Title: Prefrontal cortex dopamine transporter gene network moderates the effect of perinatal hypoxic-ischemic conditions on cognitive flexibility and brain gray matter density in children

Short title: DAT1 network and perinatal hypoxic-ischemic conditions

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Keywords: dopamine transporter gene; DAT1; hypoxic-ischemic conditions; cognitive flexibility; parallel-independent component analysis; ADHD

number of words in the abstract: 244
number of words in article body (excluding abstract, acknowledgments, financial disclosures, legends and references): 3994
number of figures: 4
number of tables: 1
supplemental information: 1

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Abstract

Background: Genetic polymorphisms of the dopamine transporter gene (*DAT1*) and perinatal complications associated with poor oxygenation are risk factors for attentional problems in childhood and may show interactive effects. **Methods:** We created a novel expression-based polygenic risk score reflecting variations in the function of the *DAT1* gene network (ePRS-DAT1) in the prefrontal cortex (PFC) and explored its interaction with perinatal hypoxic-ischemic conditions (HICs score) on cognitive flexibility and brain gray matter density in healthy children from two birth cohorts – MAVAN from Canada (n=139 boys and girls) and GUSTO from Singapore (n=312 boys and girls). **Results:** A history of exposure to several perinatal HICs was associated with impaired cognitive flexibility only in the high ePRS group, suggesting that variation in the PFC expression of genes involved in dopamine reuptake is associated with differences in this behavior. Interestingly, this result was observed in both ethnically distinct birth cohorts. Additionally, parallel-independent component analysis (MAVAN Cohort, n=40 children) demonstrated relationships between single nucleotide polymorphisms (SNP)-based ePRS and gray matter density in areas involved in executive (cortical regions) and integrative (bilateral thalamus and putamen) functions and these relationships differs in children from high or low HICs exposure. **Conclusions:** These findings reveal that the impact of conditions associated with hypoxia-ischemia on brain development and executive functions is moderated by genotypes associated with dopamine signaling in the PFC. We discuss the potential impact of innovative genomic and environmental measures for the identification of children at high risk for impaired executive functions.

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Introduction

The dopamine transporter (DAT) is a transmembrane protein responsible for the reuptake of dopamine (DA) from the synaptic cleft into the presynaptic neuron, thereby terminating DA signaling (1, 2). DAT regulates the strength and duration of dopaminergic transmission revealed by the effects of many DAT-targeted pharmacological therapies, such as methylphenidate (MPH), that improve DA dysfunction in attention-deficit/hyperactivity disorder (ADHD) (3-5). Although DAT is abundant in the striatum and sparse in the prefrontal cortex (PFC) (6, 7), several studies show that low doses of MPH (dosages that are usually more effective in treating attentional impairments than hyperactivity) preferentially increase DA release in the PFC (8-11). The PFC is highly involved in executive functions - a set of cognitive processes comprising cognitive flexibility and planning - that are typically impaired in ADHD children (12-14).

The DAT gene (*DAT1/SLC6A3*), located in the chromosome 5p15.3, is one of the most studied genes in ADHD (15). A 40-bp variable number of tandem repeats (VNTR) polymorphism and single nucleotide polymorphisms (SNPs), for example *rs2652511*, were identified as risk factors for ADHD (16-18). Although we acknowledge the contribution of studies focusing on a single candidate polymorphism, genes do not act in isolation, but in concert with other genes in molecular pathways. The principle of gene networks considers that gene expression is co-regulated by other genes, and consequently genes involved in the same network are expected to have similar expression profiles (19). Analyzing genomic data through gene sets defined by functional

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pathways represents a potentially powerful and biologically-oriented link between genotypes and phenotypes (20).

Although genetic factors contribute substantially to the etiology of ADHD, there is considerable evidence for the influence of environmental factors (21). Getahun and colleagues (22) identified a direct relationship between hypoxic-ischemic conditions (HICs) in utero and the later development of ADHD. Preeclampsia, Apgar score <7 at 1 or 5 minutes, breech/transverse presentations, prolapsed/nuchal cord and elective cesarean births were all significantly associated with ADHD (23, 24). Using an animal model of perinatal hypoxia-ischemia, we demonstrated cognitive inflexibility using the attentional set-shifting task, a task comparable to the Intra-Extra/dimensional shift in humans. Additionally, we showed that the cognitive inflexibility in this model was correlated to PFC atrophy and dopaminergic dysregulation also in the PFC, reflecting the profile reported in ADHD individuals (25).

Our rodent study suggests that perinatal hypoxia-ischemia associate both with impaired cognitive flexibility and altered PFC DA signaling. Considering that the literature has linked *DAT1* polymorphisms and ADHD, we hypothesized that a genomic measure based on a PFC-specific *DAT1* gene network would moderate the impact of perinatal HICs on cognitive flexibility in children. To test this hypothesis, we constructed an expression-based polygenic risk score that reflects the function of a prefrontal cortex *DAT1* gene network (ePRS-DAT1/PFC) and analyzed its interaction with perinatal HICs on cognitive flexibility performance and brain gray matter density in healthy children.

Methods and Materials

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Subjects

We used data from two prospective birth cohorts based in Canada (Maternal Adversity, Vulnerability and Neurodevelopment, MAVAN (26)) and Singapore (Growing Up in Singapore Towards Healthy Outcomes, GUSTO (27)).

Main Cohort (MAVAN): MAVAN is a community-based, birth cohort study of pregnant Canadian mothers and their offspring. Pregnant women aged 18 years and above were recruited in Montreal (Quebec) and Hamilton (Ontario), Canada. Approval for the MAVAN project was obtained from McGill University, Université de Montréal, Royal Victoria Hospital, Jewish General Hospital, Centre hospitalier de l'Université de Montréal, Hôpital Maisonneuve-Rosemount, St Joseph's Hospital and McMaster University. A total of 139 children of both sexes had complete data (birth records, genotype and cognitive flexibility task at 6 years of age) and were included in the study. Of this sample, 40 subjects had brain magnetic resonance imaging (MRI) used for the parallel-independent component analysis (p-ICA) (see below).

Replication Cohort (GUSTO): Pregnant aged 18 years and above were recruited at the National University Hospital and KK Women's and Children's Hospital from Singapore. The pregnant women included Chinese, Malay, or Indian ethnicity with homogeneous parental ethnic background that allow us to extend the analysis to include Southeast Asian ethnic groups (28). The study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the Sing Health Centralized Institutional Review Board (CIRB). Informed written consent was obtained from each participant. A total of 312 boys and girls had complete data (birth records, genotype and cognitive flexibility task at 4.5 years of age) and were included in the study.

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PFC *DAT1* co-expressed genes and ePRS

The expression-based polygenic risk score was created considering genes co-expressed with the dopamine transporter gene (ePRS-DAT1) in the PFC, according to the protocol previously described by Silveira et al. ((28) and see Figure S1). The genetic score was created using (a) GeneNetwork (http:// genenetwork.org), (b) BrainSpan (http://www.brainspan.org), (c) NCBI Variation Viewer (https://www.ncbi.nlm.nih.gov/variation/view) and (d) GTEx (https://www.gtex portal.org/home). A fully explanation about the processes and the final list of co-expressed genes included in the ePRS (Table S1) are described in Supplemental material. The final score in both cohorts was categorized into "low ePRS" or "high ePRS" using a median split for the behavioral analysis.

Perinatal hypoxic-ischemic conditions (HICs) Score

We aggregated information from Getahun et al (22) and Linnet et al (29), compiled by Smith et al (30) and reduced seven dichotomously scored variables using principal component analysis: 1) APGAR score at 1 minute <7 (31); 2) respiratory distress, 3) fetal dystocia, 4) occurrence of umbilical cord prolapse, 5) placental abruption, 6) breech or transverse birth presentation, 7) neonatal resuscitation. Maternal smoking during pregnancy and birth weight ratio (observed birth weight/mean populational weight adjusted by sex and gestational age)(32, 33), were tested at the unidimensional component model, but did not exhibit significant component loadings, and were not considered (see Table S2 and Figure S2). After model specification, tetrachoric correlations of dichotomous items were computed using the Item Response Theory method (34). In this procedure, scores are obtained from a linear combination between the

observed variables and the extracted component (latent variable), parceling out error variance. This method aims to maximize validity by producing scores that are highly correlated with the underlying factor, in order to obtain unbiased estimates scores, weighted for loadings that are indicative of the substantive importance of a particular variable (35).

The HICs score was used either as a continuous variable (for the behavioral outcomes) or categorized into "low HICs" or "high HICs" using a median split (for the p-ICA analysis). Low HICs indicates minimal exposure to hypoxic-ischemic conditions in the perinatal period, and High HICs suggests a history of exposure to several hypoxic-ischemic conditions.

Behavioral outcomes

Intra-/Extra-dimensional Set Shift (IED): The task comprises rule acquisition and reversal throughout nine stages with increasing difficulty. There are two dimensions used in the task (color-filled shapes and white lines) and in the first 7 stages, shape remains the relevant dimension. An extra-dimensional shift occurs in the stage 8, being the white lines the relevant dimension for a correct response, requiring cognitive flexibility (36) (Figure S3A). This task was conducted in MAVAN children at the age of 72 months and we focused specifically on stage 8 (extra-dimensional shift) that measures cognitive flexibility.

Dimensional Change Card Sort (DCCS): The DCCS, like the IED, measures the ability to shift between two dimensions, but is more readily completed by younger children. For this reason, we used this task to assess cognitive flexibility of children at 54 months in the GUSTO cohort. In the standard version of the DCCS task children are shown cards with two dimensions: different colors (red vs. blue) and shapes (rabbit vs. boat). In the first stage (pre-switch) children must sort

the cards by the color dimension, independently of the shape presented on the cards. In the following stage (post-switch) the rule changes and children must sort the cards by the shape dimension and ignore the first rule, requiring attentional flexibility (37) (Figure S3B).

Gray matter density

Parallel-independent component analysis (p-ICA): Structural MRI acquisition and data preparation were conducted previous to the p-ICA analysis (see Supplemental material). A multivariate p-ICA was applied to identify relationships between clusters of interrelated SNPs and brain gray matter information in a data-driven manner (38). We innovated because instead of investigating the relationship between the crude genotype and the gray matter-voxel based measures, we sought the relationship between the SNP based DAT1ePRS (or genotype * GTEx gene expression slope at each SNP that compose the DAT1ePRS score) and the voxel based gray matter in the whole brain (full description on supplemental material). The perinatal environment defined the groups for comparison (20 children high HIC score, 20 children low HIC score), aggregated with population stratification for adjustment (ethnicity). Loading coefficients, which describe the presence of the identified component across subjects (39), were extracted for each component, modality and subject. The mean subject-specific loading coefficients of these components between children from high and low HICs groups was compared using Student's t-test.

Validation of the prefrontal *DAT1* co-expression network

Gene expression levels at different time points: We used BrainSpan to analyze the correlation between the expression levels of all genes included in the ePRS-DAT1 in the human PFC in different time points: perinatal, childhood, and adulthood. Thus, we can investigate whether the same pattern of co-expression is maintained through the life-course. The analyses were carried out in *R* using the heatmaply package.

*Gene ontology enrichment analysis***:** Enrichment analysis for functional ontologies of the genes comprising ePRS-DAT1 was performed using Metacore® (https://portal.genego.com).

Protein-protein interaction network analysis: STRING database (https://string-db.org) was used to analyze functional interactions between the corresponding protein from our list of *DAT1* co-expressed genes (269 genes) and the same top 269 genes associated with SNPs from the genome-wide association study (GWAS) for ADHD (40). We compared the mean number of interactions of the top 20 most interactive proteins of each dataset (ePRS-DAT1 and GWAS ADHD).

Comparison to other PFC ePRS: As the creation of the ePRS-DAT1 was highly informed by the main action of a pharmacological agent (e.g. methylphenidate), we created a control PFC ePRS with the same premise and using the same methods described above. The control ePRS had the serotonin transporter as the target (ePRS-SLC6A4) considering the action of serotonin reuptake inhibitors (e.g. fluoxetine). This choice is also interesting because the methylphenidate also acts on the serotonin transporter, but with much less affinity than the dopamine transporter (41, 42).

Statistical Analysis

Data were analyzed using the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and R (https://www.r-project.org). Significance levels for all measures were set at $\alpha = 0.05$. Student's t-test was performed to compare a) the mean number of protein interactions between the ePRS and GWAS-ADHD, b) the continuous data of the sample baseline characteristics between low and high ePRS and c) the mean subject-specific loading coefficients between children from high and low HICs score (p-ICA). Chi-squared tests were performed to analyze the categorical variables of the sample baseline characteristics. Linear regressions were used to examine interaction effects of the genetic score (median split: low and high ePRS) with the perinatal hypoxic-ischemic conditions (continuous variable: HICs) on the behavioral outcomes (IED and DCCS tasks). The ePRS and HICs scores were included as main factors along with covariates of sex and population stratification. Additionally, the pre-switch performance was included as covariate for the DCCS task. Simple slope analyses were conducted to analyze the post-hoc differences.

Results

Behavioral outcomes

In both MAVAN and GUSTO datasets, children from high and low ePRS-DAT1 genetic score do not differ in the main confounding variables, chosen based on the literature (see Table 1). We considered well-established variables that affect child neurodevelopment as possible confounders: birth weight and gestational age (43-45), maternal age (46), socioeconomic status (47) and maternal education level (48).

IED task (stage 8, extra-dimensional shift): In the IED task we observed a significant ePRS x HICs interaction in predicting the latency to respond ($\beta = 32489.1$, $p < 0.001$) at the stage 8 of

the task. The simple slopes analysis showed that the high ePRS group demonstrated worse outcomes (higher latency to respond) as HICs score increases (β= 29002.6, $p < 0.05$) (Figure 1A). No significant interactions were seen for number of trials (β = 3.92, p = 0.14) and errors (β = 1.89, p = 0.29). Results for other IED stages are shown in Table S3.

DCCS task (post-switch phase): We then replicated the ePRS-DAT1/PFC x HICs interaction effect in the GUSTO cohort. The ePRS-DAT1 X HICs score interaction was observed for total accuracy (β = -0.46, $p < 0.05$) and number of commission errors (β = 0.44, $p < 0.05$) in the post-switch phase. Higher HICs was associated with lower accuracy (β = -0.50, $p < 0.001$) and higher commission errors (β =0.44, $p < 0.01$) only in the high ePRS group (Figure 1B and C, respectively). Main effects and adjusted/unadjusted analysis for IED stage 8 in MAVAN and DCCS in GUSTO are described in Table S4.

Specificity of the DAT1 gene network: We then analyzed the specificity of our findings in relation to the *DAT1* gene network. We used the same ePRS bioinformatic process (Figure S1) to create an ePRS from genes that are co-expressed with the *SLC6A4* gene in the PFC. Despite the fact that ePRS - *SLC6A4* also formed a cohesive gene network (Figure S4), there were no interactions between this genetic score and the HICs score on IED outcomes (number of trials, $\hat{\beta}$=-1074.52, p=0.11; number of errors, $\hat{\beta}$=-576.50, p=0.20 and latency $\hat{\beta}$=87428.9, p=0.97).

Gray matter density

The p-ICA identified imaging/genetic relationships between regional gray matter volume and SNP-based ePRS-DAT1 data, showing highly significant relationships between a) the genetic component 2 and MRI component 1 (r=-0.77, p=5.953e-09); b) genetic component 5 and MRI

component 7 (r=0.69, p=7.1487e-07) and c) genetic component 12 and MRI component 4 (r=-0.61, p=2.1291e-05). When comparing the mean loading coefficients of these components between children from high and low HICs groups by Student's t-test, we see statistically significant differences in the pair genetic component 2 and MRI component 1 (Figure 2), suggesting that the relationship between DAT1ePRS and gray matter volume in these brain regions is moderated by the neonatal environmental condition. Genetic component 5 was also significantly different between the groups. The pair MRI component 7 did not reach significance (p=0.069), although it is clear on Figure 2 that groups have opposite directions in loading coefficients. For the other relationship between genetic component 12 and MRI component 4, no differences between groups were observed.

To define the significant SNPs in each component, we used a threshold of >+2.5 and <-2.5. In component 2, we found 78 significant SNPs and the enrichment analysis demonstrated that these SNPs are involved especially in positive regulation of long-term synaptic potentiation (FDR q=3.635e-06), astrocyte activation (FDR q=6.529e-06), dopaminergic transmission (FDR q=2.710e-05) and GABAergic transmission (FDR q=1.867e-06). Additionally, these genes were enriched for diseases including anxiety disorders (FDR q=9.243e-05), schizophrenia (FDR q=3.269e-03) and dementia (FDR q=9.835e-03). This group of SNPs was related to differential gray matter density in areas of the putamen and thalamus (MRI component 1). In genetic component 5, we found 77 significant SNPs that were involved in nervous system development (FDR q=7.617e-04), neurogenesis (FDR q=7.365e-04) and neuron migration (FDR q=6.755e-04). This component was related to differential gray matter in cortical regions (MRI component 7).

Validation of the *DAT1* co-expression network

We used BrainSpan data to correlate the PFC expression levels of all genes included in the ePRS during the perinatal period. We observed two large clusters of highly co-expressed genes specifically at this developmental period (Figure 3A). These findings confirmed the co-expression network from the genes included in the ePRS-DAT1 in the PFC. For the developmental trajectory analysis, we kept the same order of the genes comprising the perinatal correlation matrix to visualize whether the clusters would be consistent throughout development. We observed that the general pattern of co-expression was generally maintained during the life-course (Figure 3B and C). We analyzed *DAT1* expression by age in different human brain regions using Human Brain Transcriptome (http://hbatlas.org) (49) and observed stable gene expression throughout development, with very similar levels of expression in the neocortex and striatum (Figure S5).

The gene ontology enrichment analysis showed several statistically significant enrichment processes, functions and cellular localizations and we focused on the top ten significant results (Figure S6). This analysis reveals gene ontology processes that involve neurodevelopmental processes and cell signaling among others. Similarly, molecular functions were enriched for protein binding (FDR q = 8.71e-11) and transmembrane receptor tyrosine kinase activity (FDR q = 1.28e-03). Gene ontology localizations were enriched for extracellular space, cytoplasm, adherens junction and cell junction.

The protein-protein network analysis is depicted in Figure 4, demonstrating the protein network resulting from the ePRS-DAT1 (Figure 4A), and the top genes (comparable size) from the 2017 ADHD GWAS (40) (Figure 4B). Analyzing the top 20 most interactive proteins, we found a significant higher number of interactions in our *DAT1* network compared to the GWAS

ADHD dataset ($p<0.0001$, mean *DAT1* = 11.65±5.41, mean GWAS ADHD = 2.8±1.64), suggesting that the ePRS-DAT1 represents a more cohesive gene network.

Discussion

We used a novel informatics approach to show that the association between hypoxic-ischemic conditions and executive function in childhood is moderated by genetic variants in a PFC-specific DAT1 gene network. A composite measure of perinatal HICs was related to cognitive flexibility only for children with a genetic background reflecting higher PFC activity of the DAT machinery (high ePRS-DAT1). This result was observed in two ethnically distinct birth cohorts: MAVAN (Caucasians from Canada) and GUSTO (Southeast Asians from Singapore). The SNP-based ePRS-DAT1 also moderated the relation between perinatal HICs and gray matter density in areas involved in executive (cortical regions) and integrative (bilateral thalamus and putamen) functions.

The DA system is implicated in the regulation of cognitive flexibility. In clinical trials, systemic administration of an antagonist of the dopamine receptor D2 impaired the attentional set shifting performance (50) while MPH administration improved performance (51). One of the trigger points for DA system dysfunction seems to be the DAT, and several studies reveal associations between polymorphisms in the *DAT1* gene with a higher risk for attentional problems (17, 18, 52-54). Our findings extend studies focusing on single variants to show that a *DAT1* PFC expression-based gene network moderates the impact of perinatal conditions known to increase the risk for ADHD on executive function in childhood. These findings are consistent with the

position that the analysis of gene sets defined by functional pathways is a promising approach for investigating the relationship between genotypes and phenotypes (20).

We validated our *DAT1* network using several approaches. We used databases that included gene expression levels in human PFC to demonstrate that a high proportion of the DAT1-related genes have similar expression levels in the perinatal period, confirming that the co-expression patterns within this gene network go beyond the co-expression with *DAT1* only, but form several clusters of co-expressed genes. Clusters of co-expressed genes are generally maintained throughout development, suggesting that this network is also operative at later ages. Protein network analysis resulting from the ePRS-DAT1 shows that *DAT1* network represents a more cohesive protein network with significantly more connections than the protein network resulting from the same number of top genes from most recent GWAS for ADHD (40). An ePRS based on PFC 5HTT co-expression produced a gene network that was not associated with the cognitive flexibility performance in children, emphasizing the specificity of the ePRS technique.

The ePRS method is a robust approach that goes beyond finding association between scattered genetic variants and phenotypes, but captures information about the whole gene network, and its function, in specific brain regions (28). Our enrichment analysis for the *DAT1* network included nervous system development, which is in agreement with the choice of genes overexpressed during fetal and early postnatal periods when we filtered using BrainSpan. Enrichment for many extracellular localizations, but also cytoplasmic part, adherens and cell junction, is aligned with the reported function of DAT mediating the transport of extracellular DA to the intracellular space (55, 56). Multiple intracellular and extracellular signaling pathways have been implicated in the regulation of DAT function and its expression is modulated through

internalization and recycling from the cell surface (57). Moreover, DAT is the main target site for psychostimulant drugs, and thus several binding functions observed in the enrichment analysis provide a valid representation of the *DAT1* gene network function.

Several factors such as birth asphyxia, preeclampsia, respiratory distress syndrome, low Apgar score, prolapsed/nuchal cord were significantly associated with ADHD (22-24). Considering that different, inter-correlated conditions could influence perinatal oxygenation levels, we aimed at creating a novel cumulate index of perinatal adversity, the hypoxic-ischemic-associated conditions (HICs) score. Smith and colleagues (30) have proposed that accounting for multiple ischemia-hypoxia related obstetric complications during pregnancy and birth may provide a more accurate measure of ischemia-hypoxia exposure in community-based samples. These authors recommend creating a weighted summary score of perinatal risk factors, allowing for ischemia-hypoxia exposure severity to be measured on a continuum, an approach we adopted for the current study. Other studies had used a similar approach and observed that perinatal health risk increased inattention and hyperactivity/impulsivity later in life (58-60). A strength of our prospective study is that we used birth cohorts with extensive and detailed data including gestational and birth records to create a reliable perinatal score without reliance on self-report retrospective questionnaires.

Differential exposure to perinatal HICs modifies the relationships between the SNP-based ePRS-DAT1 and gray matter volume in areas involved in information processing (cortical regions, thalamus and putamen). Our previous work using the rat model of hypoxia-ischemia demonstrate smaller total brain and gray matter volumes in areas such as cerebral cortex and striatum, in addition to attentional impairments observed in adult animals (61). Experimental studies indicate

that perinatal hypoxia/ischemia induces lasting changes in dopaminergic neurotransmission depending on the severity and duration of the hypoxic insult (62). Neuropathological and in vivo imaging studies in humans indicate that dopamine synthesis capacity is reduced in subjects exposed to "high HICs" which is positively related to brain atrophy (63, 64). Such reduced dopamine synthesis capacity could even worsen the strength and duration of dopamine transmission in general and especially in the "high ePRS DAT1 " group. In clinical studies, smaller thalamus and frontal and parietal cortex were associated with lower attention and executive functions in adolescents and adults born preterm or with low birth weight (65-67). Additionally, fronto-striato-thalamic circuitry has been implicated in ADHD pathophysiology in several studies (68-70). Considering that, we can infer that differences in gray matter density of the described structures appear to contribute to the impaired cognitive flexibility in our study, with perinatal HICs modulating the relationship between the genetic background and gray matter volumes.

One limitation of the study however is the smaller sample size for the neuroimaging study. Although the sample size at the baseline was large, it was relatively small at the follow-up study for MRI, hence neuroimaging results require replication. Independent replication and the use of falsification approach (another pathway) are strengths of this study, that together with other efforts such as pre-registration can help avoid Type-I errors in future studies using our methodology.

We demonstrated that the gene network associated with prefrontal cortex dopamine transporter interacts with the history of exposure to perinatal hypoxic-ischemic conditions impairing cognitive flexibility and modifying the relationship between genetics and gray matter density. Dopamine neurotransmission in the PFC is an essential moderator of the effects of perinatal adversity on attentional outcomes and brain development and define children's

endophenotype and risk for attentional disturbances. We innovate by proposing new ways of integrating genotype data and perinatal history of hypoxic-ischemic conditions to predict cognitive flexibility in community cohorts, which may inform practices for early detection of vulnerability to poor academic performance. The proposed research approach could be of great importance for the study of other dopamine-related gene networks and psychiatric disorders (71). Considering that we cannot modify our genetic predisposition for certain traits or disease, we highlight the importance of preventive measures to improve intrauterine and intrapartum health to avoid disturbances in the fragile fetal developing brain.

Acknowledgements

We would like to thank Professor Jingyu Liu for the technical support on the parallel-independent component analysis and all participating families for their cooperation. This work was funded by the Toxic Stress Research network of the JPB Foundation, Sackler Foundation and Ludmer Center for Neuroinformatics and Mental Health. Part of this study was conducted during a scholarship supported by the PDSE program of CAPES-Brazil (Coordination for Improvement of High Education Personnel).

Disclosure statement

The authors have no conflicts of interest to declare.

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Table 1: Description of the baseline characteristics of the MAVAN and GUSTO sample.

	MAVAN			GUSTO		
Sample characteristics	**Low ePRS (n=67)**	**High ePRS (n=72)**	**P-value**	**Low ePRS (n=150)**	**High ePRS (n=162)**	**P-value**
Males (%)	38 (56.7%)	35 (48.6%)	0.339	62 (41.3%)	82 (50.6%)	0.100
Maternal age at birth (y)	31.25 ± 5.18	31.82 ± 4.19	0.075	31.45 ± 5.21	31.62 ± 5.18	0.772
Full weeks of gestation	39.09 ± 1.28	38.78 ± 1.14	0.248	38.60 ± 1.22	38.33 ± 1.33	0.324

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Birth weight (in grams)	3404.68 ± 429.13	3366.11 ± 440.65	0.732	3131.65 ± 411.48	3067.46 ± 420.42	0.741
HICs score	0.04 ± 1.07	-0.14 ± 0.81	0.179	0.04 ± 1.04	-0.04 ± 0.96	0.473
Low SES	14 (23.3%)	8 (14.3%)	0.214	28 (19.4%)	21 (13.6%)	0.176

Data are expressed as means (standard deviations) or number of participants (percentages). Differences between low and high ePRS groups were not significant for all variables shown (Student's t-test for means and Chi-square test for percentages). Low socioeconomic status (SES) in MAVAN: maternal education attained <= high school or monthly income under low bound from the Cut Off proposed by Statistics Canada (72). Low SES in GUSTO: maternal education attained primary school or monthly income <$2000. HICs=hypoxic-ischemic-associated conditions.

Figures:

Miguel PM, Pereira LO, Barth B, de Mendonça Filho EJ, Pokhvisneva I, Nguyen TTT, Garg E, Razzolini BR, Koh DXP, Gallant H, Sassi RB, Hall GBC, O'Donnell KJ, Meaney MJ, Silveira PP. Prefrontal Cortex Dopamine Transporter Gene Network Moderates the Effect of Perinatal Hypoxic-Ischemic Conditions on Cognitive Flexibility and Brain Gray Matter Density in Children. Biol Psychiatry. 2019 Oct 15;86(8):621-630. doi: 10.1016/j.biopsych.2019.03.983

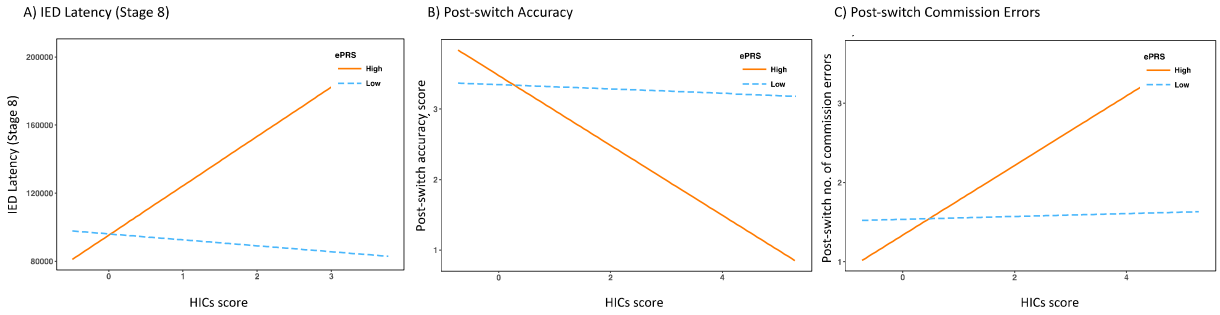

Figure 1: Cognitive flexibility performance in the Intra-/Extra-Dimensional Set Shift (IED) task in MAVAN children (A) and in the Dimensional Change Card Sort (DCCS) task in GUSTO children (B and C). Higher HICs score was associated to longer latency to respond only in the high ePRS group in the IED task (A). Higher HICs score was associated to lower accuracy and higher number of commission errors only in the high ePRS group in the DCCS task (B and C). Linear regression followed by simple slope analysis.

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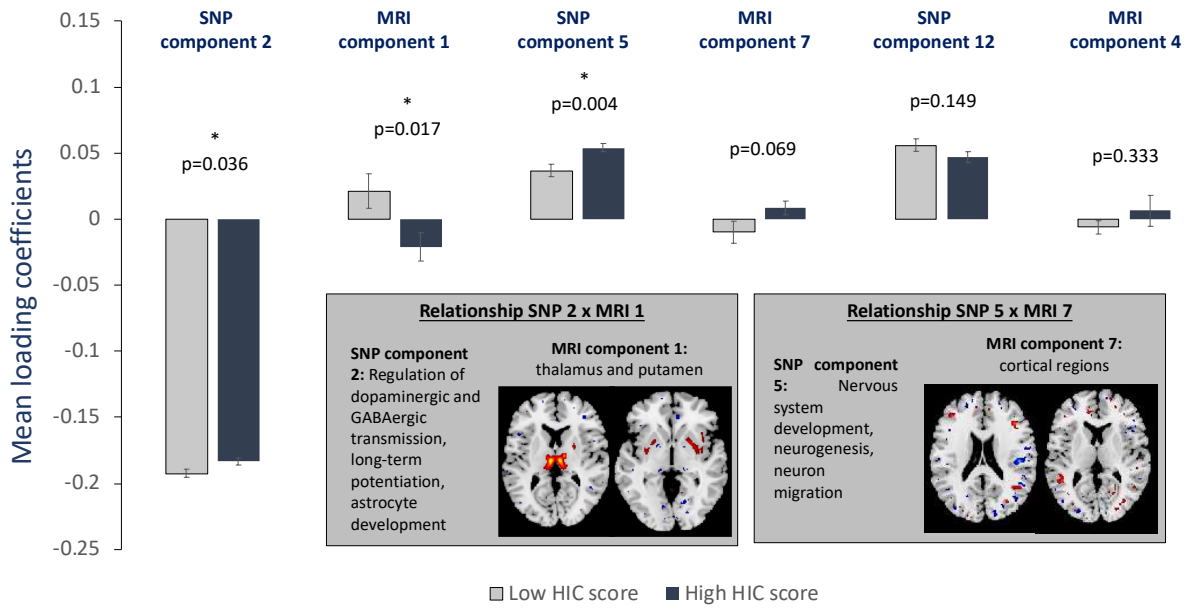

Figure 2: Bar plot of the mean loading coefficients of brain MRI component and genetic component. *indicates group differences among children with Low and High HIC score. Student's t-test. HIC=hypoxic-ischemic-associated conditions.

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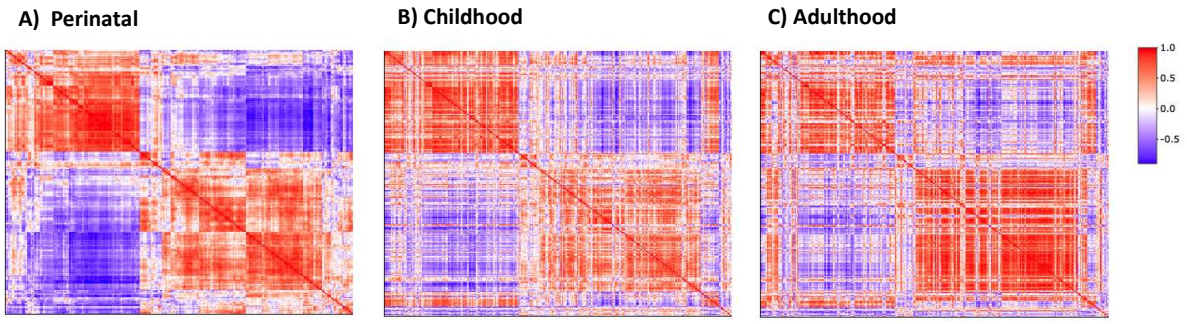

Figure 3: Heatmap of DAT1-related genes (expression levels) correlation throughout development in the human PFC. Genes from the same expression quantification tend to cluster together and could be visualized in red (positive correlation). Blue pattern indicates a negative correlation. In this analysis, the arrangement in clusters considering similar gene expression are shown in the perinatal (A), childhood (B) and adulthood (C) stages. Perinatal period ranges from 24 post conception weeks to 4 months of age (n=18); Childhood is defined as 1 to 12 years (n=26) and Adulthood 20 to 40 years (n=22).

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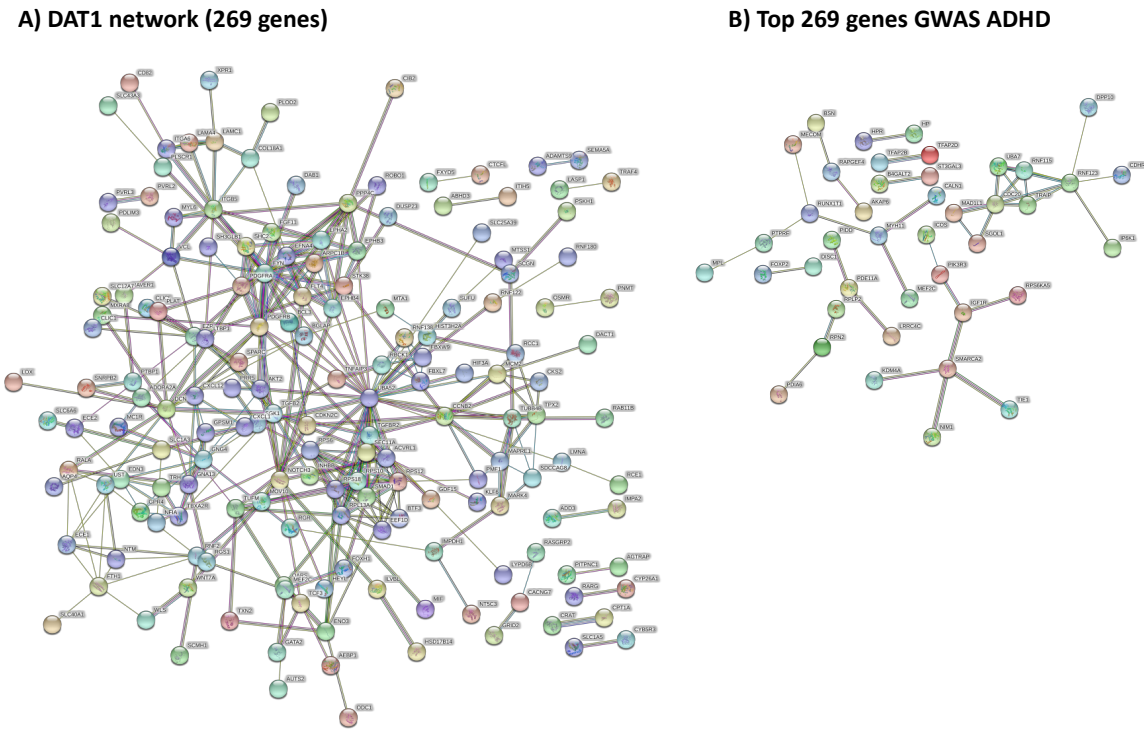

Figure 4: Protein networks from ePRS-DAT1 genes (A) and a comparable number of the top genes from the ADHD GWAS (40) (B). The ePRS-DAT1 contains proteins with a higher number of connections ($p<0.0001$; Student's t-test).

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Supplemental Material

Methods and Materials

PFC *DAT1* co-expressed genes and ePRS

The GeneNetwork is a free online resource that combines sequence data (SNPs) and transcriptome data sets (expression genetic) being useful to study complex network of genes, molecules, gene function and phenotypes (1). We used GeneNetwork to generate co-expression matrix with *DAT1* in the PFC in mice, a species with a greater amount of data (absolute value of the co-expression correlation r≥ 0.5). The gene list generated by GeneNetwork was then filtered using BrainSpan to identify consensus transcripts enriched in the fetal and early postnatal human brain. The BrainSpan is a broad developmental survey of gene expression in specific human brain regions, i.e., it is age and brain region-specific. We selected autosomal transcripts expressed in the PFC at r≥ 1.5-fold during fetal and child development (25 to 38 post conception weeks and first 5 months of age) as compared to adult samples (2). The final list included 293 genes with 13 excluded for their location on chromosome X. We used the Genotype-Tissue Expression (GTEx)

project (3), to establish the relationship between genetic variation and gene expression in the prefrontal cortex. When merged to GTEx database (see below), our final list of genes included 269 genes (Supplement Table S1).

Based on their functional annotation in the National Center for Biotechnology Information, U.S. National Library of Medicine (NCBI Variation Viewer), using GRCh37.p13, we gathered all the existing SNPs from these genes, and merged this list with SNPs from the GTEx data in human PFC (total number of SNPs: 38,509). We retained the list of common SNPs and subjected it to linkage disequilibrium clumping (r^2<0.25). It resulted in 2,328 independent functional SNPs that were weighted by the gene expression slope (expression quantitative trait loci from GTeX, in which the effect allele is the alternative allele). Based on the genotype data in MAVAN (methods described in (4) for MAVAN and (5) for GUSTO), we used a count function of the number of alleles at a given SNP weighted by the slope coefficient from the regression models associated with gene expression by SNPs in cis (Figure S1).

We aimed at replicating our findings in an ethnically distinct cohort to understand the generalizability and external validity of our findings. For that, GUSTO ePRS was created following the same steps, starting from the 269 genes. The final score was categorized into “low ePRS” or “high ePRS” using a median split for the behavioral analysis. Low ePRS indicates lower expression of genes involved in DA reuptake in the PFC with an implied higher level of DA signaling, and conversely a high ePRS implying a lower DA signaling.

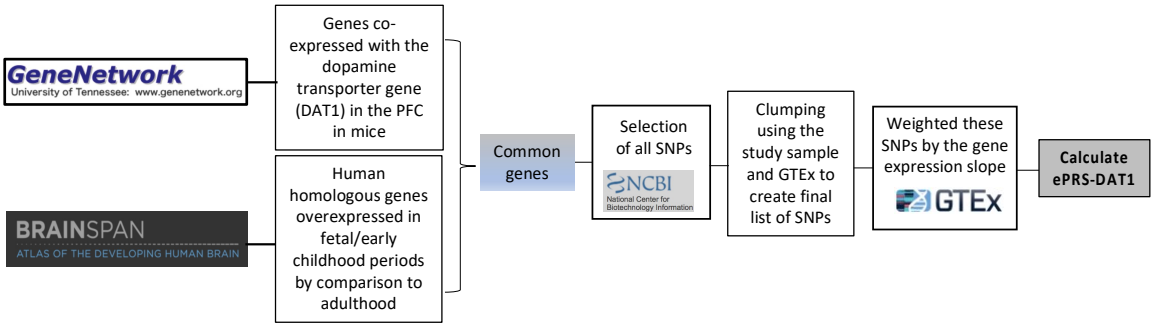

Figure S1. Flowchart depicting the bioinformatics steps involved in the creation of the polygenic risk score based on genes co-expressed with the dopamine transporter (ePRS-DAT1) in the prefrontal cortex (PFC).

Table S1: Genes co-expressed with the dopamine transporter gene and selected for composing the genetic score (DAT1-ePRS).

Symbol	Ensembl	Description
RPS18	ENSG00000226225	ribosomal protein S18 [Source:HGNC Symbol;Acc:HGNC:10401]
ECE1	ENSG00000117298	endothelin converting enzyme 1 [Source:HGNC Symbol;Acc:HGNC:3146]
TBX3	ENSG00000135111	T-box 3 [Source:HGNC Symbol;Acc:HGNC:11602]
EZR	ENSG00000092820	ezrin [Source:HGNC Symbol;Acc:HGNC:12691]
RCE1	ENSG00000173653	Ras converting CAAX endopeptidase 1 [Source:HGNC Symbol;Acc:HGNC:13721]
HEYL	ENSG00000163909	hes related family bHLH transcription factor with YRPW motif-like [Source:HGNC Symbol;Acc:HGNC:4882]
RCC1	ENSG00000180198	regulator of chromosome condensation 1 [Source:HGNC Symbol;Acc:HGNC:1913]
ZCCHC14	ENSG00000140948	zinc finger CCHC-type containing 14 [Source:HGNC Symbol;Acc:HGNC:24134]
SNHG10	ENSG00000247092	small nucleolar RNA host gene 10 [Source:HGNC Symbol;Acc:HGNC:27510]
SERINC2	ENSG00000168528	serine incorporator 2 [Source:HGNC Symbol;Acc:HGNC:23231]
GATA2	ENSG00000179348	GATA binding protein 2 [Source:HGNC Symbol;Acc:HGNC:4171]
GPSM1	ENSG00000160360	G protein signaling modulator 1 [Source:HGNC Symbol;Acc:HGNC:17858]
LTBP1	ENSG00000049323	latent transforming growth factor beta binding protein 1 [Source:HGNC Symbol;Acc:HGNC:6714]
CD72	ENSG00000137101	CD72 molecule [Source:HGNC Symbol;Acc:HGNC:1696]
SEC11A	ENSG00000140612	SEC11 homolog A, signal peptidase complex subunit [Source:HGNC Symbol;Acc:HGNC:17718]
LOX	ENSG00000113083	lysyl oxidase [Source:HGNC Symbol;Acc:HGNC:6664]

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PRPH	ENSG00000135406	peripherin [Source:HGNC Symbol;Acc:HGNC:9461]
XPR1	ENSG00000143324	xenotropic and polytropic retrovirus receptor 1 [Source:HGNC Symbol;Acc:HGNC:12827]
MSI1	ENSG00000135097	musashi RNA binding protein 1 [Source:HGNC Symbol;Acc:HGNC:7330]
CDKN2C	ENSG00000123080	cyclin dependent kinase inhibitor 2C [Source:HGNC Symbol;Acc:HGNC:1789]
LAPTM5	ENSG00000162511	lysosomal protein transmembrane 5 [Source:HGNC Symbol;Acc:HGNC:29612]
LMNA	ENSG00000160789	lamin A/C [Source:HGNC Symbol;Acc:HGNC:6636]
ROBO1	ENSG00000169855	roundabout guidance receptor 1 [Source:HGNC Symbol;Acc:HGNC:10249]
ADGRG1	ENSG00000205336	adhesion G protein-coupled receptor G1 [Source:HGNC Symbol;Acc:HGNC:4512]
LAMA4	ENSG00000112769	laminin subunit alpha 4 [Source:HGNC Symbol;Acc:HGNC:6484]
SMAD1	ENSG00000170365	SMAD family member 1 [Source:HGNC Symbol;Acc:HGNC:6767]
MOV10	ENSG00000155363	Mov10 RISC complex RNA helicase [Source:HGNC Symbol;Acc:HGNC:7200]
GPR4	ENSG00000177464	G protein-coupled receptor 4 [Source:HGNC Symbol;Acc:HGNC:4497]
DCN	ENSG00000011465	decorin [Source:HGNC Symbol;Acc:HGNC:2705]
KLF6	ENSG00000067082	Kruppel like factor 6 [Source:HGNC Symbol;Acc:HGNC:2235]
TAP1	ENSG00000224212	transporter 1, ATP binding cassette subfamily B member [Source:HGNC Symbol;Acc:HGNC:43]
FLT4	ENSG00000037280	fms related tyrosine kinase 4 [Source:HGNC Symbol;Acc:HGNC:3767]
PLPPR5	ENSG00000117598	phospholipid phosphatase related 5 [Source:HGNC Symbol;Acc:HGNC:31703]
QARS	ENSG00000172053	glutaminyl-tRNA synthetase [Source:HGNC Symbol;Acc:HGNC:9751]
TGFBR2	ENSG00000163513	transforming growth factor beta receptor 2 [Source:HGNC Symbol;Acc:HGNC:11773]
SEMA3F	ENSG00000001617	semaphorin 3F [Source:HGNC Symbol;Acc:HGNC:10728]
PLPP3	ENSG00000162407	phospholipid phosphatase 3 [Source:HGNC Symbol;Acc:HGNC:9229]
NTM	ENSG00000182667	neurotrimin [Source:HGNC Symbol;Acc:HGNC:17941]
PDGFRB	ENSG00000113721	platelet derived growth factor receptor beta [Source:HGNC Symbol;Acc:HGNC:8804]
PDZRN3	ENSG00000121440	PDZ domain containing ring finger 3 [Source:HGNC Symbol;Acc:HGNC:17704]
CIB2	ENSG00000136425	calcium and integrin binding family member 2 [Source:HGNC Symbol;Acc:HGNC:24579]
GNG4	ENSG00000168243	G protein subunit gamma 4 [Source:HGNC Symbol;Acc:HGNC:4407]
BCL9L	ENSG00000186174	B cell CLL/lymphoma 9 like [Source:HGNC Symbol;Acc:HGNC:23688]
MTSS1	ENSG00000170873	MTSS1, I-BAR domain containing [Source:HGNC Symbol;Acc:HGNC:20443]
SPARC	ENSG00000113140	secreted protein acidic and cysteine rich [Source:HGNC Symbol;Acc:HGNC:11219]
TGFB2	ENSG00000092969	transforming growth factor beta 2 [Source:HGNC Symbol;Acc:HGNC:11768]
ITGB5	ENSG00000082781	integrin subunit beta 5 [Source:HGNC Symbol;Acc:HGNC:6160]
WWTR1	ENSG00000018408	WW domain containing transcription regulator 1 [Source:HGNC Symbol;Acc:HGNC:24042]
NPEPL1	ENSG00000215440	aminopeptidase like 1 [Source:HGNC Symbol;Acc:HGNC:16244]
EFNA4	ENSG00000243364	ephrin A4 [Source:HGNC Symbol;Acc:HGNC:3224]
GRID2	ENSG00000152208	glutamate ionotropic receptor delta type subunit 2 [Source:HGNC Symbol;Acc:HGNC:4576]
MTA1	ENSG00000182979	metastasis associated 1 [Source:HGNC Symbol;Acc:HGNC:7410]
CCDC12	ENSG00000160799	coiled-coil domain containing 12 [Source:HGNC Symbol;Acc:HGNC:28332]
AGTRAP	ENSG00000177674	angiotensin II receptor associated protein [Source:HGNC Symbol;Acc:HGNC:13539]
CYP26A1	ENSG00000095596	cytochrome P450 family 26 subfamily A member 1 [Source:HGNC Symbol;Acc:HGNC:2603]
CHRNA4	ENSG00000101204	cholinergic receptor nicotinic alpha 4 subunit [Source:HGNC Symbol;Acc:HGNC:1958]
SH3GLB1	ENSG00000097033	SH3 domain containing GRB2 like, endophilin B1 [Source:HGNC Symbol;Acc:HGNC:10833]
NBEAL1	ENSG00000144426	neurobeachin like 1 [Source:HGNC Symbol;Acc:HGNC:20681]
PMF1	ENSG00000160783	polyamine modulated factor 1 [Source:HGNC Symbol;Acc:HGNC:9112]
EPHB3	ENSG00000182580	EPH receptor B3 [Source:HGNC Symbol;Acc:HGNC:3394]

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PRR5	ENSG00000186654	proline rich 5 [Source:HGNC Symbol;Acc:HGNC:31682]
ACVRL1	ENSG00000139567	activin A receptor like type 1 [Source:HGNC Symbol;Acc:HGNC:175]
MYL6	ENSG00000092841	myosin light chain 6 [Source:HGNC Symbol;Acc:HGNC:7587]
ADD3	ENSG00000148700	adducin 3 [Source:HGNC Symbol;Acc:HGNC:245]
ETV4	ENSG00000175832	ETS variant 4 [Source:HGNC Symbol;Acc:HGNC:3493]
GPM6A	ENSG00000150625	glycoprotein M6A [Source:HGNC Symbol;Acc:HGNC:4460]
IGFBPL1	ENSG00000137142	insulin like growth factor binding protein like 1 [Source:HGNC Symbol;Acc:HGNC:20081]
MCM2	ENSG00000073111	minichromosome maintenance complex component 2 [Source:HGNC Symbol;Acc:HGNC:6944]
BGLAP	ENSG00000242252	bone gamma-carboxyglutamate protein [Source:HGNC Symbol;Acc:HGNC:1043]
TOB2	ENSG00000183864	transducer of ERBB2, 2 [Source:HGNC Symbol;Acc:HGNC:11980]
RPL13A	ENSG00000142541	ribosomal protein L13a [Source:HGNC Symbol;Acc:HGNC:10304]
GNA13	ENSG00000120063	G protein subunit alpha 13 [Source:HGNC Symbol;Acc:HGNC:4381]
CRAT	ENSG00000095321	carnitine O-acetyltransferase [Source:HGNC Symbol;Acc:HGNC:2342]
FHL3	ENSG00000183386	four and a half LIM domains 3 [Source:HGNC Symbol;Acc:HGNC:3704]
EPHB4	ENSG00000196411	EPH receptor B4 [Source:HGNC Symbol;Acc:HGNC:3395]
ST6GAL2	ENSG00000144057	ST6 beta-galactoside alpha-2,6-sialyltransferase 2 [Source:HGNC Symbol;Acc:HGNC:10861]
FYN	ENSG00000010810	FYN proto-oncogene, Src family tyrosine kinase [Source:HGNC Symbol;Acc:HGNC:4037]
TUFM	ENSG00000178952	Tu translation elongation factor, mitochondrial [Source:HGNC Symbol;Acc:HGNC:12420]
CD82	ENSG00000085117	CD82 molecule [Source:HGNC Symbol;Acc:HGNC:6210]
TNFAIP3	ENSG00000118503	TNF alpha induced protein 3 [Source:HGNC Symbol;Acc:HGNC:11896]
PLSCR1	ENSG00000188313	phospholipid scramblase 1 [Source:HGNC Symbol;Acc:HGNC:9092]
SCMH1	ENSG00000010803	Scm polycomb group protein homolog 1 [Source:HGNC Symbol;Acc:HGNC:19003]
NHSL1	ENSG00000135540	NHS like 1 [Source:HGNC Symbol;Acc:HGNC:21021]
WNT7A	ENSG00000154764	Wnt family member 7A [Source:HGNC Symbol;Acc:HGNC:12786]
NECTIN2	ENSG00000130202	nectin cell adhesion molecule 2 [Source:HGNC Symbol;Acc:HGNC:9707]
PDLIM3	ENSG00000154553	PDZ and LIM domain 3 [Source:HGNC Symbol;Acc:HGNC:20767]
GJA4	ENSG00000187513	gap junction protein alpha 4 [Source:HGNC Symbol;Acc:HGNC:4278]
SLC16A3	ENSG00000141526	solute carrier family 16 member 3 [Source:HGNC Symbol;Acc:HGNC:10924]
SDCCAG8	ENSG00000054282	serologically defined colon cancer antigen 8 [Source:HGNC Symbol;Acc:HGNC:10671]
FOXH1	ENSG00000160973	forkhead box H1 [Source:HGNC Symbol;Acc:HGNC:3814]
ST6GALNAC1	ENSG00000070526	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 1 [Source:HGNC Symbol;Acc:HGNC:23614]
TTYH1	ENSG00000275650	tweety family member 1 [Source:HGNC Symbol;Acc:HGNC:13476]
NFIA	ENSG00000162599	nuclear factor I A [Source:HGNC Symbol;Acc:HGNC:7784]
KLHL23	ENSG00000213160	kelch like family member 23 [Source:HGNC Symbol;Acc:HGNC:27506]
MAPRE1	ENSG00000101367	microtubule associated protein RP/EB family member 1 [Source:HGNC Symbol;Acc:HGNC:6890]
SH3BP4	ENSG00000130147	SH3 domain binding protein 4 [Source:HGNC Symbol;Acc:HGNC:10826]
CKS2	ENSG00000123975	CDC28 protein kinase regulatory subunit 2 [Source:HGNC Symbol;Acc:HGNC:2000]
PLOD2	ENSG00000152952	procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 [Source:HGNC Symbol;Acc:HGNC:9082]
AUTS2	ENSG00000158321	AUTS2, activator of transcription and developmental regulator [Source:HGNC Symbol;Acc:HGNC:14262]
ADAMTS9	ENSG00000163638	ADAM metallopeptidase with thrombospondin type 1 motif 9 [Source:HGNC Symbol;Acc:HGNC:13202]
FBXW9	ENSG00000132004	F-box and WD repeat domain containing 9 [Source:HGNC Symbol;Acc:HGNC:28136]

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UST	ENSG00000111962	uronyl 2-sulfotransferase [Source:HGNC Symbol;Acc:HGNC:17223]
VCL	ENSG00000035403	vinculin [Source:HGNC Symbol;Acc:HGNC:12665]
SNAPC2	ENSG00000104976	small nuclear RNA activating complex polypeptide 2 [Source:HGNC Symbol;Acc:HGNC:11135]
SLC1A5	ENSG00000105281	solute carrier family 1 member 5 [Source:HGNC Symbol;Acc:HGNC:10943]
CCNB2	ENSG00000157456	cyclin B2 [Source:HGNC Symbol;Acc:HGNC:1580]
ECE2	ENSG00000145194	endothelin converting enzyme 2 [Source:HGNC Symbol;Acc:HGNC:13275]
COL18A1	ENSG00000182871	collagen type XVIII alpha 1 chain [Source:HGNC Symbol;Acc:HGNC:2195]
GPR137B	ENSG00000077585	G protein-coupled receptor 137B [Source:HGNC Symbol;Acc:HGNC:11862]
DAB1	ENSG00000173406	DAB1, reelin adaptor protein [Source:HGNC Symbol;Acc:HGNC:2661]
IMPDH1	ENSG00000106348	inosine monophosphate dehydrogenase 1 [Source:HGNC Symbol;Acc:HGNC:6052]
SLC6A6	ENSG00000131389	solute carrier family 6 member 6 [Source:HGNC Symbol;Acc:HGNC:11052]
SNRPB2	ENSG00000125870	small nuclear ribonucleoprotein polypeptide B2 [Source:HGNC Symbol;Acc:HGNC:11155]
TOR1B	ENSG00000136816	torsin family 1 member B [Source:HGNC Symbol;Acc:HGNC:11995]
DISP3	ENSG00000204624	dispatched RND transporter family member 3 [Source:HGNC Symbol;Acc:HGNC:29251]
ADORA2A	ENSG00000128271	adenosine A2a receptor [Source:HGNC Symbol;Acc:HGNC:263]
STK38	ENSG00000112079	serine/threonine kinase 38 [Source:HGNC Symbol;Acc:HGNC:17847]
ENO3	ENSG00000108515	enolase 3 [Source:HGNC Symbol;Acc:HGNC:3354]
DUSP23	ENSG00000158716	dual specificity phosphatase 23 [Source:HGNC Symbol;Acc:HGNC:21480]
FXYD5	ENSG00000089327	FXYD domain containing ion transport regulator 5 [Source:HGNC Symbol;Acc:HGNC:4029]
AKT2	ENSG00000105221	AKT serine/threonine kinase 2 [Source:HGNC Symbol;Acc:HGNC:392]
NXPH4	ENSG00000182379	neurexophilin 4 [Source:HGNC Symbol;Acc:HGNC:8078]
MEF2C	ENSG00000081189	myocyte enhancer factor 2C [Source:HGNC Symbol;Acc:HGNC:6996]
TCF3	ENSG00000071564	transcription factor 3 [Source:HGNC Symbol;Acc:HGNC:11633]
PEMT	ENSG00000133027	phosphatidylethanolamine N-methyltransferase [Source:HGNC Symbol;Acc:HGNC:8830]
CXCL12	ENSG00000107562	C-X-C motif chemokine ligand 12 [Source:HGNC Symbol;Acc:HGNC:10672]
MXRA8	ENSG00000162576	matrix remodeling associated 8 [Source:HGNC Symbol;Acc:HGNC:7542]
TOR2A	ENSG00000160404	torsin family 2 member A [Source:HGNC Symbol;Acc:HGNC:11996]
TMED9	ENSG00000184840	transmembrane p24 trafficking protein 9 [Source:HGNC Symbol;Acc:HGNC:24878]
RALA	ENSG00000006451	RAS like proto-oncogene A [Source:HGNC Symbol;Acc:HGNC:9839]
SCGN	ENSG00000079689	secretagogin, EF-hand calcium binding protein [Source:HGNC Symbol;Acc:HGNC:16941]
ARHGEF40	ENSG00000165801	Rho guanine nucleotide exchange factor 40 [Source:HGNC Symbol;Acc:HGNC:25516]
TUBB4B	ENSG00000188229	tubulin beta 4B class IVb [Source:HGNC Symbol;Acc:HGNC:20771]
HEBP2	ENSG00000051620	heme binding protein 2 [Source:HGNC Symbol;Acc:HGNC:15716]
PNMT	ENSG00000141744	phenylethanolamine N-methyltransferase [Source:HGNC Symbol;Acc:HGNC:9160]
PPP4C	ENSG00000149923	protein phosphatase 4 catalytic subunit [Source:HGNC Symbol;Acc:HGNC:9319]
TRH	ENSG00000170893	thyrotropin releasing hormone [Source:HGNC Symbol;Acc:HGNC:12298]
LAMC1	ENSG00000135862	laminin subunit gamma 1 [Source:HGNC Symbol;Acc:HGNC:6492]
SLC40A1	ENSG00000138449	solute carrier family 40 member 1 [Source:HGNC Symbol;Acc:HGNC:10909]
DNAJB5	ENSG00000137094	DnaJ heat shock protein family (Hsp40) member B5 [Source:HGNC Symbol;Acc:HGNC:14887]
MARK4	ENSG00000007047	microtubule affinity regulating kinase 4 [Source:HGNC Symbol;Acc:HGNC:13538]
HIST3H2A	ENSG00000181218	histone cluster 3 H2A [Source:HGNC Symbol;Acc:HGNC:20507]
WLS	ENSG00000116729	wntless Wnt ligand secretion mediator [Source:HGNC Symbol;Acc:HGNC:30238]
SUFU	ENSG00000107882	SUFU negative regulator of hedgehog signaling [Source:HGNC Symbol;Acc:HGNC:16466]

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DDR1	ENSG00000137332	discoidin domain receptor tyrosine kinase 1 [Source:HGNC Symbol;Acc:HGNC:2730]
ABCC9	ENSG00000069431	ATP binding cassette subfamily C member 9 [Source:HGNC Symbol;Acc:HGNC:60]
NECTIN3	ENSG00000177707	nectin cell adhesion molecule 3 [Source:HGNC Symbol;Acc:HGNC:17664]
LSR	ENSG00000105699	lipolysis stimulated lipoprotein receptor [Source:HGNC Symbol;Acc:HGNC:29572]
RGS1	ENSG00000090104	regulator of G protein signaling 1 [Source:HGNC Symbol;Acc:HGNC:9991]
RPS10	ENSG00000124614	ribosomal protein S10 [Source:HGNC Symbol;Acc:HGNC:10383]
COTL1	ENSG00000103187	coactosin like F-actin binding protein 1 [Source:HGNC Symbol;Acc:HGNC:18304]
PDAP1	ENSG00000106244	PDGFA associated protein 1 [Source:HGNC Symbol;Acc:HGNC:14634]
HSD17B14	ENSG00000087076	hydroxysteroid 17-beta dehydrogenase 14 [Source:HGNC Symbol;Acc:HGNC:23238]
COLEC12	ENSG00000158270	collectin subfamily member 12 [Source:HGNC Symbol;Acc:HGNC:16016]
OSMR	ENSG00000145623	oncostatin M receptor [Source:HGNC Symbol;Acc:HGNC:8507]
NXN	ENSG00000281300	nucleoredoxin [Source:HGNC Symbol;Acc:HGNC:18008]
TPX2	ENSG00000088325	TPX2, microtubule nucleation factor [Source:HGNC Symbol;Acc:HGNC:1249]
RGR	ENSG00000148604	retinal G protein coupled receptor [Source:HGNC Symbol;Acc:HGNC:9990]
SHC2	ENSG00000129946	SHC adaptor protein 2 [Source:HGNC Symbol;Acc:HGNC:29869]
PLAT	ENSG00000104368	plasminogen activator, tissue type [Source:HGNC Symbol;Acc:HGNC:9051]
BACH2	ENSG00000112182	BTB domain and CNC homolog 2 [Source:HGNC Symbol;Acc:HGNC:14078]
TMEM45B	ENSG00000151715	transmembrane protein 45B [Source:HGNC Symbol;Acc:HGNC:25194]
HRC	ENSG00000130528	histidine rich calcium binding protein [Source:HGNC Symbol;Acc:HGNC:5178]
ARRDC1	ENSG00000197070	arrestin domain containing 1 [Source:HGNC Symbol;Acc:HGNC:28633]
SLC25A39	ENSG00000013306	solute carrier family 25 member 39 [Source:HGNC Symbol;Acc:HGNC:24279]
EYA2	ENSG00000064655	EYA transcriptional coactivator and phosphatase 2 [Source:HGNC Symbol;Acc:HGNC:3520]
PDGFRA	ENSG00000134853	platelet derived growth factor receptor alpha [Source:HGNC Symbol;Acc:HGNC:8803]
SGK1	ENSG00000118515	serum/glucocorticoid regulated kinase 1 [Source:HGNC Symbol;Acc:HGNC:10810]
PEA15	ENSG00000162734	proliferation and apoptosis adaptor protein 15 [Source:HGNC Symbol;Acc:HGNC:8822]
UBA52	ENSG00000221983	ubiquitin A-52 residue ribosomal protein fusion product 1 [Source:HGNC Symbol;Acc:HGNC:12458]
EPHA2	ENSG00000142627	EPH receptor A2 [Source:HGNC Symbol;Acc:HGNC:3386]
HIC1	ENSG00000177374	HIC ZBTB transcriptional repressor 1 [Source:HGNC Symbol;Acc:HGNC:4909]
INHBB	ENSG00000163083	inhibin subunit beta B [Source:HGNC Symbol;Acc:HGNC:6067]
KCTD11	ENSG00000213859	potassium channel tetramerization domain containing 11 [Source:HGNC Symbol;Acc:HGNC:21302]
CXADR	ENSG00000154639	CXADR, Ig-like cell adhesion molecule [Source:HGNC Symbol;Acc:HGNC:2559]
CHCHD5	ENSG00000125611	coiled-coil-helix-coiled-coil-helix domain containing 5 [Source:HGNC Symbol;Acc:HGNC:17840]
FBXL7	ENSG00000183580	F-box and leucine rich repeat protein 7 [Source:HGNC Symbol;Acc:HGNC:13604]
SLC12A7	ENSG00000276482	solute carrier family 12 member 7 [Source:HGNC Symbol;Acc:HGNC:10915]
FGF11	ENSG00000161958	fibroblast growth factor 11 [Source:HGNC Symbol;Acc:HGNC:3667]
RAB11B	ENSG00000185236	RAB11B, member RAS oncogene family [Source:HGNC Symbol;Acc:HGNC:9761]
RNF122	ENSG00000133874	ring finger protein 122 [Source:HGNC Symbol;Acc:HGNC:21147]
RARG	ENSG00000172819	retinoic acid receptor gamma [Source:HGNC Symbol;Acc:HGNC:9866]
RNF2	ENSG00000121481	ring finger protein 2 [Source:HGNC Symbol;Acc:HGNC:10061]
CLIC5	ENSG00000112782	chloride intracellular channel 5 [Source:HGNC Symbol;Acc:HGNC:13517]
UBTD1	ENSG00000165886	ubiquitin domain containing 1 [Source:HGNC Symbol;Acc:HGNC:25683]
TXN2	ENSG00000100348	thioredoxin 2 [Source:HGNC Symbol;Acc:HGNC:17772]

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BTF3	ENSG00000145741	basic transcription factor 3 [Source:HGNC Symbol;Acc:HGNC:1125]
GIPC3	ENSG00000179855	GIPC PDZ domain containing family member 3 [Source:HGNC Symbol;Acc:HGNC:18183]
SLC1A3	ENSG00000079215	solute carrier family 1 member 3 [Source:HGNC Symbol;Acc:HGNC:10941]
SCRN2	ENSG00000141295	secernin 2 [Source:HGNC Symbol;Acc:HGNC:30381]
CXCL1	ENSG00000163739	C-X-C motif chemokine ligand 1 [Source:HGNC Symbol;Acc:HGNC:4602]
ASCL2	ENSG00000183734	achaete-scute family bHLH transcription factor 2 [Source:HGNC Symbol;Acc:HGNC:739]
PSKH1	ENSG00000159792	protein serine kinase H1 [Source:HGNC Symbol;Acc:HGNC:9529]
BCL3	ENSG00000069399	B cell CLL/lymphoma 3 [Source:HGNC Symbol;Acc:HGNC:998]
RNF180	ENSG00000164197	ring finger protein 180 [Source:HGNC Symbol;Acc:HGNC:27752]
NTHL1	ENSG00000065057	nth like DNA glycosylase 1 [Source:HGNC Symbol;Acc:HGNC:8028]
ARPC1B	ENSG00000130429	actin related protein 2/3 complex subunit 1B [Source:HGNC Symbol;Acc:HGNC:704]
SLC43A3	ENSG00000134802	solute carrier family 43 member 3 [Source:HGNC Symbol;Acc:HGNC:17466]
PTBP1	ENSG00000011304	polypyrimidine tract binding protein 1 [Source:HGNC Symbol;Acc:HGNC:9583]
ABHD3	ENSG00000158201	abhydrolase domain containing 3 [Source:HGNC Symbol;Acc:HGNC:18718]
MIF	ENSG00000276701	macrophage migration inhibitory factor [Source:HGNC Symbol;Acc:HGNC:7097]
SEZ6	ENSG00000063015	seizure related 6 homolog [Source:HGNC Symbol;Acc:HGNC:15955]
FJX1	ENSG00000179431	four jointed box 1 [Source:HGNC Symbol;Acc:HGNC:17166]
MC1R	ENSG00000258839	melanocortin 1 receptor [Source:HGNC Symbol;Acc:HGNC:6929]
LASP1	ENSG00000002834	LIM and SH3 protein 1 [Source:HGNC Symbol;Acc:HGNC:6513]
PITPNC1	ENSG00000154217	phosphatidylinositol transfer protein cytoplasmic 1 [Source:HGNC Symbol;Acc:HGNC:21045]
PACS1	ENSG00000175115	phosphofurin acidic cluster sorting protein 1 [Source:HGNC Symbol;Acc:HGNC:30032]
WSCD1	ENSG00000179314	WSC domain containing 1 [Source:HGNC Symbol;Acc:HGNC:29060]
RASSF7	ENSG00000273859	Ras association domain family member 7 [Source:HGNC Symbol;Acc:HGNC:1166]
SCARA3	ENSG00000168077	scavenger receptor class A member 3 [Source:HGNC Symbol;Acc:HGNC:19000]
FTH1	ENSG00000167996	ferritin heavy chain 1 [Source:HGNC Symbol;Acc:HGNC:3976]
CGNL1	ENSG00000128849	cingulin like 1 [Source:HGNC Symbol;Acc:HGNC:25931]
ILVBL	ENSG00000105135	ilvB acetolactate synthase like [Source:HGNC Symbol;Acc:HGNC:6041]
SPINK8	ENSG00000229453	serine peptidase inhibitor, Kazal type 8 (putative) [Source:HGNC Symbol;Acc:HGNC:33160]
DZIP1	ENSG00000134874	DAZ interacting zinc finger protein 1 [Source:HGNC Symbol;Acc:HGNC:20908]
RBCK1	ENSG00000125826	RANBP2-type and C3HC4-type zinc finger containing 1 [Source:HGNC Symbol;Acc:HGNC:15864]
IFT20	ENSG00000109083	intraflagellar transport 20 [Source:HGNC Symbol;Acc:HGNC:30989]
NOTCH3	ENSG00000074181	notch 3 [Source:HGNC Symbol;Acc:HGNC:7883]
HAPLN1	ENSG00000145681	hyaluronan and proteoglycan link protein 1 [Source:HGNC Symbol;Acc:HGNC:2380]
SRD5A1	ENSG00000145545	steroid 5 alpha-reductase 1 [Source:HGNC Symbol;Acc:HGNC:11284]
NT5C3A	ENSG00000122643	5'-nucleotidase, cytosolic IIIA [Source:HGNC Symbol;Acc:HGNC:17820]
CPT1A	ENSG00000110090	carnitine palmitoyltransferase 1A [Source:HGNC Symbol;Acc:HGNC:2328]
LUZP2	ENSG00000187398	leucine zipper protein 2 [Source:HGNC Symbol;Acc:HGNC:23206]
FLI1	ENSG00000151702	Fli-1 proto-oncogene, ETS transcription factor [Source:HGNC Symbol;Acc:HGNC:3749]
RAVER1	ENSG00000161847	ribonucleoprotein, PTB binding 1 [Source:HGNC Symbol;Acc:HGNC:30296]
BCL2L12	ENSG00000126453	BCL2 like 12 [Source:HGNC Symbol;Acc:HGNC:13787]
HNMT	ENSG00000150540	histamine N-methyltransferase [Source:HGNC Symbol;Acc:HGNC:5028]
EPS8	ENSG00000151491	epidermal growth factor receptor pathway substrate 8 [Source:HGNC Symbol;Acc:HGNC:3420]

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PIGQ	ENSG00000007541	phosphatidylinositol glycan anchor biosynthesis class Q [Source:HGNC Symbol;Acc:HGNC:14135]
HIST1H1C	ENSG00000187837	histone cluster 1 H1 family member c [Source:HGNC Symbol;Acc:HGNC:4716]
TSC22D4	ENSG00000166925	TSC22 domain family member 4 [Source:HGNC Symbol;Acc:HGNC:21696]
PPP1R35	ENSG00000160813	protein phosphatase 1 regulatory subunit 35 [Source:HGNC Symbol;Acc:HGNC:28320]
EDN3	ENSG00000124205	endothelin 3 [Source:HGNC Symbol;Acc:HGNC:3178]
CYB5R3	ENSG00000100243	cytochrome b5 reductase 3 [Source:HGNC Symbol;Acc:HGNC:2873]
NXPH1	ENSG00000122584	neurexophilin 1 [Source:HGNC Symbol;Acc:HGNC:20693]
HAAO	ENSG00000162882	3-hydroxyanthranilate 3,4-dioxygenase [Source:HGNC Symbol;Acc:HGNC:4796]
LYPD6B	ENSG00000150556	LY6/PLAUR domain containing 6B [Source:HGNC Symbol;Acc:HGNC:27018]
CLIC1	ENSG00000230685	chloride intracellular channel 1 [Source:HGNC Symbol;Acc:HGNC:2062]
RASGRP2	ENSG00000068831	RAS guanyl releasing protein 2 [Source:HGNC Symbol;Acc:HGNC:9879]
SOX12	ENSG00000177732	SRY-box 12 [Source:HGNC Symbol;Acc:HGNC:11198]
SLC27A5	ENSG00000083807	solute carrier family 27 member 5 [Source:HGNC Symbol;Acc:HGNC:10999]
EEF1D	ENSG00000273594	eukaryotic translation elongation factor 1 delta [Source:HGNC Symbol;Acc:HGNC:3211]
CSRNP1	ENSG00000144655	cysteine and serine rich nuclear protein 1 [Source:HGNC Symbol;Acc:HGNC:14300]
RBM42	ENSG00000126254	RNA binding motif protein 42 [Source:HGNC Symbol;Acc:HGNC:28117]
AQP4	ENSG00000171885	aquaporin 4 [Source:HGNC Symbol;Acc:HGNC:637]
NKD2	ENSG00000145506	naked cuticle homolog 2 [Source:HGNC Symbol;Acc:HGNC:17046]
H19	ENSG00000130600	H19, imprinted maternally expressed transcript (non-protein coding) [Source:HGNC Symbol;Acc:HGNC:4713]
NINJ1	ENSG00000131669	ninjurin 1 [Source:HGNC Symbol;Acc:HGNC:7824]
ITGA6	ENSG00000091409	integrin subunit alpha 6 [Source:HGNC Symbol;Acc:HGNC:6142]
SNHG11	ENSG00000174365	small nucleolar RNA host gene 11 [Source:HGNC Symbol;Acc:HGNC:25046]
SEMA5A	ENSG00000112902	semaphorin 5A [Source:HGNC Symbol;Acc:HGNC:10736]
AKAP7	ENSG00000118507	A-kinase anchoring protein 7 [Source:HGNC Symbol;Acc:HGNC:377]
HIF3A	ENSG00000124440	hypoxia inducible factor 3 subunit alpha [Source:HGNC Symbol;Acc:HGNC:15825]
RNF138	ENSG00000134758	ring finger protein 138 [Source:HGNC Symbol;Acc:HGNC:17765]
IMPA2	ENSG00000141401	inositol monophosphatase 2 [Source:HGNC Symbol;Acc:HGNC:6051]
GDF15	ENSG00000130513	growth differentiation factor 15 [Source:HGNC Symbol;Acc:HGNC:30142]
TBXA2R	ENSG00000006638	thromboxane A2 receptor [Source:HGNC Symbol;Acc:HGNC:11608]
ODC1	ENSG00000115758	ornithine decarboxylase 1 [Source:HGNC Symbol;Acc:HGNC:8109]
ITIH5	ENSG00000123243	inter-alpha-trypsin inhibitor heavy chain family member 5 [Source:HGNC Symbol;Acc:HGNC:21449]
AEBP1	ENSG00000106624	AE binding protein 1 [Source:HGNC Symbol;Acc:HGNC:303]
TRAF4	ENSG00000076604	TNF receptor associated factor 4 [Source:HGNC Symbol;Acc:HGNC:12034]
RPS6	ENSG00000137154	ribosomal protein S6 [Source:HGNC Symbol;Acc:HGNC:10429]
CACNG7	ENSG00000105605	calcium voltage-gated channel auxiliary subunit gamma 7 [Source:HGNC Symbol;Acc:HGNC:13626]
RPS12	ENSG00000112306	ribosomal protein S12 [Source:HGNC Symbol;Acc:HGNC:10385]
DACT1	ENSG00000165617	dishevelled binding antagonist of beta catenin 1 [Source:HGNC Symbol;Acc:HGNC:17748]
SBF2	ENSG00000133812	SET binding factor 2 [Source:HGNC Symbol;Acc:HGNC:2135]
FCHSD2	ENSG00000137478	FCH and double SH3 domains 2 [Source:HGNC Symbol;Acc:HGNC:29114]
ARHGAP15	ENSG00000075884	Rho GTPase activating protein 15 [Source:HGNC Symbol;Acc:HGNC:21030]
SURF2	ENSG00000281024	surfeit 2 [Source:HGNC Symbol;Acc:HGNC:11475]

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Table S2: Variables used to create the hypoxic-ischemic associated conditions (HICs) score. Component loadings are indicative of the substantive importance of a particular variable to the component.

	Hypoxic-ischemic conditions scoring		Component Loading	
	0 Point	1 Point	Mavan	Gusto
Neonatal Resuscitation	No	Yes	0.78	0.83
APGAR score at 1 minute	7 to 10	0 to 6	0.76	0.71
Fetal dystocia	No	Yes	0.43	0.13
Occurrence of placental abruption	No	Yes	0.38	0.35
Respiratory distress	No	Yes	0.34	0.60
Prolapse of umbilical cord	No	Yes	0.22	-0.13
Breech or transversal presentation at birth	No	Yes	0.06	0.27

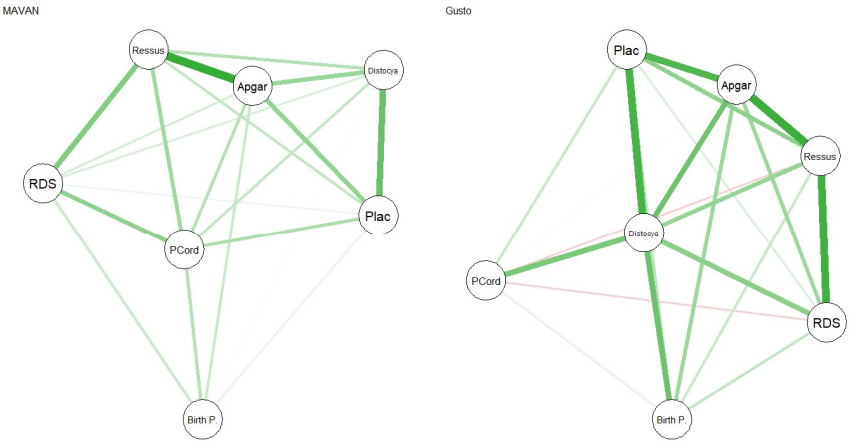

Figure S2. Correlation networks of the birth hypoxic-ischemic conditions (HICs) score for the two cohorts. Ressus = Neonatal Resuscitation, Apgar = APGAR score at 1 minute, Dystocia = Fetal dystocia, Plac = Placental abruption, RDS = Respiratory distress, PCord = Prolapse of umbilical cord, Birth P = Breech or transversal presentation at birth.

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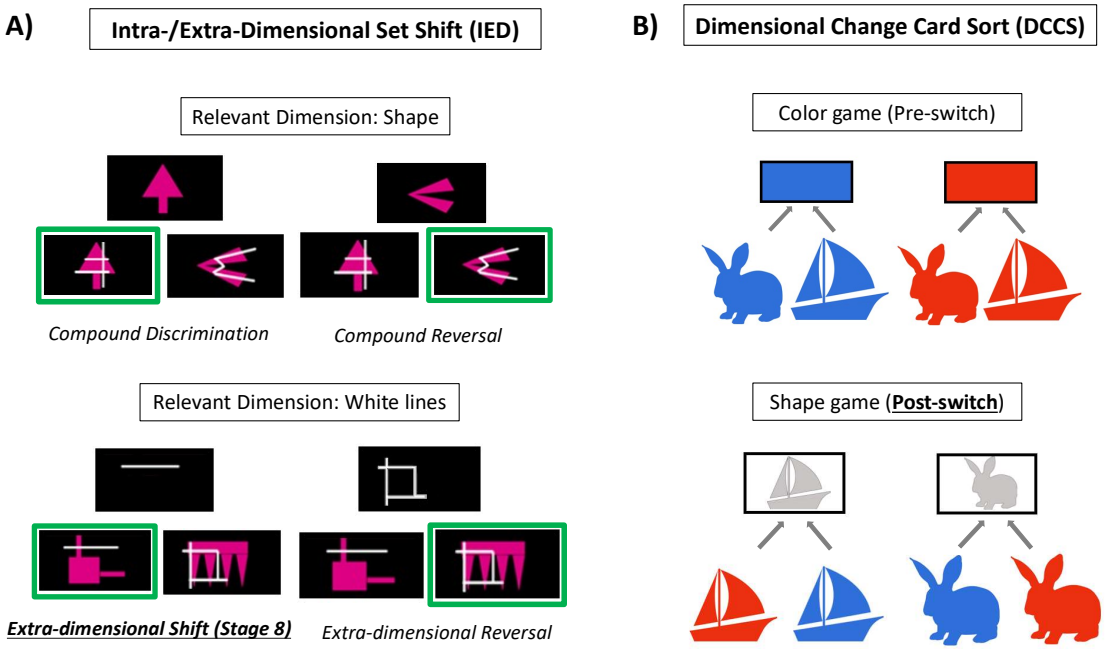

Figure S3: Schematic representation of the attentional flexibility tasks: (A) Intra-/Extra-dimensional Set Shift (IED) and (B) Dimensional Change Card Sort (DCCS). The IED was applied to MAVAN children and in this task the first relevant dimension is the shape presented in the cards, ignoring the white lines. After an extensive training discrimination using this rule, in the stage 8 (extradimensional shift) the rule changed and children must respond to the other dimension (white lines). In the DCCS task, applied to GUSTO children, there are only 2 stages: pre-switch and post-switch. In the pre-switch, children must sort the cards by color, ignoring the shape of the objects but in the post-switch stage the new rule considers the shape of the objects and not anymore the color. IED image was adapted from the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Gray matter density

Structural MRI acquisition and data preparation: High-resolution T1-weighted images for the whole brain were acquired using a 3T trio Siemens scanner available at Cerebral Imaging Center, Douglas Mental Health Institute (Montreal, Canada) and a GE MR750 Discovery 3T MRI scanner at the Imaging Research Centre, St Joseph's Healthcare (Hamilton, Canada). The

following parameters were used: 1 mm isotropic 3D MPRAGE, sagittal acquisition, 256 x 256 mm grid, TR=2300ms, TE=4ms, FA=9degrees (Montreal); a 3D inversion recovery-prepped, T1-weighted anatomical data set, fSPGR, axial acquisition, TE/TR/flip angle = 3.22/10.308/9, 512 x 512 matrix with 1mm slice thickness and 24cm FOV (Hamilton). Computational Anatomy Toolbox (CAT12) from the Statistical Parametric Mapping software (SPM12) was used to process the T1-weighted images. In the preprocessing step, the images were normalized and segmented into gray matter and white matter. After a high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) normalization, a smoothing process was applied using 8mm full width half maximum kernel.

Parallel-independent component analysis (p-ICA): The Fusion ICA Toolbox (http://mialab.mrn.org/software/fit/) within MATLAB® R2014 was used to run the analysis. The number of independent components estimated using minimum description length criteria (37, 38) was 16 for genetic data and 8 for MRI data. Talairach coordinates were used to identify the anatomical classification of brain areas included in the MRI components. To define the significant SNPs in each component, we used a threshold of >+2.5 and <-2.5 and to identify underlying biological pathways and functions of the relevant SNPs, we used Metacore®.

Statistical Analysis

The population structure of the MAVAN and GUSTO cohorts were evaluated using principal component analysis of all autosomal SNPs that passed the quality control, without low allele frequency (MAF>5%) and are not in high linkage disequilibrium (r2>0.2) within a window of 50 SNPs at each step size of 5 (43). Based on the inspection of the scree plot, the first three

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principal components were the most informative of population structure in both cohorts and were included in all analysis.

Results

Table S3: Adjusted linear regression effects on the IED outcomes in MAVAN Cohort.

Variable	ePRSScore		HICsScore		HICsScore x ePRS Score	
	β	*p*	β	*p*	β	*p*
Latency 1	-2512	0.529	256.146	0.918	-1442.448	0.768
Error 1	0.159	0.615	0.109	0.579	-0.104	0.788
Trials 1	0.143	0.841	0.219	0.624	-0.121	0.891
Latency 2	-3706	0.087	538.692	0.688	855.902	0.746
Error 2	-0.372	0.23	0.018	0.924	0.029	0.939
Trials 2	-1.1	0.19	-0.154	0.768	-0.025	0.981
Latency 3	1088.5	0.619	1205.399	0.377	2117.768	0.43
Error 3	0.454	0.12	0.101	0.578	-0.203	0.57
Trials 3	1.073	0.129	0.194	0.66	-0.094	0.913
Latency 4	-1443	0.487	1773.08	0.172	2179.849	0.392
Error 4	-0.188	0.272	0.096	0.37	-0.053	0.802
Trials 4	-0.675	0.244	0.614	0.09	-0.092	0.897
Latency 5	-376.3	0.839	1320.103	0.254	1208.943	0.595
Error 5	-0.03	0.867	-0.074	0.515	0.003	0.988
Trials 5	-0.261	0.663	-0.043	0.908	-0.586	0.425
Latency 6	-3088	0.31	1272.52	0.502	491.278	0.895
Error 6	-0.428	0.329	-0.033	0.904	-0.055	0.918
Trials 6	-1.061	0.253	-0.049	0.933	-0.613	0.59
Latency 7	-2102	0.524	1414.727	0.492	-289.744	0.943
Error 7	-0.687	0.244	0.1	0.785	-0.42	0.561
Trials 7	-1.284	0.271	0.098	0.893	-0.904	0.527
Latency 8	-741.1	0.926	-3486.597	0.486	32489.246	0.001
Error 8	-0.882	0.542	-1.177	0.192	1.847	0.295
Trials 8	-1.652	0.453	-2.248	0.102	3.924	0.144

* Significant effect ($p<0.05$).

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Table S4: Main effects adjusted and unadjusted linear regression effects in MAVAN and GUSTO Cohorts.

		Adjusted						Unadjusted					
Cohort	Variable	ePRSScore		HICsScore		HICsScore x ePRS Score		ePRSScore		HICsScore		HICsScore x ePRS Score	
		β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Mavan	Latency 8	-741.09	0.93	97026.32	3.33	32489.25	<0.001	-563.08	0.94	-3978.69	0.42	32598.07	<0.001
	Error 8	-0.88	0.54	20.10	1.05	1.89	0.29	-0.74	0.62	-1.37	0.15	1.12	0.54
	Trials 8	-1.65	0.45	40.41	1.47	3.92	0.14	-1.54	0.50	-2.43	0.09	2.74	0.32
Gusto	DCCS Total Accuracy (post-switch)	0.03	0.88	-0.04	0.76	-0.46	0.03	0.04	0.87	-0.05	0.72	-0.45	0.03
	DCCS commission errors (post-switch)	-0.06	0.76	0.01	0.93	0.44	0.03	-0.07	0.76	0.02	0.87	0.43	0.03

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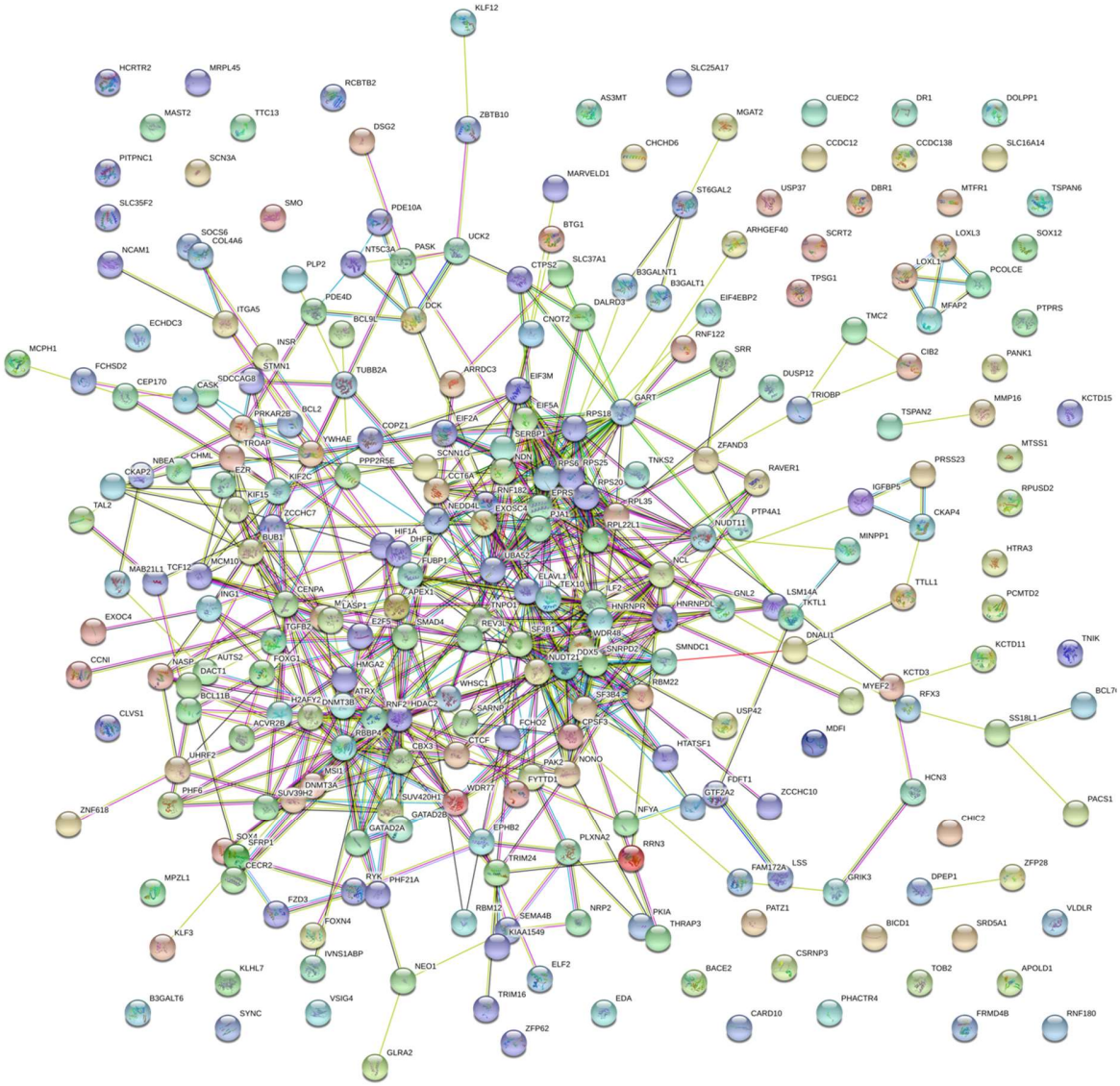

Figure S4: ePRS-SLC6A4 gene network in the PFC (String database). This gene network was not associated with the cognitive flexibility performance in children.

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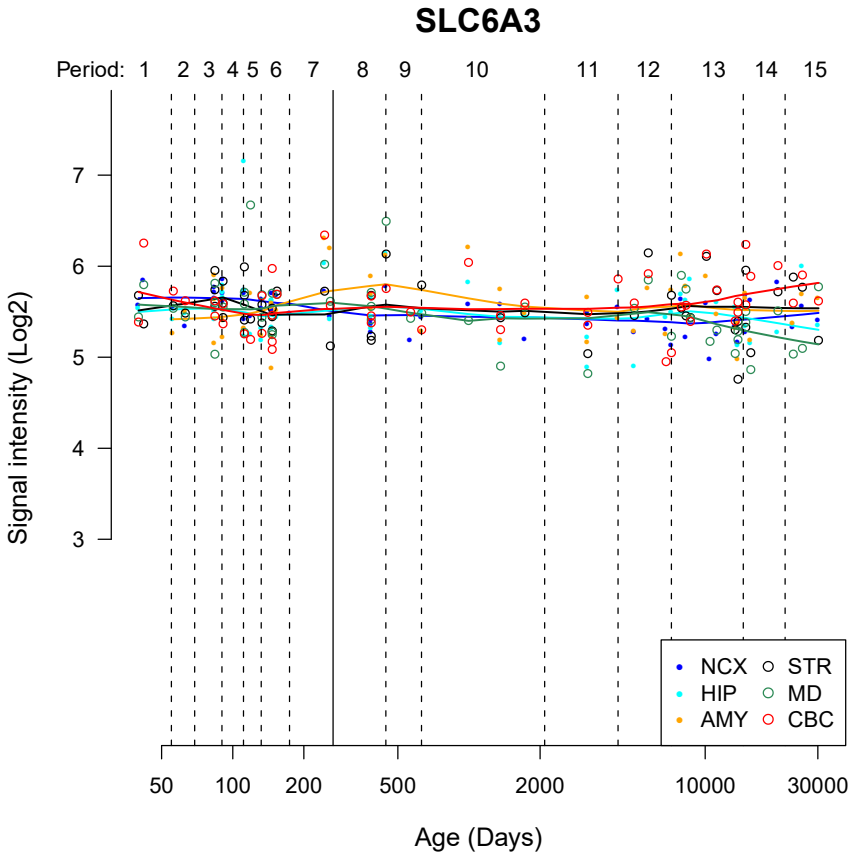

Figure S5: Dynamic DAT1/SLC6A3 expression along the entire development and adulthood in different human brain regions – data from the Human Brain Transcriptome project.

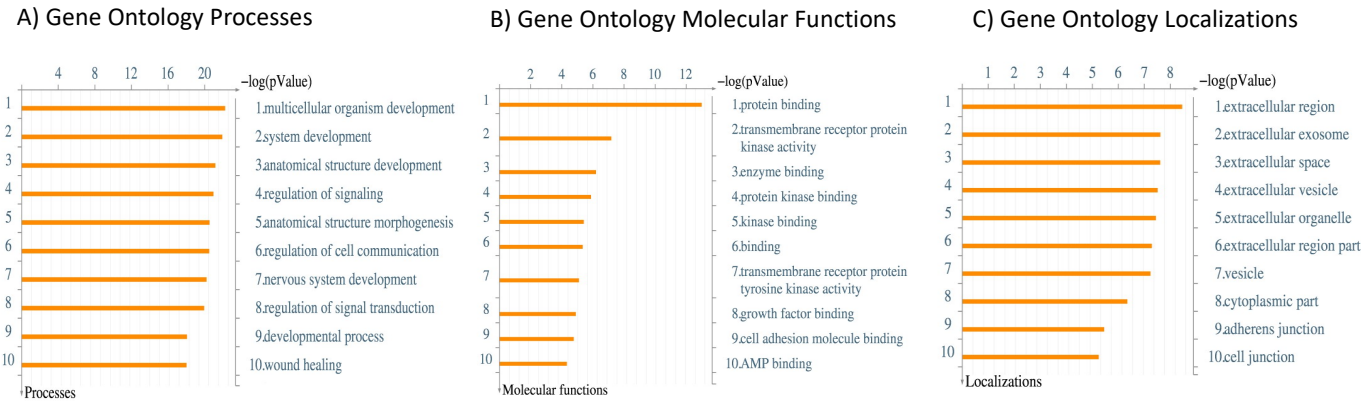

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Figure S6: Gene ontology enrichment analysis of DAT1 co-expressed genes using Metacore®.

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