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PTPRD: neurobiology, genetics, and initial pharmacology of a pleiotropic contributor to brain phenotypes

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Abstract

Receptor-type protein tyrosine phosphatase, receptor type D (PTPRD) has likely roles as a neuronal cell adhesion molecule and synaptic specifier. Interest in its neurobiology and genomics has been stimulated by results from human genetics and mouse models for phenotypes related to addiction, restless leg syndrome, neurofibrillary pathology in Alzheimer's disease, cognitive impairment/intellectual disability, mood lability, and obsessive-compulsive disorder. We review PTPRD's discovery, gene family, candidate homomeric and heteromeric binding partners, phosphatase activities, brain distribution, human genetic associations with nervous system phenotypes, and mouse model data relevant to these phenotypes. We discuss the recently reported discovery of the first small molecule inhibitor of PTPRD phosphatase, the identification of its addiction-related effects, and the implications of these findings for the PTPRD-associated brain phenotypes. In assembling PTPRD neurobiology, human genetics, and mouse genetic and pharmacological datasets, we provide a compelling picture of the roles played by PTPRD, its variation, and its potential as a target for novel therapeutics.

Graphical abstract

Receptor-type protein tyrosine phosphatase, receptor type D (PTPRD) is a neuronal cell adhesion molecule and synaptic specifier that has possible roles in addiction, Alzheimer's disease, cognitive impairment, mood lability, and obsessive-compulsive disorder. This article reviews PTPRD's discovery, gene family, candidate binding partners, phosphatase activities, brain distribution, human genetic associations with nervous system phenotypes, and mouse model data relevant to these phenotypes.

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Competing interests

The authors declare no competing interests.

Keywords

cell adhesion molecule; cocaine; addiction; neurofibrillary tangles; restless leg syndrome; obsessive compulsive disorder; neurotherapeutics

Context

Classical genetic studies support both genetic and environmental influences on vulnerability to virtually all common brain-based disorders and traits [1]. Molecular genetic association studies now propose a modest number of oligogenic and large numbers of polygenic influences on these disorders. For each disorder or trait, the genetic influences thus typically arise from variations in a group of genes. There frequently are disease-associated variants in several distinct regions of each gene. There often is pleiotropy: effects of common functional variations that are sufficient to alter one brain-based phenotype often alter other phenotypes as well.

Here, we focus on receptor type protein tyrosine phosphatase, receptor type D (PTPRD) and the roles for its variants in brain, behavioral, and neurological disorders. We review this gene and some of the likely roles of PTPRD and its variants in brain. Data now support a working hypothesis that common and rarer PTPRD variants make pleiotropic contributions of differing strength to a number of brain phenotypes and disorders. Understanding the genomics and genetics of PTPRD is thus important for understanding the biology of interesting phenotypes for substance use disorders, restless leg syndrome, mood lability, cognitive abilities, and the neurofibrillary neuropathology of Alzheimer's disease. Substance disorder phenotypes include dependence (polysubstance, opiate, alcohol), rewarding properties (stimulants), effects experienced during the first drinking sessions (alcohol), and ability to quit smoking (see references below). We thus review PTPRD, place its function and its variation in the context of these genetic findings, and describe the implications of these findings for improved understanding of pathogenesis and novel therapeutic opportunities. The recent elucidation of the actions of a novel small molecule inhibitor of PTPRD phosphatase [2] adds support for PTPRD roles in addiction-related phenotypes and solidifies PTPRD as an emerging target for novel therapeutics for addiction and possibly other PTPRD-associated disorders.

What is PTPRD?

Discovery

PTPRD was identified in 1990 by the low stringency screening of a human cDNA library with a *Drosophila* receptor-type protein tyrosine phosphatase (RPTP) hybridization probe [3]. PTPRD contains extracellular immunoglobulin and fibronectin III domains, a transmembrane domain, and D1 and D2 intracellular phosphatase-like domains (Fig. 1). The D1 phosphatase domain is catalytically active (Fig. 1). PTPRD mRNAs and protein were identified in specific brain regions [4–6] and in the kidney. Human RNAseq data has now identified the highest expression in brain, followed by kidney, ovary, placenta, and intestine [7]. Overall, the brain expresses moderate levels of PTPRD, with reads per kilobase per

million (RPKM) values of about 18, compared to 90 for the mRNA encoding the very abundant brain protein THY1. The working hypothesis that PTPRD is one of the 400–500 genes that encode a cell adhesion molecule/synaptic specifier [8–9] initially arose from PTPRD's homologies with other genes that serve these functions. This hypothesis has received substantial additional support, as we describe below.

PTPRD gene and protein

The *PTPRD* gene is found on the short arm of human chromosome 9 (9p), at 8,314,246 to 10,612,841 basepairs (build 109, NC_000009.12). Its 5' transcriptional start is centromeric to its telomeric 3' last exon [10]. There are many splicing and other variations; at least 50 *PTPRD* mRNA isoforms are described. As many as 49 exons that encode portions of mRNA-sense transcripts and two that encode natural antisense transcripts are annotated [11]. The canonical *PTPRD* gene model contains 1912 amino acids, with a predicted mass of 215 kDa [12]. Amino acids 24–114, 126–224, and 236–318 are immunoglobin-like (Ig) sequences; residues 325–415, 420–516, 518–607, 612–709, 714–822, 823–916, 921–1016, and 1020–1106 are fibronectin type III (FNIII) domains; and amino acids 1357–1612 and 1644–1903 represent the active D1 and inactive D2 protein tyrosine phosphatase–like sequences, respectively. The region of amino acids 180–189 is postulated to interact with IL1RAPL1 (see below). Functionally important splicing variants include those that include or exclude miniexons A and B and encode amino acids 181–189 and 227–230, respectively. Alternate splicing at the regions that encode fibronectin domains 4 to 7 yields long (Ig1–3, FNIII1–8) or short (Ig1–3, FNIII1–3,8) isoforms that are predominantly expressed postnatally in most brain regions [13].

PTPRD mRNAs include several that encode only extracellular sequences and might provide decoy soluble translation products. Such soluble isoforms could conceivably compete for binding interactions that might otherwise occur between PTPRD-containing membrane-bound homo- or hetero-oligomers [14].

Gene family

PTPRD is a member of a three-gene DSF mammalian subfamily of receptor type protein tyrosine phosphatases that also includes PTPRS (also known as PTPR sigma, PTPσ, or PTPRσ) and PTPRF (also known as leukocyte related antigen or LAR). Single *Drosophila* (*Dlar*) and *C. elegans* (*ptp-3*) genes [3, 15] encode homologs of these DSF family members, helping to explain the success of the homology cloning strategy that initially identified PTPRD.

Functions: Extracellular domains and binding partners

PTPRD's immunoglobulin and fibronectin extracellular architecture (Fig. 1) suggested roles as a cell adhesion molecule and synaptic specifier. Wang and Bixby's results from PTPRD expression in cultures support cell adhesion molecule roles for homophilic PTPRD–PTPRD interactions [16]. Embryonic neuronal subpopulations from forebrain, retina, ciliary ganglion, and cerebellum bound to PTPRD-containing substrates and elaborated many more neuronal processes when plated on PTPRD-containing substrates, supporting positive neurotrophic and adhesive roles for PTPRD–PTPRD interactions. While this important data has not been

substantially extended, the results provide significant evidence that homophilic PTPRD–PTPRD interactions can promote neuronal process growth.

In addition to the evidence for PTPRD homomeric binding, there is support for other candidate physiological PTPRD ligands (Table 1). Most evidence comes from studies of PTPRD interactions with the SLIT- and NTRK-like (SLITRK) proteins [17–18]. Takahashi *et al.* screened candidate proteins for interactions with SLITRK3 and found that it bound to PTPRD, though not to neurexins, NCAM, CHL1, neurofascin, PTPRF, NTRK2 (also known as TRKB), or CNTNAP1 (also known as CASPR)). Each of the six SLITRKs displayed an affinity for PTPRD. Cells that express either SLITRK2 or −3 caused aggregation of PTPRD and of the vesicular GABA transporter, a marker for synaptic specialization, in contacting,expressing cells [18]. Crystallographic structures of PTPRD/SLITRK1 and of PTPRD/SLITRK2 complexes are now available. These structures point to key roles for a PTPRD splice variant that includes amino acids encoded by miniexon B, lying between immunoglobulin domains 2 and 3, in facilitating strong PTPRD binding to SLITRK's leucine-rich repeat domain [17, 19].

Binding to PTPRD was also detected when investigators sought ligands for interleukin 1 receptor accessory protein (IL1RAP, also known as IL-1RAcP) and interleukin 1 receptor accessory protein like 1 (IL1RAPL1). These proteins contain extracellular immunoglobulin domains and single transmembrane regions, and display substantial expression in the brain. Testing for candidate ligands of IL-1RAcP and IL1RAPL1, including neurexins, SynCAMs, synaptic adhesion-like molecules (SALMs), and receptor-type protein tyrosine phosphatases, identified good interactions only with PTPRD [20]. This binding again depends on PTPRD miniexon splicing. Crystallography confirms complexes between PTPRD immunoglobulin domains and the immunoglobulin domains of IL1RAPL1 and IL1RAP, again in a miniexon-dependent fashion [21].

Attention to PTPRD interactions with LRRC4B (also known as NGL-3) came from extensions of work that identified functional interactions between PTPRF and LRRC4B/NGL-3 [22]. Extracellular domains from PTPRD and expression constructs limited to PTPRD's extracellular fibronectin domains I and II both interacted with LRRC4B in binding assays. However, these PTPRD sequences were weaker NGL-3 binders than analogous PTPRF or PTPRS sequences. These PTPRD sequences also failed to induce aggregation of the postsynaptic marker PSD-95, although PTPRF sequences triggered such aggregation in the same assay.

SALMs, especially those that are products of the *LRFN1* and *−5* genes, can also serve as binding partners of DSF family members, including PTPRD [23–26].

There are reported interactions between PTPRD and cytoplasmic proteins, including PPFIA1 [5]. However, follow-up work provides better evidence of interactions with other DSF family members than with PTPRD. Reported interactions of MTSS1 with cytoplasmic PTPRD sequences and actin filaments provide a plausible direct link between PTPRD and neuronal process formation [27]. However, evidence for the effects of altered MTSS1

expression on neuronal process formation comes largely from studies of cerebellar neurons, which do not substantially express PTPRD [28].

Functions: Intracellular domains and phosphatase activity

PTPRD's physiological functions are likely to derive from its dephosphorylation of phosphotyrosine residues in a group of cytoplasmic proteins. Its D1 phosphatase domain, proximal to the membrane, mediates this phosphatase activity. While the D2 domain displays sequence homology to phosphatases, it is largely inactive enzymatically but binds to and downregulates the activity of the D1 domains of PTPRD and several other related receptor type protein tyrosine phosphatases (especially in *in vitro* studies with PTPRA, PTPRE and PTPRS) [29–30].

Analysis of the selectivity of PTPRD's D1 phosphatase domain reveals: (1) lack of a highly specific consensus sequence for the amino acids that surround the phosphotyrosine; (2) preference for large hydrophobic amino acids, especially adjacent (−1) to the phosphotyrosine; (3) preference for acidic residues in the vicinity of the phosphotyrosine; (4) aversion to basic residues at these locations; (5) relatively lower affinity for phosphotyrosine substrates when compared to the affinities of other protein tyrosine phosphatases; and (6) good catalytic activities (k_{cat} values) that are close to those of other protein tyrosine phosphatases and thus the potential to act as a highly efficient enzyme with a high k_{cat}/K_M ratio [31].

The selectivity of the PTPRD phosphatase is likely reflected in the sequences of 45 *C. elegans* proteins whose phosphotyrosine residues are conserved in human homologs. Phosphorylation of these *C. elegans* proteins is altered with knockout of *ptp-3* [32] (A Pandey, personal communication, 2015).. PTPRD-mediated changes in the phosphorylation of STAT3 tyrosine 705 alter STAT3's abilities to homodimerize, move into the nucleus, and change transcription of other genes [33]. Altered tyrosine phosphorylation of FYN and SRC in homozygous *Ptprd* knockout mice has been related to differential elaboration of basal dendrites by layer V cortical pyramidal cells that normally express PTPRD [34].

As we discuss below, inhibition of the PTPRD D1 phosphatase domain provides an apparently successful route to modulating PTPRD activity. It is also theoretically possible to increase phosphatase activity of PTPRD by reducing the inhibitory effect of D2 domain binding to the active D1 phosphatase domain.

PTPRD distribution in the brain

Reports of the brain distribution of PTPRD mRNA or immunoreactivity (e.g. Ref. [35]) fit well with Allen Brain Atlas images that describe the largely neuronal distribution of *PTPRD* mRNA in a number of brain regions whose function can often be related to human phenotypes associated with *PTPRD* variation [36]. These data in turn mesh reasonably well with available single cell RNAseq datasets. We can thus describe pictures of the multifocal distribution of *PTPRD* mRNA and of the brain circuits that are likely to display altered activity when PTPRD function changes (Table 2).

We can relate some prominent neuronal *PTPRD* mRNA expression patterns to neurotransmitter phenotypes in the fore- and midbrain. Likely cholinergic neurons of the nucleus basalis, diagonal band, septum, striatum/accumbens, and reticular formation express high densities of *PTPRD* mRNA hybridization signal. Likely dopaminergic neurons of the substantia nigra pars compacta and the ventral tegmental area express *PTPRD* mRNA with moderately high hybridization signal densities. Human RNAseq data from pigmented, presumed dopaminergic neurons from ventral midbrain confirms this dopaminergic *PTPRD* mRNA localization [37].

Other areas of prominent *PTPRD* mRNA expression are easiest to characterize based on their relatively high levels of *PTPRD* mRNA hybridization in many or even most neurons. Most neurons of the reticular thalamic nucleus and specific olfactory bulb (inner plexiform) and pyriform cortex (layer 2) layers express relatively high densities of *PTPRD* mRNA.

Expressing neurons are also scattered in a number of other brain regions. There are scattered expressing neurons in several hypothalamic nuclei, in hippocampus, and in amygdaloid nuclei, especially in cortical and lateral amygdala. RNAseq data confirm higher hippocampal expression in CA2 neurons [38]. This data supports levels of expression in hippocampal pyramidal neurons that lie in the highest decile of levels of expression for all cell adhesion molecules annotated by these authors [9].

Within neocortical regions, scattered neurons, especially in laminae II-III and V-VI, show moderate *PTPRD* mRNA hybridization densities. RNAseq data from the visual cortex [39] support *PTPRD* colocalization [40] with neurons containing vasoactive intestinal peptide, L4 and L5 (while somatostatin-expressing neurons express much less PTPRD). However, there is also significant *PTPRD* expression in opalin-expressing cells, suggesting some oligodendroglial expression that has also been demonstrated elsewhere [41]. Such expression might modulate neuronal–oligodendroglial interactions in ways that have been supported by studies of other cell adhesion molecules [42].

Within the brainstem, there is moderately dense *PTPRD* mRNA hybridization in cholinergic neurons throughout, including parabigeminal and cranial nerve motoneurons. There is dense expression in olivary nuclei (especially inferior olive). There is modest expression in some dorsal raphe and locus coeruleus neurons and in scattered neurons in other brainstem regions.

In spinal cord, there is dense expression in motoneurons and significant expression in scattered dorsal horn neurons.

While it is not possible to comprehensively summarize these expression patterns in a simple fashion, patterns of expression do provide emphasis on (1) dopamine and acetylcholine systems that are implicated in reward, mnemonic, and motor functions in ways that involve substantial subcortical–cortical (and hippocampal) interactions; (2) thalamo-cortical interactions mediated through reciprocal reticular thalamic–cortical interactions; (3) likely roles in cortical interconnectivities; (4) roles in the strong cerebellar connections that emanate from the inferior olive; and (5) brainstem and spinal cord motoneuronal pools. PTPRD homomeric and heteromeric interactions could play differential roles in these

circuits. We thus describe highlights of the distributions of expression of several candidate heteromeric PTPRD ligands below.

Brain distributions of other candidate PTPRD ligands

The mouse brain distribution of *IL-1RAcP* mRNA appears highest in the hippocampus, especially the dentate gyrus. There is moderate expression in many thalamic nuclei [43]. There is also hybridization signal in pyriform cortex and in ventral midbrain areas, including the substantia nigra.

There is more hybridization signal for *IL1RAPL1* mRNA, with prominent expression in many areas of the olfactory bulb and pyriform cortex, cerebral cortex (especially layers II and III), hippocampus (especially dentate gyrus), and mammillary body. There is moderate expression in cells of the striatum, many thalamic nuclei, hypothalamus, areas of the brainstem, including modest to moderate expression in ventral midbrain, and many spinal cord dorsal horn and motoneurons [44].

SLITRKs are also expressed in interesting brain patterns. We focus here on SLITRK3 since there is better documentation of its role as a PTPRD binding partner, as well as SLITRK1 and −2. *SLITRK3* mRNA expression is abundant in many brain regions. *SLITRK3* mRNA is expressed in the cerebral cortex (especially layer II), hippocampus (especially CA1/2 and dentate gyrus), olfactory bulb and tract, many thalamic regions, hypothalamic regions, midbrain regions (including ventral midbrain and red nucleus), and multifocal regions in the pons and medulla [45].

Much of the expression of *SLITRK1* mRNA overlaps with the patterns of expression of *PTPRD* mRNA, including expression in likely cholinergic neurons of the basal forebrain, striatum, and brainstem motor nuclei, and in dopaminergic midbrain neurons [46]. There is also abundant expression in the olfactory and pyriform cortex, cerebral cortex (especially layers II-III and V-VI), septum, many thalamic regions (including anterodorsal nucleus), hypothalamic regions (including supraoptic, paraventricular, and suprachiasmatic nuclei), hippocampal regions (especially dentate gyrus), and most amygdala regions.

SLITRK2 mRNA expression is also highest in the pyriform cortex, olfactory regions, and hippocampus (especially dentate gyrus) [47]. There is again expression in presumed cholinergic neurons in the basal forebrain and brainstem, with moderate levels of expression in cortical layers I–VI, and thalamic, hypothalamic, and amygdaloid nuclei.

PTPRD genomic variation and *PTPRD* associations with human disorders and phenotypes

PTPRD *genomic variation and association with levels of* PTPRD *brain mRNA expression and possible mechanism*

A recent search of the dbSNP database identifies 700,229 *PTPRD* single nucleotide polymorphism (SNP) variants, with 56,540 involving short insertion or deletion variants. Of these, 1,346 are missense/nonsense or result in a premature stop codon. Though minor allele frequencies (MAFs) have not been determined for most, only a relatively few missense

SNPs are known to display average MAFs above 2%. The SNP rs10977171 changes amino acid (aa) 444 in PTPRD's second fibronectin type III domain from Q to E. The MAF of rs10977171 is above 0.11 in Asian samples but only 0.001 in African samples [48]. The SNP rs35929428 changes aa 995 in the seventh fibronectin domain from R to either G or to C, with the MAF again lower in African samples (0.005) than in samples with European or Asian ancestries (MAF 0.08–0.14) [49]. We are not aware of any experimental or *in silico* studies that elucidate the functional consequences of these relatively common missense variations. Nevertheless, their relative proximity (22,268 basepairs apart) and the similar distributions of their MAFs in different populations do suggest that they may mark an extended haplotype. The database of genomic variants lists 39 gold standard copy number variants (CNVs), of which all but two are deletions [50].

There is modest evidence for parent-of-origin effects at the locus, and thus possible imprinting. The associations between SNPs in *PTPRD* introns 7–9 with a metabolic trait, triglycerides in medium low density lipoproteins, display significantly less variation in homozygotes than in heterozygotes, one way in which parent-of-origin effects can manifest themselves [51].

We have sought evidence for *cis* effects of human *PTPRD* haplotypes on levels of *PTPRD* mRNA expression in postmortem human cerebral cortex samples. There are robust individual differences in levels of expression of *PTPRD* mRNA in these brain samples [52], with 70% differences in levels of *PTPRD* expression in brains from carriers of major versus minor alleles at an intron 10 SNP, rs2381970 ($P = 0.002$, remaining significant following Bonferroni correction; Fig. 2). There was also a nominal significance of $P \leq 0.05$ for association with levels of *PTPRD* mRNA expression with SNPs rs4626664 (intron 9, $P = 0.04$) and rs1975197 (intron 12, $P = 0.05$; see discussion below of restless leg syndrome), as well as rs7470838 (intron 3, $P = 0.04$), rs2296094 (intron 36, $P = 0.01$), and rs10115782 (intron 39, $P = 0.003$).

These data support the possibility that *cis*-regulatory elements lie in several *PTPRD* genomic regions. The data do not indicate that any major toxicity is caused by the 70% differences in levels of human *PTPRD* expression noted above [52]. The data also raise questions about genomic mechanisms, such as balancing selection, that might maintain such common, functional *PTPRD* gene variants in the population. Analyses of genomic variants do identify signatures of balancing selection [53]. *PTPRD* variants, including a SNP in intron 9, display associations with human fecundity [54] that could plausibly contribute to balancing selection at this locus.

Association of PTPRD *genomic markers with addiction phenotypes*

Addiction phenotypes provided the first evidence for polygenic association with *PTPRD* variants [55] (Fig. 2). *PTPRD* has now been identified in human genome-wide SNP and CNV association studies [56–58] of several addiction-related phenotypes, usually by clusters of nearby SNPs or CNVs that each display association with a nominal significance of $10^{-8} < P < 10^{-2}$. Such associations were first identified with the 10K SNP array study of associations with polysubstance dependence (1 of 38 SNPs reported; now known to map to the 3' flanking region of *PTPRD*) [55] and continued with studies that included 600K SNP array

associations with polysubstance dependence (1 of 119 genes) [59], 1M SNP array associations for illegal substance abuse in African-American subjects from two independent samples (1 of 97 genes) [60], 1M SNP array studies of alcohol use disorder in an epidemiological sample (1 of 9 genes identified in both European- and African-American samples) [61], and genes identified by both SNP and CNV associations for opiate dependence (1 of 3 genes) [62].

The ability to quit smoking in clinical trial settings displayed *PTPRD* associations in several studies (1 of 33 genes in Ref. [63] and 1 of 116 genes in Ref. [64]).

PTPRD was identified by one of the top two GWAS peaks in a study of acute responses to amphetamine administered in a research laboratory setting [65] (A Hart and A Palmer, personal communication, 2014). It was one of 156 genes identified by association with responses to drinking during the “first five” occasions for alcohol consumption [66].

PTPRD variants that reduce expression appear to be associated with reduced vulnerability to substance use disorder phenotypes. Rare CNVs likely to reduce *PTPRD* expression are more frequent in controls than in opiate-dependent individuals [62]. Common haplotypes marked by the SNPs associated with lower *PTPRD* brain expression are associated with reduced addiction vulnerabilities [52]. Some of the $10^{-8} < P < 10^{-2}$ SNP associations with addiction phenotypes do lie in regions of the *PTPRD* locus in which genomic markers have not been tested for associations with levels of *PTPRD* mRNA expression or do not display such associations.

Association of PTPRD *genomic markers with restless leg syndrome*

Variation at the *PTPRD* locus has provided robust, oligogenic associations with vulnerability to restless leg syndrome (RLS; also known as Willis-Ekbom disorder) [67–70]. The magnitude of these association signals is consistent with observations that an RLS linkage peak was centered at the 9p location of the *PTPRD* gene in a family study [71]. The two SNPs that displayed initial association and are the subject of most follow-up work, rs4626664 and rs1975197, lie in *PTPRD* introns 9 and 12 (Fig. 2). These SNPs display associations with both the RLS diagnoses and the periodic limb movements that are key features of this diagnosis [70]. In different samples, the extent of the association signal differs from one of these SNPs to the other. In recent work corrected for covariates, rs1975197 alleles provided odds ratios of about 1.3 for either RLS diagnosis or periodic limb movements [70].

While *PTPRD* variants thus provide an oligogenic influence on the vulnerability to developing idiopathic RLS, effects on symptomatic RLS associated with other conditions are less clear. This may be due in part to smaller sample sizes in many of these studies. There is negative data from association efforts relevant to putative migraine and multiple sclerosis comorbidities with RLS [72–73]. There was a nominally significant association of *PTPRD* rs4626664 alleles (odds ratio of 1.5) with symptomatic RLS in a sample of uremic patients, but no significant association of rs1975197 [74]. There was no association with either SNP in another report [75]. Though reported as negative, rs1975197 associations with Parkinson’s disease, a RLS comorbidity, displayed odds ratios of 1.3 and 2 under recessive and dominant models, respectively. Suggestive odds ratios for *PTPRD* markers came from evaluation of association with age of Parkinson’s disease onset and dopamine-related

symptoms (rigidity, bradykinesia) but not from association with tremor, a symptom less tightly tied to dopamine function [76].

While addiction phenotypes thus represent the first reported replicable associations with *PTPRD*, RLS provides the strongest *PTPRD* associations that have been repeatedly replicated. Furthermore, the two most RLS-associated SNPs display nominal/borderline-significant associations with levels of *PTPRD* expression and flank rs2381970, the *PTPRD* SNP that is the most strongly associated with these individual differences in levels of expression. Dopamine is involved in both addiction and RLS [77], and dopamine agonists are major RLS therapeutics [78]. Virtually all addictive substances enhance dopamine release in the striatum [79]. Though dopaminergic activities do not completely explain either disorder, the effects of PTPRD variation on dopaminergic brain systems could contribute to the noted associations with both addiction and RLS.

Association of PTPRD *genomic markers with densities of neurofibrillary pathology in Alzheimer's disease brain*

A recent report examined genomic correlates of the densities of neurofibrillary tangles and of senile plaques in the brains of well-characterized patients who died with Alzheimer's disease [80]. There was a robust association of *PTPRD* SNPs with neurofibrillary tangle density. The strongest association was for the intron 10 SNP rs560380. There was specificity; there was no such association with the densities of senile plaques. The site of this association signal within the *PTPRD* gene provides a clear link with levels of *PTPRD* expression (Fig. 2). The *PTPRD* SNPs accounted for 3% of the individual differences in neurofibrillary pathology. The only other oligogenic influence was that of the well-known *APOE4*/*TOMM40* variants. There was nominal association with Alzheimer's pathological diagnosis in this report, though *PTPRD* has not previously displayed robust associations with Alzheimer's disease diagnoses [81]. MAPK5, a kinase associated with tangle-related tau hyperphosphorylation, is a likely PTPRD dephosphorylation target based on *ptp-3* knockout data [32]. This possible pathogenic link supports the hypothesis that *PTPRD* variants provide oligogenic influences on a key neurodegenerative pathogenic component. These data provide one robust link between *PTPRD* variation and neuropathology, since neither addicted nor RLS brains display reproducible neuropathological changes [82]. The results present the exciting possibility that common *PPTRD* level-of-expression variants might influence neurofibrillary contributions to other neurodegenerative diseases.

Association of PTPRD *genomic markers with self-reported mood lability*

A recent report describes a robust genetic association between *PTPRD* SNPs and individual differences in response to the question "Does your mood often goes up and down?" in UK biobank participants [83]. A >0.5 Mb zone in the 5' flanking region of *PTPRD* is covered by SNPs with nominally significant association, with the minimal *P* value at rs10959826 (Fig. 2). The effect was the largest reported for mood lability in this sizable sample.

Association of PTPRD *genomic markers with personality phenotypes*

There are reports of associations between *PTPRD* genomic variants and personality phenotypes. SNPs in the *PTPRD* telomeric/3' flanking region display genome-wide

significant associations with openness in a female Korean sample [84] and with agreeableness (but not openness) in another Korean meta-analysis [85]. A *PTPRD* intron 1 SNP displayed polygenic association with the N6 vulnerability neuroticism subscale in Korean samples [86]. However, *PTPRD* is not identified by meta-analyses of personality data genetics in samples of largely U.S. origin [87]. Impulsivity or venturesomeness, personality phenotypes that are related to addictions [88], have not been associated with *PTPRD*. However, such traits might be tested in future studies of the impulsiveness that is associated with substance use disorders.

Association of PTPRD *genomic markers with obsessive compulsive disorder*

SNPs in the 5' flanking region of *PTPRD* were among those most highly associated with obsessive compulsive disorder (OCD) diagnosis in one report (minimal *P* value at rs2821204) [89]; there was a more modest signal in a subsequent meta-analysis [90]. These findings are reinforced by linkage of OCD to the chromosome 9p region that contains *PTPRD* [91–92], and by observations of a greater number of *PTPRD* copy number variants in pediatric OCD than in controls [93].

Association of PTPRD *deletions with cognitive abilities*

In each parent in a well-studied family, deletions of parts of one copy of *PTPRD* failed to cause any notable disability [94]. However, their son displayed defects in both *PTPRD* copies, microcephaly, and failure to develop normal cognitive abilities. These data support human gene dose–dependent effects of *PTPRD* deletion on cognitive abilities. Failure of GWASs for cognitive abilities to identify *PTPRD* [95–96] is consistent with the lack of any large effect on cognitive abilities from the common variation that provides 70% individual differences in levels of *PTPRD* expression.

Mouse models: characterization and support for human *PTPRD* associations

Mouse model for Ptprd *variation: initial characterization*

Uetani and colleagues produced *Ptprd* knockout mice [97] in which the knockout cassette inserts into the tyrosine phosphatase domain of PTPRD. These workers focused largely on differences between wild-type and homozygous knockouts. Homozygotes were smaller than wild-type littermates. For survival, they required food placement on cage floors. Homozygotes were unable to learn the Morris water maze task. Performance on reinforced alternation and radial arm mazes was also reduced in homozygotes. Tests of hippocampal electrophysiological function identified enhanced long term potentiation in CA1 and CA3 hippocampal subfields in slices prepared from brains of homozygous *Ptprd* knockouts.

Initial histological analyses of brains of homozygous knockouts failed to identify gross or light microscopic differences from brains of wild-type mice [97], though more recent work identified less elaboration of basal dendrites in homozygous knockout cortical pyramidal neurons [34]. Even *Ptprd* knockout combined with knockout of its subfamily member, *Ptprs*, produced no gross brain histological changes [98]. However, spinal motoneurons were substantially lost between embryonic days 13.5 and 18.5 in mice with combined

homozygous losses of both *Ptprd* and *Ptprs*. There was thus uniform lethality at C-section or birth that appeared to result from respiratory failure. Chick embryos treated with *PTPRD* antisense RNAs also displayed disorganization of certain peripheral nerves [99]. While abnormalities increase in mouse models as knockout of *Ptprd* is added to knockout of *Ptprs*, abnormalities decrease in chick models as antisense RNA targets more PTPRD-related RPTPs. There may thus be different interactions between products of PTPRD-related genes in these two species.

Support for human PTPRD *associations with mouse model data: addiction phenotypes*

Consistent data now supports influences of the reduced *Ptprd* expression found in heterozygous *Ptprd* knockout mice on each of two models of stimulant reward [2, 100]. Each of these reward models, conditioned place preference (CPP) [101] and self-administration [102], reliably separates virtually all of the substances that humans abuse from those with little human abuse potential, thus displaying substantial validity. Appropriate control experiments for the confounding factors that could muddy the interpretation of results are understood for each of these two tests.

Heterozygous *Ptprd* knockout mice, which express half of the wild-type levels of *Ptprd*, display reduced preference for places paired with effects of normally highly rewarding 10 mg/kg doses of cocaine [52] (Fig. 3). Tests of strength, motor function, anxiety, and mnemonic function reveal no obvious confounding effects [52]. These results provide additional support for human GWAS observations that variation at the *PTPRD* locus contributes to both vulnerability to develop a substance use disorder and to individual differences in the rewarding properties of amphetamine doses administered in a laboratory setting.

These CPP results have recently been reinforced by findings from self-administration assays [2]. *Ptprd* heterozygous knockout mice took longer to establish high rates of 1 mg/kg/infusion cocaine self-administration than wild-type littermate controls. During the last three of eight successive three-hour sessions in which up to 50 cocaine infusions were available on fixed ratio 1 (FR1) schedules, heterozygotes self-administered about half of the maximal amounts available, while wild-type littermates self-administered about 70% of the maximal available drug. Heterozygotes continued to self-administer at lower rates than wild-type mice on days 6–8. There were no differences in control responding on inactive levers during FR1 responding.

There is additional support from the results of subsequent progressive ratio studies [2]. After several days of experience with these progressive ratio schedules, *Ptprd* heterozygous knockouts displayed significantly lower break points. They thus self-administered about half the number of infusions that were self-administered by wild-type littermate control mice. Taken together, CPP and self-administration data provide strong support for the polygenic PTPRD associations identified in the human GWAS datasets.

Support for human PTPRD *associations with mouse model data: RLS phenotypes*

Mice with reduced *Ptprd* expression display behavioral evidence of sleep disruption during the beginning of the sleep period, the time period when sleep abnormalities are easiest to identify in humans with RLS [52]. In assessments of sleep behaviors in the hour prior to and

the hour following “lights on” (the start of the normal mouse sleep phase), mice with reduced *Ptprd* expression had a decreased number of sleep bouts, which decreased total sleep duration and increased the length of sleep bouts, providing evidence of sleep deprivation. While these observations provide face validity in relation to human RLS-associated sleep disturbances, there is a less clear relationship between RLS-associated periodic limb movements and either the twitch-like or the slower movements that can be quantified in mice. We found no effect of PTPRD genotype on either slower or faster twitch-like movements in the hour prior to or the hour after “lights on”. There were effects of *Ptprd* genotype on overall locomotor activity in several settings. Overall, there is thus good mouse model evidence that validates the effects of human *PTPRD* variation on sleep but no clear mouse model evidence to validate the effects of *PTPRD* variation on human periodic limb movements.

Support for human PTPRD *associations with mouse model data: other phenotypes*

There are striking parallels between the gene dose–dependent effects of reducing *Ptprd* expression and data relating to human cognitive abilities. Heterozygous knockout mice, humans with the common *PTPRD* variation that alters expression by perhaps 70%, and humans with a single *PTPRD* copy deletion all do not display abnormal cognitive test results. The case report of severe intellectual impairment when both copies of human *PTPRD* are deleted [94] accords well with the severe difficulties displayed by homozygous *Ptprd* knockout mice in the water maze task [52]. Expression of at least 30–50% of wild-type levels of *PTPRD* appears sufficient for the development of apparently normal cognitive function.

Support for some other human *PTPRD* associations is not available, based in part on the lack of well-validated mouse models for mood instability, personality phenotypes, OCD, or neurofibrillary Alzheimer’s disease pathology.

Potential for future support of (as yet unelucidated) human motoneuron phenotypes by mouse model data

In mice, combined homozygous deletion of both *Ptprd* and *Ptprs* causes remarkable lethality [98]. Even mice delivered by Caesarean section are paralyzed, never observed to breathe, and die with severe muscle dysgenesis and loss of spinal cord motoneurons. Phrenic nerves emerge normally from the cervical spinal cord, but stall on reaching the diaphragm. Preservation of a single functional copy of either the *Ptprd* or *Ptprs* genes allows significant survival in the background of a homozygous knockout of the other gene, though there were significantly reduced motoneuron densities in $Ptprd^{+/-}$ $Ptprs^{-/-}$ mice. These data predict that combined homozygous deletions of both the chromosome 9 sequence encoding *PTPRD* and the chromosome 16 sequence encoding *PTPRS* would cause severe motoneuron phenotypes, though there is no report of such humans. They also predict functional redundancy that should allow substantial differences in function of PTPRD or of PTPRS, individually, without any large consequence for motoneuron or neuromuscular physiologies.

Discovery and effects of the initial PTPRD ligand

Sites for targeting small molecule PTPRD ligands

As noted above, binding of PTPRD by its extracellular ligands is likely to alter the phosphatase activity of its key intracellular D1 phosphatase domain [103]. Phosphatase activity of this D1 domain is likely to be reduced by binding interactions with the inactive D2 phosphatase-like domain [30]. PTPRD could thus be targeted by compounds that could (1) bind extracellularly in ways that increase its phosphatase activity (e.g., agonist-like); (2) bind extracellularly in ways that decrease its phosphatase activity (e.g., antagonist-like): (3) bind to the active D1 phosphatase domain to decrease its phosphatase activity (e.g., inhibitor-like); or (4) disinhibit the active D1 phosphatase domain by reducing its inhibitory interactions with the D2 domain. Other interactions (e.g., allosteric effects, binding to other extracellular or intracellular modulators) are possible. Interest in the phosphatase portion of PTPRD as a drug target has been increased by the nonconservative amino acid differences between PTPRD and its other DSF subfamily members[104].

Small molecule PTPRD phosphatase inhibitor

We have focused on inhibitors of PTPRD's phosphatase domain as a novel approach to "drugging" PTPRD for several reasons [2] Natural product library screening identified ligands that inhibit PTPRF's phosphatase activity. Illudalic acid displays micromolar K_i [105–106] in inhibiting PTPRF's phosphatase. Illudalic acid analogs thus provided exciting clues to possible PTPRD ligands.

We were able [2] to (1) synthesize a 7-butoxy illudalic acid analog (7-BIA, Fig. 4); (2) produce enzymatically active recombinant human PTPRD and PTPRS D1 phosphatase domain fusion proteins; (3) develop *in vitro* assays for the activities of the PTPRD and PTPRS phosphatase domain proteins; and (4) use these assays to document significant 7-BIA potency in inhibiting PTPRD and PTPRS phosphatases. IC_{50} values for 7-BIA preincubated with the fusion protein are about 3 μM (PTPRD) and 40 μM (PTPRS)in assays in which preincubated protein is diluted 10-fold No tested precursor significantly inhibited PTPRD phosphatase fusion protein's activity. 7-BIA failed to provide significant inhibition of any of the more than 85 transporter, receptor, enzymatic, or other sites assessed by Eurofins and Dr. A. Janowsky. Based on observation, behavioral tests, autopsy by an experienced veterinarian, and major organ histology evaluated by experienced veterinary pathologists, we found no dose-related behavioral or organ toxicity or peritoneal inflammation in mice sacrificed minutes or weeks following injections of doses limited by 7-BIA solubility in DMSO and maximal 5% DMSO volumes that mice could receive.

Small molecule PTPRD phosphatase inhibitor reduces cocaine reward in two behavioral tests

Effects of 7-BIA on cocaine conditioned place preference.—We administered 7-BIA 90 min prior to each of the two 10 mg/kg cocaine conditioning sessions [2]. Mice pretreated with DMSO vehicle displayed preferences for places paired with 10 mg/kg cocaine that were similar to those that we have previously reported in wild-type C57BL/6 mice [107]. However, these preferences for cocaine-paired environments were significantly

reduced in mice pretreated with 7-BIA (Fig. 5, top). There were no significant 7-BIA effects on locomotor speed or distance traveled. Apparent transient inhibition of PTPRD phosphatase activity influenced a measure of cocaine reward with behavioral specificity. This did not appear to be caused by preference or aversions induced by 7-BIA itself. Pairing with effects of 7-BIA provided no change in preference/aversion for environments in which it was administered.

Effects of 7-BIA on well-established cocaine self-administration.—Wild-type and *Ptprd* heterozygous mice were allowed to self-administer 0.5–1 mg/kg/infusion cocaine for at least 20 sessions so that they were self-administering >40 doses during 3-hour sessions with a 50-dose limit [2]. 7-BIA–pretreated mice failed to obtain at least 40 cocaine doses during 52% of sessions, compared to the about 20% of sessions in which vehicle/non-pretreated mice failed to obtain at least 40 doses (Fig. 5, bottom). Mice also failed to self-administer at least 40 cocaine doses during the next session (1–2 days following single 7-BIA treatments) and returned to >40 doses/session in subsequent sessions. Most, if not all, of these 7-BIA effects appear to be attributable to the compound's influences on PTPRD. Heterozygous *Ptprd* knockout mice treated with 7-BIA only failed to obtain >40 cocaine doses in 9% of sessions

PTPRD variation and brain phenotypes: current support

Substance reward and substance use disorders

There is compelling evidence for PTPRD roles in addiction that comes from the combination of data from: (1) human *PTPRD* associations with individual differences in (a) responses to stimulant and alcohol administration, (b) vulnerability to develop a substance use disorder, and (c) ability to quit smoking; as well as (2) mouse studies of effects of (a) lifelong alterations of the levels of PTPRD expression and (b) acute pharmacological inhibition of PTPRD's phosphatase activity.

There remain caveats for the human findings by themself since no single *PTPRD* SNP provides consistent $P < 10^{-8}$ association or any evidence for oligogenic influences on these addiction-related phenotypes. Taken together with the mouse model genetic and pharmacological data, however, there seems little *a posteriori* doubt that (1) *PTPRD* variation plays polygenic roles in human addiction-related phenotypes and that (2) changes in mouse PTPRD expression or activity can play larger roles in stimulant reward (when, of course, there is more control for genetic background and environmental influences than in human studies). PTPRD provides a novel and interesting target for anti-addiction medications development.

Restless leg syndrome

The combination of human and mouse model data also provides strong support for the roles of individual differences in *PTPRD* expression on the sleep disruption associated with RLS. Human data also supports roles for *PTPRD* variation in the RLS-associated periodic limb movements in sleep. The oligogenic human associations with RLS, indeed, are of at least as impressive magnitude as the significant, though moderate, differences in sleep parameters

observed in mice with reduced *Ptprd* expression. There is no well-validated, well-established mouse model for periodic limb movements. Thus, it may not be surprising that our efforts to assess quicker and slower limb movements in mice around the "lights on" natural start of their sleep cycles might not reflect either *bona fide* RLS pathophysiology or PTPRD effects on this physiology. It is notable that studies of a mouse models of another RLS oligogene, *Btbd9*, also identified effects on sleep [108]. Mice with altered expression of *Btbd9*, the RLS oligogene *Meis1* [109], and *Ptprd* [52] each exhibited increased locomotion (termed "restlessness" in one report), but none manifest clear-cut periodic limb movements.

Cognitive abilities

Human and mouse data provide mutual support for both effects of altered PTPRD expression on cognitive abilities and for gene dose-response relationships. Deletion of all PTPRD expression provides marked cognitive deficits in both mouse models and the very rare humans homozygous for such deletions. By contrast, the scope for substantial variation in levels of PTPRD function before deficits in cognitive function become notable is strongly supported by (1) the failure of human deletion heterozygotes or mouse *Ptprd* knockout heterozygotes to demonstrate significant cognitive impairments; (2) the failure to identify *PTPRD* in cognitive function GWAS; and (3) our findings that common haplotypes confer 70% individual differences in levels of *PTPRD* expression. Such data provide reassurance for the development of compounds that transiently reduce PTPRD function.

Neurofibrillary Alzheimer's pathology, personality, and obsessive compulsive disorder

The careful recent report that identified *PTPRD* association with the extent of neurofibrillary pathology in Alzheimer's disease brain specimens is impressive [110]. However, this association comes from only a single publication to date. There is no supporting mouse model data of which we are aware. Personality associations are variable in human studies; there are only a few mouse models with substantial validation. There are a number of face-valid models for features of OCD, but relatively few of these models have been validated pharmacologically [111] and none have been applied to PTPRD, to our knowledge. These associations thus merit efforts for replication in humans and generalization to mouse models.

A note about cancer and other systemic phenotypes

There are reported associations between *PTPRD* variation and a number of cancers or their responses to treatment [112–128]. While the details of these associations are beyond the scope of this paper, we note that most come from genotyping tumors or tumor-derived cell lines and that none of these associations focuses on the mid-gene regions that we have associated with a number of brain phenotypes and levels of *PTPRD* expression. Neither we nor others have identified any tumors in studies of thousands of mice with altered *Ptprd* expression.

There are also reported associations with susceptibilities to diabetes [129], treatment-resistant hypertension [130], weight gain associated with neuroleptic treatments [131], and craniofacial abnormalities with hearing deficits [94], though neither we nor others have identified these phenotypes in mice with altered *Ptprd* expression.

As we and others continue to develop drugs that target PTPRD, we must nevertheless continue to be alert to potential for unwanted carcinogenesis and other systemic phenotypes (as for all drugs that engage novel targets).

Neurobiology and genetics of PTPRD and brain phenotypes

The neurobiology of PTPRD, even incompletely understood, places this receptor type protein tyrosine phosphatase in a central position in regulating the development and modulation of interesting, PTPRD-expressing brain circuits. Clearer understanding of this neurobiology, and the consequences of acute and chronic modulation of PTPRD function, sharpens our pictures of the complex physiology and pathophysiology of PTPRD-expressing neurons and circuits.

PTPRD genetics, also partially understood, is consistent with both major/oligogenic and modest/polygenic contributions of common and rare *PTPRD* variation on common disorders: substance use disorders, RLS, Alzheimer's disease and perhaps other neurodegenerative diseases. Mouse models link lifetime alterations in brain PTPRD expression to human phenotypes. Our lead compound work (gratifyingly) supports the idea that even acute changes in PTPRD function can have specific effects on important phenotypes, including in mouse models of stimulant reward.

Recent bioinformatic work has underscored the ways in which availability of pharmacological tools, publications, and grant funding focus on the products of a modest fraction of the genome, in ways that have not included PTPRD to date [132]. PTPRD remains an interesting molecule, an apparently druggable drug target and a marker for and an important constituent of brain circuits of likely importance for major brain-based phenotypes. This interesting gene is thus a prime candidate target for funding, pharmacological work, and increasing therapeutic advances in addictions and other disorders.

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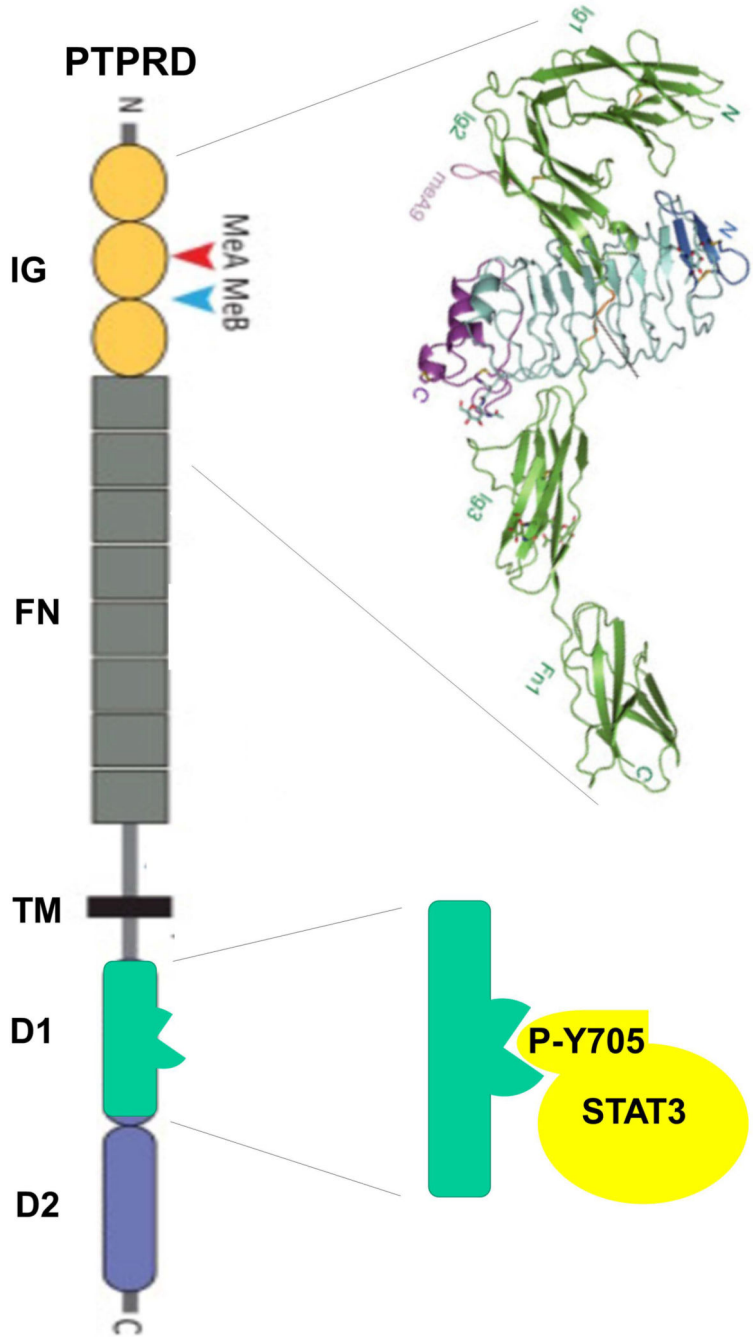

Figure 1.

PTPRD domains. Immunoglobulin (IG, with miniexons (Me) A and B shown), fibronectin type III (FN), transmembrane (TM), active tyrosine phosphatase domain (D1), and enzymatically inactive regulatory domain (D2). Upper right: structure of the complex between the PTPRD IG and first FN domains with the leucine-rich repeat region of SLITRK2. Lower right: D1 domain dephosphorylation of phosphotyrosine 705 in STAT3, an example of PTPRD activity.

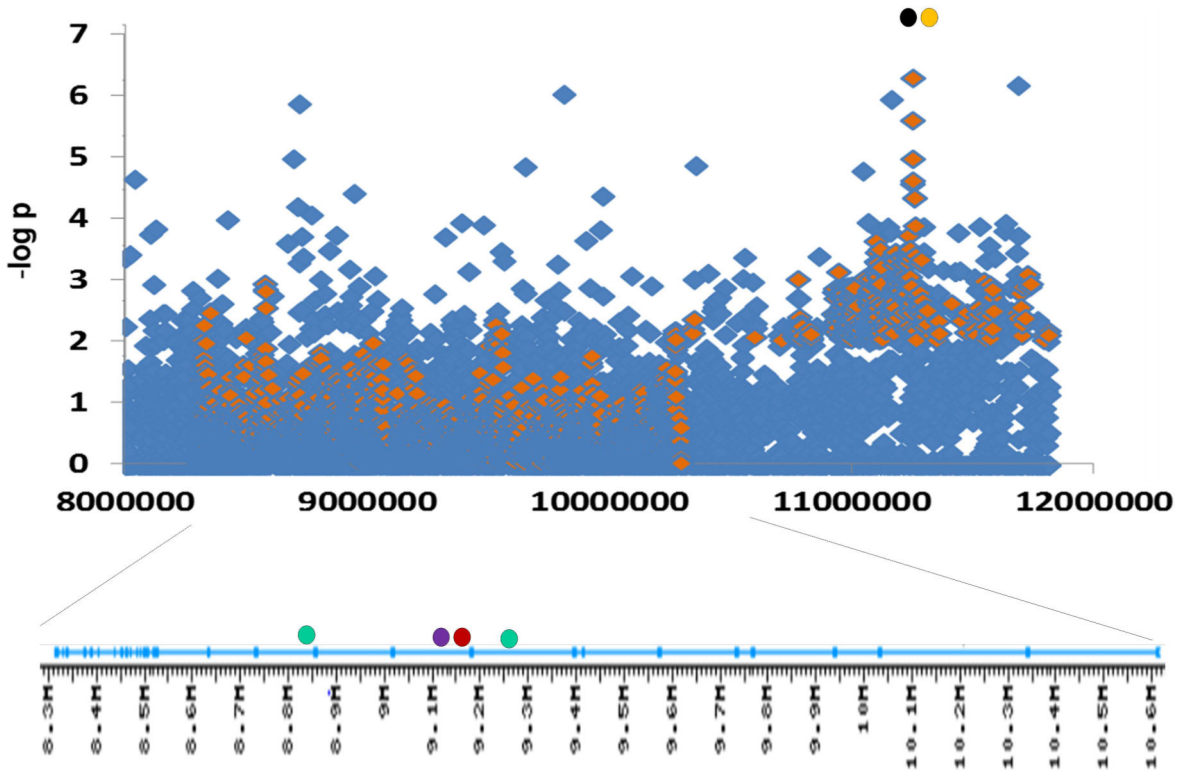

Figure 2.

Associations at *PTPRD* locus (top) and *PTPRD* introns (bottom) (Manhattan plot). Diamonds: –log *P* values for addiction-related phenotypes: smoking cessation success (blue; Uhl *et al.*, unpublished observations) and positive responses to amphetamine (orange; data kindly provided by A. Hart). Filled circles: Intron positions of SNPs most strongly associated with RLS (green), levels of brain *PTPRD* mRNA expression (red), and neurofibrillary tangle density in Alzheimer's disease brains (purple), and positions of SNPs most strongly associated with mood lability (orange) and obsessive-compulsive disorder (black). Left is telomeric and 3', including the most 3' exon encoding the 3' untranslated region. Right: 5' exons 1–12 encode the 5' untranslated region of common adult brain transcripts.

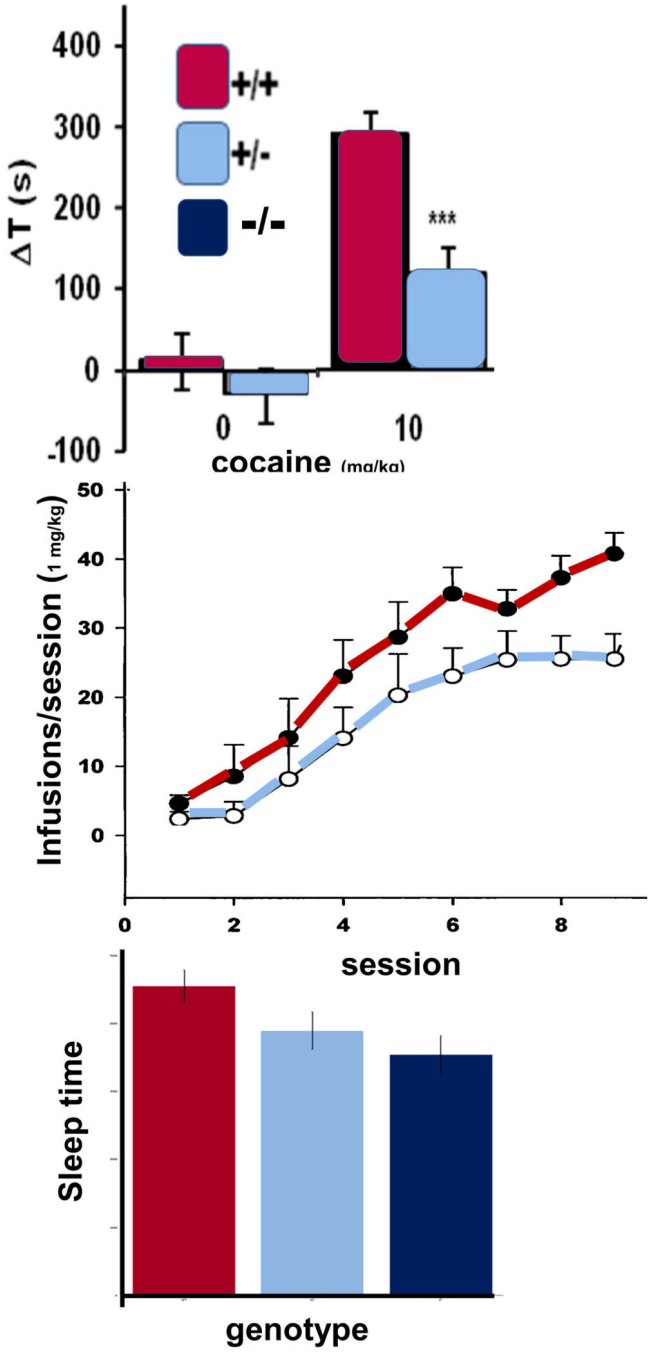

Figure 3.

Heterozygous *Ptprd* knockout mice display reduced cocaine-conditioned place preference (top), cocaine self-administration (middle, fixed ratio 1 schedule) and sleep (bottom, 2h around "lights on"). Homozygotes display larger sleep deficits than heterozygotes. All differences are statistically significant.

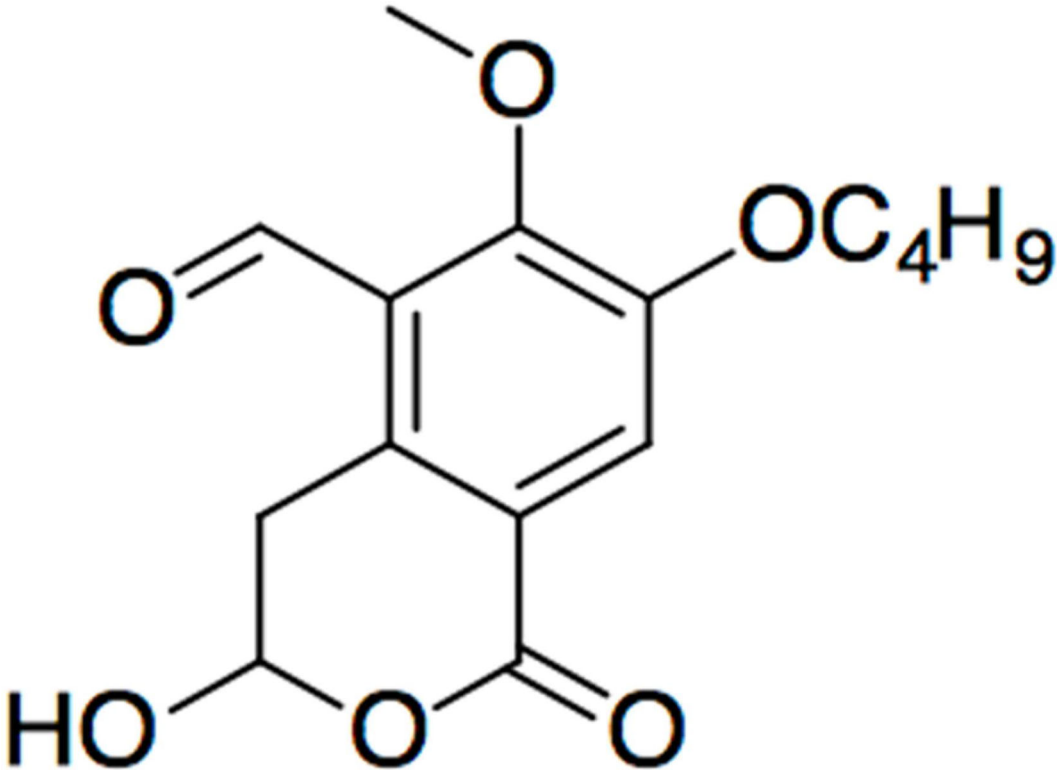

Figure 4.
Structure of the first PTPRD phosphatase inhibitor 7-BIA (7-butoxy illudalic acid analog).

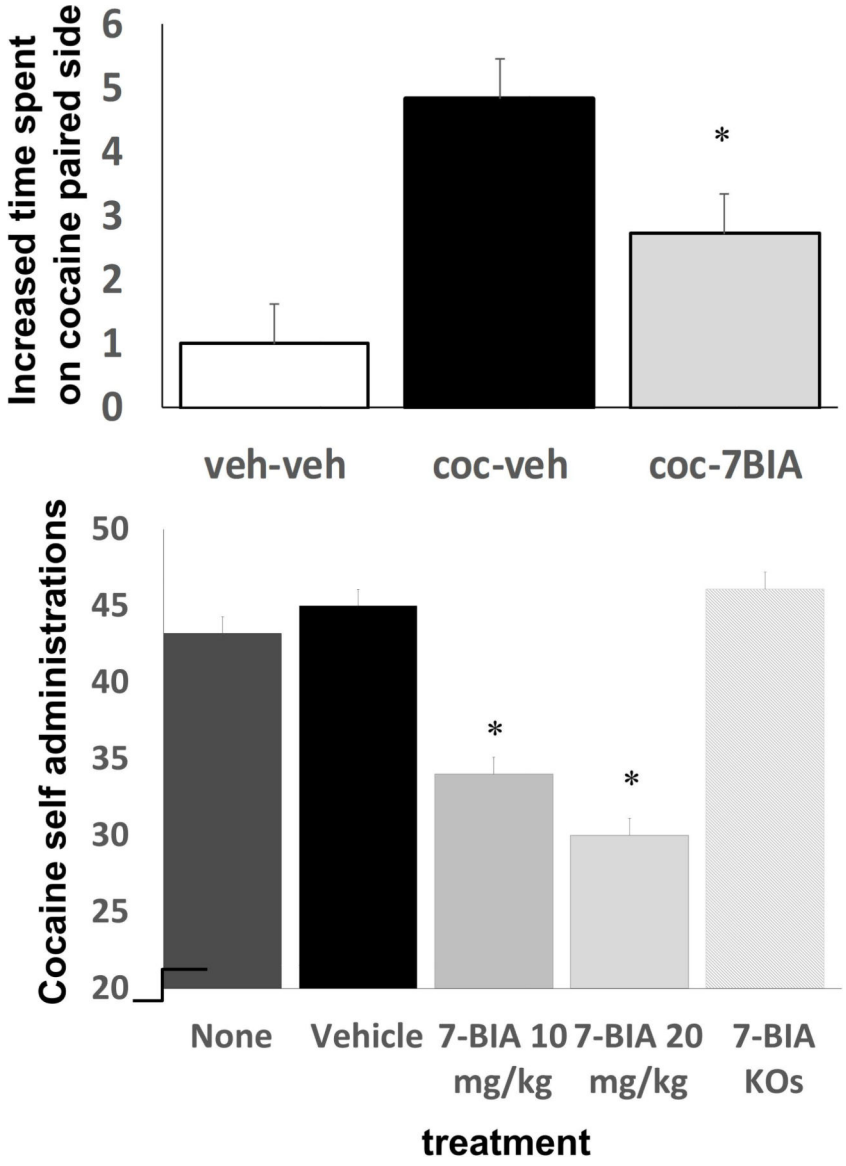

Figure 5.

7-BIA pretreatment reduces cocaine-conditioned place preference (top) and self-administration (bottom) in wild-type but not *Ptprd* knockout (KO) mice.

Table 1.

Some candidate homomeric and heteromeric PTPRD binding partners

Homomeric
PTPRD
Heteromeric
SLITRK1
SLITRK2
SLITRK3
IL-1RAcP
IL1RAPL1
NGL3
LRFN1
LRFN5

Table 2.

Some of the neuronal types that express PTPRD mRNA[2]

Neuronal type	PTPRD expression
Acetylcholine	Many, dense
Dopamine	Many, dense
Reticular thalamic	Many, dense
Cerebral cortical	Scattered, moderate
Olfactory bulb (inner plexiform)	Many, dense
Pyriform cortex (layer 2)	Many, dense