Connecting DCX, COMT and FMR1 in social behavior and cognitive impairment

Anna Delprato[1*] , Emily Xiao[1,2†] and Devika Manoj[1,3†]

Abstract

Genetic variants of *DCX*, *COMT* and *FMR1* have been linked to neurodevelopmental disorders related to intellectual disability and social behavior. In this systematic review we examine the roles of the *DCX*, *COMT* and *FMR1* genes in the context of hippocampal neurogenesis with respect to these disorders with the aim of identifying important hubs and signaling pathways that may bridge these conditions. Taken together our findings indicate that factors connecting *DCX*, *COMT,* and *FMR1* in intellectual disability and social behavior may converge at Wnt signaling, neuron migration, and axon and dendrite morphogenesis. Data derived from genomic research has identified a multitude of genes that are linked to brain disorders and developmental differences. Information about where and how these genes function and cooperate is lagging behind. The approach used here may help to shed light on the biological underpinnings in which key genes interface and may prove useful for the testing of specific hypotheses.

Keywords: Intellectual disability, Social behavior, Neurogenesis, Hippocampus, Wnt signaling, *COMT*, *DCX*, *FMR1*

Introduction

The aim of this systematic review is to gain an understanding of the genetic underpinnings linking intellectual disability (ID) and social behavior in the context of three critical risk factor genes *DCX*, *COMT*, and *FMR1*. In the study by Kwan et al. [1] the authors used a method similar to ours which involved identifying signaling pathways associated with Autism Spectrum Disorder (ASD) and ID based on risk factor genes linked to these disorders that were identified in genomic studies. In this study we have started with three risk factors genes associated with a multitude of neuro-related disorders and have found through a review of the literature that they converge in Wnt signaling, neuron migration, axon, and dendrite morphogenesis. To provide further insight we use systems biology methods to investigate how these genes

could interface at the molecular and cellular level. Our approach employs a literature review and an assessment of legacy RNA-Seq datasets to identify genes with correlative expression patterns to *DCX*, *COMT*, *and FMR1* in the developing hippocampus [2]. The gene correlates were evaluated using integrative genomics methods which include an analysis of gene set intersection [3] and functional enrichment [4]. Additional insight concerning the relationship between *DCX*, *COMT* and *FMR1* was obtained by an evaluation of protein–protein interaction (PPI) networks [5, 6].

Hippocampal neurogenesis and Wnt signaling

In neurogenesis, neural stem cells proliferate, migrate, and differentiate into mature neurons. The production of new neurons is most active during development but continues throughout life in many species including humans [7, 8]. Hippocampal neurogenesis occurs in the subgranular zone of the dentate gyrus (DG) in a tightly regulated and sequential manner [9]. It is well established that dysregulation of hippocampal neurogenesis is linked to a variety of neurological disorders such as ASD, Fragile-X

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Syndrome (FXS) and ID [10–12]. This is not surprising given the role of the hippocampus in learning, long term memory, and the processing of emotional response [13].

Hippocampal neurogenesis is regulated by Wnt signaling which has been suggested as a conserved feature in both embryonic and adult neurogenesis [14–16]. The Wnt signaling pathway regulates cell fate decisions, tissue patterning, neuronal differentiation, axon outgrowth and guidance, dendrite development, synaptic function, and neuronal plasticity [17, 18].

Wnt proteins are involved in all aspects of the developing brain [19]. In neuronal development Wnt proteins bind Frizzled receptors, Tyrosine kinase receptors or the Insulin-like growth factor receptor to activate Dishevelled which results in different fates depending on the cellular context [20]. This includes gene transcription, regulation of axon and dendrite morphology and pre synaptic function via small GTPases of the Rho family, which in turn modulate neuronal polarity, dendritic spine morphology and synapses [21, 22]. The Wnt/Dishevelled axis may also proceed through a calcium signaling pathway or other pathway intermediates to modulate the guidance and branching of dendrites and axons, as well as synapse formation and remodeling [20, 23]. There is a great deal of evidence derived from genetically altered animals, cell based, and human studies supporting the role of Wnt signaling in ID and ASD [24–28]. In individuals with ASD, ID varies widely. However, in cases where [29] the two conditions coexist the *GSK3* and *CTNNB1* genes are strongly implicated [26, 30, 31]. The *CTNNB1* gene, which encodes β-catenin, is a main modulator of the canonical Wnt signaling pathway and is linked to sporadic ASD and ID [1, 29, 32]. In mice, a conditional knockout of *Ctnnb1* deleted in parvalbumin interneurons significantly impaired object recognition and social interactions and increased repetitive behaviors [24]. Moreover, data derived from large scale exome sequencing studies investigating ASD and ID have identified nonsense and missense mutations in CTNNB1 [30, 33].

DCX, *FMR1*, and *COMT* in hippocampal neurogenesis
i. Role of DCX in hippocampal neurogenesis and disease
The *DCX* gene product, doublecortin, stabilizes microtubules and stimulates their polymerization to facilitate the migration of post mitotic neurons and cortical layering in the developing brain [34]. Doublecortin acts via microtubules to form a scaffold within the cell that elongates in a specific direction, altering the cytoskeleton and moving the neuron to a targeted location [35, 36]. Doublecortin is used as a neuronal differentiation and migration marker to assess the various stages of the neurogenic process in the sub granular zone (SGZ) of the hippocampus [37]. A lack of normal doublecortin affects

the stability, organization and movement of microtubules which impairs their ability to move neurons [36]. Migrating neurons in the developing brain are particularly affected because they are mis-localized which disrupts connectivity resulting in neurological problems [38].

While the role of doublecortin in microtubule stabilization and neuronal migration is well established [39]. There is evidence that doublecortin is also involved in axon guidance via actin association and dendrite branching and complexity [35, 40, 41].

Dcx knockout mice have a simplified dendrite morphology in hippocampal pyramidal neurons [37]. Knockdown of *Dcx* in cultured rat neurons also led to a simplified dendrite morphology [15, 19]. Conversely, overexpression of doublecortin increases dendrite complexity [37]. Interestingly, daily mild stress exposure in mice altered dendrite length and complexity in doublecortin positive immature neurons of the dentate gyrus [42].

Several diseases are linked to *DCX* variants such as Isolated Lissencephaly Sequence (ILS) which is a disorder characterized by abnormal brain development that results in the brain having a smooth surface (lissencephaly) instead of normal gyri and sulci [43, 44]. This causes severe neurological issues such as ID and recurring seizures which begin in infancy. Most of the *DCX* gene mutations that cause ILS are a result of a single amino acid substitution in doublecortin producing a protein with little or no function [45].

Subcortical Band Heterotopia (SBH) is another disorder associated with mutation in the *DCX* gene [46]. This condition causes abnormal brain development that is less severe than ILS but has a similar pathology. In people with subcortical band heterotopia, some neurons that should be part of a certain region of the brain do not reach their destination [47]. Neurons stop their migration process in areas of the brain where they are not supposed to be and form band-like clusters of tissue. Male and female differences have been noted in lissencephaly and SBH related to *DCX* mutations which predominantly causes lissencephaly in hemizygous males and SBH in heterozygous females. Both males and females exhibit language impairment and epileptic seizures however cognitive ability varies between the two sexes. Males exhibit early and severe cognitive impairment whereas cognitive ability ranges from mild to severe in females [48, 49].

ii. Role of COMT in hippocampal neurogenesis and disease
The *COMT* gene encodes the enzyme, catechol-*O*-methyltransferase which catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines in several neurotransmitters such as dopamine, epinephrine, and norepinephrine. This *O*-methylation results in

one of the major degradative pathways of the catecholamine transmitters.

COMT has both soluble and membrane-bound isoforms and is expressed in many different tissues. The membrane bound form (MB-COMT) has a preference for brain tissue and especially the hippocampus [50]. MB-COMT is located on axons and neuron cell bodies in pre and postsynaptic structures [51]. Analyses of MB-COMT orientation with computer simulation, flow cytometry, and a cell surface enzyme assay indicates that the C-terminal catalytic domain of MB-COMT is in the extracellular space, which suggests that MB-COMT can inactivate synaptic and extrasynaptic dopamine on the surface of presynaptic and postsynaptic neurons [51].

MB-COMT is expressed by postsynaptic neurons and/or surrounding glia (Gogos et al. 1998; Schott et al. 2010; Rivett et al. 1983b; Karhunen et al. 1995a; Matsumoto et al. 2003) where it modulates synaptic dopamine levels. Dopamine levels are increased by as much as 60% in *Comt* knock-out mice [7] (e.g., Chen et al. 2004; Lebedeva et al. 2009; Grigorenko et al. 2007).

COMT localization has also been observed in dendrites [51, 52] Localization of COMT in rats using immunoelectron microscopy results in the presence of reaction product in dendritic processes and spines associated with postsynaptic membranes [50]. COMT is particularly important in the prefrontal cortex, the region of the brain associated with personality, executive function, inhibition of behaviors, abstract thinking, emotion, and working memory [53, 54]. Several studies have also demonstrated its relevance in the hippocampus [55–57] and neurogenesis [53, 58, 59]. Copy number elevation of *COMT* is associated with reduced proliferation of neural stem/progenitor cells in vitro and the migration of their progeny in the hippocampus granular layer in vivo [58] as well as hippocampal volume changes in the CA2/CA3 regions [59]. The *COMT* genotype influenced the maturation of working memory associated with problem solving and knowledge acquisition skills in both mice and humans [40, 41].

COMT and Wnt signaling are both linked to schizophrenia which has been postulated to arise from abnormal neurogenesis associated with embryonic neural stem cells [60–62]. The relationship between COMT and Wnt signaling in the context of neurogenesis may be based on dopamine regulation. The *COMT* gene has long been considered a candidate gene for schizophrenia because it degrades dopamine and individuals with schizophrenia have increased dopamine levels [63]. Wnt signaling is associated with schizophrenia, particularly via the *GSK3* gene which acts downstream of the dopamine (D2) receptor [64, 65]. Drugs that induce psychosis increase D2 receptors and drugs that are used to treat psychosis

alter GSK3 signaling. GSK3 phosphorylates CTNNB1 resulting in its degradation and the down regulation of the Wnt signal [66].

COMT is also associated with 22q11.2 Deletion Syndrome which results from a deletion of a region of chromosome 22 that contains 30–40 genes [58]. Learning disabilities and psychiatric disturbances such as ASD, schizophrenia, and attention deficit hyperactivity disorder (ADHD) are associated with 22q11.2 Deletion Syndrome [67, 68].

Individuals with this disorder have only one copy of the *COMT* gene in each cell instead of the usual two copies making them more likely to develop neuropsychiatric disorders. *COMT* variants and dopamine levels have been linked to ASD [69]. In a study of 52 individuals diagnosed with ASD, *COMT* genotypes and dopamine levels correlated with ASD phenotype severity [69]. In another study investigating dopaminergic effects in two mouse models of ASD, differential expression of tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine biosynthesis, was observed between the strains. There was a reduction of TH in BTBR/J mice and normal levels in *Fmr1*-KO animals. Striatal dopamine transporter expression was reduced in both strains. Interestingly, application of intranasal dopamine to *Fmr1*-KO animals alleviated their impairment of social novelty, in altered association with reduced striatal TH [70]. (https://molecularbrain.biomedcentral.com/articles/10.1186/s13041-020-00649-7).

Besides schizophrenia, ID, and ASD, COMT function in the context of dopamine regulation is also associated with addiction and depression [71–73].

iii. Role of FMR1 in hippocampal neurogenesis and disease

The *FMR1* gene encodes the FMRP protein. Results from many years of research indicate that FMRP acts as a transporter carrying mRNA from the nucleus to areas of the cell where proteins are assembled [74]. Altered neurogenesis has been reported in an *Fmr1*-/-knockout mouse model. Animals displayed an increase in neuronal differentiation in the DG but no significant difference in the number of neurons added to the DG [12]. The connection between *FMR1* and Wnt signaling is supported by the finding that GSK3β, a negative regulator of Wnt signaling, is elevated in FXS animal models [65]. Correction of the increased GSK3 activity with lithium or GSK3β inhibitors in mice rescues neurobehavioral and brain morphological abnormalities [75]. Furthermore, inhibition of GSK3β is reported to improve hippocampus-dependent spatial learning tasks and restore neurogenesis in a mouse model of FXS [65].

FMRP localizes to axons and dendrites [76]. Studies involving both humans and mice support the role of

FMRP expression in normal spine morphological development [77, 78]. The data obtained from human post mortem tissue derived from donors with FXS and animal models in which FMRP is underexpressed or not expressed at all indicate an increase in spine density, spine length and immature spine morphology [76, 79].

FMRP has an inhibitory effect on mRNA translation and regulates translation in pre- and post-synaptic terminals [80]. A possible explanation of the effects of FMRP in spine dynamics and morphology is by influencing local mRNA translation [81]. A trinucleotide repeat mutation in the *FMR1* gene is the underlying cause of FXS [82]. The CGG repeat disrupts gene expression and as a consequence little or no protein is produced [82]. FXS is one of the most commonly inherited forms of ID and monogenic causes of ASD [83, 84].

Methods
Literature review
The literature review for identifying common themes associated with *DCX*, *COMT*, and *FMR1* was performed using PubMed, Google Scholar, and the Online Mendelian Inheritance in Man database [85]. Repositories and databases were searched using keywords associations.

Gene sets and evaluation
Microarray data were collected from the Allen Brain Database Developing Human Brain Atlas (https://human.brain-map.org/, https://human.brain-map.org/). To obtain the data, a gene search for *DCX*, *COMT*, and *FMR1* was performed. Each of these genes were used to query the atlas for correlates to the developing hippocampus.

Genes whose expression pattern correlated with DCX, COMT, and FMR1 were collected for analysis. Correlates with a range of Pearson r values from |0.7 to 1.0| were considered in the analysis (Additional file 1: Workbook S1). The rationale was to investigate genes with a similar expression pattern in order to identify correlates specific and common to DCX, COMT, and FMR1 associated with neurogenesis, Wnt signaling, ID, and social behavior.

Each gene set was evaluated using Gene Ontology (GO) enrichment via the Database for Annotation, Visualization and Integrated Discovery (DAVID, version 6.8) [86]. Gene Set overlap among the correlates for DCX, COMT, and FMR1 was assessed using Venny 2.0 [87], an online program that compares lists of items to determine the shared and unique genes.

Network analysis
The String database (version 11.0) was used to build a protein–protein interaction network (PPI) for DCX, COMT, and FMRP [5, 88]. The network was constructed based on experimentally validated interactions using the medium confidence score of 0.4. The combined scores for the interactions are computed by combining the probabilities from the different evidence channels and corrected for the probability of randomly observing an interaction. First and 2nd shell interactions are included in the network. The network was exported from STRING and analyzed in Cytoscape (version 3.7) [6, 89]. Network clusters and enriched themes were identified with Cytoscape plugins MCODE (version 1.6.1) and ClueGo (version 2.5.7) [4, 90]. The nodes in the networks have been manually arranged for proper visibility.

Results
To investigate how these genes may interact we performed a literature review which supported that Wnt signaling, neuron migration, and axon and dendrite morphogenesis were common factors in connecting *DCX*, *COMT*, and *FMR1* in ID and social behavior. Based on the results of the literature review, we examined RNA-Seq datasets of genes with correlating expression patterns to *DCX*, *COMT*, and *FMR1* in the developing hippocampus in order to gain further insight. GO annotation was used to identify gene correlates associated with Wnt signaling, neurogenesis, social behavior, and ID. Among the correlates, many genes are linked to Wnt signaling, neurogenesis, and ID and to a lesser extent social behavior (Tables 1, 2, 3, 4). All of the results from the GO analysis which includes biological processes, cellular localization, molecular function, as well as pathway and disease information are provided in Additional file 2: Workbook S2.

The results from the analyses of gene set overlap which was performed to shed light on how these genes might interact at the molecular level, consisted of identifying common genes among the correlates for *DCX*, *COMT*, and *FMR1*. Findings indicate that there were many shared relevant genes inversely correlated with *COMT*, *DCX*, and *FMR1* expression patterns particularly in the context of ID (*CHAMP1*, *DCHS1*, *EML1*, *MCPH*, *TCF4*, *CTCF*, *FAT4*, *FXR2*, *GATAD2B*, *KIAA2022*, *SETBP1*, *TAF2*, *BCAP31*, *BRWD3*, *NUFIP1*, *ATRX*) and to a lesser extent social behavior (*AUTS2*, *PCM1*). Other shared correlating genes with relevance are linked to neurogenesis, Wnt signaling, transcription regulation, microtubule and axon related processes (Table 5 and Additional file 2: Workbook S2).

The majority of ID related genes are shared between *DCX* positive and *COMT* negative correlates. A possible

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Table 1 Wnt pathway genes associated with DCX, COMT and FMR1 correlates in the hippocampus

DCX +	ACTB, ACTG1, ACVR1B, ARID1A, ARID1B, BCL9, CDH2, CELSR3, CSNK1E, CSNK1G1, CSNK2A1, DACT1, DCHS1, FAT4, FZD7, GNB1, GNG2, HDAC2, MYCN, PCDHB12, PCDHB14, PCDHB2, PCDHB8, PCDHB9, PPP2R5E, PYGO1, SIAH1, SMAD1, SMAD4, SMARCA4, SMARCB1, SMARCD1
DCX −	CDH19, DCHS1, GNA14, GNA15, GNG13, GNG7, KREMEN2, MYH13, MYH7B, WNT10A, WNT6, WNT9B
COMT +	BMPR1B, GNA14, ITPR3, KREMEN2, NFATC1, NFATC2 PPARD, PPP2R5A, SMARCD2, TCF7
COMT −	CELSR3, CSNK1G1, CSNK1G3, DACT1, FAT4, GSK3B, HDAC2, MAP3K7, PCDHB3, PPP2R5E, PRKCI
FMR1 +	LRP6, PPP2CA, PRKCI, SMARCA5, TBL1XR1
FMR1 −	DVL1, DVL1P1

Positive and negative associations are indicated with "+" and "−" respectively

Table 2 DCX, COMT and FMR1 gene correlates associated with intellectual disability

DCX +	ACTB, ACTG1, ADNP, ARID1A, ARID1B, AUTS2, BBS9, CASK, CHAMP1, CTCF, DCHS1, DYRK1A, EDC3, EFTUD2, EHMT1, EML1, EXT2, FAT4, FGD1, FOXG1, FRMD4A, FTSJ1, FXR2, GATAD2B, GNB1, IGBP1, KAT6A, KIAA2022, LMAN2L, MCPH1, NONO, OPHN1, POGZ, RBMX, RSPRY1, SETBP1, SMARCA4, SMARCB1, SMC3, SOX11, TAF2, TCF4, TTI2, TUBGCP4, ZC4H2, ZEB2, ZNF711
DCX −	BCAP31, MAP2K1
COMT +	BCAP31, CHI3L2, CLIC2, HEPACAM, PGAP3, PIGV, PPIC, SLC6A8, TECR, VWA3B
COMT −	ATP8A2, ATRX, AUTS2, BRWD3, CHAMP1, CTCF, DDX3X, EML1, FAT4, FXR2, GATAD2B, KDM6A, KIAA2022, MCPH1, MED13L, NUFIP1, PAK3, PGAP1, SETBP1, SOX5, TAF2, TCF4, TTC21B, UPF3B
FMR1 +	AMMECR1, ATRX, BRWD3, COG6, CRBN, CUL4B, FMR1, KIAA0196, KIAA1033, NIPBL, NUFIP1, NUFIP2, RAB3GAP2, RAD21, RBBP8, RPS6KA3, TBL1XR1, TDP2, TTC21B, USP9X, ZDHHC15
FMR1 −	No associated genes

Positive and negative associations are indicated with "+" and "−" respectively

Table 3 DCX, COMT and FMR1 gene correlates associated with social behavior

DCX +	DNAJC9, AUTS2, EIF4, EBP2
DCX −	SHANK3, ANXA7, MYH14, NPAS4
COMT +	DRD4, UCN
COMT −	KRAS, AUTS2, PCM1
FMR1 +	PCM1
FMR1 −	DVL1

Positive and negative associations are indicated with "+" and "-" respectively

explanation could be related to the roles of *COMT* and *DCX* and their effects on brain structure and neurogenesis. In patients with schizophrenia the *COMT Val* allele is associated with smaller temporal and frontal brain areas [91] and as described in the Introduction, *DCX* variants cause severe lamination defects in the cortical and hippocampus regions [92]. In addition, there is supporting evidence that increased dopamine neurotransmission stimulates neurogenesis [93, 94].

The shared genes between *COMT* and *FMR1* are also inversely correlated and are associated with similar relevant themes (Table 5). There were no relevant genes common between *FMR1* and *DCX*.

To gain further insight, an analysis of protein–protein interaction networks of experimentally validated

Table 4 DCX, COMT and FMR1 neurogenesis related gene correlates

DCX +	AKT1, ARID1A, ARID1B, BCL11B, BZW2, CEP120, DACT1, DBN1, DCHS1, DOCK7, DPYSL2, DYNLT1, EFNB2, EPHB1, EPHB2, FAT4, FOXN4, GPSM1, IGSF9, INA, INSM1, ISLR2, KDM1A, KIAA2022, KIDINS220, NEUROD2, NGFR, OPHN1, RBM45, SEMA3A, SEMA3C, SEMA4C, SMARCA4, SMARCB1, SMARCD1, SOX11, SRGAP2, STMN1, TCF4, XRCC5
DCX −	BCL6, CHN1, CIT, GLDN, HAP1, NPAS4, NTRK1, PAX5
COMT +	BCL6, CSPG5, HAP1, METRN, MT3, NDRG2, PLXNB3, SIRT2, ZC3H12A
COMT −	ARHGEF2, BCL11B, BHLHB9, BZW2, CEP120, DACT1, EFNB2, EIF2AK4, EPHA4, EPHA7, FAT4, FBXO45, GSK3B, KIAA2022, KIDINS220, KIF2A, NEUROD6, PCM1, PRDM8, ROBO2, SEMA3A, SEMA3C, SPAST, STMN1, TCF4, XRCC5
FMR1 +	CCDC88A, EIF2AK4, HOOK3, IMPACT, PCM1, PHF10 SETX, ZEB1
FMR1 −	RFNG

Positive and negative associations are indicated with "+" and "−" respectively
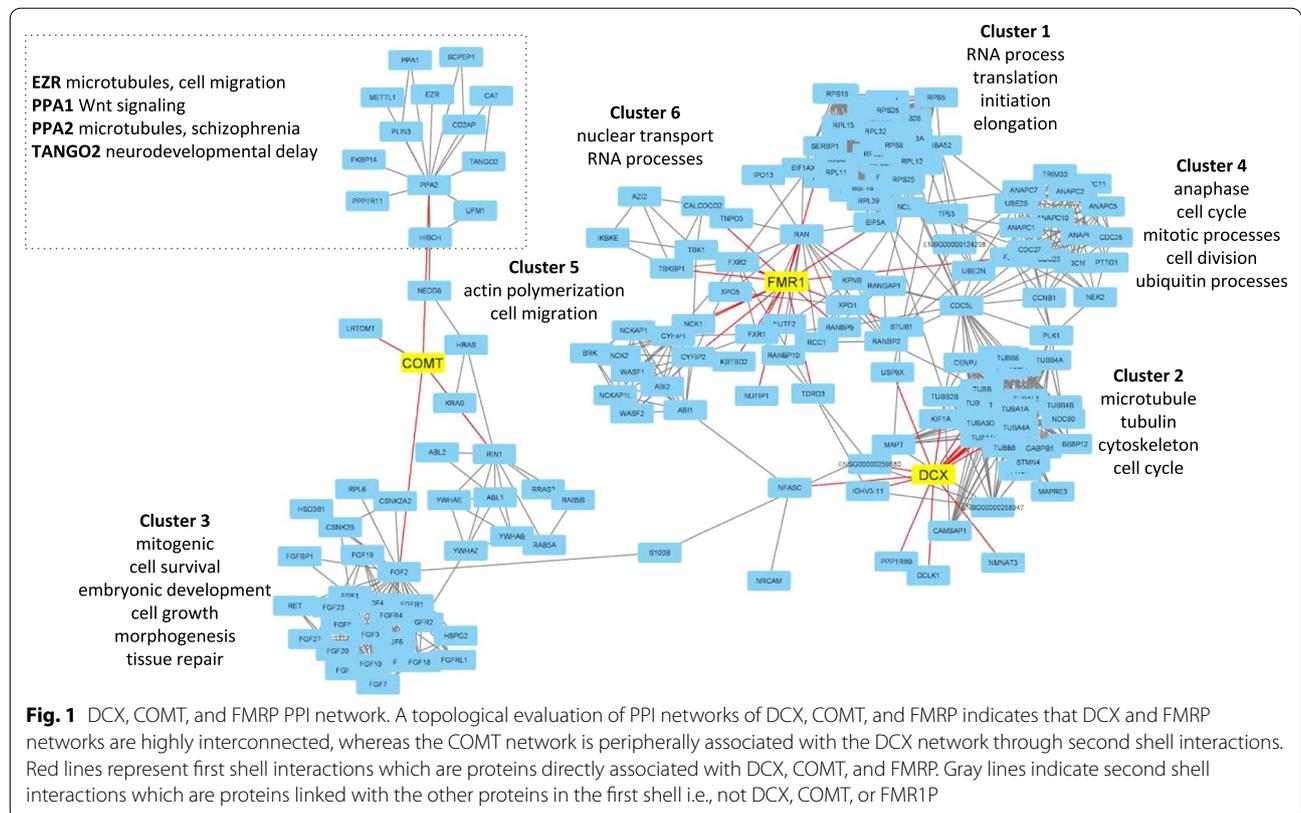
interactions for *DCX*, *COMT*, and *FMRP* was performed. An assessment of network topology and connectivity indicates that the individual PPI networks for these genes connect (Fig. 1, Additional file 3: Workbook S3).

The DCX and FMRP networks are more highly interconnected via proteins associated with RNA binding and cell cycle such as FXR1/2 and CYFIP2, whereas the

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Table 5 Relevant shared gene correlates for DCX, COMT and FMR1

COMT +/DCX −		
	BCAP31	Apoptosis, ubiquitin dependent catabolic process protein transport, X-linked mental retardation, dystonia, cerebral hypomyelination
	BCL11B	Neurogenesis, axon guidance, neuron projection, transcription, splicing, methylation
	GNA14	Signal transduction phospholipase C-activating dopamine receptor signaling pathway
	HAP1	Synaptic transmission axonal transport, cerebellum development, cell projection organization, neurogenesis, transport along micro-tubules
	KREMEN2	Wnt signalling
COMT −/DCX +		
	AUTS2	Transcription regulation, Autism, mental retardation/ID
	BZW2	Nervous system development, cell–cell adhesion, neurogenesis
	CELSR3	Neuron migration, axonal fasciculation, dopaminergic serotonergic neuron axon guidance, Wnt signaling pathway
	CEP120	Regulation of centrosome duplication, cerebral cortex development, neurogenesis, astral microtubule organization
	CHAMP1	Protein localization to kinetochore, protein localization to microtubule, attachment of mitotic spindle microtubules to kinetochore
	CSNK1G1	Endocytosis, regulation of cell shape, Wnt and Hedgehog signaling
	CTCF	Transcription regulation, DNA methylation, mental retardation, Mental retardation, autosomal dominant 21
	DACT1	Transcription regulation, Wnt signaling
	EFNB2	Cell adhesion, axon guidance, neurogenesis
	EML1	Microtubule cytoskeleton organization, epilepsy, mental retardation
	FAT4	Neurogenesis, cerebral cortex development, cell adhesion, mental retardation/ID
	FXR2	RNA transport, negative regulation of translation, Fragile X mental retardation
	GATAD2B	Transcription, DNA methylation, mental retardation/ID
	HDAC2	Transcription regulation, chromatin remodeling neuron projection and dendrite development
	KIAA2022	Nervous system development, X-linked mental retardation, neurogenesis mental retardation, X-linked 98, neurite extension and migration
	KIDINS220	Dendrite morphogenesis, neuron projection development, neurogenesis
	MCPH1	Mitotic spindle orientation, regulation of gene expression, cerebral cortex development, mental retardation, Microcephaly 1, primary, autosomal recessive
	SEMA3A	Neuron migration, axon guidance, neurogenesis
	SEMA3C	Neuron migration, axon guidance, neurogenesis
	SETBP1	DNA binding, Schinzel-Giedion midface retraction syndrome, mental retardation, autosomal dominant 29
	STMN1	Microtubule depolymerization, mitotic spindle organization, axongenesis, neurogenesis
	TAF2	Transcription regulation, mental retardation/ID Mental retardation, autosomal recessive 40
	TCF4	Transcription regulation, neurogenesis, epilepsy, mental retardation, Pitt-Hopkins syndrome
	XRCC5	Transcription, DNA recombination, neurogenesis
FMR1 +/COMT −		
	ATRX	DNA methylation, chromatin remodeling, transcription, Mental retardation: alpha-thalassemia/mental retardation syndrome, mental retardation-hypotonic facies syndrome, X-linked 52/intellectual development disorder
	BRWD3	Transcription regulation, mental retardation X-linked intellectual developmental disorder
	EIF2AK4	Translation, ribosome structure and biogenesis, learning and long-term memory
	NUFIP1	RNA processing, transcription fragile X mental retardation-interacting protein 1
	PCM1	Neuron migration, microtubule organization and anchoring, social behavior, negative regulation of neurogenesis
	TTC21B	Transcription regulator, smoothened signaling pathway regulation
FMR1 −/COMT +		
	GAS6	Dendritic cell differentiation, apoptosis
	KIF19	Axon, microtubule depolymeriation
	NDUFS7	Synapse, neuron projection

Positive and negative correlative gene expression patterns are indicated with "+" and "−" respectively

Fig. 1 DCX, COMT, and FMRP PPI network. A topological evaluation of PPI networks of DCX, COMT, and FMRP indicates that DCX and FMRP networks are highly interconnected, whereas the COMT network is peripherally associated with the DCX network through second shell interactions. Red lines represent first shell interactions which are proteins directly associated with DCX, COMT, and FMRP. Gray lines indicate second shell interactions which are proteins linked with the other proteins in the first shell i.e., not DCX, COMT, or FMR1P

COMT network is linked to the DCX and FMRP networks via the neurotrophic factor S100B which enhances hippocampal neurogenesis in rodent models, as well as the microtubule associated proteins MAPT, which promotes microtubule assembly and stability and TUBA1A which is a fundamental component of microtubules [95–98].

Assignment of over-represented themes based on GO and pathway analysis of the PPI network modules are: Module 1. RNA process translation initiation elongation, Module 2. Microtubule tubulin cytoskeleton cell cycle, Module 3. Mitogenic cell survival embryonic development cell growth morphogenesis tissue repair, Module 4. Anaphase cell cycle mitotic, cell division and ubiquitin processes, Module 5. Actin polymerization cell migration, Module 6. Nuclear transport, RNA processes (Fig. 1).
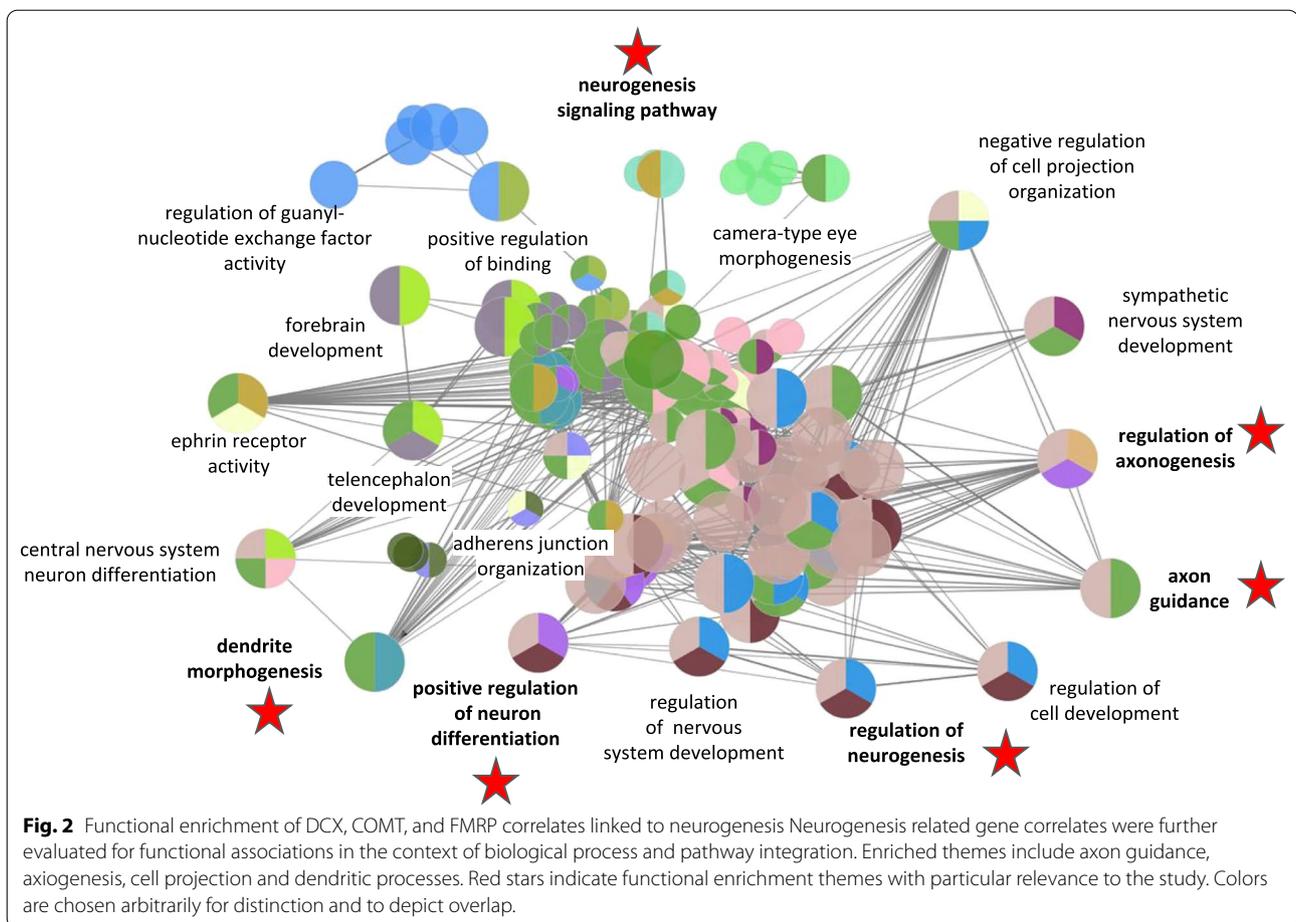
An analysis of neurogenesis related genes from the *DCX*, *COMT*, and *FMR1* correlates in the context of enriched functional categories results in thirty-two groups and within those groups one hundred and ninety-one GO annotations. Among the categories there are many related to axon, dendrite, and neuron processes as

well as several other relevant classifications (Fig. 2 and Additional file 4: Workbook S4).

Conclusions

Polymorphisms in the *DCX*, *COMT*, and *FMR1* genes are associated with severe and diverse brain development and neuropsychiatric disorders. Each of these genes has been linked to ID and social behavior. To investigate how these genes may interact we performed a literature review which pointed to Wnt signaling, neuron migration, and axon and dendrite morphogenesis as common factors.

Based on the results from the literature review, we analyzed gene expression patterns in the developing hippocampus to gain additional support and insight into the relationship between these genes in the context of identifying molecular interactions and signaling pathways that may connect them. The findings from these analyses support the results obtained from the literature review and provide useful information for follow up studies.

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Fig. 2 Functional enrichment of DCX, COMT, and FMRP correlates linked to neurogenesis Neurogenesis related gene correlates were further evaluated for functional associations in the context of biological process and pathway integration. Enriched themes include axon guidance, axiogenesis, cell projection and dendritic processes. Red stars indicate functional enrichment themes with particular relevance to the study. Colors are chosen arbitrarily for distinction and to depict overlap.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12993-022-00191-7.

Additional file 1: Workbook S1. *DCX*, *COMT*, and *FMR1* hippocampal gene correlates.

Additional file 2: Workbook S2. Gene Ontology analysis of *DCX*, *COMT*, and *FMR1* hippocampal gene correlates.

Additional file 3: Workbook S3. DCX, COMT, and FMRP protein–protein interaction network.

Additional file 4: Workbook S4. *DCX*, *COMT*, and *FMR1* functional enrichment categories for neurogenesis genes.

Availability of data and materials
All data are provided with the manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Not applicable.

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