Coexpression of the discoidin domain receptor 1 gene with oligodendrocyte-related and schizophrenia risk genes in the developing and adult human brain

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Abstract

Background: Discoidin domain receptor tyrosine kinase 1 (DDR1) is present in multiple types of epithelial cells and is highly expressed in the nervous system. Previous studies have revealed that DDR1 is involved in schizophrenia (SCZ). Although the expression of DDR1 in oligodendrocytes has been described, its role in brain myelination is not well understood. In this study, we aimed to explore the coexpression network of DDR1 in the human brain and to compare the list of DDR1 coexpressing genes with the list of genes containing single nucleotide polymorphisms (SNPs) that are associated with SCZ.

Materials and Methods: We used a weighted gene coexpression network analysis (WGCNA) of a dataset from four brain areas (the dorsolateral prefrontal cortex, primary motor cortex, hippocampus, and striatum) and from four different intervals (I) of life (I-1 = 10–38 weeks postconception, I-2 ≥ 0 to < 6 years, I-3 ≥ 6 to < 40 years, and I-4 ≥ 40 years of age). We compared the list of genes that are associated with SCZ in the GWAS Catalog with the list of genes coexpressing with DDR1 in each interval.

Results: Our study revealed that DDR1 was coexpressed with oligodendrocyte-related genes mainly in I-2 (adjP = 5.66e-24) and I-3 (adjP = 2.8e-114), which coincided with the coexpression of DDR1 with myelination-related genes (adjP = 9.04e-03 and 2.51e-08, respectively). DDR1 was also coexpressed with astrocyte-related genes in I-1 (adjP = 1.11e-71), I-2 (adjP = 2.12e-20) and I-4 (adjP = 9.93e-52) and with type 2 microglia-related genes in I-1 (adjP = 2.84e-08), I-2 (adjP = 5.68e-16) and I-4 (adjP = 3.66e-10). Moreover, we observed significant enrichment of SCZ susceptibility genes within the coexpression modules containing DDR1 in I-1 and I-4 (P = 1e-04 and 0.0037, respectively), during which the DDR1 module showed the highest association with the astrocytes.
**1 | INTRODUCTION**

Discoidin domain receptor tyrosine kinase 1 (DDR1) is a membrane-anchored protein activated by fibrillar collagens (Leitinger, 2014). In adult human brain tissue, DDR1 expression is detected mainly in oligodendrocytes, but it is also found in astrocytes, activated microglia and endothelial cells (Roig et al., 2010; Vilella et al., 2019). DDR1 is also expressed in the peripheral nervous system, presumably in Schwann cells, and in other tissues and cell types (Leitinger, 2014; Vilella et al., 2019). During mouse neurodevelopment, DDR1 is maximally expressed in oligodendrocytes throughout the myelination period (Franco-Pons et al., 2006). It has been shown that remyelination following experimentally induced demyelination induces DDR1 upregulation (Franco-Pons et al., 2009). Recent single-cell RNA-seq studies in rodent models reported that ddr1 expression peaks in the period in which newly formed oligodendrocytes differentiate into myelinating oligodendrocytes (Vilella et al., 2019). Data from these studies demonstrated that genes encoding the membrane receptors Ephrinb3 (Enfb3), plexinb3 (Pxnrb3), ERBB3 (Erbb3) and semaphorin 4D (Sema4D); ligands (such as gelsolin [Gsn] and collagen 11 alpha 2 chain [Col11a2]); and classical myelin proteins (such as myelin-associated oligodendrocyte basic protein [Mobp]), among others, are coexpressed with DDR1 (Vilella et al., 2019). Nevertheless, the specific role of DDR1 in myelination has not yet been identified.

Humans exhibit the highest level of brain myelination among mammals (including primates), which allows for a high capacity of information processing (Bartzokis, 2011). Myelin deficiencies have been observed in several psychiatric disorders, including schizophrenia (SCZ), through neuroimaging, genetic, molecular, and anatomical studies (Bartzokis, 2011; Chen et al., 2018; Koshiyama et al., 2019).

DDR1 variations have been found to be associated with human schwannomas (benign tumors of myelin-producing Schwann cells) (Agnihotri et al., 2016) and SCZ (Benkovits et al., 2016; Gas et al., 2018; Roig et al., 2007). Moreover, genome-wide association studies (GWAS) have found associations between DDR1 and multiple sclerosis (Mo et al., 2019), neuroticism (Kim et al., 2017), and SCZ (Pardiñas et al., 2018), although this latter study did not include the DDR1 locus in the final analyses because it falls inside (1100 kb apart) of a linkage disequilibrium (LD) region wherein the highest SCZ-associated locus is located. Differentially expressed levels of the DDR1c isoform (Q08345_5, 919aa) have been observed in brain tissues from patients with SCZ, compared to healthy controls, with contradictory results (Gandal et al., 2018; Roig et al., 2012). However, detailed studies on the coexpression of DDR1 with other genes during human brain development are lacking.

Here, with the primary hypotheses that DDR1 is upregulated during oligodendrocyte myelination and that DDR1 is itself or through its interaction with other genes associated with SCZ, we aimed to identify the genes coexpressed with DDR1 in human brain tissue in different neurodevelopmental periods and to test whether DDR1 is coexpressed with SCZ-associated genes.

**2 | MATERIALS AND METHODS**

**2.1 | Data**

Publicly available spatiotemporal transcriptome data of the human brain were used for this study (Kang et al., 2011). Raw data files were retrieved from the GEO database (GSE25219), which consisted of genome-wide transcriptome data from 16 brain regions analyzed with the Affymetrix GeneChip Human Exon 1.0 ST Array. Samples were selected according to the following criteria: brain region, number of subjects available and tissue quality (RNA integrity number, RIN ≥8). We evaluated gene coexpression patterns in three brain regions that are involved in SCZ symptomatology, as well as one unrelated region. The first region was the dorsolateral prefrontal cortex (DFC), which is associated with high cognitive processing and was previously shown to be involved in SCZ (Friston, 1992; Lewis & Mirmics, 2006). The second region, the hippocampus (HIP), is involved in memory and other cognitive processes, which are impaired in SCZ (Geuze et al., 2005). The third region was the striatum (STR), which, due to its high dopaminergic activity, has been related to positive psychotic symptoms in SCZ (McCuttacon et al., 2019). Finally, the primary motor cortex (M1C), which is not associated with SCZ, was chosen as the “noncognitive” region. We grouped the 15 original periods (Kang et al., 2011) into four developmental intervals (I) considering both specific neurodevelopmental periods and to test whether DDR1 is coexpressed with SCZ-associated genes.

**Conclusions:** Our study confirmed that DDR1 is coexpressed with oligodendrocyte- and myelin-related genes in the human brain but suggests that DDR1 may contribute mainly to SCZ risk through its role in other glial cell types, such as astrocytes.

**KEYWORDS**

astrocytes, coexpression, DDR1, human brain, microglia type 2, oligodendrocytes
Gene expression overlapping with SCZ susceptibility genes

Weighted gene coexpression analysis

RESULTS

3.1 DDR1 expression

Our study focused on DDR1 expression during brain development and in adulthood. Relative whole-transcript DDR1 levels in several brain
regions in the I-1 to I-4 periods were retrieved from both the Human Brain Atlas and the Human Brain Development database, and these levels are shown in Supporting Information Figure S1. DDR1 expression diminished over time in all the studied regions. In general, a time-dependent decrease was observed in the expression of COL1A1 and COL4A1, which code for components of collagens, the extracellular matrix ligands that activate DDR1 (Supporting Information Figure S1). However, the expression of the classical oligodendrocyte and myelin markers OLIG2, CNP, MAG, and MBP increased perinatally and was maintained at a relatively stable level until adulthood (Supporting Information Figure S1).

### 3.2 WGCNA to identify DDR1 coexpression networks

WGCNA performed to identify gene coexpression networks in each development interval, and the lowest values that allowed more than 85% similarities in topological models of the four intervals were used as soft thresholds (I-1 = 5; I-2 = 6; I-3 = 6; and I-4 = 10), resulting in the detection of 8, 11, 9, and 16 modules for each of the intervals, respectively (Figure 1). Genes that were not correlated strongly enough with any module were considered background (denoted by the color gray and named hereafter as module 0, Figure 1 and Supporting Information...
### Table 1: DDR1-module cell-type enrichments in each time interval

|                | I-1 10 - 38 PCW | I-2 ≥0 - < 6 years | I-3 ≥6 - < 40 years | I-4 ≥ 40 years |
|----------------|-----------------|-------------------|--------------------|---------------|
| DDR1 module   | M3 (brown)      | M3 (brown)        | M5 (red)           | M3 (brown)    |
| Cell type module<br> |                 |                   |                    |               |
| Astrocytes    | 1.11e-71        | 2.12e-20          | ns                 | 9.93e-52      |
| Microglia (Type 1) | 3.26e-04   | ns                | ns                 | ns            |
| Microglia (Type 2) | 2.84e-08   | 5.68e-16          | ns                 | 3.66e-10      |
| Oligodendrocytes | 1.53e-13    | 5.66e-24          | 2.18e-114          | 1.45e-02      |
| Myelin         | ns              | 9.04e-03          | 2.51e-08           | ns            |
| Neuron         | ns              | ns                | ns                 | ns            |
| PVALB Interneurons | ns       | ns                | ns                 | ns            |
| Glutamatergic Synapse | ns   | ns                | ns                 | ns            |
| Nucleus        | ns              | ns                | ns                 | ns            |
| Mitochondria   | ns              | ns                | ns                 | ns            |
| Ribosome       | ns              | ns                | ns                 | ns            |

*DDR1 module according to Figure 1.*

*Cell type modules according to Miller and colleagues (Miller et al., 2010).*

*Myelin genes according to GO.*

ns = nonsignificant.

In I-1, I-2, and I-4, DDR1 was found in M3 (brown module) with 812, 553, and 398 genes, respectively (Supporting Information Table S3). However, DDR1 clustered in M5 (red module) with 527 genes in I-3 (Supporting Information Table S3). Within each period, we evaluated the correlation of the detected modules with sample traits such as sex, age, hemisphere, region, pH, PMI, and RIN. The complete list of the correlations of the modules with external traits is shown in Supporting Information Figure S2. Multiple modules were associated with one or more traits, but no module was correlated with hemisphere at any period. Although we found significant correlations with some of the external traits, we did not further analyze the data to correct for them as our study was not focused on correlation strength. All of the networks resulting from all the DDR1 modules showed a protein-protein interaction (PPI) enrichment value < 1e-16 (data not shown), indicating that the proteins were strongly biologically connected.

### 3.3 DDR1 module cell-type enrichments

To investigate the role of DDR1 during neurodevelopment as well as in the adult human brain, the function userListEnrichment was used to assess cell-type enrichments using the human brain networks described by Miller and colleagues (Miller et al., 2010). We also evaluated the enrichment of a list of myelin-related genes from the GO database and explored whether conventional glial cell type genes overlapped with the DDR1 module. Table 1 shows the cell-type enrichments in DDR1 modules in each period, and Supporting Information Figure S3 shows the cell-type enrichments in all modules. DDR1 module showed coexpression with oligodendrocyte genes in all four intervals, with the highest correlation in I-3 (P = adjP = 1.53e-13, adjP = 5.66e-24, adjP = 2.18e-114, and adjP = 1.45e-02, respectively). Notably, in I-3 DDR1 was contained in M5 and the module matches exclusively with oligodendrocyte and myelin gene profiles. In I-1, I-2, and I-4, DDR1 was contained in M3 with a high correlation with astrocyte gens (adjP = 1.11e-71, adjP = 2.12e-20, and adjP = 9.93e-52, respectively), microglia type 2 (adjP = 2.84e-08, adjP = 5.68e-16, and adjP = 3.66e-10, respectively) and to a lesser extent to microglia type 1, which was only significant in I-1 (adjP = 3.26e-04). Notably, M14 in I-4, which does not contain DDR1, was strongly enriched in oligodendrocyte markers (adjP = 2.62e-60) and myelin-related genes (adjP = 1.48e-05) (Supporting Information Figure S3). Altogether, these results suggest that the principal role of DDR1 in brain is in non-mature oligodendrocytes, but some function is also associated with astrocytes and microglia.

Conventional glial cell type gene markers and collagen genes were localized within the modules at each interval (Supporting Information Table S4). In summary, M3 at I-1 contained classical markers for OPC, OLs-myelin, astrocytes, and microglia. M3 in I-2 contained gene markers for OPC, OLs-myelin and astrocytes; M5 at I-3 contained exclusively OL-myelin markers; and M3 in I-4 contained OL-myelin and astrocyte markers. These results corroborate the cell-type enrichments shown in Table 1. Finally, the enrichments in the DDR1 modules were validated using mouse brain networks from Cahoy and colleagues (Cahoy et al., 2008) (Supporting Information Table S5), which confirmed that the DDR1 module corresponded to astrocytes in I-1 and I-4, to astrocytes and oligodendrocytes in I-2 and to oligodendrocytes in I-3. Confirmatory data were retrieved from the Human Developmental Brain project, which demonstrated that DDR1 in the adult brain...
Pathway enrichment in DDR1 modules

We then performed pathway enrichment analysis of DDR1 modules in each period (Supporting Information Tables S6–S9). The most common enriched GO term for the DDR1 module was gliogenesis, which was significant in all periods (I-1 to I-4; adjP = 2.94e-07, 5.91e-04, 2.68e-07, and 4.08e-04). In I-1, the DDR1 module (M3) was also enriched in regulation of cell adhesion (adjP = 2.6e-07), the ERK1 and ERK2 cascades (adjP = 1.05e-07), and extracellular matrix organization (adjP = 1.27e-06) (Supporting Information Table S6). In I-2, the DDR1 module (M3) was significantly enriched in categories such as cell substrate adhesion (adjP = 6.3e-07) (Supporting Information Table S7). In I-3, the DDR1 module (M5) was highly enriched in the ensheathment of neurons (adjP = 3.13e-06), the myelin sheath (FDR = 8.26e-03) and the actin cytoskeleton (adjP = 8.26e-03) (Supporting Information Table S8). Finally, in I-4, the DDR1 module (M3) showed enrichment in GO categories such as negative regulation of nervous system development (adjP = 4.08e-04) (Supporting Information Table S9).

Overlap with SCZ risk genes

As both DDR1 variants and myelin impairments are involved in SCZ, we evaluated whether genes previously found by GWASs to be associated with SCZ were enriched in the DDR1 modules in each period (Figure 2). We generated 10,000 random gene lists of the same length, one for each period (the DDR1 module contained 812, 553, 527, and 398 genes for intervals 1, 2, 3, and 4, respectively) and evaluated the number of SCZ genes in the bootstrapped module (Supporting Information Table S10). We found that M3, which contained DDR1 in I-1 and I-4, was enriched in SCZ-associated genes (empirical p-value = 1e-04 and 0.0037, respectively). In I-1 the overlapping list of 49 genes is represented by functions such as cell and tissue development, calcium signaling, energy metabolism, synopsis, and genes coding for proteins of the dystrophin-associated proteins complex (DAPC). In I-4, the overlapping list consists of 24 genes coding for proteins involved in axon growth/guidance, calcium and cell signaling, intracellular stress response and transcriptional repression. The DDR1 modules in I-2 and I-3 were not enriched in SCZ susceptibility genes (empirical p-values = 0.45 and 0.21, respectively).

4 DISCUSSION

Although in situ hybridization, immunohistochemical and RNA-seq studies have mapped DDR1 to white matter in humans and rodents (Vilella et al., 2019), a complete coexpression analysis of DDR1 in human brain development has not been published. Here, we show that DDR1 (whole-transcript) is expressed at similar levels between four different brain regions (the DFC, HIP, STR, and M1C) and decreases in an age-dependent manner (from the embryonic-fetal stage to > 40 years of age).

The most relevant result shown here is that DDR1-containing modules were significantly enriched in oligodendrocyte-related genes in the human brain in all four-time intervals. These results are consistent with previous findings in mice (Franco-Pons et al., 2006; Vilella et al., 2019) and in the human brain (Roig et al., 2010). The highest correlation of DDR1 expression with oligodendrocyte genes was observed in I-3 (≥6 to < 40 years of age), followed by I-2, I-1, and I-4. These results are also congruent with previous data in mice brain showing that ddr1 expression peaks on postnatal days 15–17 (Franco-Pons et al., 2006; Zhang et al., 2014), coinciding with the peak of myelination (Bumann & Pham-Dinh, 2001). DDR1-containing modules were also significantly enriched in myelin-related genes in I-2 and I-3, with the highest levels being observed in I-3, but the enrichment was lower for this module than for the oligodendrocyte module. One possible interpretation of this result, a part of a sample power explanation, is that the DDR1 expression pattern is similar to that of oligodendrocyte markers other than myelinating oligodendrocyte markers. This interpretation is in line with the results found in mice, in which ddr1 expression peaks between the periods in which late newly formed oligodendrocytes and myelinating oligodendrocytes are present (Marques et al., 2016; Zhang et al., 2014). Therefore, higher enrichment in oligodendrocyte-related genes than myelin-related genes (genes expressed in mature myelinating oligodendrocytes) is expected, and it suggests that in the human brain DDR1 is relevant in differentiated oligodendrocytes that are not yet myelinating or that are myelinating but not mature. Myelin deficiencies have been observed in psychiatric disorders, such as psychosis (Mighdoll et al., 2015) and depression (Zhou et al., 2021). Recently, genome-wide based studies have shown that myelin gene expression and regulation are altered in SCZ (Hegyi, 2017). In addition,
experience-induced myelination is known to be necessary for brain function (Fields, 2008). As an example, a recent study in mice demonstrated that remote fear memory recall depends on new myelination (Pan et al., 2020). In summary, compelling evidence supports the importance of myelin integrity for brain function and its link with psychiatric diseases.

DDR1-containing modules also showed significant enrichment in microglia-related genes, in type 2 microglia-related genes specifically, in I-1, I-2, and I-4. Likewise, DDR1-containing modules were highly correlated with astrocyte-related genes in I-1, I-2, and I-4. Coexpression of DDR1 with astrocyte- and microglia-related genes could be interpreted to mean that DDR1 is expressed in these types of cells, as has already been reported (Vilella et al., 2019). Additionally, the periods of maximal enrichment (I-1 and I-2) can be inferred as the developmental periods of neurogenesis, gliogenesis, synaptic formation, and synaptic pruning. All of these processes require high activity of tissue remodeling involving both astrocytes (Nutma et al., 2020) and type 2 microglia (Tang & All of these processes require high activity of tissue remodeling involving both astrocytes (Nutma et al., 2020) and type 2 microglia (Tang & All of these processes require high activity of tissue remodeling involving both astrocytes (Nutma et al., 2020) and type 2 microglia (Tang &

We did not observe significant expression of neuronal genes (glutamatergic synapses, neurons, or PVALB interneurons), nuclear genes, mitochondria-related genes or ribosome-related genes in the DDR1 module. In rodents, ddr1 has been observed in proliferative and differentiating areas during neurogenesis in early neurodevelopment (Vilella et al., 2019); however, under the conditions studied here we could not detect covariations in the expression of DDR1 and neuronal genes in the human brain, suggesting that expression of DDR1 in fetal stages is not regulated within the main neuronal pathways.

The pathway enrichment analysis revealed that in I-1, I-2, and I-4, the top pathways associated with the DDR1 module were cell substrate adhesion and extracellular matrix interactions. However, in I-3 (≥6-40 years of age), the top enriched pathways were neuron ensheathment and the myelin sheath. Moreover, in I-3, conventional myelin markers (CNP, MAG, MBP, PLP1, and SOX10) were found in the DDR1 module (M5). Notably, Rho GTPase and actin binding were also significantly enriched in M5, which suggests, according to previous data (Yeh et al., 2019), that the role of DDR1 in oligodendrocytes is mediated by the Rho GTPase system and impacts actin cytoskeleton remodeling. This indicates cell movement that could be associated with oligodendrocyte process extension and the beginning of axon ensheathment.

As we previously demonstrated that SNP variants of DDR1 are associated with SCZ (Gas et al., 2018; Roig et al., 2007), we also tested whether SCZ susceptibility genes are significantly more common in DDR1-containing modules. We found that the overlap of the 2 lists of genes was significant in I-1 (fetal) and I-4 (≥40 years). Interestingly, in I-1 and I-4, the DDR1 module was highly correlated with astrocytes. The neurodevelopmental hypothesis of SCZ states that disturbances in the molecular development of the brain are the first step that confers susceptibility to the disease, which manifests later in life with the outbreak of psychotic symptoms (Weinberger, 1987). Currently, this hypothesis is supported by the identification of genetic risk (Owen & O’Donovan, 2017). Based on the present data, we hypothesize that, prenatally, DDR1 modestly contributes to SCZ risk and is mainly expressed in astrocytes and oligodendrocytes and involved in CNS architecture including synaptic pruning and myelination. In addition, DDR1 could contribute to SCZ risk through astrocytes’ modulation of the glutamatergic neurotransmission (Mei et al., 2018). Conversely, later in adulthood DDR1 is mainly expressed in astrocytes and microglia and could be involved in degenerative processes related to cognitive impairments also observed in chronic SCZ. This hypothesis is supported by the recent results showing that astrocyte and microglia genes as well as neuronal genes contribute to the differences in cortical thickness in schizophrenia (Patel et al., 2020). The fact that the list of genes does not significantly overlap with SCZ susceptibility genes in I-2 and I-3, when the DDR1 module is highly correlated with oligodendrocyte and myelin function, suggests that myelin-related genes do not contribute importantly to the SNP-associated risk of SCZ development, which is in agreement with recent data pointing to neurons (Skene et al., 2018; Toker et al., 2018) and astrocytes (González-Peñas et al., 2019; Toker et al., 2018). However, these interpretations are speculative, and further investigation is needed to address them.

Some limitations to our study exist. First, while the sample size allowed for sufficient statistical power, we could not further analyze subgroups of data based on, for instance, sex or shorter developmental time periods. Second, separate expression data for individual DDR1 transcripts were not obtained; therefore, we could not explore which DDR1 isoform is most associated with oligodendrocyte- and myelin-related genes. Finally, WGCNA identifies clusters of genes with expression levels that are highly correlated in a given sample, but gene coexpression does not always mean that the affected genes are expressed spatially close to each other. Future functional studies assessing the exact role of DDR1 transcripts in oligodendrocytes and other cell types in the human brain are needed.

Regarding the possible translation of these observations, Fowler and colleagues (Fowler et al., 2020) suggested that DDR1 could be a therapeutic target for neurological diseases. The author’s proposal was based upon their results showing that by inhibiting DDR1, the changes in brain tissue seen in Parkinson’s diseases such as inflammation, neuronal injury, autophagy and vesicular transport are reversed. Therefore, in the near future, with exhaustive description of the role of DDR1 in brain cells, the receptor can become a therapeutic target in psychiatry.

In summary, we provide convincing evidence for the involvement of DDR1 in oligodendrocytes and for a role for this gene in myelination during human brain development. Additionally, and against our primary
hypothesis, the data suggest that DDR1 can contribute to SCZ susceptibility through coexpression with astrocyte-related genes.

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CONFLICT OF INTEREST
All of the authors declared no conflicts of interest.

DATA ACCESSIBILITY LINKS
For this study, we used the publicly available spatiotemporal transcriptome of the human brain dataset (Kang et al., 2011); raw data files were retrieved from the GEO database (GSE25219), https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse25219.

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