 mRNA was transiently upregulated in the SN 4 days post-6-OHDA administration in the medial forebrain bundle lesion model in rats (Collins et al., 2014). Besides, DUSP1 mRNA expression was increased in rat striatum treated with 6-OHDA followed by injection of SKF38393, a selective dopamine receptor D1 agonist (Berke et al., 1998). DUSP1 has been shown to promote the growth and elaboration of dopaminergic neuronal processes, protecting them from the neurotoxic effects of 6-OHDA (Collins et al., 2013). This study indicates that DUSP1 may have a neuroprotective effect, at least in PD rodent models (Collins et al., 2013).

4.3. Huntington’s disease (HD)

HD is a devastating heritable neurological disease characterized primarily by progressive motor and cognitive impairments, as well as psychiatric symptoms, including affective disorder symptoms that often precede other symptoms (Julien et al., 2007). HD is typically induced by a highly polymorphic CAG trinucleotide repeat expansion in exon-1 of the gene encoding the huntingtin protein (Bano et al., 2011). Huntington protein is widely expressed during development and exhibits a complex and dynamic distribution within cells (Schulte and Littleton, 2011). Besides genetic factors, cerebral vitamin B5 deficiency is a potential cause of HD (Patassini et al., 2019). Most European populations show a relatively high prevalence (4–8 per 100,000), but HD is notably rare in Finland and in Japan (Harper, 1992). The underlying neuropathology is characterized by neuronal loss, striatum microglial activation, and neuro-inflammation within the striatum (Novak and Tabrizi, 2011; Reiner et al., 2011). Many genetically modified animal models of HD recapitulate some of the pathophysiological features observed in humans, but many drug designs based on animal models of HD have failed in clinical trials (Menalled and Brunner, 2014).

4.3.1. DUSP1 and HD

Reduced DUSP1 levels were observed in animal models of HD (Collins et al., 2015), and enhancing DUSP1 expression has been shown to significantly reduce neuronal cell death in HD animal models induced by lentiviral infection and expression of a mutated huntingtin gene. In a cell culture study comprising primary striatal rat neurons exposed to a pathological construct comprising of the N-terminal fragment of polyglutamine-expanded huntingtin (Htt171–82Q), overexpression of DUSP1 inhibited apoptosis (Taylor et al., 2013).

This DUSP1-mediated neuroprotection has been suggested to be dependent on the activity of phosphatases and occur through direct regulation of JNKs and p38 (Taylor et al., 2013). Mutant DUSP1 selectively targeting JNK or p38, preserves significantly fewer NeuN-positive cells in primary striatal neurons exposed to Htt171–82Q fragments than in wild-type DUSP1 primary neuron HD models, indicating that dual targeting of JNK and p38 by DUSP1 may exert neuroprotective effects (Taylor et al., 2013). These findings suggest that this DUSP1 regulated pathway may represent a novel candidate as a therapeutic target in HD.

4.3.2. PTEN and HD

Elevated PTEN expression, together with amplification of BDNF signaling, seems to result in neuroplasticity abnormalities in the indirect pathway of the spiny projection neurons from brain slice of the BACHD mouse model and Q175 knock-in mouse model of HD (Plotkin and Surmeier, 2014). Furthermore, plasticity and LTP aberrations were rescued by inhibiting PTEN in indirect pathway spiny projection neurons of a transgenic HD mouse model (Plotkin et al., 2014).

PTEN deletion combined with PTPN11 deletion in mice, exhibited increased levels of apoptotic cells in the striatum. Thus, PTEN and p53 prolong neuronal survival upon nucleolar disruption (Kreiner et al., 2013). The upregulation of PTEN impairs kinase mammalian/mechanistic target of rapamycin function in medium spiny neurons (Kreiner et al., 2013).

Future studies investigating PTEN regulation will contribute to understanding the etiology of HD and to the development of new therapeutic strategies targeting PTEN.

4.4. Epilepsy

Epilepsy is characterized by recurrent unprovoked seizures and accounts for the highest disability-adjusted life year rates among neurological disorders (Beghi, 2016). Epilepsy is caused by various factors, including genetic influence, head trauma, brain disease like brain tumors or strokes, infectious diseases, prenatal injury, or developmental disorders. Epilepsy affects more than 65 million people worldwide (Singh and Trevick, 2016). Gliosis, imbalance of ion and water homeostasis, increased extracellular glutamate, altered neural circuits, damaged blood-brain barrier are omnipresent in epilepsy in animal models or patients (Patel et al., 2019). Antiepileptic drugs are the first-line treatment, but alternative treatments, including surgical resection of the seizure focus, ketogenic diets, vagus nerve stimulators, and implantable brain neurostimulators are available for patients with seizures that are not controlled with medication (Liu et al., 2017).

4.4.1. Lafortin and Lafora disease (LD)

LD is a progressive neurological disorder characterized by intractable myoclonic seizures, emotional disturbance, and cognitive decline. Hallmarks of this disease are primarily attributed to the accumulation of hyperphosphorylated insoluble poly-glucosan called Lafora bodies (LBs). LBs are caused by mutations in either the atypical DUSP Laforin, EPM2A, or NHLRC1. Lafortin genes encode phosphatases that dephosphorylate glycogen. Glycogen, a potent energy storage molecule in animals, is degraded by glycogen phosphorylase and glycogen debranching enzyme. In the brain, the accumulation of glycogen in neurons can lead to neuronal loss, locomotive defects, and neurodegeneration in mice and Drosophila. As such, a reduction of glycogen synthesis may prevent LB formation and subsequent neurodegeneration and seizure susceptibility, thus preventing LD progression (Duran and Guinovart, 2015; Kecmanovic et al., 2016; Roach, 2015).

4.4.2. PTEN and epilepsy

PTEN mutations have been observed in patients with epilepsy and a variety of comorbidities, including cancer (de Souza et al., 2015; Schick et al., 2006). PTEN sequence analysis performed on a case where the individual suffered from both epilepsy and Cowden syndrome, an
inherited disorder characterized by noncancerous growths, identified a heterozygous missense mutation in PTEN (Ueno et al., 2019). Resection of high-grade glioma tissue from patients with seizures exhibited reduced PTEN expression compared to patients with glioma without seizures (Yang et al., 2016).

PTEN mutations have also been reported and used in several animal models of cortical dysplasia, which is also a contributor to epilepsy in adults (Elia et al., 2012). For instance, the inhibition of PTEN rescued neuronal death in a mouse model of temporal lobe epilepsy, implying an excitotoxic role for PTEN. This inhibition has also been shown to exert potent anti-inflammatory and neuroprotective effects (Grande et al., 2014). These results confer additional support to the role of PTEN in neuronal dysfunction.

4.4.3. DUSP1 and epilepsy

A study on kainic acid-induced limbic seizures in rats reported that DUSP1 protein expression was transiently induced in the dentate granule cells of the hippocampus, outer layers of the neocortex, and neurons of the lateral nucleus of the bed of the stria terminalis in rat with the seizures as compared to untreated controls (Gass et al., 1996). On a subcellular level, DUSP1 colocalizes with its substrate, MAP kinase, in neuronal nuclei, which has been linked to inhibition of the seizure response in an animal model of temporal lobe epilepsy (Gass et al., 1996; Tai et al., 2017). Given these results, DUSP1 induction seems to have a partial role in the inhibition of MAP kinase activity following seizures.

5. Conclusions

This review provides an extensive overview of research findings of the role of several DUSP genes and their involvement in the onset and development of certain mental and neurological disorders. The body of literature on DUSP genes does show the great diversity of biological processes in which DUSP genes are involved, and it is therefore not surprising that genomic variations in DUSP genes have been linked to several mental and somatic disorders.

It is furthermore noteworthy that the first wave of epigenetic studies has identified epigenetic changes in particularly one DUSP gene, i.e., DUSP22, to be linked to a range of mental as well as neurological disorders, i.e., altered methylation in the heterozygous missense mutation in PTEN (Ueno et al., 2019). Resection of an inherited disorder characterized by noncancerous growths, identified a subset of cyclin-dependent kinase (Cdk) sites containing phosphoserine. J. Biol. Chem. 287, 1662–1668.

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