Deep multitask learning of gene risk for comorbid neurodevelopmental disorders

Ilayda Beyreli[1,#], Oguzhan Karakahya[1,#], and A. Ercument Cicek[1,2,*]

[1] Department of Computer Engineering, Bilkent University, Ankara, Turkey 06800
[2] Computational Biology Department, Carnegie Mellon University, Pittsburgh, PA 15213

Abstract. Autism Spectrum Disorder (ASD) and Intellectual Disability (ID) are comorbid neurodevelopmental disorders with complex genetic architectures. Despite large-scale sequencing studies only a fraction of the risk genes were identified for both. Here, we present a novel network-based gene risk prioritization algorithm named DeepND that performs cross-disorder analysis to improve prediction power by exploiting the comorbidity of ASD and ID via multitask learning. Our model leverages information from gene co-expression networks that model human brain development using graph convolutional neural networks and learns which spatio-temporal neurovelopmental windows are important for disorder etiologies. We show that our approach substantially improves the state-of-the-art prediction power in both single-disorder and cross-disorder settings. DeepND identifies mediodorsal thalamus and cerebral cortex brain region and infancy to childhood period as the highest neurodevelopmental risk window for both ASD and ID. We observe that both disorders are enriched in transcription regulators. Despite tight regulatory links in between ASD risk genes, such is lacking across ASD and ID risk genes or within ID risk genes. Finally, we investigate frequent ASD and ID associated copy number variation regions and confident false findings to suggest several novel susceptibility gene candidates. DeepND can be generalized to analyze any combinations of comorbid disorders and is released at `http://github.com/ciceklab/deepnd`.
# Equal contribution.*Correspondance: cicek@cs.bilkent.edu.tr

1 Introduction

Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder with a complex genetic architecture in which around a thousand risk genes have a role [35]. Large consortia efforts have been paving the way for understanding the genetic, functional and cellular aspects of this complex disorder via large scale exome [18, 41, 80, 71, 70, 66, 40] and genome [31, 22, 20, 58, 1, 4] sequencing studies. Latest and also the most comprehensive study to date analyzed $\sim 36k$ samples (6,430 trios) to pinpoint 102 risk genes ($FDR \leq 0.1$) [81]. Overwhelming evidence suggests that genetic architectures of neuropsychiatric disorders overlap [63, 78, 54]. For instance, out of the twenty five SFARI Cat I ASD risk genes (i.e., highest risk), only five are solely associated with ASD. Genes like *CHD2*, *SCN2A* and *ARID1B* are associated with six neurodevelopmental disorders. Intellectual Disability (ID) is one of such comorbid disorders which manifests itself with impaired mental capabilities. Reminiscent of ASD, ID also has a complex genetic background with hundreds of risk genes involved and identified by rare *de novo* disruptive mutations observed in whole exome and genome sequencing studies [17, 23, 25, 76, 83, 89, 100]. ASD and ID are frequently observed together [64]. In 20, CDC reported that 31% of children with ASD were also diagnosed with ID and 25% were borderline [6]. They also share a large number of risk genes [55]. Despite these similarities, Robinson *et al.* also point to differences in genetic architectures and report that intelligence quotient (IQ) positively correlates with family history of psychiatric disease and negatively correlates with *de novo* disruptive mutations [77]. Yet, the shared functional circuitry behind is mostly unknown.

The current lack of understanding on how comorbid neuropsychiatric disorders relate mostly stems from the incomplete profiling of individual genetic architectures. Statistical methods have been used to assess gene risk using excess genetic burden from case-control and family studies [35] which are recently extended to work with multiple traits [68]. Yet, these tools work with genes with

observed disruptive mutations (mainly *de novo*). It is often of interest to use these as prior risk and obtain a posterior gene interaction network-adjusted risk which can also assess risk for genes with no prior signal. Network-based computational gene risk prediction methods come handy for (i) imputing the insufficient statistical signal and providing a genome-wide risk ranking, and (ii) finding out the affected cellular circuitries such as pathways and networks of genes [35, 29, 24, 37, 69, 27, 26, 67, 10]. While these methods have helped unraveling the underlying mechanisms, they have several limitations. First, by design, they are limited to work with a single disorder. In order to compare and contrast comorbid disorders such as ASD and ID using these tools, one approach is to bag the mutational burden observed for each disorder assuming two are the same. However, disorder specific features are lost as a consequence [29]. The more common approach is to perform independent analyses per disorder and intersect the results. Unfortunately, this approach ignores valuable source of information coming from the shared genetic architecture and lose prediction power as per-disorder analyses have less input (i.e., samples, mutation counts) and less statistical power [81, 12, 37]. Second, current network-based gene discovery methods can work with one or two integrated gene interaction networks [27, 57, 37, 49]. This means numerous functional interaction networks (e.g., co-expression, protein interaction etc.) are disregarded which limits and biases the predictions. Gene co-expression networks that model brain development are a promising source of diverse information regarding gene risk, but currently cannot be fully utilized, as the signal coming from different networks cannot be deconvoluted. Usually, investigating such risky neurodevelopmental windows is an independent downstream analysis [95, 49]. Should this process be integrated within the risk assessment framework, it has potential to provide valuable biological insights and also to improve the performance of the genome-wide risk assessment task.

Here, we address these challenges with a novel cross-disorder gene discovery algorithm (Deep Neurodevelopmental Disorders algorithm - *DeepND*.) For the first time, DeepND analyzes comorbid neurodevelopmental disorders simultaneously over multiple gene co-expression networks and explicitly learns the shared and disorder-specific genetic features using multitask learning. Thus, the predictions for the disorders *depend* on each other's genetic architecture. The proposed DeepND architecture uses graph convolution to extract associations between genes from gene co-expression networks. This information is processed by a mixture-of-experts model that can self-learn critical neurodevelopmental time windows and brain regions for each disorder etiology which makes the model interpretable. We provide a genome-wide risk ranking for each disorder and show that the prediction power is improved in both singletask (single disorder) and multitask settings. DeepND identifies mediodorsal thalamus and cerebral cortex brain region and infancy to childhood period as the highest neurodevelopmental risk window for both disorders. We observe that top percentile risk genes for both disorders are enriched in transcription regulators. Despite tight regulatory links in between ASD risk genes, we observe loose connectivity across ASD and ID risk genes or within ID risk genes. Finally, we investigate frequent ASD and ID associated copy number variation regions and confident false findings to suggest several novel risk gene candidates. The software is released at `http://github.com/ciceklab/deepnd`. This neural network architecture can easily be generalized to other disorders with a shared genetic component and can be used to prioritize focused functional studies and possible drug targets.

2 Results

Using a deep learning framework which combines graph convolutional neural networks with a mixture of experts model, we perform a genome-wide risk assessment for ASD and ID simultaneously in

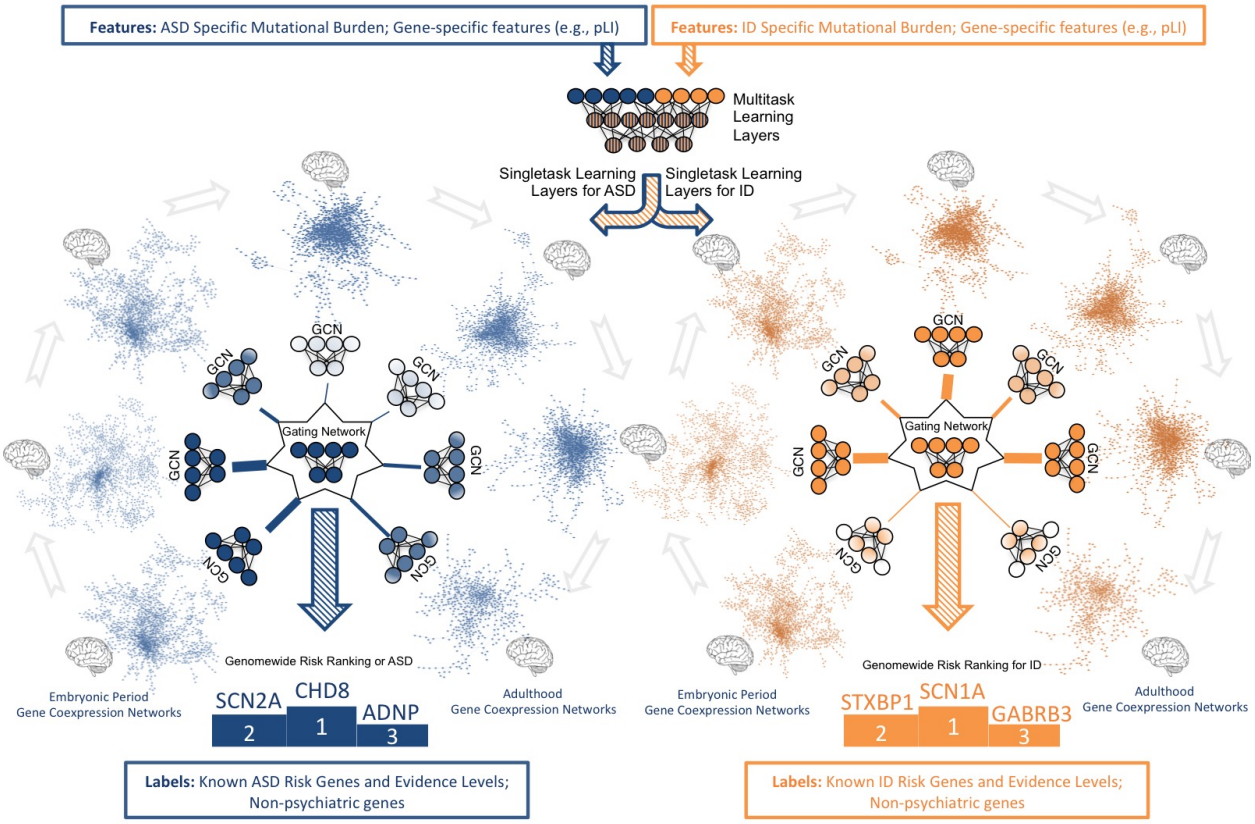

Fig. 1: System model of the proposed deep learning architecture for genome-wide cross-disorder risk assessment (DeepND). The algorithm takes the following information as input: (i) disorder specific features for every gene (e.g., *de novo*/transmitted loss of function/missense mutation counts from family etc.) as well as non-disorder related features (e.g., pLI); (ii) disorder specific ground truth genes that are labeled as positive with varying level of evidence based on a literature search; and (iii) non-psychiatric genes which are labeled as negative. The features are passed through fully-connected multitask layers that learn shared weights for both disorders and produces a new feature representation. This new representation is then input to singletask graph convolutional neural networks (GCNs), each processing one of fifty-two gene co-expression networks that represent different brain regions and neurodevelopmental time windows. The output of GCNs are then weighted by the Gating Network to learn which networks are informative for the gene risk assessment (shade of the network indicates importance). Thus, DeepND learns which neurodevelopmental windows confer more risk for each disorder's etiology. The final output is a genome-wide risk probability ranking per disorder, which are then used for various downstream analyses to understand the underlying functional mechanisms and to compare/contrast both disorders. The singletask layers are exclusively trained with the ground truth genes of the disorder they belong. Thus, they learn only disorder specific parameters and disorder-specific networks that implicate risk.

a multitask learning setting and detect neurodevelopmental windows that are informative for risk assessment for each disorder. Our results point to the shared disrupted functionalities and novel risk genes which provides a road map to researchers who would like to understand the ties between these two comorbid disorders.

2.1 Genome-wide Risk Prediction for ASD and ID

To have a model of evolving gene-interactions throughout brain development, we extracted 52 gene co-expression networks from the BrainSpan dataset [85, 45] using hierarchical clustering of brain regions and a sliding window approach [95]. These networks are used to assess the network-adjusted posterior risk for each gene given the prior risk features. As for prior risk features, we used various (i) gene specific features (e.g., pLI), and (ii) ASD and ID mutation burden indicators (e.g., number of *de novo* loss-of-function mutations) obtained from large-scale WES studies for each disorder (Methods).

The deep neural network architecture (DeepND) performs a semi-supervised learning task, which means a set of positively and negatively labeled genes are required as ground truth per disorder. As also done in [49], we obtained 594 ASD-positive genes (Supplementary Table 1) from public databases which are categorized into 4 evidence levels based on the strength of evidence in the literature (e.g., SFARI Gene - http://gene.sfari.org - categorization providing the highest level of evidence, whereas text mining based evidence from Gene2Mesh - http://gene2mesh.ncibi.org - has the lowest confidence). For ID, we curated a ground truth ID risk gene set of 237 genes using landmark review studies on ID gene risk [25, 32, 88, 39, 14] (Supplementary Table 2). We generated two evidence level sets similar to the ASD counterpart: E1 and E2 sets where each set includes genes which are recurrently indicated in multiple studies. As for the negatively labeled genes, we use 1074 non-mental-health related genes for both disorders which is curated by Krishnan et al., (2016) (Supplementary Table 1).

DeepND uses the multitask learning paradigm where multiple tasks are solved concurrently (i.e., genome wide risk assessment for ASD and ID). Thus, the network learns a shared set of weights for both disorders and also disorder-specific set of weights (Figure 1). First, the model inputs the prior risk features of a gene for both disorders (i.e., concatenated) and using fully-connected layers produces a transformed feature set per gene. The set of weights learnt in these layers are affected by the ground truth labels for both disorders, and thus, are shared. Then, the architecture branches out to 2 single task layers, one per disorder (blue for ASD and yellow for ID in Figure 1). For each single task branch, these transformed features are input to 52 graph-convolutional neural networks (GCNs). Each GCN processes a co-expression network that represents a neurodevelopmental window and and extracts network-adjusted gene risk signatures (i.e., embeddings) [81, 67] (Methods). Finally, these embeddings are fed into a fully-connected gating network along with the prior risk features. The gating network assigns a weight to each GCN which is proportional to the informativeness of the embedding coming from each neurodevelopmental window. Thus, the model also learns which windows are important for prediction of and ASD/ID risk genes. This also means they are important in the etiology of the disorder. In the end, each disorder-specific subnetwork produces a genome-wide ranking of genes being associated with that disorder along with risk probabilities . To quantify the contribution of the co-analyzing comorbid disorders (i.e., multitask) as opposed to individual analysis (i.e., singletask), we also present our results of DeepND when it is run on a single task mode (DeepND-ST). In this mode, the fully connected layers that transform feature sets are removed and feature sets are directly fed into the GCNs (Methods). We show that the genome-wide risk assessment of DeepND is robust, precise and sensitive and substantially improves the state of the art both in terms of performance and interpretability of the predictions.

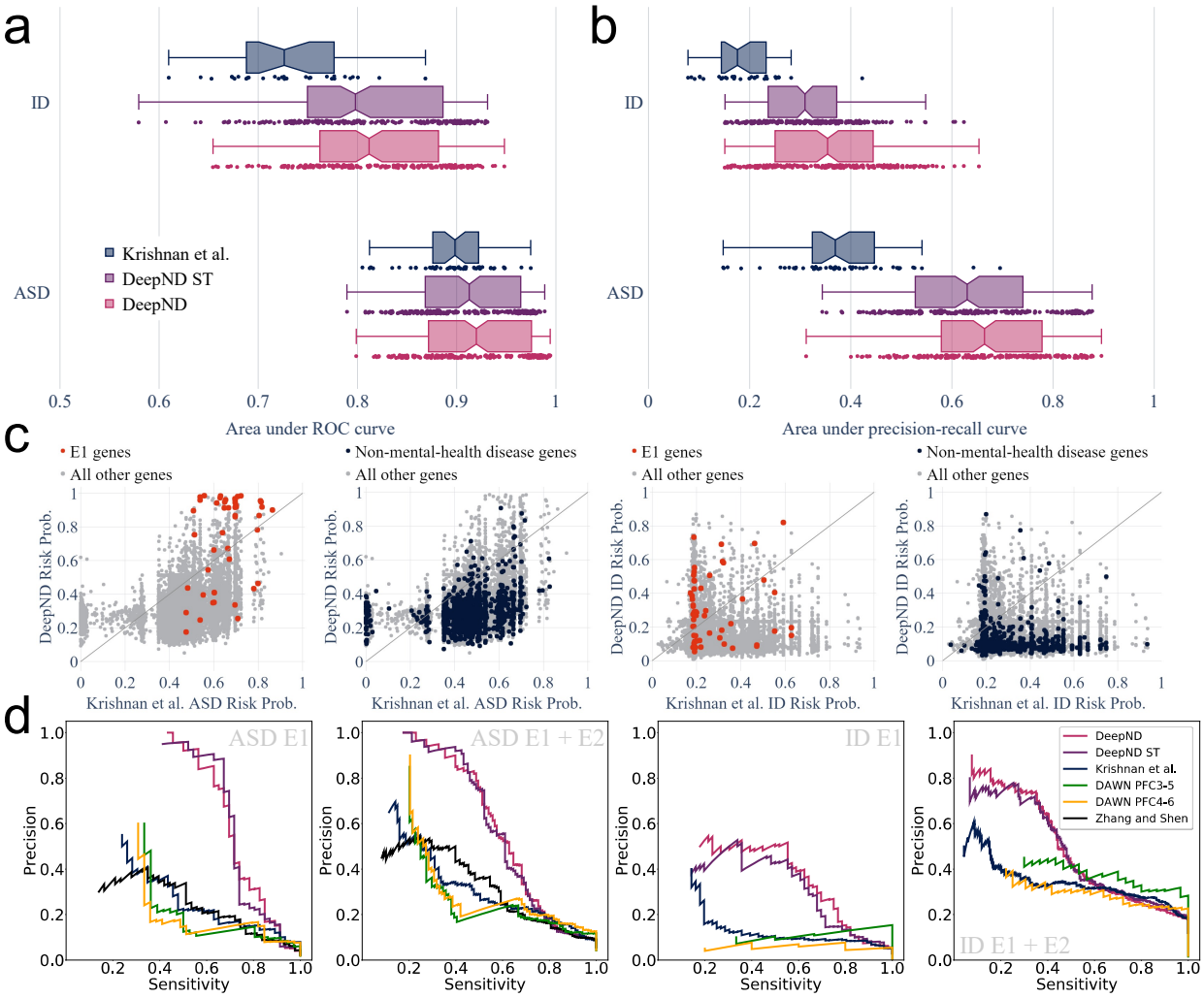

Fig. 2: Evaluation of DeepND genome-wide risk assessment for ASD and ID. (**a**) The area under ROC curve distributions of Krishnan *et al.*, DeepND and DeepND-ST for ASD and ID genome-wide risk assessments. Every point corresponds to the performance on a test fold in the repeated cross validation setting (**b**) The area under precision-recall curve distributions for the same methods as in (**a**). Center line: median; box limits: upper and lower quartiles; whiskers: 1.5x interquartile range; points: outliers. (**c**) ASD and ID risk probabilities assigned to each gene (dots) by the DeepND and Krishnan *et al.* methods. Red: E1 genes; Black: Non-mental-health disease genes; and Grey: all other genes. A better assessment method would have the E1 genes towards its side of the diagonal and have the black genes on the other side of the diagonal. (**d**) Precision - Recall curves to compare DeepND, DeepND - ST, Evidence weighted SVM of Krishnan *et al.*, DAWN, and DAMAGES score of Zhang and Shen. Results for ASD and ID shown when (i) E1 genes are used as the true risk genes and (ii) E1+E2 genes are considered as the true risk genes.

We benchmark the performances of DeepND and other gene discovery algorithms for neurodevelopmental disorders. First, we compare DeepND and the state of the art algorithm by Krishnan *et al.* using their experimental settings. Evaluating performances of the algorithms using E1 genes through 5-fold cross shows that DeepND achieves a median AUC of 92% (Wilcoxon rank-sum test, $P = 1 \times 10^{-6}$) and a median AUPR of 66% (Wilcoxon rank-sum test, $P = 1 \times 10^{-6}$) for ASD, which correspond to 2% and 30% improvements over the evidence weighted SVM algorithm of Krishnan *et al.*, respectively (Figures 2a and 2b). Similarly for ID, DeepND achieves a median AUC of 81% and a median AUPR of 35%, which improves the state of the art by 9% and 18%, respectively. We observe that even the singletask mode DeepND-ST performs better than Krishnan *et al.*'s algorithm (up to 7%) in all settings. As expected, the multitask setting of DeepND performs better than DeepND-ST and leads to improved AUC (up to 1.4%) and AUPR (up to 5%) for both disorders.

We also compare DeepND and Krishnan *et al.*'s approach gene-by-gene for both disorders. Figure 2c shows the probabilities assigned to each gene (red: E1 genes; black: non-mental health genes; and grey: all other genes). The better performing algorithm would have the E1 genes on its own side of the diagonal (i.e., relatively higher risk probability assigned) and have the black genes on the other side (i.e., relatively lower risk probability assigned). We observe that DeepND consistently assigns higher probabilities to E1 genes and lower probabilities to non-mental health relate genes and thus, provides a better risk assessment (Wilcoxon Rank Sum test, DeepND ASD $P = 3.35 \times 10^{-22}$, DeepND ID $P = 5.07 \times 10^{-19}$, Krishnan *et al.* ASD $P = 5.07 \times 10^{-20}$ and Krishnan *et al.* ID $P = 7.12 \times 10^{-9}$).

Finally, we compare DeepND, DeepND-ST and Krishnan *et al.* with other neurodevelopmental disorder gene discovery algorithms from the literature that had output a genome-wide risk ranking: DAWN [57] and DAMAGES [98] (Methods). We compare them using precision-recall (PR) curves over the final genome-wide predictions of all methods. We consider 2 scenarios, where in the first one E1 genes are considered as true risk genes and in the second both E1 and E2 genes are considered as the ground truth. (Figure 2d). For both disorders, DeepND consistently performs better than others and the singletask version provides the second best result.

2.2 Critical neurodevelopmental windows for ASD and ID Risk

We observe that the top percentile genes in the DeepND ASD and ID rankings have a significantly high overlap with a Jaccard index of 15% (Chi-Square test, $P = 1.6 \times 10^{-15}$). The overlap declines sharply for the rest of the ranking. Unsurprisingly, top 3 deciles also have relatively high overlap with Jaccard indices $0.2, 0.24$, and 0.2, respectively (Supplementary Figure 1).

To further investigate the shared genetic component, we focus on the spatio-temporal neurodevelopmental windows that are deemed important by DeepND for accurate ranking of risk genes for both disorders. The neural network analyzes co-expression networks that represent 13 neurodevelopmental time windows (from embryonic period to late adulthood; Figure 3a) and 4 brain region clusters (PFC-MSC: Prefrontal and motor-somatosensory cortex; MDCBC: Mediodorsal nucleus of the thalamus and cerebellar cortex; V1C-STC: Primary visual and superior temporal cortex; SHA: Striatum, Hippocampus, Amygdala) generated using Brainspan RNA-Seq dataset [45] in accordance with Willsey *et al.* [95] (Methods; Figure 3b).

We investigate using which neurodevelopmental windows more confidently distinguish disorder risk genes. Figure 3c shows normalized average probabilities assigned to top percentile risk genes (Methods). First, we focus on DeepND-ST. We observe that the networks of the MDCBC brain region, spanning several time windows from late/late-mid fetal to young adulthood periods consistently are better predictors for ASD and ID risk. This is inline with the fact that ID or ASD linked genes are

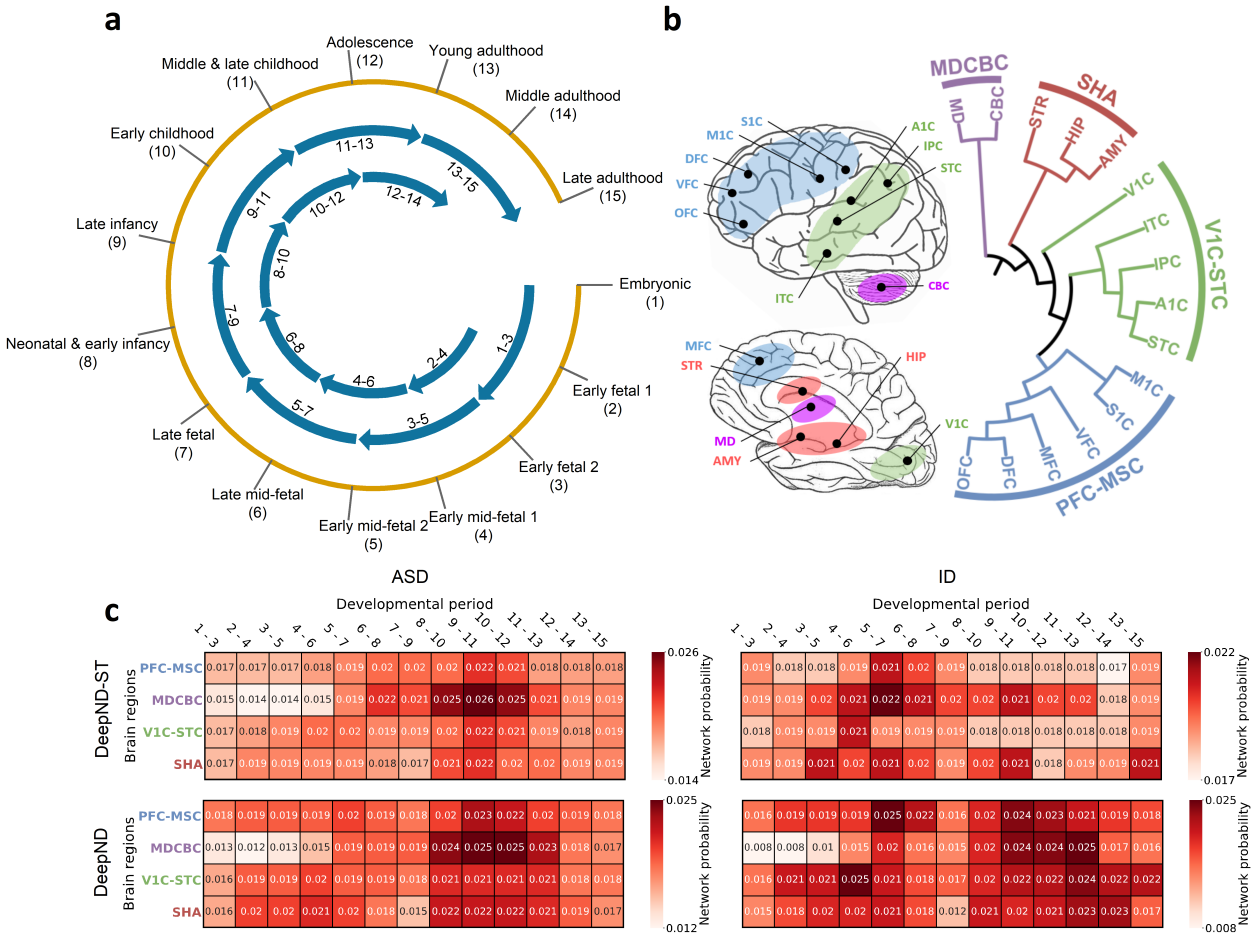

Fig. 3: The BrainSpan dataset which models the spatiotemporal gene expression of human neurodevelopment [45] is used to obtain gene co-expression networks. This dataset contains samples from 12 brain regions and spans 15 time points from early fetal period to late adulthood. **(a)** We generate 13 neurodevelopmental time-windows using a sliding window of length 3 which provides sufficient data in each window as also done by Willsey *et al.* [95]. **(b)** We obtain 4 brain region clusters based on transcriptional similarity during fetal development which also reflects topographical closeness and functional segregation. The brain regions considered are as follows. HIP: Hippocampal anlage (for (1)–(2)), Hippocampus (for (3)–(15)); OFC: Orbital prefrontal cortex; DFC: Dorsal prefrontal cortex; VFC: Ventral prefrontal cortex; MFC: Medial prefrontal cortex; M1C: Primary motor cortex; S1C: Primary somatosensory cortex; IPC: Posterior inferior parietal cortex; A1C: Primary auditory cortex; STC: Superior temporal cortex; ITC: Inferior temporal cortex; V1C: Primary visual cortex; AMY: Amygdala; STR: Striatum; MD: Mediodorsal nucleus of the thalamus; CBC: cerebellar cortex. **(c)** Heatmaps show which spatio-temporal windows lead to assignment of higher risk probabilities to top percentile genes for respective disorders. The numbers in boxes are softmaxed outputs of each respective GCN, averaged for top percentile genes and then normalized. The weights assigned to each co-expression network by the MoE lets each GCN learn to make a better prediction. Top panels are the results for the DeepND-ST model for ASD (left) and ID (right). Bottom panels are are the results for the DeepND model for ASD (left) and ID (right). Results show that for both disorders, in all settings, MD-CBC early infancy to mid-late childhood is consistently the most informative network and could be the point where the etiologies of the disorders converge.

highly expressed during prenatal and early postnatal time windows in development [62, 51]. For both disorders these neurodevelopmental windows confer the highest risk due to the cross-talk between their corresponding risk genes. The shared most informative period is 9-11. The period 8-10 was also previously indicated as one of the highest risk regions and was subject to network analyses for ASD gene discovery [95, 57]. Prefrontal cortex mid-fetal (PFC-MSC 3-5) window was another region deemed important in the same study for ASD, but no such significant signal is picked up by DeepND-ST. Overall, we observe that earlier time windows are relatively more important for ID compared to ASD.

Next, we use DeepND which co-analyzes ASD and ID in the multitask setting. We observe that in this setting, the change in the informativeness of networks for ASD is subtle compared to the singletask setting. For ID, we see a more scattered picture and a more diverse set of networks are more informative when cross-talk among ID and ASD genes are considered. This is also evident in the higher prediction performance gain in ID compared to ASD (Figure 2). We see that later periods become more informative, yet keeping the MDCBC infancy - childhood region as one of the most important. Investigating the probabilities for the E1 genes for both disorders yields a similar picture (Supplementary Figure 2).

DeepND architecture associates a weight with each network which is proportional to its informativeness for the ranking task at hand. We observe that MDCBC late/late-mid fetal to late childhood/adolescence periods are consistently attended the most by the algorithm (Supplementary Figure 3), indicating these regions are the most informative. MDCBC 9-11 window is the top in 3 out of 4 analyses indicating that this region and this time period is critical for the etiology of both disorders. The weakest source of information is MDCBC 2-4 network. We observe roughly 12.5k links between top percentile ASD and ID genes. The network contains close to 37.5m links. On the other hand, MDCBC 9-11 contains close to 13m edges. Yet, there exists close to 30k links between top percentile ASD and ID genes which is the reason behind DeepND focusing on this window as its top predictor. These two networks are visualized side by side in Supplementary Figure 4. Visualization of the top 30 genes for each disorder in MDCBC 9-11 network with only very high co-expression links ($r^2 > 0.95$) is provided in Figure 5a.

2.3 Enrichment Analysis of the Predicted Risk Genes

In addition to the prediction performance benchmark above, we also evaluate the enrichment of our ASD and ID gene risk rankings in gene lists which are shown to be related to these disorders. That is, while these gene sets are not *ground truth* sets, they have been implicated as being associated with the etiology of either disorder. Thus, enrichment of members of these sets in the higher deciles of the genome-wide risk ranking of DeepND is an indication of the wellness of the ranking and also provides a means of comparing and contrasting the disrupted circuitries affected by ASD and ID. These lists are (i) targets of transcription regulators like CHD8 [15], FMRP [16, 5, 18], RBFOX [90, 94, 18] and TOP1 [46]; (ii) Susceptibility pathways like WNT signaling [44] and MAPK signaling [75]; and (iii) affected biological processes and molecular functions like, post-synaptic density complex [8, 101], histone modification [18, 42]).

The first decile of ASD-risk genes has the highest enrichment in all categories. All enrichments are significant with respect to Binomial test (Figure 4; Methods). We observe the same trend for ID that the top decile of the genome-wide risk ranking is the most enriched in most categories but the P values are more subtle. For the CHD8 targets, the fifth decile of the ID risk ranking is the most enriched set and the distribution into deciles is not significant (Binomial test, $P = 5.9 \times 10^{-2}$). $CHD8$

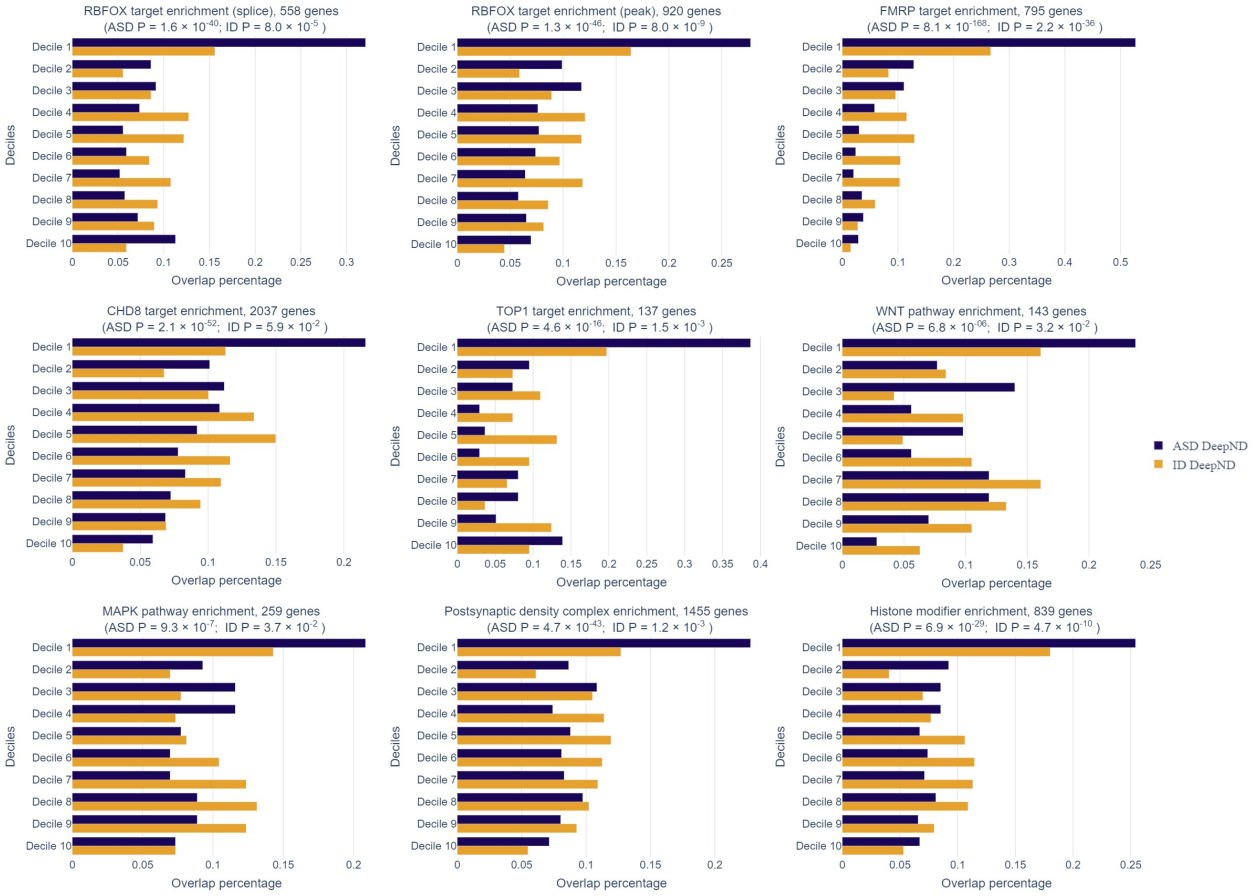

Fig. 4: The enrichment of our ASD and ID gene risk rankings in various disease-related gene lists (i.e., each panel) are shown: (i) ASD and/or ID-related transcription regulators, (ii) ASD and/or ID-related pathways, and (iii) ASD and/or ID-related biological functions or protein complexes. While these do not fully contain ground truth genes, they have been indicated in the literature as being enriched with risk genes for either disorder. Percentage of genes in the corresponding gene set (x axis) that occurred within each decile of the genome-wide risk ranking per ASD (blue) and ID (yellow) are shown. The gene sets used are as follows: (i) Targets of RBFOX (splice), (ii) Targets of RBFOX (splice target), (iii) Targets of FMRP (all peak), (iv) Targets of CHD8, (v) Targets of TOP1, (vi) WNT Pathway, (vii) MAPK Signaling Pathway, (viii) GTPase regulator activity, (x) Postsynaptic density complex genes, (xi) Synaptic genes (xii) Histone modifier genes.

(Chromodomain Helicase DNA Binding Protein 8) is the highest ASD-risk gene known to date with the highest mutation burden in large ASD cohorts [18, 81] and with downstream functional analysis [15]. Accordingly, DeepND ranks $CHD8$ as the third top risk gene whereas Krishnan *et al.* ranks it 1943th genome-wide. While it has a solid association to ASD etiology, the ties to ID is not well-established. Bernier *et al.* reports that 9 out of 15 ASD probands with mutations in $CHD8$ also has ID. While it is a comorbid condition to ASD, $CHD8$ is not a well-established susceptibility gene for ID. Lower enrichment of ID genes in CHD8 targets is in line with this hypothesis. In accordance, DeepND places CHD8 as the 150th highest risk gene for ID.

We also perform an untargeted enrichment analysis of the top percentile predictions using the Enrichr system [13, 52]. We find that for both disorders *regulation of transcription from RNA polymerase II promoter* is the top enriched Biological Process GO term (Fisher's exact test, $P = 6.4 \times 10^{-19}$ for ASD and $P = 6.1 \times 10^{-13}$ for ID) which indicates that transcriptional regulation is a shared function that is disrupted in the etiology of both disorders (Supplementary Table 3). As for the GO Molecular Function enrichment, two disorders diverge in the mechanism: the top function affected for ASD is *RNA polymerase II transcription co-factor activity* whereas for ID the top affected function is *histone-lysine N-methyltransferase activity*. As the top predicted genes are responsible for regulating gene activity, we further investigate if there are any master transcription regulators upstream that regulate the high risk genes for ASD and ID in the ChEA Database [53]. We find that DMRT1 is the top transcription factor with 77 of its targets coincide with 258 the top percentile DeepND predicted ASD risk genes (Chi-Square test, $P = 2.84 \times 10^{-18}$). It is the top third regulator for ID by regulating 46 of 258 top percentile ID risk genes (Chi-Square test, $P = 1.74 \times 10^{-4}$), 22 targets are shared among ASD and ID. Note that only 69 genes overlap in top percentile ASD and ID risk genes. This means 30% of the shared set of genes among two disorders are targeted by DMRT1 (Supplementary Table 3). When the union set of the top percentile genes for ASD and ID are considered (447 genes), we find that the top transcription factor targeting these is again DMRT1 (105 out of 2071 targets; Chi-Square test, $P = 2.33 \times 10^{-15}$).

While $DMRT1$ is not ranked as a high risk gene, Pinto *et al.* report a rare experimentally-validated *de novo* CNV (deletion) in an ASD proband which encompasses 9p24.34-p24.2 and $DMRT1$ [75]. $DMRT1$ is in the 9p region with the following genes: $DOCK8$,$DMRT2$,$DMRT3$,$VLDLR$, and $ANKRD15$ and several works indicate that mutations affecting these these genes might be related to neurodevelopmental disorders [72, 87, 86, 96]. DMRT1 is a transcriptional regulator and plays role in male sex determination. This finding suggests an interesting link between *DMRT1* and the strong male bias in ASD [93] and ID [43, 84] prevalence.

2.4 Regulatory Interactions between ASD and ID Genes

After observing that top percentile genes for both ASD and ID are enriched in gene expression regulators, and that there is a common upstream regulator, we further investigate the regulatory relationships among the risk genes of the two disorders. The union of the top percentile risk genes contain 447 genes and 25 of them are found in the ChEA Database as transcription factors (TF) with experimental target information (permutation test, $P < 1 \times 10^{-3}$). Out of this set of 25 TFs, 9 are ASD-only risk genes, 9 are ID-only risk genes, and 7 of them are ASD & ID risk genes. We generate a transcription factor regulation subnetwork between only genes in these three groups and investigate whether they interact more than expected by chance. Using a stringent matched randomization technique which is based on mutation rate, pLI and gene length, we generate 1000 random ASD-only, ID-only and ASD & ID gene sets such that the sizes of each set is preserved and these sets

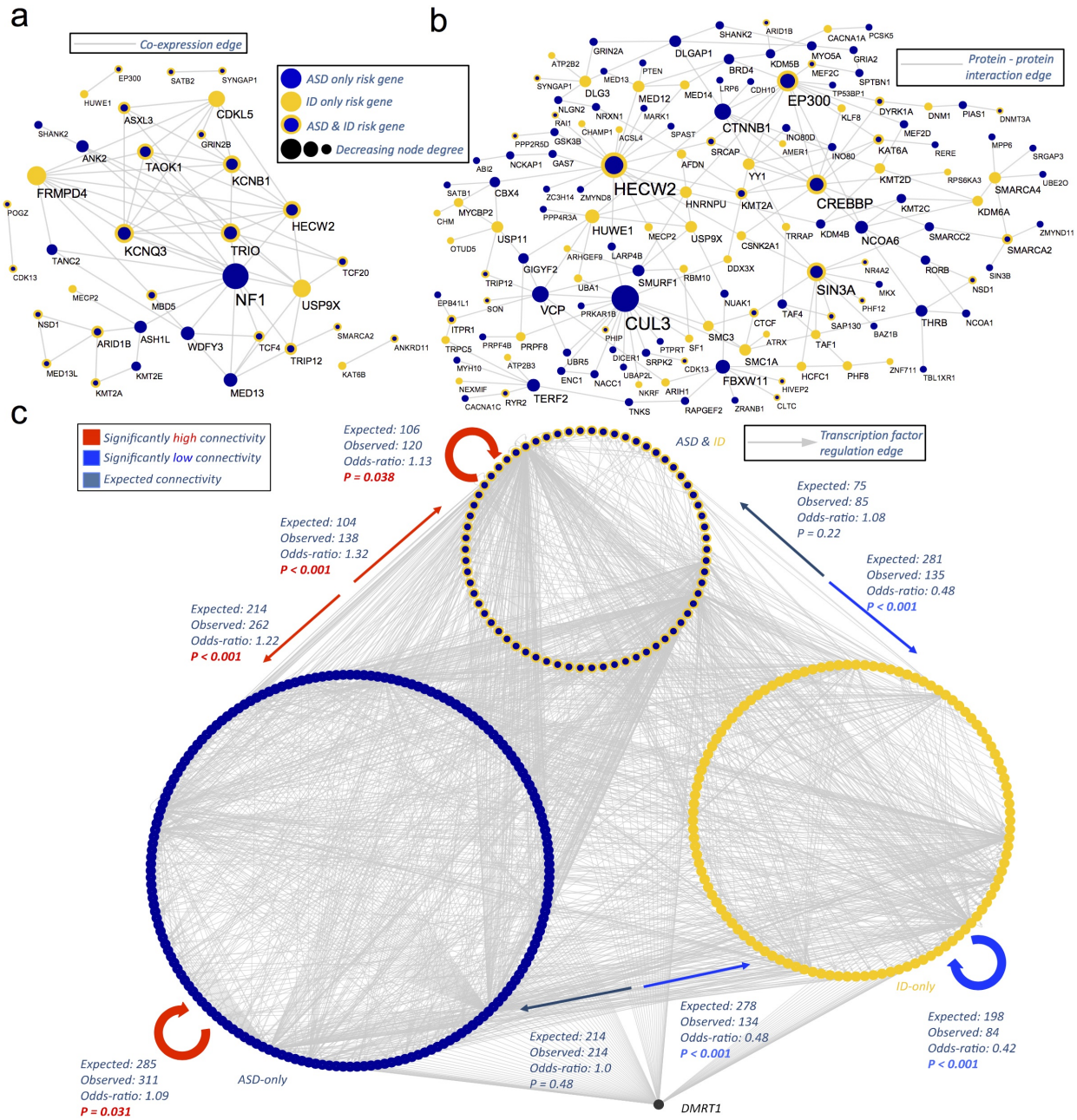

Fig. 5: Network Analyses of the risk genes. (a) The co-expression relationships between top 30 ASD and ID risk genes in MDCBC 9-11 region. This is found as the most informative co-expression network for DeepND. Only links for at least 0.95 absolute correlation and genes with at least one connection are shown. (b) The protein-protein interactions between the top percentile risk genes are shown. The PPIs are obtained from the tissue specific PPI network of frontal cortex in DifferentialNet database [7] Only interactions between the top percentile risk genes are shown. (c) The regulatory relationships between the top percentile ASD-only and ID-only risk genes in the ChEA transcription factor regulation database are shown. 69 genes are ranked in the top percentile for both disorders. Only the risk genes with at least one connection are shown (180 ASD-only, 114 ID-only and 66 ASD & ID). $DMRT1$ is found to be an upstream regulator which significantly regulates both groups. ASD risk genes and ID risk genes contain 9 TFs each and the shared risk genes contain 7 TFs. Using a permutation test, we check the connectivity between pairs of these groups. Red arrows indicate that the TFs in the source has more targets than expected by chance in the target group. Cobalt blue arrows indicate that the TFs in the source has less targets than expected by chance in the target group. Finally, aegean blue arrows indicate expected connectivity. The figure shows that the connectivity within and between ASD-only and ASD&ID risk genes are significantly high. On the contrary, TFs in these two groups have significantly less connections to ID-only than expected. Also, the connections within the ID-only group is also significantly scarce.

contain the same TFs in the original risk gene sets, respectively (Methods). We observe that the most strongest connection is in between ASD-only and ASD & ID risk gene sets both ways. TFs in both groups regulate each other significantly (permutation test - 1000 draws, $P < 1 \times 10^{-3}$; Figure 5). While TFs in ASD-only set regulate the genes in its group more frequently than expected by change, the significance is lower (permutation test - 1000 draws, $P = 3.1 \times 10^{-2}$). The same is true for TFs in ASD & ID set (permutation test, $P = 3.8 \times 10^{-2}$). This is in striking contrast with the relationships between ASD-only/ASD & ID TFs and ID-only risk genes. The strength of the connectivity is significantly less than expected (permutation test, $P < 1 \times 10^{-3}$). Similarly, TFs in the ID-only risk set do not significantly interact with other groups.

We further investigate the protein-protein interactions (PPI) between the top percentile risk genes in tissue specific PPI network for frontal cortex obtained from DifferentialNet database [7] using the NetworkAnalyst system [99]. This analysis reveals several hub proteins such as HECW2, EP300, CUL3, and CTTNB1 as shown in Figure 5. In this list, $HECW2$ gene stands out as it has the highest degree in this network and has very low prior risk for both ASD (TADA $P = 0.95$) and ID (extTADA $Q = 0.97$). Yet, it is the top 4th ID risk gene identified by DeepND and in the top percentile for ASD risk. Note that DeepND did not use any PPI network information in its reasoning, and yet, was able to identify this hub protein which has been linked with ASD [41] and ID [33] via *de novo* disruptive mutations in simplex families.

2.5 Identification of Novel Candidates within ASD and ID Associated CNV Regions

Recurrent copy number variations in several regions of the genome are associated with ASD and ID etiology. However, these are large regions and it is not clear which genes in particular are driver genes. We investigate the DeepND risk ranking of genes within (i) six regions which frequently harbor ASD-related CNVs (16p11.2, 15q11-13, 15q13.3, 1q21.1 and 22q11) [49], and (ii) six regions which were reported to harbor mental retardation related CNVs (16p11.2, 1q21.1, 22q11.21, 22q11.22, 16p13 and 17p11.2) [60]. Note that these CNVs in these regions might confer risk for both disorders (Supplementary Table 4).

DeepND highly ranks several novel genes for ASD and ID, which (i) are within these CNV regions, (ii) have low prior risk (e.g., E2 or lower, low TADA P value etc.), and (iii) low posterior risk assigned by other algorithms (Supplementary Table 4).

For ASD, while *GABRG3* is ranked as the 250th genome-wide by DeepND despite very slim prior risk indicators. It is an E3-E4 level risk gene. It does not participate in any of the relevant gene sets (e.g., risk pathways) and it has a low TADA $P = 0.75$. This is also a novel finding as none of the other algorithms rank it in the top thousand (Krishnan *et al.*, 1297th, DAWN 3257th, DAMAGES score 1472nd). (Supplementary Table 1). Yet, we find that this gene is assigned a *SFARI Gene Score* 2 which means it is in top 400 risk genes in SFARI Gene Database (accessed on May 2020). Moreover, links between variants in this gene and ASD were found in Caucasian [61] and Chinese cohorts [91].

MICAL3, a gene related to actin and Rab GTPase binding, ranked in as the 352nd for ASD risk despite having TADA $Q = 0.77$ and not being in relevant risk gene groups. Krishnan *et al.* rank it 3165th and DAMAGES score ranks it 1916th. DAWN provides no ranking as it is not co-expressed with other is networks of interest for DAWN. While disruption in Rab GTPase cycle gene could lead intellectual disability [82], there are no established ties between *MICAL3* and ASD or ID. However, MICAL family genes are related to cytoskeletal organization which recently has been deemed an important molecular function in ASD etiology [81, 69]. *MICAL2* is an ASD-risk gene and also ranked in the top percentile by DeepND. Unlike others, DeepND utilizes multiple co-expression networks

concurrently and is able to capture the link between *MICAL2* and *MICAL3* in 7 networks spanning late fetal to adolescence in SHA and V1C-STC regions. This enables DeepND to predict it as a risk gene in a relevant CNV region (22q11).

FOXO3B is located in 17p11.2 which is one of the ID related CNV regions. While this gene does not even have a prior TADA score in Nguyen *et al.* [67], DeepND marks it as the 57th risk gene. Deletion of FOXO transcription factors is shown to cause axonal degeneration and elevated mTORC1 activity [38] which was previously associated with several neurological and neurodevelopmental disorders including autism and epilepsy. Krishnan *et al.* ranks this gene in the fifth decile and DAWN cannot capture it due to lack of correlation in prefrontal cortex during mid-fetal period. Interestingly, all discussed genes, *GABRG3, MICAL3* and *FOXO3B* have similar RNA expression patterns in brain as they are either most expressed or second most expressed in cerebral cortex [2] (Supplementary Figure 5).

2.6 Evaluation of Novel Predictions

Here, we focus on the most confident predictions of DeepND which are clashing with the current consensus; such as ground truth risk genes classified as non-risk genes and vice versa (Supplementary Table 1). While it is always interesting to discover new disorder risk genes, it maybe is as important to pinpoint non-ASD/non-ID genes. This is because many neurodevelopmental disorders overlap and specificity is import.

SLC9A9 is a sodium/hydrogen exchange protein with a record of rare variants in an ASD cohort [65, 3]. While, it was listed as an E1 risk gene [49], DeepND consistently ranks it in the last decile with 0.175 probability of being an ASD risk gene. Other algorithms rank it in the fifth decile at the lowest. The protein and RNA expressions of *SLC9A9* are enriched in the spinal cord which makes it an unlikely ASD risk candidate [2] which is a testament to the ability of DeepND to distinguish true risk genes from noise despite a potentially incorrect ground truth label (Supplementary Figure 6).

CACNA1H is another ASD E1 risk gene [49] ranked in the 9th decile ($22,102^{nd}$) by DeepND with 0.246 probability of being an ASD-risk gene. DAWN ranks it as the 300th risk gene while others put it into the 3rd decile as the lowest. This gene shows higher protein and RNA expression levels in basal ganglia and pituitary gland with respect to other brain regions [2] which lowers the chances of *CACNA1H* to be an ASD risk gene when combined with its low prior probability.

Finally, DeepND assigns *TAT* (an ID E1 gene) a very low risk probability (0.074) and ranks it in the last decile. Although it is listed as an ID risk gene in multiple studies [14, 25, 32, 39, 88], *TAT* encodes a tyrosine aminotransferase and is mainly expressed in liver which makes it a questionable candidate as an ID risk gene.

There are also examples where genes in the negative ground truth set are listed in the top quartile by DeepND. *GIGYF2* encodes a protein with stretches of polyglutamine residues and is located in 2q37.1, which is linked to Parkinson disease type 11 [73]. GIGYF2 is argued to play a role in regulation of tyrosine kinase receptor signaling and it has been placed in top percentile by DeepND with an ASD risk probability of 0.906. Likely gene disrupting mutations in *GIGYF2* has linked it to ASD in a Chinese cohort [92].

3 Discussion

Neurodevelopmental disorders have been challenging geneticist and neuroscientists for decades with complex genetic architectures harboring hundreds of risk genes. Tracing inherited rare and *de novo*

variation burden has been the main driver of risk gene discovery. However, overlapping genetic components and confounding clinical phenotypes make it hard to pinpoint disorder-specific susceptible genes and to understand differences. For instance, Satterstrom *et al.* pinpoint 102 ASD risk genes with FDR < 10% with the largest ASD cohort to date covering nearly 6.5k trios [81]. Yet, they still need to manually segregate these risk genes into two groups as (i) 53 ASD predominant risk genes which are distributed across a spectrum of ASD phenotypes, and (ii) 49 neurodevelopmental delay risk genes causing impaired cognitive, social, and motor skills. Thus, comorbidity is a further obstacle to be reckoned with in addition to identifying individual susceptible genes. Nevertheless, the shared risk genes and biological pathways offer opportunities for computational risk assessment methods which were not explored before. So far, only disorder specific analyses were possible by design of the network-based gene discovery algorithms. These are limited in power due to distinct datasets which lead to limited cohort sizes. Here, we proposed a novel approach which can co-analyze comorbid neurodevelopmental disorders for gene risk assessment. The method is able to leverage the shared information using multitask learning paradigm for the first time for this task. DeepND learns both a shared and a disorder-specific set of weights to calculate the genome-wide risk for each disorder. DeepND is a multitask deep learner which uses state-of-the-art techniques underneath such as graph convolution and mixture of experts to learn non-linear relationships of genes on 52 brain co-expression networks. The model is also interpretable as it is able to learn which neurodevelopmental windows (i.e., networks) provide more information for distinguishing high risk genes, and thus, are important for understanding disease etiology. Our benchmarks show these techniques enable DeepND to outperform existing gene discovery methods even when working in singletask mode. Multitask mode has the best performance overall.

We focus on ASD and ID in this study and identify similarities such as shared affected pathways and neurodevelopmental windows, and differences such as regulatory relationships and novel risk genes. We think the findings in this paper will help guiding neuroscientists researching ASD and ID in prioritizing downstream functional studies and identifying drug targets. DeepND is not an algorithm specific to these disorders though. It can easily be extended to consider other comorbid disorders such as schizophrenia and epilepsy by adding similar singletask layers for each disorder. It can also be used for other comorbid disorders that are not related to neurodevelopment at all.

We demonstrated the advantage of being able to employ multiple co-expression networks and pointed to cases where, for instance, DAWN was not able to capture relationships between genes as they are limited with a single co-expression network. For the clarity of discussion and interpretability, we focused on only networks produced from BrainSpan dataset. However, DeepND can also employ any combination of other types of gene interaction networks such as protein interaction networks.

4 Methods

4.1 Ground Truth Risk Gene Sets

Our genome-wide gene-risk prediction algorithm is based on a semi-supervised learning framework in which some of the samples (i.e., genes) are labeled (as ASD/ID risk gene or not) and they are used to learn a ranking for the unlabeled samples.

We obtain the labels for ASD as also done in Krishnan *et al.* (2016) for a fair comparison. The ASD related genes are collected from from various sources: SFARI [3], OMIM [34], HUGE [97], Gene2Mesh (http://gene2mesh.ncbi.org/), GAD [9] and DGA [74]. These genes are classified into four

evidence levels indicating the quality of the evidence (E1 - E4, E1 indicating the highest risk). The list contains 46 E1 genes (from SFARI Cat I/II and OMIM), 67 E2 genes (from SFARI Cat III), 525 E3 (from HUGE and GAD databases) and E4 genes (from text mining studies Gene2Mesh/DGA and SFARI Cat IV) as positively labeled ASD-risk genes. We also obtain 1,185 non-mental health related genes from OMIM and Krishnan *et al.* as negatively labeled genes. The list and corresponding evidence levels are listed in Supplementary Table 1. In the loss calculations during training of the model, genes in these categories are assigned the following weights: E1 genes (1.0), E2 genes (0.50), E3/E4 genes (0.25) and negative genes (1.0). The performance is evaluated only on E1 genes for the sake of compatibility with other methods.

For ID, we rely on review studies from the literature which provide in depth analyses and lists of ID risk genes. We considered the *known gene* lists from 2 landmark review studies as our base ground truth ID risk gene list [25, 32]. We divide this set into 2 parts (i.e., E1 and E2) with respect to evidence obtained from 3 other studies [88, 39, 14]. The genes which are indicated by all 5 studies are assigned to the highest risk class, E1. Remaining genes which are indicated by 4 studies are assigned to the second highest risk class, E2. See Supplementary Table 2 for a detailed breakdown of evidence for each gene. We use the same set of negative genes as ASD which are non-mental health related genes. Overlapping genes within the E1 and E2 lists are removed from the negative list. Consequently, we have 56 E1 and 131 E2 genes and 1,074 negative genes for ID. See Supplementary Table 1 for a complete list of ground truth genes for both disorders. The weights we use per gene class are as follows: E1 genes (1.0), E2 genes (0.50), and negative genes (1.0). For the sake of consistency, we also report the performance of the model on E1 genes for ID.

4.2 Gene Risk Features

The disorder specific features we use are as follows. First, for ASD we obtain the mutation burden information from the latest and largest whole exome study to date [81]. For every gene, we use the following information as features related to ASD-risk: (i) the number of *de novo* loss of function mutations, (ii) the number of damaging missense loss of function mutations, (iii) the number of protein protein truncating variants (PTVs) for ASD case and control groups, (iv) the number of transmitted loss of function mutations, (v) the number of *de novo* protein truncating variants (PTVs) and missense mutations in published ASD probands, (vi) frequency of *de novo* variants in ASD individuals. For ID, a similar set of features are obtained from [67]. For every gene, DeepND learns the ID-risk from the following features: (i) the number of *de novo* loss of function mutations, (ii) the number of damaging missense loss of function mutations, (iii) extTADA Bayes factor which is calculated using an extension of TADA, (iv) the number of *de novo* PTVs and missense mutations in published ID/DD (developmental delay) probands, (v) frequency of *de novo* variants in ID/DD individuals. We use the gene pLI and mutation rate for both disorders. See Supplementary Table 5 for the complete list of features and values used for each gene.

4.3 Gene Co-expression Networks

We used the BrainSpan dataset of the Allen Brain Atlas [85, 45] in order to model gene interactions through neurodevelopment and generated a spatio-temporal system of gene co-expression networks. This dataset contains 57 postmortem brains (16 regions) that span 15 consecutive neurodevelopmental periods from 8 postconception weeks to 40 years. To partition the dataset into developmental periods and clusters of brain regions, we follow the practice in Willsey *et al.* (2013) [95]. Brain regions

were hierarchically clustered according to their transcriptional similarity and four clusters were obtained (Figure 3b): (i) V1C-STC (primary visual cortex and superior temporal cortex), (ii) PFC-MSC (prefrontal cortex and primary motor-somatosensory cortex), (iii) SHA (striatum, hippocampal anlage/hippocampus, and amygladia), and (iv) MDCBC (mediodorsal nucleus of the thalamus and cerebellar cortex). In the temporal dimension, 13 neurodevelopmental windows (Figure 3a) were obtained using a sliding window approach (i.e., [1–3], [3–5], $\cdots$, [13–15]). A spatio-temporal window of neurodevelopment and its corresponding co-expression network is denoted by the abbreviation for its brain region cluster followed by the time window of interest, e.g. "PFC-MSC(1-3)" represents interactions among genes in the region PFC-MSC during the time interval [1–3].

Using the above-mentioned partitioning, we obtained 52 spatio-temporal gene co-expression networks, each of which contain 25,825 nodes representing genes. An undirected edge between two nodes is created if their absolute Pearson correlation coefficient $|r|$ is greater than or equal to 0.8 in the related partition of BrainSpan data.

4.4 DeepND Model

Problem Formulation Each 52 co-expression network j described in Section 4.3 is represented as a graph $G_j = (V, E_j)$, where the vertex set $V = (v_1, \cdots, v_n)$ contains genes in the human genome and $E_j \in \{0,1\}^{n \times n}$ denotes the binary adjacency matrix. Note that $n = 25,825$. Let $X_D \in \mathbb{R}^{n \times d}$ be the feature matrix for disorder D where each row $X_D[i]$ is a list of d features associated with gene (and node) $i, \forall i \in [1,n]$. Let y_{ASD} be an l dimensional vector, where y_{ASD}[i] = 1 if the the node i is a risk gene for ASD, and y_{ASD}[i] = 0 if the gene is non-mental health related, $\forall i \in [1,l], l < n$. Note that, in this semi-supervised learning task, only first l genes out of n have labels. y_{ID} is defined similarly for ID, using its ground truth risk and non-risk gene sets. The goal of the algorithm is to learn a function $f(X_{ASD}, X_{ID}, y_{ASD}, y_{ID}, G_1, \cdots, G_{52}) \rightarrow P \in \mathbb{R}^{n \times 2}$. $P[i][ASD]$ denotes $p(y_{ASD}[i] = 1)$, and $P[i][ID]$ denotes $p(y_{ID}[i] = 1), \forall i \in [1,n]$.

Graph Convolutional Network Model Convolutional Neural Networks (CNNs) have revolutionized the computer vision field by significantly improving the state-of-the art by extracting local patterns on grid-structured data [50]. Applying the same principle on arbitrarily structured graph data have also enjoyed success [11, 21, 36]. While all these spectral approaches have proven useful, they are computationally expensive. Kipf and Welling have proposed an approach (graph convolutional network - GCN) to approximate the filters as a Chebyshev expansion of the graph Laplacian [19] and let them operate on the 1-hop neighborhood of each node [48]. This fast and scalable approach extracts a network-adjusted feature vector for each node (i.e. ,embedding) which incorporates high-dimensional information about each node's neighborhood in the network. The convolution operation of DeepND is based on this method. Given a gene co-expression network G_j, GCN inputs the normalized adjacency matrix $\hat{E}_j$ with self loops (i.e., $\hat{E}_j[i,i] = 1, \forall i \in [1,n]$) and the feature vector $X_D[i]$, for gene i and for disorder D. Then, the first layer embedding $H^1[i] \in \mathbb{R}^{d_1}$ produced by GCN is computed using the following propagation rule $H_1[i] = ReLU(\hat{D}^{-0.5}\hat{E}\hat{D}^{-0.5}X_D[i]W_0)$ where W_0 is the weight matrix at the input layer to be learnt, $ReLU$ is the rectified linear unit function and $\hat{D}$ is the normalized version of a diagonal matrix where $\hat{D}_{ii} = \sum_j \hat{E}_{ij}$. We pick $d_1 = 4$ in this application. Each subsequent layer k is defined similarly as follows: $H_k[i] = ReLU(\hat{D}^{-0.5}\hat{E}\hat{D}^{-0.5}H_{k-1}[i]W_{k-1})$. Thus, the output of a k-layered GCN, for gene i on co-expression network j is denoted as follows: $GCN(G_j, X_D[i]) = H_k[i] \in \mathbb{R}^{d_k}$. In this application, we use 2 GCN layers and $d_2 = 1$. The final layer

is softmax to produce probabilities for the positive class. That is, the output of a GCN model j, for a gene i is $GCN(G_j, X_D[i]) = softmax(H_2[i]) = v_i^j \in \mathbb{R}$.

Mixture of Experts Model Mixture of experts model (MoE) is an ensemble machine learning approach which aims to find out informative models (experts) among a collection [59]. Specifically, MoE inputs the features and assigns weights to the outputs of the experts. In DeepND architecture, individual experts are the 52 GCNs which operate on 52 gene co-expression networks as explained above ($G_1, \cdots, G_{52}$). For every gene i, MoE inputs $X_D[i]$ and produces a weight $\vec{w}$ of length 52 which is passed through a softwax layer (i.e., $\sum_{h=1}^{52} \vec{w_i}[h] = 1$). The output of the GCNs are weighted by this network and the weighted sum is used to produce a risk probability for every gene i using softmax. That is, the $MoE(X_D[i]) = \vec{w}_i \in \mathbb{R}^{52}$. The GCNs produce 52 v_i^j values (one per co-expression network) which are concatenated to produce $\vec{v}_i \in \mathbb{R}^{52}$. Finally, the following dot product is used to produce the risk probability of gene i for disorder D: $\vec{w}_i \cdot \vec{v}_i = P[i][D]$.

Multitask Learning Model Above-mentioned GCN and MoE cascade inputs $X_D[i]$ and co-expression networks $G_1, .., G_{52}$ along with labels for a single disorder to predict the risk probability for every gene. Thus, it corresponds to the single-task version of DeepND (i.e., DeepND-ST.) On the other hand, DeepND is designed to work concurrently with multiple disorders (i.e., ASD and ID.) DeepND employs one DeepND-ST cascade per disorder and puts a multi-layer perceptron (MLP) as a precursor to two DeepND-ST subnetworks. The weights learnt on these subnetworks are only affected by the back-propagated loss of the corresponding disorder, and hence, these are single task parts of the architecture. On the contrary, the weights learnt on the MLP part are affected by the loss back-propagated from both subnetworks. Thus, this part corresponds to the multitask component of the DeepND architecture. The MLP layer inputs the union of X_{ASD} and X_{ID} and passes it through a fully connected layer followed by Leaky ReLU activation (negative slope = -1.5) to learn a weight matrix W_{MLP} and output a d' dimensional embedding to be input DeepND-ST instead of $X_{ASD}[i]$ and $X_{ID}[i]$. That is, $MLP(X_{ASD}[i] \cup X_{ID}[i]) = LRELU(W_{MLP}^{\intercal} \cdot (X_{ASD}[i] \cup X_{ID}[i]) + \vec{b}_{MLP})$.

Learning and the Cross Validation Setting of DeepND To evaluate both DeepND-ST and DeepND approaches, we use a five-fold cross-validation scheme. All labeled genes are uniformly and randomly distributed to the folds. At each training iteration, we leave one fold for validation and one fold for testing. We train the model on the remaining three folds of the labeled genes. For all the genes in the left-out fold, their feature vectors are nullified when input to training in order to prevent information leakage.

The model is trained up to 1000 epochs with early stop which is determined with respect to the loss calculated on the validation fold using only E1 genes as the positives and all negative genes. Once the model converges, the test performance is reported on the test fold in the same manner as in the validation fold. The model uses cross entropy loss (evidence weighted) and ADAM optimizer [47] for updating the weights which are initialized using Xavier initialization [28]. DeepND-ST uses a fixed learning rate of 7×10^{-4} for both disorders. DeepND uses the learning rates of 7×10^{-4}, 7×10^{-4} and 7×10^{-3}, for the shared layer, ASD single task layer, and ID single task layer, respectively. To ensure proper convergence of DeepND, should one of the singletask subnetworks converge, the learning rate of that subnetwork and the shared layer are cut down twenty folds. This lets the yet underfit subnetwork to keep learning till early stop or the epoch limit.

Above-mentioned procedure produces 20 results as for every left-out test fold, all remaining 4 folds are used as validation. We repeat this process 10 times with random initialization to obtain a

total of 200 results for performance comparison (Figure 2). For ASD, positively labeled genes' weights equal to 1.00 (E1), 0.50 (E2), 0.25 (E3) and 0.25 (E4). For ID, positively labeled genes' weights equal to 1.00 (E1) and 0.50 (E2). For both disorders, negatively labeled genes have weight 1.00. Note that this procedure is in line with the setting of Krishnan *et al.* for fairness of comparison.

4.5 Genome-wide risk prediction for ASD and ID and Comparison with Other Methods

We compare the performance of DeepND-ST and DeepND with other state-of-the-art network based neurodevelopmental disorder gene risk assessment methods from the literature which output a genome-wide risk ranking: Krishnan *et al.* [49], DAWN [56], and DAMAGES score [98].

We run Krishnan *et al.*'s approach as described in their manuscript [49]. This is an evidence-weighted Support Vector Machine (SVM) classifier which identifies risk genes based on similarity of network features. They use a human brain-specific functional interaction network to generate features as input [30]. Note that, the ground truth gene set is the same as ours as well as the evidence weights for ASD. We perform a 5-fold cross validation. That is, for each iteration, we train their SVM model on 80% of the labeled genes and evaluate the model on E1 genes and all negative genes in the left-out 20% of the labeled genes as suggested. We repeat this procedure 10 times. We post-process SVM outputs to produce risk probabilities using isotonic regression which ensures that the gene ranking is preserved. We use the pLI value of each gene as the dependent variable. In a 10-fold cross validation setting, we detect *knots* on the left-out fold, and fit another isotonic regression line to interpolate the knots. We use SVM output for all genes to produce a gene risk probability values for the corresponding disorder and produce the genome-wide risk ranking. We compare this method and DeepND-ST/DeepND with respect to (i) the area under receiver operating curve (AUC) and area under precision recall curve (AUPR) distributions calculated on the left-out fold at each cross validation iteration (Figure 2a-b) and (ii) probabilities assigned to the ground truth genes with respect to the final rankings (Figure 2c).

DAWN is a hidden Markov random field based approach that assigns a posterior, network-adjusted disorder risk score to every gene based on guilt by association principle. It inputs TADA p-values as prior features along with a partial co-expression network to assess connectivity. We input the TADA p-values to DAWN which are also used by DeepND as one of the features [81, 67]. The method also uses partial co-expression networks. We use two networks which the authors suggest as the most useful for this task in their manuscript [56]. These represent prefrontal cortex/mid-fetal period (i.e., PFC-MSC 3-5 and PFC-MSC 4-6). We generate these networks using the RNA-Seq data in the BrainSpan dataset. Note that DeepND utilizes the same dataset and uses these networks and 50 others. Instead of partial co-expression networks, DeepND uses co-expression networks. The DAMAGES score is a principal component analysis based technique that assess the risk of genes based on (i) the similarity of their expression profiles in 24 specific mouse central nervous system cell types, (ii) the enrichment of mutations in cases as opposed to controls, and (iii) the pLI score of the gene. We directly obtain the risk ranking from Shen and Zhang, 2017 [98]. We compare all above mentioned methods with DeepND-ST/DeepND with respect to precision-recall curves in Figure 2d.

All algorithms are trained and tested on a SuperMicro SuperServer 4029GP-TRT with 2 Intel Xeon Gold 6140 Processors (2.3GHz, 24.75M cache), 251GB RAM, 6 NVIDIA GeForce RTX 2080 Ti (11GB, 352Bit) and 2 NVIDIA TITAN RTX GPUs (24GB, 384Bit). For DeepND-ST, we used 3 2080 RTX and 1 TITAN RTX cards and the cross validation setup took approximately 5 hours. For DeepND, we used 5 RTX 2080 and 1 TITAN RTX cards and the cross validation setup took approximately 16 hours.

4.6 Enrichment Analyses

We evaluate the enrichment of DeepND's ASD and ID gene risk rankings in gene lists which are known to be enriched in disorder-risk genes in the literature. These lists are (i) targets of transcription regulators like CHD8 [15], FMRP [16, 79], RBFOX1 [90, 94] and TOP1 [46]; (ii) Susceptibility pathways like WNT signaling [44] and MAPK signaling [75]; and (iii) affected biological processes and molecular functions like, post-synaptic density complex [8, 101], histone modification [18, 42]). We use the binomial test to determine whether the top decile in the corresponding ranking significantly deviate from uniform enrichment (Figure 4).

We perform a Gene Ontology term enrichment analysis of the top percentile predictions using the Enrichr system [13, 52] with respect to Biological Process terms and Molecular Function terms. As both analyses point to *transcription factor regulation*, we investigate the connectivity of the high risk genes in the ChEA Database [53] which is a large repository that lists experimentally validated transcriptional regulation relationships in various organisms. Again using the Enrichr system, we find that *DMRT1* is a significant upstream regulator with respect to Chi-Square test.

We investigate the regulatory relationships among 258 top-percentile risk genes for each disorder. First, we obtain three risk gene groups: ASD-only (9 genes; 9 are TFs), ID-only (9 genes; 9 are TFs), and ASD&ID (69 genes, 7 are TFs) (Supplementary Table 1). Then, we use a permutation test to assess various enrichment categories. First, we draw random risk gene sets. That is, we generate 1000 random gene sets with size 9 to mimic ASD-only set; 1000 random gene sets with size 9 to mimic ID-only set; and 1000 random gene sets with size 69 to mimic ASD&ID gene set. We ensure that the original TFs are in each respective set are preserved in the random sets. For instance, if a TF is in the ASD-only set, it is also in all of the 1000 random sets generated for to mimic the ASD-only set. We use a matched randomization strategy to randomly pick the remaining genes other than the TFs. The genes are matched with respect to (i) pLI, (ii) gene length, (iii) protein truncating variant (PTV) rate, and (iv) brain expression. First, the genes are partitioned into 3 pLI groups: $[0, .5)$, $[.5, .9)$, and $[.9, 1.0]$. These bins contain 12152, 4227, and 62 genes, respectively. Second, 15 gene length groups for each kb range are formed. For instance, genes that are [1000, 1999] bp-long are assigned to bin 1. All genes that are longer than 14kb are put in a single group. These bins contain 64, 6962, 2622, 1111, 451, 269, 132, 93, 55, 34, 17, 13, 14, 20, and 30 genes, respectively. Finally, 3 PTV rate groups are formed: $[0, 1.6 \times 10^{-6})$, $[1.6 \times 10^{-6}, 3.8 \times 10^{-6})$, and $[3.8 \times 10^{-6}, 1]$. These bins contain 6994, 6994, and 3496 genes, respectively. For a gene X to be randomly matched, a random brain expressed gene that shares all corresponding partitions with X is selected without replacement. These features for genes are listed in Supplementary Table 6. Then the permutation test checks if the TFs in one group (e.g., ASD-only) are significantly connected to the genes in another group (e.g., ID-only) as follows: (i) We count the number of connections between the actual sets; (ii) we count the number of connections in between each of the corresponding 1000 random sets; and finally, (iii) we assign an empirical p-value to the connectivity using the ranking of the actual number of connections among 1000 random draws (Figure 5).

4.7 Spatio-Temporal Network Analyses

We investigate which GCNs (i.e., neurodevelopmental windows) are better predictors of gene risk for each disorder. For each gene i, the average risk probability assigned by the corresponding GCN is calculated over all iterations such that i is in the test fold. The average values for (i) top percentile genes for each disorder are shown in Figure 3; and (ii) E1 genes for each disorder are shown in Supplementary Figure 2. Both DeepND-ST and DeepND results are provided. We also investigate

which GCNs are attended by the MoE model the most. That is, we calculate the mean of the weights assigned to GCN j for each gene i (i.e., W_i^j) by the MoE. Again, only the iterations in which gene i is in the test fold is used. Results are shown in Supplementary Figure 3.

Code Availability. DeepND is implemented and released at http://github.com/ciceklab/deepnd. We provide the environment which contains all dependencies for an easy setup. We give a small example to train and test both DeepND-ST/ DeepND models. Finally, we provide the code and links to the full set of datasets to reproduce the results (genomewide risk rankings and data for heatmaps) presented in this manuscript for ASD and ID.
Data Availability. All datasets used in this study are publicly available, which are referenced in the relevant methods subsections. The Genotype-Tissue Expression (GTEx) Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The GTEx data used for the analyses described in this manuscript were obtained from the GTEx Portal on Feb 2020. All data supporting the key findings such as gene risk evidence levels and gene risk predictions are available within the article and corresponding supplementary tables.

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Author Contributions. AEC conceived, designed, and supervised the study. IB and OK implemented the DeepND software. IB, OK and AEC performed the computational experiments and wrote the manuscript.

Competing Financial Interests. Authors declare no competing financial interests.

Supplementary Figure and Table Legends.

Supplementary Figure 1. (a) The percentage overlap between corresponding deciles of the ASD and ID genome-wide risk rankings are shown. (b) The percentage overlap between corresponding percentiles of the ASD and ID genome-wide risk rankings are shown.

Supplementary Figure 2. Heatmaps show which spatio-temporal windows lead to assignment of higher risk probabilities to E1 genes for respective disorders. The numbers in boxes are softmaxed outputs of each respective GCN, averaged for E1 genes and then normalized. Top panels are the results for the DeepND-ST model for ASD (left) and ID (right). Bottom panels are are the results for the DeepND model for ASD (left) and ID (right). The categorization of brain regions and time windows are provided in Figure 3.

Supplementary Figure 3. Heatmaps show which spatio-temporal windows are focused by the Mixture of Experts model to have better predictions for the top percentile genes for respective disorders. The numbers in boxes are the weights assigned to each GCN, averaged for top percentile genes. Top panels are the results for the DeepND-ST model for ASD (left) and ID (right). Bottom panels are are

the results for the DeepND model for ASD (left) and ID (right). The categorization of brain regions and time windows are provided in Figure 3.

Supplementary Figure 4. (a) The co-expression relationships between top percentile genes in each disorder on (a) MDCBC 2-4 network and (b) MDCBC 9-11 network. MDCBC 2-4 is the weakest source of information for DeepND and MDCBC 9-11 is the strongest source of information. In panel (a) there are roughly 12.5k links as opposed to approximately 30k links in panel (b). Note that the full MDCBC 2-4 network contains close to 37.5m links compared to 13m links in MDCBC 9-11, indicating the importance of MDCBC 9-11 for the etiologies of these disorders.

Supplementary Figure 5. Median RNA expression patterns for *GABRG3* (top), *MICAL3* (down-left) and *FOXO3B* (down-right) across various tissues in the GTEx dataset [2] (transcripts per million). These genes are either most expressed or second most expressed in the cerebral cortex.

Supplementary Figure 6. Median RNA expression patterns for confident novel predictions of DeepND across various tissues in the GTEx dataset [2] (transcripts per million): *SLC9A9* (top-left), *CACNA1H* (top-right), *TAT* (bottom-left) and *GIGYF2* (bottom-right).

Supplementary Table 1. Genome-wide risk probability predictions and rankings of DeepND for ASD and ID. The table marks the gold standard genes: 594 positively and 1185 negatively labeled genes for ASD; and 237 positively and 1074 negatively labeled genes for ID are given along with their evidence levels (E1 - E4, E1 indicating the highest risk). The table also provides the rankings from other gene discovery algorithms from the literature. Finally, for each gene, participation in disorder-related gene sets are provided (e.g., WNT pathway, *CHD8* targets etc.).

Supplementary Table 2. The table provides information about the studies used to generate the ground truth labels for ID. For each gene, the base studies which indicates it as a risk gene are provided.

Supplementary Table 3. The table lists (i) the GO enrichment analysis for the top percentile risk genes for both disorders (Biological Process and Molecular Function). It also provides lists of top transcription factor (TF) regulators whose targets are enriched with the top percentile ASD and/or ID risk genes, respectively. The TF enrichment results are based on the experimentally validated TF-gene relationships in ChEA 2016 database. All results are obtained using the EnrichR system.

Supplementary Table 4. DeepND risk rankings for the genes within 6 ASD related (16p11.2, 15q11-13, 15q13.3, 1q21.1 and 22q11) (Krishnan et al., 2016) and 6 mental retardation related CNV regions (16p11.2, 1q21.1, 22q11.21, 22q11.22, 16p13 and 17p11.2). Frequency of these CNV regions within ASD and ID individuals are provided when available.

Supplementary Table 5. The input feature data used to train DeepND-ST and DeepND models are provided for each gene for replication purposes. The sources in the literature which are used to compile the data are stated. The complete list of 29 features listed are used to train the multitask model. Subsets of this list are used to train singletask models respectively for each disorder and the columns are marked accordingly.

Supplementary Table 6. The information for gene-gene interaction plots in Figure 5 are provided for (a) the co-expression subnetwork for the top 30 risk genes in the MDCBC 9-11 network with a correlation coefficient of at least .95, (b) the top percentile risk genes with a connection in the DifferentialNet frontal-cortex PPI network, and (c) top percentile risk genes which are regulated by a TF gene in the same list or by DMRT1. The list of nodes and edges are listed in the corresponding tabs.

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