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Precision Autism: Genomic Stratification of Disorders Making Up the Broad Spectrum May Demystify its "Epidemic Rates"

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Abstract: In the last decade, Autism has broadened and often shifted its diagnostics criteria, allowing several neuropsychiatric and neurological disorders of known etiology. This has resulted in a highly heterogeneous spectrum with apparent exponential rates in prevalence. We ask if it is possible to leverage existing genetic information about those disorders making up Autism today and use it to stratify this spectrum. To that end, we combine genes linked to Autism in the SFARI database and genomic information from the DisGeNet portal on 25 diseases, inclusive of non-neurological ones. We use the GTEx data on genes' expression on 54 human tissues and ask if there are overlapping genes across those associated to these diseases and those from Autism-SFARI. We find a compact set of genes across all brain-disorders which express highly in tissues fundamental for somatic-sensory-motor function, self-regulation, memory, and cognition. Then, we offer a new stratification that provides a distance-based orderly clustering into possible Autism subtypes, amenable to design personalized targeted therapies within the framework of Precision Medicine. We conclude that viewing Autism through this physiological (Precision) lens, rather than from a psychological behavioral construct, may make it a more manageable condition and dispel the Autism epidemic myth.

Keywords: autism; genes; tissues; stratification; neurodevelopment; neurological disorders; neuropsychiatric disorders

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1. Introduction

According to the CDC, in the span of 16 years, the US moved from 6.7/1000 to 18.5/1000 autistics in the population of school age children [1]. Reportedly, this increase continues to move along an exponential rate, while maintaining a near 5:1 males-to-females ratio [2]. This ratio prevents researchers from spontaneously reaching statistical power in any random draw of the population, when attempting to characterize the autistic female phenotype. Yet, motor features derived from endogenous neural signals in motor patterns, do identify the female phenotype [3-6]. This is the case even when digitizing the current clinical criteria that would otherwise miss females because of exclusive reliance on external observation [7, 8]. Likewise, subtle cultural biases built into the social-appropriateness criteria of the current instruments skew identification of underserved populations [1]. Consequentially, current interventions are far from being inclusive, or advocating for neurodiversity in the clinical data driving best-practices and evidence-based criteria for treatment recommendation [9, 10].

Despite sparse sampling in certain sectors of society, the shifts in diagnostic criteria have significantly broadened the detection rates to include now children with sensory issues and to allow comorbidity with ADHD under the Diagnostic Statistical Manual (DSM-5) [10]. This inclusion of ADHD in ASD contrasts with the former DSM-IV criteria,

which would not allow comorbidities of ASD and ADHD, nor would it recognize sensory issues in Autism.

The challenges that broadening the diagnostics criteria bring to the science and practices of Autism are manifold [11], albeit discouragement by some clinicians from trying to stratify the spectrum into subtypes [12, 13]. Under current standards, motor, kinesthetic sensing, and vestibular issues are not part of the core symptoms of the original diagnosis in the DSM. These criteria also remain absent from psychological instruments like the ADOS test, currently used to diagnose different age groups [9, 14, 15]. However, kinesthetic sensing and motor/vestibular issues define several of the many disorders that today received the Autism diagnosis. Among them are Cerebral Palsy [16, 17], the Dystonias [18, 19], Tourette's Syndrome [20] and obsessive-compulsive disorders (OCD) thought to be related to ADHD [21]. Besides these neurological disorders in ASD [22], others of known genetic origins enter in the broad criteria for Autism. Among them, various types of Ataxias [23] and Fragile X [24, 25] make up for a large percentage of individuals with Autism today. Despite profound physiological, systemic alterations and somatic-sensory-motor differences, these individuals will very likely go on to receive behavioral modification treatments during early interventions. Furthermore, these behavioral modification interventions in the US, will continue later at the school, through the individualized education plan. Such treatments neither recognize, nor address individual phenotypic physiological features of these disorders of known genetic origins that, nevertheless, do enter in the Autism spectrum today.

Phenotypically, these disorders that currently go on to receive the Autism diagnosis, are precisely defined by somatic, sensory-motor issues [26, 27] that manifest throughout the lifespan [28]. This scientific finding is nevertheless at odds with the current clinical "gold standard" criteria. In the DSM-5 [10] we read "*Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).*" And in the DSM criteria, motor issues are excluded owing to the confounds of symptoms induced by psychotropic medication, "*Medication-induced movement disorders are included in Section II because of their frequent importance in 1) the management by medication of mental disorders or other medical conditions and 2) the differential diagnosis of mental disorders (e.g., anxiety disorder versus neuroleptic-induced akathisia; malignant catatonia versus neuroleptic malignant syndrome). Although these movement disorders are labeled 'medication induced', it is often difficult to establish the causal relationship between medication exposure and the development of the movement disorder, especially because some of these movement disorders also occur in the absence of medication exposure. The conditions and problems listed in this chapter are not mental disorders.*" This is despite scientific evidence that even without medication, there are profound motor issues in Autism [4] that intensify with aging [28].

Further sidelining sensory-motor issues in Autism, within the ADOS booklet [9], under the guidelines for selecting a module, we read "*Note that the ADOS-2 was developed for and standardized using populations of children and adults without significant sensory and motor impairments. Standardized use of any ADOS-2 module presumes that the individual can walk independently and is free of visual or hearing impairments that could potentially interfere with use of the materials or participation in specific tasks*".

Despite these caveats explicitly stated on their manuals, children with profound and highly visible motor, kinesthetic sensing and vestibular issues [29] go on to receive the Autism diagnosis that places them on a behavioral modification therapeutic pipeline that does not consider the brain-body physiology [30]. Clearly, there is a contradiction between the somatic-sensory-motor medical-physiological criteria and the social-appropriateness behavioral-psychological criteria explicitly denying the former. *Which one is it? And why are these important medical-physiological factors deemed secondary or co-morbid, when they are at the core of the basic building blocks necessary to develop and maintain social behaviors?*

To better understand this tension between psychological criteria (dominating Autism research, diagnostics, therapies and services) and medical-physiological issues reported by peer-reviewed science [31], we here examine the genes linked to these neurological and neuropsychiatric disorders making up a large portion of the autistic population today and manifesting profound somatic and sensory-motor differences.

We examine the pool of genes linked to a purely behavioral diagnosis of Autism attained through instruments that sideline the somatic sensory-motor physiology (*i.e.*, the ADOS/DSM-5). Specifically, the ADOS-2 research criteria inform the studies that support the confidence scores of the Autism-linked genes hosted by the Simons Foundation Research Initiative (SFARI). We leverage this research-based data repository of Autism-linked genes and use it as reference to compare its gene pool to the genes from other sources identifying neurological and neuropsychiatric disorders making up the Autism spectrum today. Given that those other disorders of known genetic origin are visibly affected by somatic-sensory-motor differences, but also receive the Autism diagnosis, we here ask if the gene pool of those disorders could help us stratify the broad spectrum of Autism into subtypes.

We find that we can indeed automatically and categorically stratify Autism through the gene pool of neurological and neuropsychiatric disorders that make up its broad spectrum today. We discuss our results in the context of the Precision Medicine (PM) model (Figure 1A) aimed at the development of personalized targeted treatments that integrate several layers of the knowledge network [32]. Under this PM platform we can better situate the person on the landscape of existing disorders for which there are more effective treatments than those currently offered in Autism. Based on this genomic stratification of Autism, we here propose a paradigm shift whereby the pipeline of diagnosis-to-treatment is based on the known physiology of these disorders (Figure 1B), addressing specific capabilities, predispositions and needs of each neurological phenotype. This new line of scientific inquiry not only leverages existing genomic information but more importantly, it responds to the quest of the autistic community to improve the prognosis and the future lives of those who receive this diagnosis.

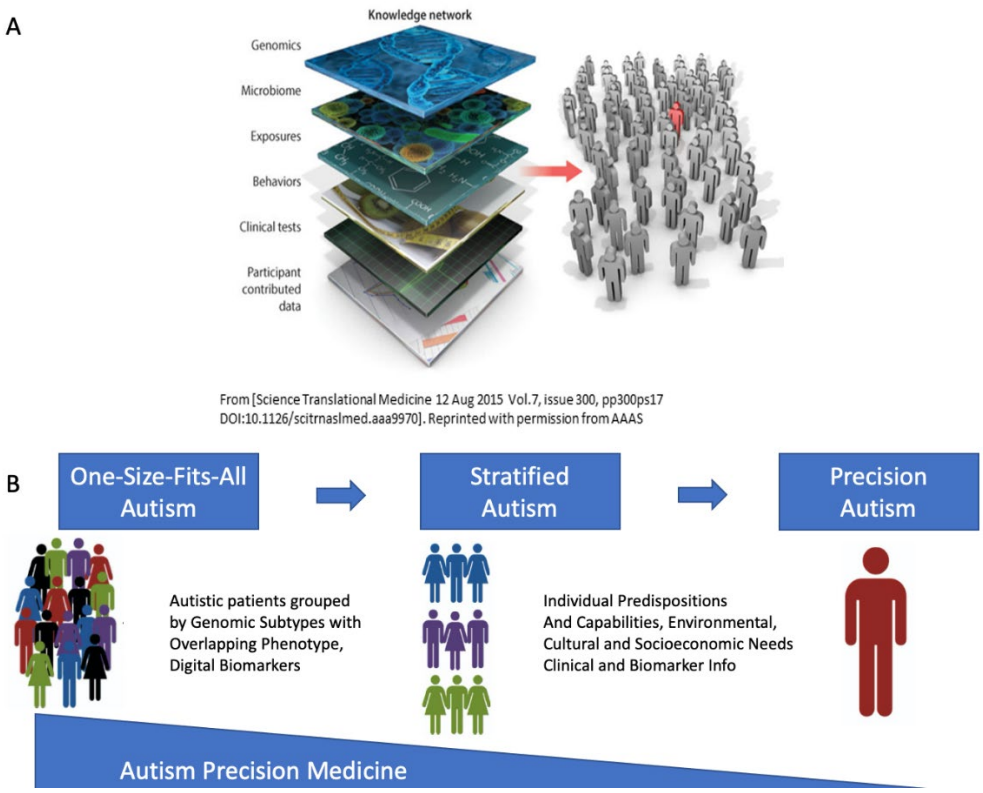

Figure 1. Leveraging existing genomic data to stratify the broad Autism Spectrum. (A) The Precision Medicine model [32] aims at the design of personalized targeted treatments that integrate all layers of the knowledge network to support the person's needs under the genetic and epigenetic individual makeup. (B) Proposed model to stratify the broad spectrum of Autism based on existing genomic information causally defining the origins of neurological and neuropsychiatric disorders making Autism today. This Precision Autism model can identify, relative to other disorders of known origin, the person's best predispositions and capabilities, the environmental, cultural, and socio-economic needs, and design a personalized treatment that targets the medical-physiological issues rather than modifying behavior to conform to a grand average norm -a norm arbitrarily defined by current clinical criteria.

2. Materials and Methods

We examine the genetic data base from the Simons Foundation Research Initiative (SFARI), which has been scored according to the evidence provided in the scientific literature linking the behavioral Autism diagnosis with a pool of genes. We then extract from that pool of genes those genes that overlap with the pool of genes linked to other disorders that are fundamentally defined by somatic-sensory-motor issues. Among them we use the genes associated with cerebral palsy (CP), Dystonia, Attention Deficit Hyperactivity Disorder (ADHD), obsessive compulsive disorder (OCD), Tourette's, the Ataxias (autosomal dominant, recessive and X-linked) and Fragile X (FX). We also use the genes associated with Parkinson's disease (PD) [33, 34], as symptoms of Parkinsonism abound in autistic adults after 40 years of age [28, 35].

While the SFARI genes circularly depend on the ADOS and the DSM behavioral Autism criteria (*i.e.,* they were obtained precisely based on those clinical inventories describing presumed socially *inappropriate* behaviors), the latter genes come from the disease-association network (the DisGeNet portal) which did not rely on an Autism diagnosis. These individuals are likely to receive an Autism diagnosis at present, because of the shifts and broadening of the criteria [21, 22, 36-40]. However, they have their own clinical definition and known genetic origins [17, 41].

In Autism research, when the person has both diagnoses (ASD and a neurological or neuropsychiatric one) the former is coined idiopathic Autism, whereas the latter are called Autism of known etiology. Yet in a random draw of the population, we have identified clusters differentiating subtypes by relying on gait [5, 42], voluntary reaches [3, 26, 43, 44] and involuntary head motions [4, 6, 28, 45, 46].

We blindly took these genes associated to other disorders of the nervous system (clinically and physiologically defined) and interrogated them in terms of their expression on brain and bodily tissues. We asked how much overlapping we would find (if any) with the SFARI Autism-linked genes (coined hereafter SFARI-Autism) defined by observation and descriptions of behaviors.

Upon this compilation of genes from several sources in the DisGeNet portal and the literature, we used the Genotype-Tissue Expression (GTEx) project involving human RNA-seq, expressed in Transcripts Per Million (TPM) to examine the genes' expression across the 54 tissues sampled in their database [47] (Figure 2A). Using this atlas of genetic regulatory effects across human tissues, we compare across diseases, for those genes overlapping with the SFARI Autism-linked genes, the common tissues where the expression of these genes is maximal. To zoom into these overlapping genes expressed on tissues from the GTEx project (Figure 2A), we included the 11 distinct brain regions along with other 7 tissues representative of three fundamental muscle types: cardiac, smooth, and skeletal (Figure 2B), supporting the generation and maintenance of all physiological processes underlying all human functions and behaviors. Specifically, brain tissues included: the amygdala, the anterior cingulate cortex, the basal ganglia (caudate, putamen, nucleus accumbens), the brain cortex and the brain frontal cortex, the cerebellum and the cerebellar cortex, the hippocampus, the hypothalamus, and the substantia nigra.

Representative tissues of the different muscle types are: (cardiac) the heart left ventricle and the heart atrial appendage, (smooth) the esophagus muscularis and the bladder,

(skeletal) muscle skeletal. We also examined these genes' expression on the tibial nerve and the spinal cord (Figure 2A).

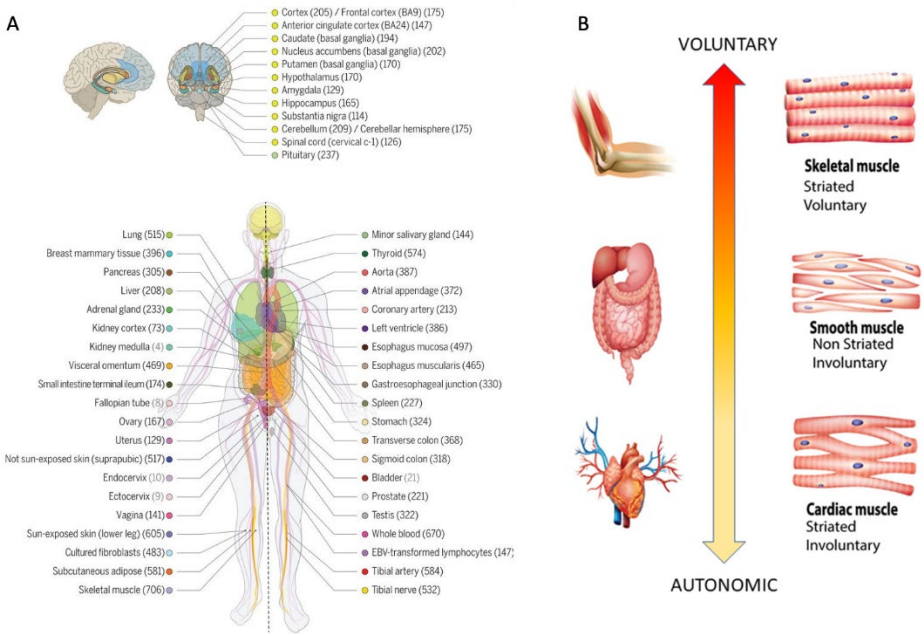

Figure 2. Genomic and Physiological criteria used in this study. (A) GTEx v8 study atlas of 54 tissues including 11 distinct brain regions and two cell lines. Genotyped sample donors numbers in parenthesis and color coding to indicate the tissue in the adjacent circles (Figure used with permission from AAAS [47].) (B) Three fundamental types of muscles supporting autonomic, involuntary and voluntary actions in humans can help us categorize behavioral functional levels according to related tissues affected [23].

The SFARI Autism categories that we used to determine the level of confidence that the gene is linked to Autism, were those reported as of 03-04-2020. Quoting from their site:

CATEGORY 1

Genes in this category are all found on the SPARK gene list. Each of these genes has been clearly implicated in Autism Spectrum Disorders, ASD—typically by the presence of at least three de novo likely-gene-disrupting mutations being reported in the literature—and such mutations identified in the sequencing of the SPARK cohort are typically returned to the participants. Some of these genes meet the most rigorous threshold of genome-wide significance; all at least meet a threshold false discovery rate of <0.1.

CATEGORY 2

Genes with two reported de novo likely-gene-disrupting mutations.

A gene uniquely implicated by a genome-wide association study, either reaching genome-wide significance or, if not, consistently replicated and accompanied by evidence that the risk variant has a functional effect.

CATEGORY 3

Genes with a single reported de novo likely-gene-disrupting mutation.

Evidence from a significant but unreplicated association study, or a series of rare inherited mutations for which there is not a rigorous statistical comparison with controls.

SYNDROMIC (former category 4)

The syndromic category includes mutations that are associated with a substantial degree of increased risk and consistently linked to additional characteristics not required for an ASD diagnosis. If there is independent evidence implicating a gene in idiopathic ASD,

it will be listed as "#S" (e.g., 2S, 3S). If there is no such independent evidence, the gene will be listed simply as "S".

The GTEx dataset is as the 06-05-2017 v8 release [47]. For every gene in the disorders and diseases of interest, we first confirmed the presence of the gene in the GTEx dataset and then incorporated it into the analyses.

The genes from the DisGeNet portal were found by interrogation of their dataset under disease type and saving the outcome to excel files containing all pertinent information.

We follow our previously proposed roadmap to adapt the Precision Medicine platform [32] to Autism research and treatments [48] linking other disorders to the broad Autism phenotype (Figure 1). We first isolate the genes common to Autism and each disorder under consideration, sort them according to their median gene expression over the above mentioned 18 tissues of interest and then, for each tissue of interest, we highlight the top genes with expression above (log(e^{60}) TMP (using the natural logarithm, Euler's base 2.7183), to further help visualize common top genes across these diseases. We note that this is an arbitrary threshold used only to help visualize the top genes, since other thresholds could be used to visualize more genes in common. We report in the supplementary material the full set of genes common to these disorders and the SFARI-Autism set. Then, for each of the 54 tissues, we obtain the gene in the unique intersection set with the maximal expression and plot this information for the brain tissues of interest along with the SFARI-Autism score assigned to that gene.

In addition to genes linked to neurological disorders, we examined genes linked to neuropsychiatric conditions such as depression, schizophrenia, ADHD, and post-traumatic stress syndrome (PTSD), the latter owing to the tendencies in ASD to develop trauma and depression reportedly induced by current behavioral therapies [49], and to the known overlap between Autism and schizophrenia [50]. Furthermore, since the DSM 5 now accepts ASD and ADHD as coexisting diagnoses, we included ADHD-linked genes and asked about their overlap with Autism. We also tallied the shared genes pairwise across all the neurological and neuropsychiatric disorders under consideration, to learn about shared genes across these diseases.

Finally, other non-neurological and non-neuropsychiatric diseases were considered, to ascertain their overlap with the Autism-linked genes and with the genes linked to the neurological and neuropsychiatric disorders. We tallied their genes in common and interrogated the genes' expression reported in the GTEx tissues. These included several forms of cancer (colon 49 genes, breast 488 genes, pancreas 114 genes), diabetes 5,545 genes, autoimmune disorders (lupus systemic 1,743 genes, psoriasis 1,221 genes, irritable bowel syndrome 1,483 genes), and congenital heart disease 252 genes, totaling 10,895 genes in addition to 8,070 genes associated to neural disorders (a random draw across 25 diseases of 18,965 genes and their expression on 54 tissues). Here we hypothesized that the overlap between the genes linked to Autism and those linked to neurological and neuropsychiatric conditions would be much higher than the overlap between the Autism-linked genes and the genes linked to other non-neurological diseases.

Methods to Obtain Pairwise Comparisons of Genes' Expression in Autism and Various Disorders

We obtained for each set of reported DisGeNet genes liked to each disorder, their expression across the 54 tissues from the GTEx project. This yielded a matrix of N genes x 54 tissues, where each entry in the matrix is the gene's expression in that tissue. Taking the median across all rows (*i.e.*, the number of genes in the disorder) gives a 1 x 54 vector array of median genes' expression per tissue, which we normalize by the total number of genes in that disorder (scaling it to range between 0 and 1 unitless quantity). This is depicted in stem form in Figure 3A for each of 3 different representative disorders (ASD, ADHD and Lupus Systemic.) We then take the histogram of the values (represented by red dots in Figure 3A) and obtain the Earth Mover's Distance (EMD) [51-53] between histograms, to code the distance in some probability space where we can represent these histograms according to an empirically fit continuous family of probability distributions.

We obtain the EMD quantity pairwise between disorders, normalize it by the maximum value across the entire set, and represent it in matrix form for neuropsychiatric, neurological disorders and non-neurological diseases. We ask if clusters self-emerge from this representation of the median genes' expression across the 54 tissues.

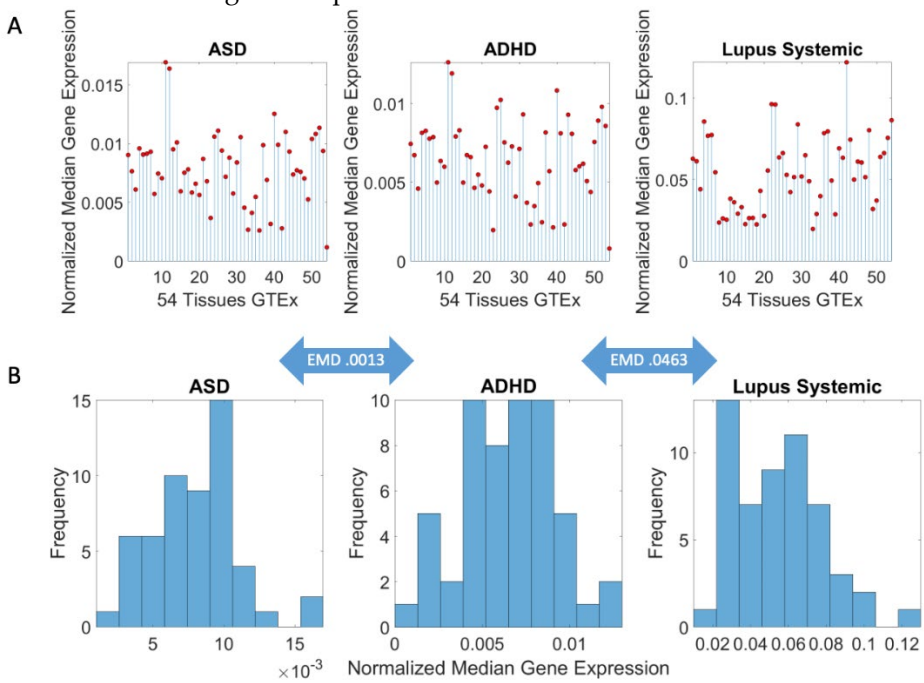

Figure 3. Pipeline of analysis to obtain pairwise similarity measurements between disorders. (A) The matrix of N genes x 54 tissues whereby is *ij* entry is the gene expression from the row *i* in the tissue *j*, is transformed into a 1 x 54 vector of median gene expression values (across the matrix rows) represented here in stem form, from the normalized values accounting for the number of genes in each disorder. Each red dot represents the median gene expression at the jth tissue. Three representative disorders are shown. (B) Histogram of the genes' normalized expression correspond to the step plots of panel (A). We take the earth mover's distance (EMD) pairwise between two disorders (represented in the arrow) and build a matrix of EMD values representing the distance (similarity) between two disorders in the precise sense of genetic information contributing to genes' expression on tissues.

3. Results

Neuropsychiatric Disorders and Autism Share Common Genes Expressed in Brain Tissues for Motor, Emotional and self-Regulatory Control.

Quantification of genes common to Autism and neuropsychiatric disorders is depicted in Table 1. Figure 4A shows the distribution of genes common to the Autism linked SFARI database and each of the neuropsychiatric disorders under consideration, schizophrenia, ADHD, depression, and bipolar depression. Figure 4B shows the same information color-coded (in log N color scale, where N is the number of genes in common with the Autism-linked SFARI set.) Notice that ADHD and Schizophrenia share the highest number of genes followed by depression and bipolar depression. Interestingly, we included PTSD owing to the tendency of trauma reported in Autism [49, 54, 55] and found 55 genes of those linked to PTSD in the Autism-SFARI set.

Table 1: Overlap between Autism-linked genes in SFARI and known neuropsychiatric disorders.

Neuropsychiatric Condition	Number of Genes in DISGENET	Number of Genes Shared with SFARI ASD-linked Genes
ADHD	795	188
Schizophrenia	2,697	336

Bipolar Depression	116	33
Depression	1,407	158
PTSD	395	55

Neurological Disorders and Autism Share Common Genes Expressed in Brain Tissues for Motor, Emotional and Regulatory Control

Likewise, quantification of genes linked to well-known neurological disorders and present in the Autism-linked SFARI dataset yielded between 1-98 overlapping genes. These are depicted in Table 2 and Figure 4. We computed as well, pairwise, the number of overlapping genes between each of the neuropsychiatric and neurological disorders. These numbers are depicted in the color-coded map of Figure 4B, where surprisingly, 12/17 genes reported in Parkinson's disease are present in the schizophrenia set, while 15/17 are present in dystonia. This figure depicts the shared gene pool across these disorders that also show their genes overlapping with Autism-linked genes.

Examination of the Maximal Gene Expression on the Tissues for Genes Common to Autism and These Disorders Revealed a Compact Gene Pool.

We found that 12 genes common to Autism and these disorders are maximally expressed on the 54 tissues. They are depicted in Table 3 along with the tissues where they maximally express. We discuss later some of the literature on these known genes. We also provide supplementary files with the pairwise genes in common between Autism and each disorder or disease under consideration.

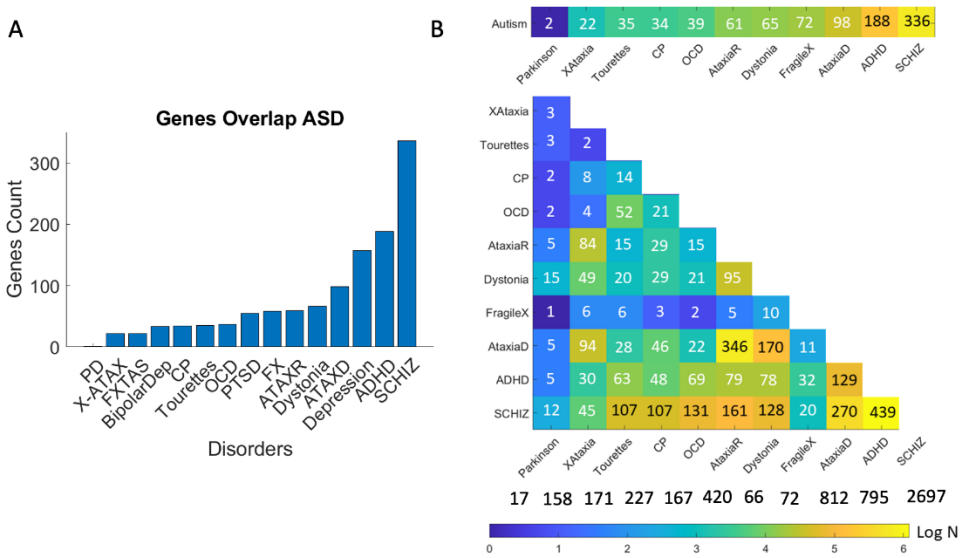

Figure 4. Number of genes common to Autism and neuropsychiatric and neurological disorders. (A) Bar plot tallying the number of genes in each disorder that are also present in the SFARI dataset linking genes to Autism according to a confidence score (see methods.) (B) Colormap depicting the number of genes in Autism and each disorder and obtained pairwise between disorders. Color is in log N, where N is the number of genes common to Autism and the disorder, or common to a disorder and another disorder (pairwise intersect.)

Table 2: Overlap between Autism-linked genes in SFARI and known neurological disorders of genetic origins.

Neurological Disorder	**Number of Genes Reported in DISGENET**	**Number of Genes Shared with SFARI ASD-linked Genes**

CP	227	34
FX	72	58
OCD	167	37
Tourette's	171	35
Ataxia Autosomal Dominant	812	98
Ataxia Autosomal Recessive	420	59
X-Ataxia	158	22
Dystonia	419	66
Progressive Cerebellar Ataxia	134	13
Parkinson's	17	1
FXTAS	63	22

Table 3: Compact set of genes common to Autism and the neurological and neuropsychiatric disorders maximally and selectively expressed across the 54 tissues.

Genes Common to ASD and Neuro-Disorders	**Tissue with Max Expression**
ACTB	Liver
AFF2	Adipose Subcutaneous, Adipose Visceral Omentum, AdrenalGland, Artery Aorta, Artery Coronary, Artery Tibial, Bladder, Breast Mam Tiss, Cervix Ectocervix, Cervix Endocervix, Colon Sigmoid, Colon Transverse, Esophag GastroesophagJunct, Esophagus Muscularis, Fallopian Tube,Heart AtrialAppendage, Kidney Cortex, Kidney Medulla, Lung, Minor Saliv Gland, Nerve Tibial, Pituitary, Prostate, Small Int lIleum, Spleen, Stomach, Thyroid, Uterus, Vagina
AKAP9	WholeBlood
ALDH5A1	Esophagus Mucosa
ATP2B2	Heart Left, Ventricle, Ovary, Cerebellar Hemi, Cerebellum
AVPR1A	Muscle Skeletal
CACNA1E	Ant Cingulate Cortex
CHD7	Pancreas, SkinNotSunExp Suprapubic, SkinSunExp LowerLeg
CREBBP	Cortex, FrontalCortex, Fibroblasts, Cell-Lymphocytes
FOXP1	NAccumbens-BG
MECP2	Amygdala, Caudate-BG, Hippocampus, Hypothalamus, Putamen-BG, SpinalC-Cervical, Subs Nigra
SMAD4	Testis

Genomic Stratification of Neurological and Neuropsychiatric Diseases Making Up Autism Today

The EMD taken pairwise between Autism and each disorder, and pairwise across all neuropsychiatric, neurological disorders and non-neurological diseases revealed an orderly stratification of disorders, whereby a common gene pool and expression on the

tissues can clearly separate neuropsychiatric and neurological from non-neurological diseases. This is shown in Figure 5A, where we also appreciate that in the non-neurological diseases, the autoimmune ones share a common gene pool and tissue expression. Notably, colon cancer is also close in a probability distance sense, to neurological disorders of known genetic origin, namely, Fragile X, FXTAS, the ataxias, dystonia, and Parkinson's disease.

Zooming into the entries with lowest EMD value, corresponding to the neuropsychiatric and neurological disorders, we see in Figure 5B, that other patterns self-emerge further refining the clusters. There, we can appreciate that ASD is close to ADHD and Schizophrenia, as well as close to Depression, PTSD and Cerebral Palsy. Furthermore, OCD and Tourette's cluster close together, also showing a common gene pool and genes' expression across the tissues. In the group of the neurological disorders of known etiology, we can visualize self-grouping of FX and the ataxias (dominant and recessive), while X-ataxia, dystonia, Progressive cerebellar ataxia, and Parkinson self-cluster and separate from FXTAS.

To further test this visualization, we run a common clustering procedure using MATLAB linkage function using Euclidean distance and plot the output as a dendogram showing the orderly binary tree structure of these genes-tissues grouping. This is appreciated in Figure 5C, where we see that the two main branches of the binary tree, *i.e.*, the two subtrees in which each branch is comprised of the neuropsychiatric and the neurological disorders, respectively. Further refinement reveals FXTAS as a leaf of its own, close to PD and the progressive cerebellar ataxia. We also see that dystonia and X-ataxia fall under the same subtree branch as PD, and that autosomal recessive ataxia is closer to Fragile X than to autosomal dominant ataxia, though all are branches of the same subtree of the binary tree. At the other end, we see that Tourette's and OCD group in a branch and bipolar depression is a leaf of its own, while schizophrenia and Autism fall the closest together in one branch of the same subtree. That subtree also groups PTSD, Depression and ADHD under one branch and shows CP as a leaf of its own. These gene pools and their expression on the 54 GTEx tissues define an orderly stratification aided by genes common to Autism Spectrum Disorders, according to DisGeNet and SFARI genomic reports.

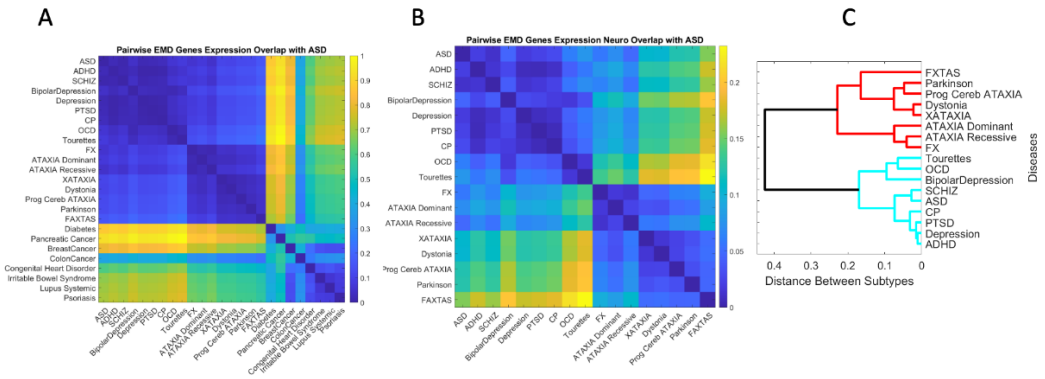

Figure 5. Genomic stratification of Autism and diseases obtained by leveraging the gene pool that overlaps with other known neurological and neuropsychiatric diseases and their expression on the 54 tissues defined by GTEx. (A) Separation between neuropsychiatric, neurological disorders and non-neurological diseases, also identifying common gene pool in autoimmune diseases. (B) Zooming into the neuropsychiatric and neurological diseases whose gene pool overlaps with Autism, we see different self-emerging subclusters further refining the stratification. (C) Dendogram showing the binary tree orderly organization that groups and categorizes diseases according to genes' overlap and tissue expression with respect to ASD. ASD is closest to schizophrenia and groups within a cluster containing ADHD, Depression, PTSD and CP.

Figures 6 and 7 reveal the genes expression for values above (log(e^{60}) TPM) with the SFARI confidence score on the horizontal axis and the expression value log TPM on the vertical axis. Figure 6 shows the brain tissues and genes above this level of expression along with the confidence score in the SFARI data repository. Tissues that are fundamental for the development and maintenance of motor learning, motor coordination and motor adaptation include the substantia nigra (maximal expressed gene AFF2-AUT1 signifying this gene is scored in SFARI as score 1 confidence), basal ganglia with caudate, putamen and nucleus accumbens also with AFF2-AUT1 as top expressing gene. Other tissues involved in motor control are the cerebellar hemisphere (ATP2B2-AUT2) and the cerebellum (CREBBP-AUT1). Tissues known to be involved in executive function are the brain frontal cortex (MECP2-AUT1) and the brain cortex (CACNA1E-AUT2). Tissues known for their involvement in emotions (amygdala (AFF2-AUT1)) and memory (hippocampus (BRSK2-AUT1)) and the anterior cingulate cortex (BRSK2-AUT1) are also depicted in Figure 6, along with the schematics of the brain from Figure 1 with the locations of these areas.

In Figure 7 we also reveal those genes' expression and SFARI scores for the cardiac (heart left ventricle and the heart atrial appendage), skeletal (muscle skeletal), and smooth muscle (esophagus muscularis and bladder) tissues and for the nerve tibial. The latter is critical to develop kinesthetic reafference and proper gait. Common to all these disorders are well known genes in the Autism literature with SFARI score confidence 1 (*e.g.*, MECP2, AFF2, FOXP1, CREBBP, CACNA1E, CHD7, TRIO and SHANK3, among others.) We will later discuss the known roles of some of these genes in the development of synapses and circuits necessary to form and dynamically maintain neural networks.

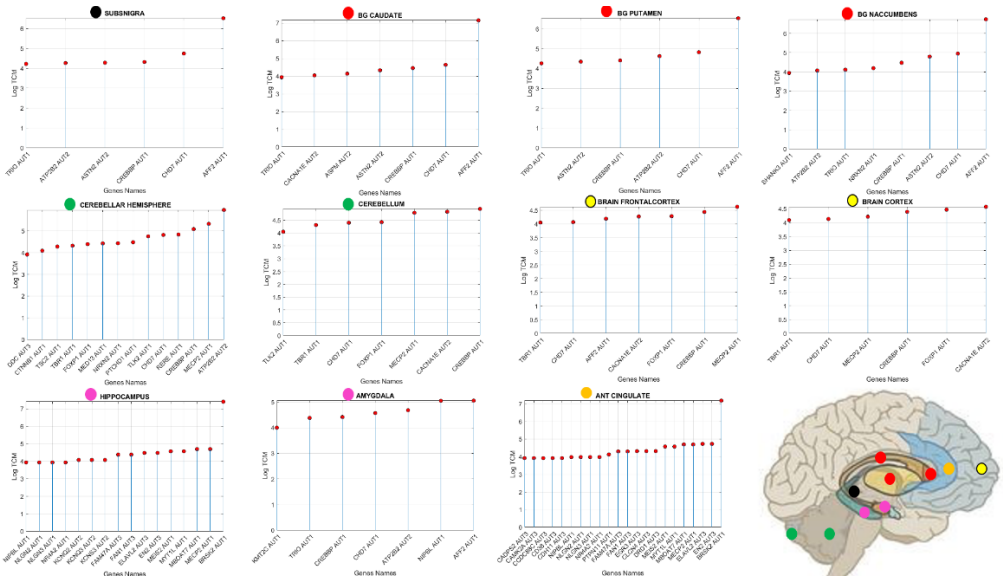

Figure 6. Common genes to Autism and all other neurological and neuropsychiatric disorders maximally express on brain tissues involved in the initiation, generation, control, coordination, and adaptation of movements, as well as in tissues necessary for the creation, retrieval and maintenance of memories and executive function. Genes' expression is threshold above log(e^{60}) to show the top expressing genes from DisGenNet overlapping with those in the SFARI set. The AUT# reflects the confidence score assigned to the gene at the SFARI repository. Horizontal axis shows the genes above threshold and vertical axis the expression level (log transcripts count per million, TCM.) Each colored dot is shown at the brain tissue in Figure 2A schematic form.

We further plot in Supplementary Figures 1-3 genes common to Autism and some of the disorders, for the top 20 genes with maximal expression (in log TCP units) across the brain and spinal cord tissues, as well as tissues involving muscle skeletal, cardiac, and smooth muscle types. These figures in the Supplementary Material show the matrix with

genes across the rows (top 20 expressed genes) and 18 tissues across the columns. Each entry is color coding the expression of these genes in log TCM units. From these plots, we note that *e.g.*, MECP2 is present at the highest expression on the spinal cord in Autism and Schizophrenia, Autism and Depression, Autism and ADHD, Autism and OCD, Autism and Cerebral Palsy, Autism and Dystonia, Autism and Autosomal Dominant Ataxia, Autism and Autosomal Recessive Ataxia, Autism and Fragile X, Autism and X-ataxia, Autism and PTSD but not in Tourette's & Autism, where MECP2 is not among the top 20 genes expressed on these tissues. Instead, CHD2 is expressed on the spinal cord, and highly expressed on the cerebellum and cerebellar hemisphere. Indeed, Tourette's is closer to OCD (Figure 5) than to the cluster formed by ASD, ADHD and Schizophrenia (though located on the same branch as these neuropsychiatric disorders.)

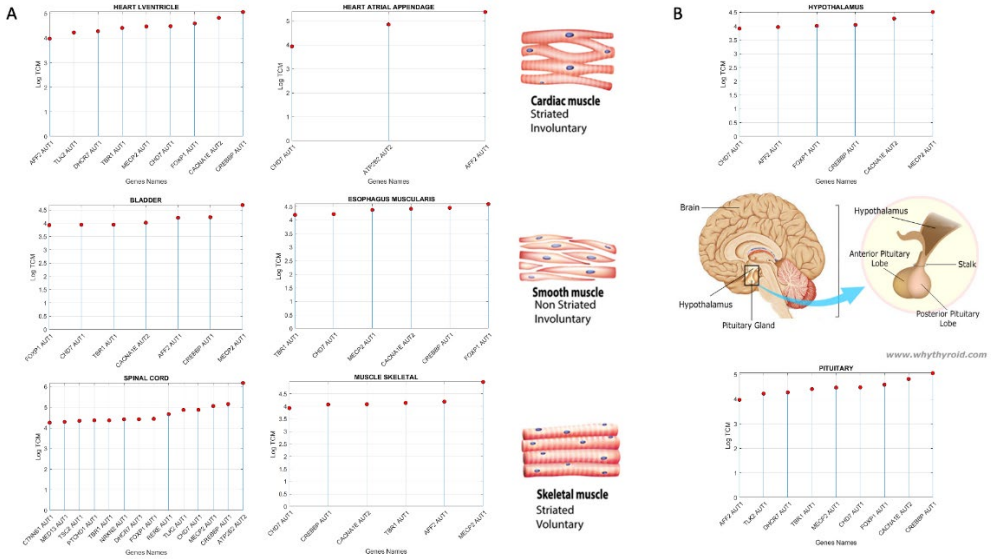

Figure 7. Genes present in Autism and all other neurological and neuropsychiatric disorders maximally expressed (above log(e^{60}) on tissues involved in all vital functions associated with cardiac, smooth, and skeletal muscles and the spinal cord (A), and with self-systemic regulation (B). Top genes and corresponding SFARI confidence score are also plotted on the horizontal axis. Vertical axis reflects the expression in log TCM units. Schematics reflect the locations of the hypothalamus and pituitary gland in the brain (from www.whythyroide.com)

Discussion

This work provides support to the idea of reframing Autism under the model of Precision Medicine [23, 48], while also addressing the notion of an "Autism epidemic" recently portrayed as an exponential rise in prevalence [56] and its costly consequences [56]. Re-examining Autism as the conglomerate of disorders and diseases, many of known origins, comprising this heterogeneous spectrum, we conclude that such "*epidemic*" or "*tsunami*" is bound to be an artifact of the current behavioral diagnosis-to-treatment pipeline. This pipeline allows such comorbidities and often shifts criteria, discouraging stratification. We argue that stratifying the spectrum according to underlying genetic, causal information provides far more viable strategies to cope with the overall increase in neurodevelopmental disorders in general, than continuing the use of Autism as a blanket label grouping all these disorders. Furthermore, we argue that several of the disorders in question already have therapies designed to address issues in their corresponding phenotype. As such, the general Autism label could leverage the accommodations and support pertinent to each of the neurological and neuropsychiatric groups conforming its broad spectrum today.

Autism serves as an umbrella term encompassing many disorders and diseases, some of which have precise etiology (e.g., Down Syndrome [57], Fragile X Syndrome [58], etc.). In this work we posit that this broad spectrum affords subtyping and that given a random

draw of genes linked to disorders with high penetrance in Autism, we could find self-emerging clusters at their intersection, using (probabilistic) distances from those overlapping genes specifically linked to Autism and their expression in brain-body tissues. We here adopted this proposed strategy, by combining multiple open access data sets with the label of Autism and with the label of a disorder or disease that often receives the Autism diagnosis. We included neuropsychiatric disorders, and neurological and non-neurological diseases associated with some set of genes. Then, we applied common computational techniques to attempt to automatically and orderly stratify a cohort of 25 diseases and 18,965 genes expressed on 54 brain-bodily tissues.

We found genes common to Autism and these diseases, leading to self-emerging clusters that clearly differentiated neuropsychiatric and neurological disorders from non-neurological diseases and within the brain-related disorders, we established an orderly distance to Autism in the sense of overlapping genes and their expression on tissues critical for motor control (initiation, learning, coordination, and adaptation), cognition, memory, and self-regulation.

Our overall conclusion from our results is twofold: (1) Autism prevalence rates are an artifact of current surveillance methods relying exclusively on the clinical (behavioral) diagnosis that welcomes other disorders, using fundamentally flawed statistics in the criteria, thus inflating false positives [8]; (2) The broad spectrum of Autism, as we know it today, *i.e.,* inclusive of disorders and diseases of known etiology, share a common set of genes with those disorders and consequentially can be stratified into Autism subtypes. These genetically-based subtypes might be more manageable and less costly to treat and service, than forecasted by current epidemiological accounts relying only on the psychological construct of "appropriate" social behaviors [56].

The Genetically Informed Autism Subtypes

Given a mixture of genes and their median expression on the 54 tissues defined by GTEx, across multiple neuropsychiatric and neurological disorders, we found that Autism-linked genes in SFARI (Autism-SFARI) overlap with genes defining these disorders in DisGeNet, which would also likely receive the Autism label. Such overlapping showed an orderly stratification using a binary tree structure that rendered schizophrenia as the closest to Autism-SFARI (sharing 363/906 genes reported in SFARI) and FXTAS as the farthest (nonetheless sharing 22/906 genes reported in SFARI.) We note that DisGeNet ASD (Autism Spectrum Disorders; CUI: C1510586) is a superset of SFARI, 1,071 *vs.* 906 genes and SFARI genes are ranked according to the literature. We also note that since our last download, the number of genes in SFARI may have increased.

In good concordance with clinical criteria, two main subtypes automatically self-emerged according to the distance metric that we used (Figure 5) comprising neuropsychiatric and neurological disorders, all sharing a compact set of genes described below. The neuropsychiatric branch includes the Autism linked genes in DisGeNet (overlapping with a subset of those in SFARI) and disorders in the Diagnostic Statistical Manual, 5th edition, DSM-5 and the International Classification of Diseases, 10th edition, ICD-10. In order of distance to Autism-SFARI, these are schizophrenia (the closest), ADHD (allowed to be co-diagnosed with Autism in the DSM5), depression, PTSD, CP, OCD, Tourette's syndrome, and bipolar depression (the farthest in this branch of the binary tree). Among the neurological disorders conforming the second branch of the binary tree, we found, in order of distance from Autism, dystonia and X-ataxia, Fragile X and Ataxia autosomal recessive in a common branch, progressive cerebellar ataxia and Parkinson's (in a common branch), Ataxia autosomal dominant as a leaf of the subtree comprising FX and the recessive ataxia and FXTAS as a leaf of the subtree farthest from the Autism-schizophrenia branch. This natural breakdown of the (Autism) spectrum according to the shared genetic pool and genes' expression on tissues fundamental to form the building blocks of any human behavior, is far more manageable (using medical knowledge today) than

considering the full spectrum in a monolithic form, as suggested by surveillance methods [1, 56] and the behaviorists' recommendations [12].

The Genes Common to Autism and Each Subtype

Each neuropsychiatric or neurological subtype identified by the genes-tissue analysis shared genes with the Autism-SFARI. The full list in Supplementary Materials for each disorder/disease, offers clues with regards to the tissues whereby these intersecting genes maximally express. It will be interesting to track their evolution on induced pluripotent stem cell models, as cells develop into neuronal classes. Research along those lines is warranted [59].

Autism and schizophrenia, Autism and ADHD, Autism and Depression, Autism and OCD, Autism and FX, Autism and ataxia-X, Autism and PTSD, Autism and CP, Autism and dystonia, Autism and Ataxia autosomal dominant and Autism and Ataxia autosomal recessive, all share METHYL-CpG-binding protein 2, MECP2, with cytogenetic location at Xq28 (according to the Online Mendelian Inheritance in Man, OMIM site). It is reported as implicated in severe neonatal encephalopathy, mental retardation and Rett syndrome, as well as to have high Autism susceptibility. MECP2, binds methylated CpGs. It is a chromatin-associated protein that can both activate and repress transcription; it is required for maturation of neurons and is developmentally regulated [60].

Furthermore, Autism and schizophrenia and Autism and ADHD (the two top neuropsychiatric disorders sharing the highest percentages of genes with the genes linked to Autism-SFARI) shared the CREP-Binding Protein (CREBBP), among the top 10 genes expressed maximally across the 54 tissues and common to the Autism and Schizophrenia gene pool. It is located in 16p12.3, a chromosomal region linked to Autism.

Autism and Tourette's syndrome did not share MECP2, but shared CHD2 as the top gene maximally expressed across all 18 tissues of the brain, spinal cord and tissues associated with cardiac, smooth, and skeletal muscles. Maximal expression at the cerebellar hemisphere and the cerebellum suggest involvement in motor control, coordination, and adaptation, while high expression in other tissues for memory, cognition, and self-systemic regulation suggest that this gene is rather important. Indeed, prior work in Autism [61] and other neurodevelopmental disorders [62] had conferred importance to this gene for neural development.

Among highly expressed genes in Autism and other disorders, we also found AFF2 [63] and BRSK2 [64], both with score 1 in SFARI and reportedly critical for neurodevelopment. Indeed, the X-linked gene AFF2 has been found in patients with fragile X E (FRAXE) intellectual disability, while the gene encoding the serine/threonine-protein kinase BRSK2 was recently detected in individuals with developmental and intellectual disability.

The Genes Common to Autism and All Subtypes

MECP2 and CREBBP were found to be shared pairwise with Autism and the above-mentioned disorders, but also at the intersection taken across disorders. MECP2 expressed maximally in tissues related to emotion (amygdala) and memory (hippocampus) and tissues important for motor control (basal ganglia's caudate and putamen regions, the substantia nigra and the spinal cord) and for self-regulation (hypothalamus.) CREBBP was found to be maximally expressed at the cortex and frontal cortex, both of which are important for high-level cognitive and executive functions. Another important forkhead transcription factor FOXP1 was found to be maximally expressed in the basal ganglia's nucleus accumbens, a structure important for developing striatal function and differentiation in medium spiny neurons from precursors to maturity [65-67]. CACNA1E was found maximally expressed across disorders in the anterior cingulate cortex, a region associated with impulse control, emotion and decision making, and previously known in connection to epilepsy, Autism, schizophrenia, and major depressive disorder [68-70].

Implications of This Genomic Categorization for Treatment Selection in Autism

Approaching Autism as genotypically defined orderly subtypes may also be more humanely relevant to the affected individuals. Today, they receive recommendations for a "one-size-fits-all" behavioral-modification or conversion-therapy to reshape "socially inappropriate behaviors" without informing such treatments by brain-body physiological and medical issues. This approach disregards possible adverse effects linked to their genomic characteristics [71]. Indeed, despite advances in genetics, it has been reported that the current paradigm neglects the physiological phenotypes in favor of psychological constructs [31]. The literature reports that this paradigm for Autism treatment selection promotes stigma, causes harm in the form of trauma, increases the person's stress and ultimately results in PTSD [72]. Along those lines, here we show that there is a pool of genes linked to PTSD and depression overlapping with a subset of the Autism-SFARI data set, and very close to the Autism branch of the binary tree in Figure 5C. These genes may interact in ways that could increase the predisposition of the Autistic system to develop PTSD and depression, explaining the rise as well in suicidal ideation [49, 73-75].

The outcome of this work highlights the relevance of considering, when choosing treatments, the medical and physiological issues linked to the phenotypic characteristics that these genes forecast. This proposed approach contrasts with choosing treatments that exclusively focus on the social appropriateness criteria. The latter model has been said to lead to high societal cost [56, 76], to offer no future to the affected individuals and their families and has recently been shown to be polluted with conflict of interests and nonscientific practices [77, 78].

In the present study, we reasoned that stratifying Autism based on the genetic makeup of the diseases that today go on to receive the Autism clinical diagnosis, could help us in various ways. One was to find the diseases genetically closer to Autism itself (as defined by the SFARI genes). Another was to leverage existing clinical information in other fields, amenable to create support and accommodations for the individuals affected by those diseases. Such accommodations could then be tailored to the individual with the Autism label, according to the phenotype that these genetic pools express for each of these other diseases of known etiology. Furthermore, we reasoned that since Autism today includes all these other disorders in its broad spectrum, utilizing the information that has already been verified (*e.g.,* in the SFARI repository) would bring us a step closer to the Personalized Medicine approach that we propose for a new platform that we would like to coin *Precision Autism* (Figure 1B.)

The current diagnosis of Autism follows criteria that sideline somatic-sensory-motor issues as secondary (or comorbid) to social communication and repetitive, ritualistic behaviors [9, 10]. These are behaviors that are deemed inappropriate by psychologists and psychiatrists. As such, the individuals are subject to behavioral modification therapies that do not consider the physiological neurodevelopmental issues [30, 79]. Owing to its high cost in both clinical and research settings, it has been recently proposed that the behavioral definition of Autism, which recommends against stratifying the spectrum [12], feeds the Autism Industrial Complex (AIC) [76] and opens a behavioral diagnosis-to-treatment pipeline contributing to their claimed societal burden [56].

Here the stratification of Autism revealed by the gene pool under consideration underscores the need to seriously consider the somatic-sensory-motor issues in the spectrum. This spectrum of disorders today includes diseases of known origins (*e.g.,* Timothy Syndrome, SYNGAP1, SHANK3 deletion syndrome, Cerebral Palsy and Dystonia, among others) with life-threatening conditions that could seriously harm the child under the type of stress that a behavioral modification technique has been said to bring to their nervous systems [54, 71, 80].

To demonstrate that physiological constructs should guide the choice of therapies in Autism (rather than being secondary to psychological constructs of social appropriateness), we showed sets of overlapping genes co-occurring in those disorders that likely receive the Autism label, and those linked to Autism-SFARI genes. The latter inform their classification from the psychological construct of Autism, while the former classifies

disorders under a variety of medical criteria, which may also independently arrive at a clinical Autism diagnosis. For those genes common to both SFARI-Autism and each one of the diseases in question, we showed shared patterns of genes' expression on tissues in the brain and the body, important for somatic-sensory-motor function underlying all *physiological building blocks* of social behavior and cognitive development (involving memory and executive function.) We also showed a compact set of top genes shared by SFARI-Autism and all diseases demonstrating that they too share tissues critical for (*i*) somatic-sensory-motor functioning, (*ii*) memory and cognition and (*iii*) systemic self-regulation.

This compact set of genes for each of these functions in (*i-iii*) underlying all critical physiological ingredients for social communication and smooth, well-coordinated actions is essential to all human autonomic, involuntary, and voluntary behaviors. As such, they should not be sidelined when recommending and selecting treatments for Autism. We provided a distance from each disorder to SFARI-Autism based on the genes' expression on these 54 tissues defined by GETx, in the hopes of offering new ways to converge to truly personalized interventions that agree with the individual's physiological phenotype and with the endophenotype of a genetically informed group.

We concluded from these analyses that the highly publicized exponential rate in prevalence reported by the US CDC surveillance network is a myth. This myth has been built by broadening and shifting the criteria over time and by allowing diseases of known etiology be part of the Autism spectrum. The increase in neurodevelopmental disabilities (including intellectual disability) is as real as it gets, as evidenced by the compact set of genes identified to be common to SFARI-Autism and all other diseases under consideration. All these genes play a fundamental role on the development of synapses via proteins that are necessary for channels functioning and neurotransmitters balance, neuronal differentiation, the formation of circuits and networks, etc., during neurodevelopment [81]. Yet, these disorders exist independent of Autism. Calling them Autism may be doing more harm than benefit, stigmatizing the affected individuals [56], their families and negatively impacting the entire ecosystem inclusive of research, services and education [72]. By neglecting the physiology of the disorders that make up Autism today, the current approach skews the therapy recommendations for Autism in ways that may in fact harm their nascent nervous systems.

Given these results, we invite rethinking the epidemiology of Autism Spectrum Disorders, to go beyond the behavioral diagnosis when surveying the spectrum to estimate prevalence. We also offer a new avenue to adapt the platform of Precision Medicine to Autism and disclose the implications of these results for the design of truly personalized therapies aimed at helping the affected individuals improve their overall quality of life.

The Importance of Reframing Autism under the Precision Medicine Paradigm

This notion of personalized medicine for Autism that we have proposed [23, 48], contrasts with the current behavioral diagnosis-to-treatment pipeline that discourages stratification of Autism and advocates for a general (one-size-fits-all) model of behavioral modification. Indeed, the last study from the U.S. National Academy of Science (NAS) considering how to educate autistic children, recommended that Autism shall not be stratified [12]. Since then, practice and services do not distinguish *e.g.*, between a child with Cerebral Palsy and a child with ADHD. Both receive the Autism diagnosis, and both will receive a form of behavioral modification to reshape social behaviors in compliance with a set of social norms. As mentioned, such norms were never informed, in any way, by the nervous systems physiology [8]. The accreditation programs enabling such behavioral diagnoses and interventions in fact lack training on basic neuroscience[1]. In the US, these treatments will be administered at the school and the home, under a type of insurance coverage that other therapies do not have.

[1] https://accreditation.abainternational.org/apply/accreditation-standards.aspx

https://www.wpspublish.com/ados-2-autism-diagnostic-observation-schedule-second-edition

Our results show that contrary to the recommendations of the 2001 NAS study, such stratification is not only possible today, but more importantly, it is much needed to help guide and inform the design of new targeted therapies for Autism. Such new therapies could be truly personalized to address phenotypic features of the CNS, including tissues linked to self-regulating systemic structures, memory, cognition, and motor control. They would consider the physiology of numerous networks in the human brain-body complex, serving as the building blocks of all behaviors.

The methods used in this work are rather simple and parsimonious. They also rely on open access data sets. These sets are reliable and provide the grounds for reproducibility of this and related works [23, 48]. We encourage the community to stratify Autism into the appropriate phenotypes with capabilities, predispositions and needs causally linked to the genetic origins of each subtype. If we follow the medical and physiological scientific path, we will be able to progress in Autism research, treatments, and services. But if we continue to follow the circular behaviorist approach, we will not make headways in identifying personalized targeted treatments. Worse yet, will continue to cause trauma to the individual in the spectrum.

An alternative route to the current research paradigm in Autism is possible, by leveraging the work from other fields of science and engineering, and by stratifying the broad spectrum that otherwise keeps exponentially growing [1, 56]. Contrary to archaic recommendations from behaviorists [12], here we show that Autism can and should be stratified to take the first steps toward a paradigm shift toward *Precision Autism*.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Colormaps of top 20 genes expressed in 54 tissues at the intersection of Autism-SFARI and other disorders-I, Figure S2: Colormaps of top 20 genes expressed in 54 tissues at the intersection of Autism-SFARI and other disorders-II, Figure S3: Colormaps of top 20 genes expressed in 54 tissues at the intersection of Autism-SFARI and other disorders-III.

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Data Availability Statement: Data supporting the results can be found at https://www.sfari.org/resource/sfari-gene/, https://gtexportal.org/home/ and https://www.disgenet.org/.

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References

1. Maenner MJ, S.K., Baio J, et al., *Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States,*, CDC, Editor. 2020, Morbidity and Mortality Weekly Report MMWR Surveill Summ 2020. p. 1-12.
2. Mandy, W., et al., *Sex differences in autism spectrum disorder: evidence from a large sample of children and adolescents.* J Autism Dev Disord, 2012. **42**(7): p. 1304-13.
3. Torres, E.B., et al., *Strategies to develop putative biomarkers to characterize the female phenotype with autism spectrum disorders.* J Neurophysiol, 2013. **110**(7): p. 1646-62.

4. Torres, E.B. and K. Denisova, *Motor noise is rich signal in autism research and pharmacological treatments.* Sci Rep, 2016. **6**: p. 37422.
5. Torres, E.B., et al., *Characterization of the Statistical Signatures of Micro-Movements Underlying Natural Gait Patterns in Children with Phelan McDermid Syndrome: Towards Precision-Phenotyping of Behavior in ASD.* Front Integr Neurosci, 2016. **10**: p. 22.
6. Torres, E.B., et al., *Stochastic Signatures of Involuntary Head Micro-movements Can Be Used to Classify Females of ABIDE into Different Subtypes of Neurodevelopmental Disorders.* Front Integr Neurosci, 2017. **11**: p. 10.
7. Bokadia, H., R. Rai, and E.B. Torres, *Digitized ADOS: Social Interactions beyond the Limits of the Naked Eye.* J Pers Med, 2020. **10**(4).
8. Torres, E.B., et al., *Hidden Aspects of the Research ADOS Are Bound to Affect Autism Science.* Neural Comput, 2020. **32**(3): p. 515-561.
9. Lord, C., et al., *The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism.* J Autism Dev Disord, 2000. **30**(3): p. 205-23.
10. *American Psychiatric Association: Diagnostic and statistical manual of mental disorders (5th ed.).* 2013, American Psychiatric Association: Arlington, VA.
11. Mottron, L., *A radical change in our autism research strategy is needed: Back to prototypes.* Autism Res, 2021.
12. Council, N.R., *Educating Children with Autism.*, in *Division of Behavioral and Social Sciences and Education.*, C. Lord and P. McGee, Editors. 2001, National Academy of Science: Washington DC.
13. Constantino, J.N., *Response to "A Radical Change in Our Autism Research Strategy is Needed: Back to Prototypes" by Mottron et al. (2021).* Autism Res, 2021.
14. Gotham, K., A. Pickles, and C. Lord, *Standardizing ADOS scores for a measure of severity in autism spectrum disorders.* J Autism Dev Disord, 2009. **39**(5): p. 693-705.
15. Esler, A.N., et al., *The Autism Diagnostic Observation Schedule, Toddler Module: Standardized Severity Scores.* J Autism Dev Disord, 2015. **45**(9): p. 2704-20.
16. Sanger, T.D. and S.N. Kukke, *Abnormalities of tactile sensory function in children with dystonic and diplegic cerebral palsy.* J Child Neurol, 2007. **22**(3): p. 289-93.
17. Pham, R., et al., *Definition and diagnosis of cerebral palsy in genetic studies: a systematic review.* Dev Med Child Neurol, 2020. **62**(9): p. 1024-1030.
18. Lin, J.P. and N. Nardocci, *Recognizing the Common Origins of Dystonia and the Development of Human Movement: A Manifesto of Unmet Needs in Isolated Childhood Dystonias.* Front Neurol, 2016. **7**: p. 226.
19. Xiao, R., et al., *Abnormal Cerebellar Development Is Involved in Dystonia-Like Behaviors and Motor Dysfunction of Autistic BTBR Mice.* Front Cell Dev Biol, 2020. **8**: p. 231.
20. Geurts, H.M., et al., *Intra-individual variability in ADHD, autism spectrum disorders and Tourette's syndrome.* Neuropsychologia, 2008. **46**(13): p. 3030-41.
21. Zablotsky, B., M.D. Bramlett, and S.J. Blumberg, *The Co-Occurrence of Autism Spectrum Disorder in Children With ADHD.* J Atten Disord, 2020. **24**(1): p. 94-103.
22. Bell, L., A. Wittkowski, and D.J. Hare, *Movement Disorders and Syndromic Autism: A Systematic Review.* J Autism Dev Disord, 2019. **49**(1): p. 54-67.
23. Torres, E.B., *Reframing Psychiatry for Precision Medicine.* J Pers Med, 2020. **10**(4).
24. Hagerman, R., G. Hoem, and P. Hagerman, *Fragile X and autism: Intertwined at the molecular level leading to targeted treatments.* Mol Autism, 2010. **1**(1): p. 12.
25. Wang, L.W., E. Berry-Kravis, and R.J. Hagerman, *Fragile X: leading the way for targeted treatments in autism.* Neurotherapeutics, 2010. **7**(3): p. 264-74.

26. Torres, E.B., et al., *Autism: the micro-movement perspective.* Front Integr Neurosci, 2013. **7**: p. 32. 742
27. Torres, E.B., *Atypical signatures of motor variability found in an individual with ASD.* Neurocase, 2011. **19**(2): p. 150-65. 743
28. Torres, E.B., C. Caballero, and S. Mistry, *Aging with Autism Departs Greatly from Typical Aging.* Sensors (Basel), 2020. **20**(2). 744
29. Bermperidis, T., et al., *Optimal Time Lags from Causal Prediction Model Help Stratify and Forecast Nervous System Pathology.* BioRxvi, 2021. 745 746
30. Torres, E.B. and C. Whyatt, *Autism : the movement sensing perspective*. 2018, Boca Raton: CRC Press/Taylor & Francis Group. xviii, 386 pages. 747 748
31. Whyatt, C.P. and E.B. Torres, *Autism Research: An Objective Quantitative Review of Progress and Focus Between 1994 and 2015.* Front Psychol, 2018. **9**: p. 1526. 749 750
32. Hawgood, S., et al., *Precision medicine: Beyond the inflection point.* Sci Transl Med, 2015. **7**(300): p. 300ps17. 751
33. Scott, W.K., et al., *Complete genomic screen in Parkinson disease: evidence for multiple genes.* JAMA, 2001. **286**(18): p. 2239-44. 752
34. Klein, C. and A. Westenberger, *Genetics of Parkinson's disease.* Cold Spring Harb Perspect Med, 2012. **2**(1): p. a008888. 753
35. Starkstein, S., et al., *High rates of parkinsonism in adults with autism.* J Neurodev Disord, 2015. **7**(1): p. 29. 754
36. Pahlman, M., et al., *Autism spectrum disorder and attention-deficit/hyperactivity disorder in children with cerebral palsy: results from screening in a population-based group.* Eur Child Adolesc Psychiatry, 2020. **29**(11): p. 1569-1579. 755 756
37. Riccio, M.P., et al., *Dystonic Movement Disorder as Symptom of Catatonia in Autism Spectrum Disorder.* Case Rep Psychiatry, 2020. **2020**: p. 8832075. 757 758
38. Dell'Osso, L., et al., *Autism spectrum in patients with schizophrenia: correlations with real-life functioning, resilience, and coping styles.* CNS Spectr, 2021: p. 1-11. 759 760
39. Gecz, J. and J.G. Berry, *Cerebral palsy with autism and ADHD: time to pay attention.* Dev Med Child Neurol, 2021. **63**(3): p. 247-248. 761 762
40. Ghaziuddin, M. and N. Ghaziuddin, *Bipolar Disorder and Psychosis in Autism.* Psychiatr Clin North Am, 2021. **44**(1): p. 1-9. 763
41. Pan, P.Y., et al., *Neurological disorders in autism: A systematic review and meta-analysis.* Autism, 2021. **25**(3): p. 812-830. 764
42. Bermperidis, T., et al., *Optimal Time Lags from Causal Prediction Model Help Stratify and Forecast Nervous System Pathology.* BbioRxvi, 2021. 765 766
43. Torres, E.B., P. Yanovich, and D.N. Metaxas, *Give spontaneity and self-discovery a chance in ASD: spontaneous peripheral limb variability as a proxy to evoke centrally driven intentional acts.* Front Integr Neurosci, 2013. **7**: p. 46. 767 768
44. Wu, D., et al., *A Biomarker Characterizing Neurodevelopment with applications in Autism.* Sci Rep, 2018. **8**(1): p. 614. 769
45. Caballero, C., et al., *Characterization of Noise Signatures of Involuntary Head Motion in the Autism Brain Imaging Data Exchange Repository.* Front Integr Neurosci, 2018. **12**: p. 7. 770 771
46. Caballero, C., S. Mistry, and E.B. Torres, *Age-Dependent Statistical Changes of Involuntary Head Motion Signatures Across Autism and Controls of the ABIDE Repository.* Front. Integr. Neurosci., 2020. **14**(23): p. 1-14. 772 773
47. Consortium, G.T., *The GTEx Consortium atlas of genetic regulatory effects across human tissues.* Science, 2020. **369**(6509): p. 1318-1330. 774 775
48. Torres, E.B., et al., *Toward Precision Psychiatry: Statistical Platform for the Personalized Characterization of Natural Behaviors.* Front Neurol, 2016. **7**: p. 8. 776 777
49. Haruvi-Lamdan, N., D. Horesh, and O. Golan, *PTSD and autism spectrum disorder: Co-morbidity, gaps in research, and potential shared mechanisms.* Psychol Trauma, 2018. **10**(3): p. 290-299. 778 779
50. Pettersson, E., et al., *Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls.* Psychol Med, 2019. **49**(7): p. 1166-1173. 780 781
51. Monge, G., *Memoire sur la theorie des deblais et des remblais.*, in *Histoire de l' Academie Royale des Science; avec les Memoires de Mathematique et de Physique;* . 1781, De L'imprimerie Royale: Paris, France. 782 783

52. Rubner, Y., C. Tomasi, and L.J. Guibas. *Metric for Distributions with Applications to Image Databases.* in *Proceedings of the ICCV*. 1998. Bombay, India. 784 785
53. Stolfi, J. and L.J. Guibas, *The earth mover's distance as a metric for image retrieval.* . Int. J. Comput. Vis., 2000. **40**: p. 99-121. 786
54. Hoover, D.W. and J. Kaufman, *Adverse childhood experiences in children with autism spectrum disorder.* Curr Opin Psychiatry, 2018. **31**(2): p. 128-132. 787 788
55. Stack, A. and J. Lucyshyn, *Autism Spectrum Disorder and the Experience of Traumatic Events: Review of the Current Literature to Inform Modifications to a Treatment Model for Children with Autism.* J Autism Dev Disord, 2019. **49**(4): p. 1613-1625. 789 790
56. Blaxill, M., T. Rogers, and C. Nevison, *Autism Tsunami: the Impact of Rising Prevalence on the Societal Cost of Autism in the United States.* J Autism Dev Disord, 2021. 791 792
57. Bradbury, K.R., et al., *Co-occurring Down Syndrome and Autism Spectrum Disorder: Cognitive, Adaptive, and Behavioral Characteristics.* J Autism Dev Disord, 2021. 793 794
58. Salcedo-Arellano, M.J., et al., *Overlapping Molecular Pathways Leading to Autism Spectrum Disorders, Fragile X Syndrome, and Targeted Treatments.* Neurotherapeutics, 2021. **18**(1): p. 265-283. 795 796
59. Torres, E.B., et al. *Dynamic Interrogation of Stochastic Transcriptome Trajectories (DIST2)*. in *Information Theory and Applications Workshop (ITA), 2020*. 2020. San Diego, CA: IEEE. 797 798
60. Swanberg, S.E., et al., *Reciprocal co-regulation of EGR2 and MECP2 is disrupted in Rett syndrome and autism.* Hum Mol Genet, 2009. **18**(3): p. 525-34. 799 800
61. Platt, R.J., et al., *Chd8 Mutation Leads to Autistic-like Behaviors and Impaired Striatal Circuits.* Cell Rep, 2017. **19**(2): p. 335-350. 801
62. Talkowski, M.E., et al., *Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries.* Cell, 2012. **149**(3): p. 525-37. 802 803
63. Mondal, K., et al., *Excess variants in AFF2 detected by massively parallel sequencing of males with autism spectrum disorder.* Hum Mol Genet, 2012. **21**(19): p. 4356-64. 804 805
64. Hiatt, S.M., et al., *Deleterious Variation in BRSK2 Associates with a Neurodevelopmental Disorder.* Am J Hum Genet, 2019. **104**(4): p. 701-708. 806 807
65. Tamura, S., et al., *Foxp1 gene expression in projection neurons of the mouse striatum.* Neuroscience, 2004. **124**(2): p. 261-7. 808
66. Hisaoka, T., et al., *The forkhead transcription factors, Foxp1 and Foxp2, identify different subpopulations of projection neurons in the mouse cerebral cortex.* Neuroscience, 2010. **166**(2): p. 551-63. 809 810
67. Precious, S.V., et al., *FoxP1 marks medium spiny neurons from precursors to maturity and is required for their differentiation.* Exp Neurol, 2016. **282**: p. 9-18. 811 812
68. Peng, J., Y. Zhou, and K. Wang, *Multiplex gene and phenotype network to characterize shared genetic pathways of epilepsy and autism.* Sci Rep, 2021. **11**(1): p. 952. 813 814
69. Liao, X. and Y. Li, *Genetic associations between voltage-gated calcium channels and autism spectrum disorder: a systematic review.* Mol Brain, 2020. **13**(1): p. 96. 815 816
70. Yoshino, Y., B. Roy, and Y. Dwivedi, *Altered miRNA landscape of the anterior cingulate cortex is associated with potential loss of key neuronal functions in depressed brain.* Eur Neuropsychopharmacol, 2020. **40**: p. 70-84. 817 818
71. Bottema-Beutel, K., et al., *Adverse event reporting in intervention research for young autistic children.* Autism, 2021. **25**(2): p. 322-335. 819 820
72. Thompson-Hodgetts, S., et al., *Helpful or harmful? A scoping review of perceptions and outcomes of autism diagnostic disclosure to others.* Research in Autism Spectrum Disorders, 2020. **77**: p. 101598. 821 822
73. Chen, Y.Y., Y.L. Chen, and S.S. Gau, *Suicidality in Children with Elevated Autistic Traits.* Autism Res, 2020. **13**(10): p. 1811-1821. 823 824

74. Costa, A.P., C. Loor, and G. Steffgen, *Suicidality in Adults with Autism Spectrum Disorder: The Role of Depressive Symptomatology, Alexithymia, and Antidepressants.* J Autism Dev Disord, 2020. **50**(10): p. 3585-3597.
75. Hand, B.N., T.W. Benevides, and H.J. Carretta, *Suicidal Ideation and Self-inflicted Injury in Medicare Enrolled Autistic Adults With and Without Co-occurring Intellectual Disability.* J Autism Dev Disord, 2020. **50**(10): p. 3489-3495.
76. Broderick, A.A. and R. Roscigno, *Autism, Inc.: The Autism Industrial Complex.* Journal of Disability Studies in Education, 2021: p. 1-25.
77. Bottema-Beutel, K., et al., *Research Review: Conflicts of Interest (COIs) in autism early intervention research - a meta-analysis of COI influences on intervention effects.* J Child Psychol Psychiatry, 2021. **62**(1): p. 5-15.
78. Dawson, M. and S. Fletcher-Watson, *Commentary: What conflicts of interest tell us about autism intervention research-a commentary on Bottema-Beutel et al. (2020).* J Child Psychol Psychiatry, 2021. **62**(1): p. 16-18.
79. Torres, E.B., *Objective biometric methods for the diagnosis and treatment of nervous system disorders*. 2018, London: Academic Press. x, 568 pages.
80. Sandbank, M., et al., *Project AIM: Autism intervention meta-analysis for studies of young children.* Psychol Bull, 2020. **146**(1): p. 1-29.
81. Carroll, L., et al., *Autism Spectrum Disorders: Multiple Routes to, and Multiple Consequences of, Abnormal Synaptic Function and Connectivity.* Neuroscientist, 2021. **27**(1): p. 10-29.

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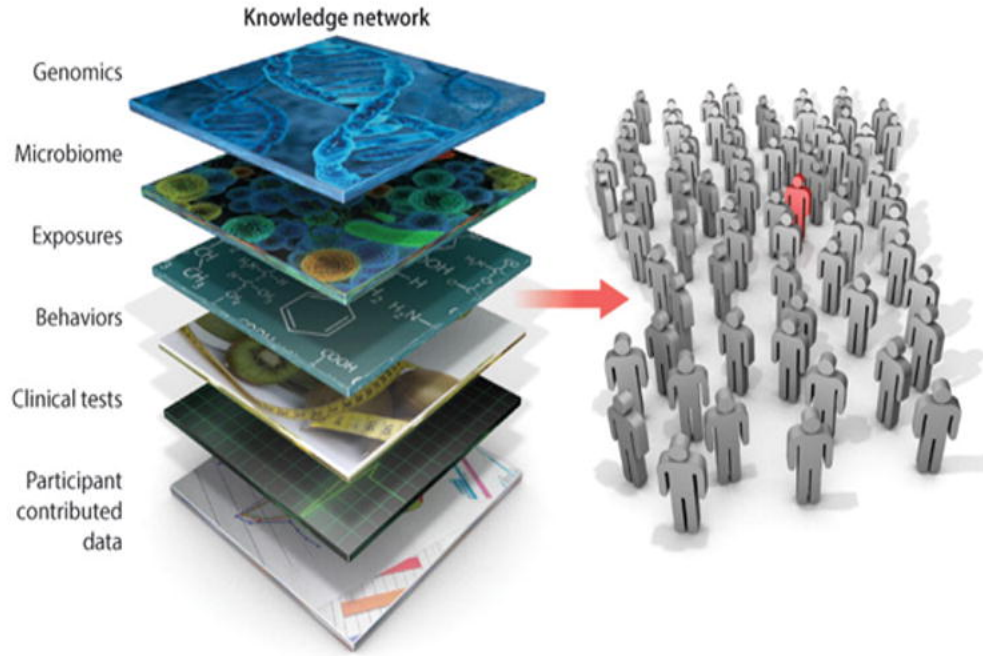

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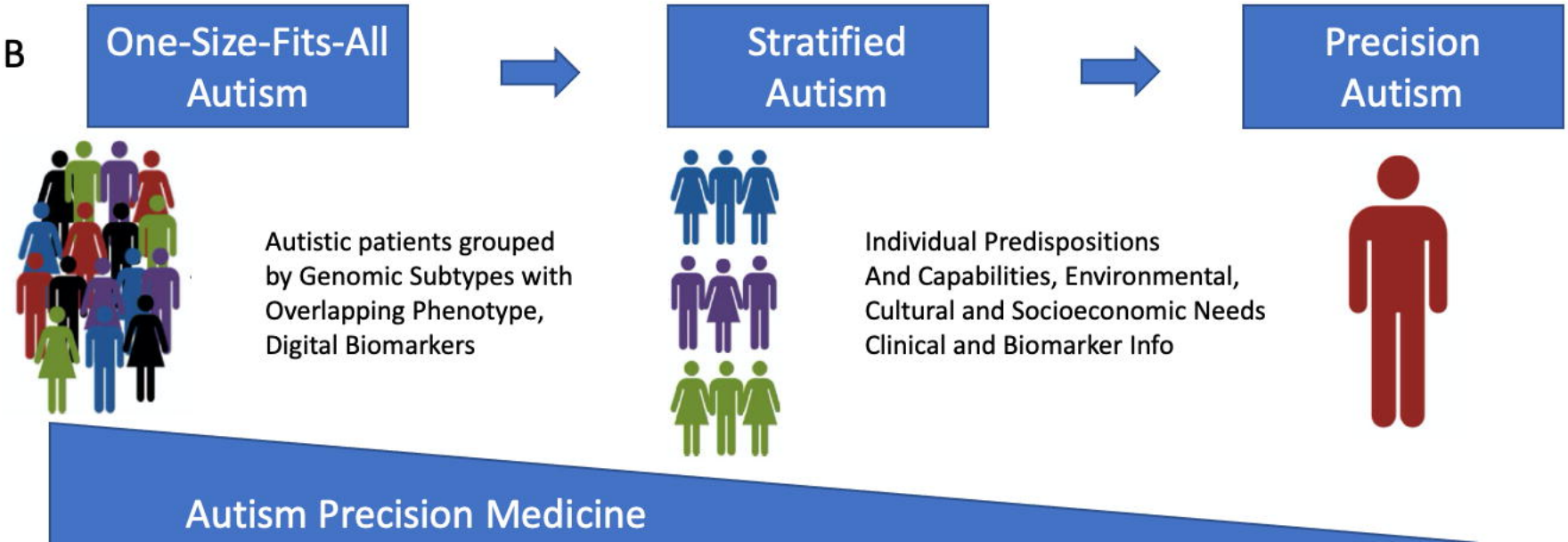

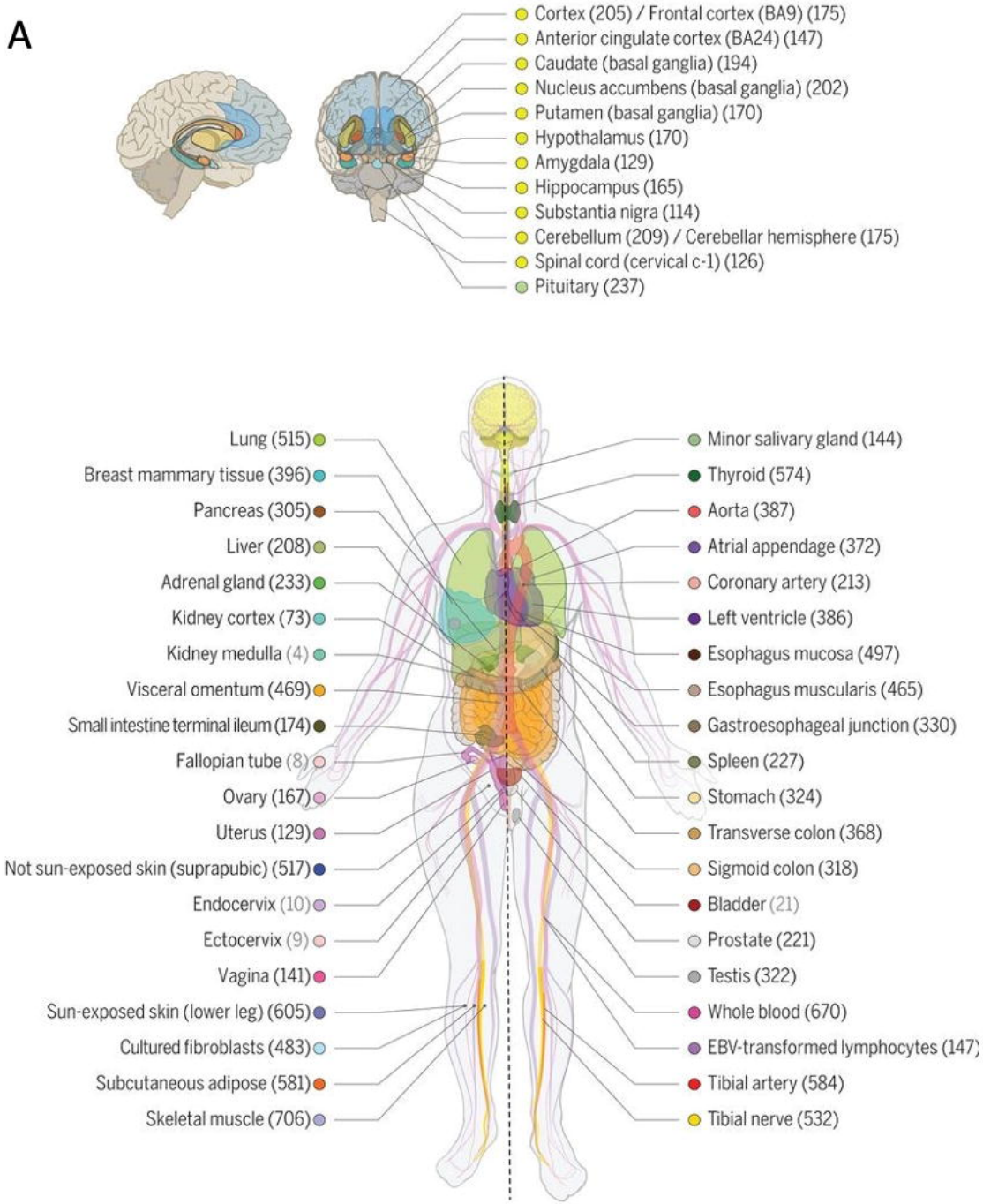
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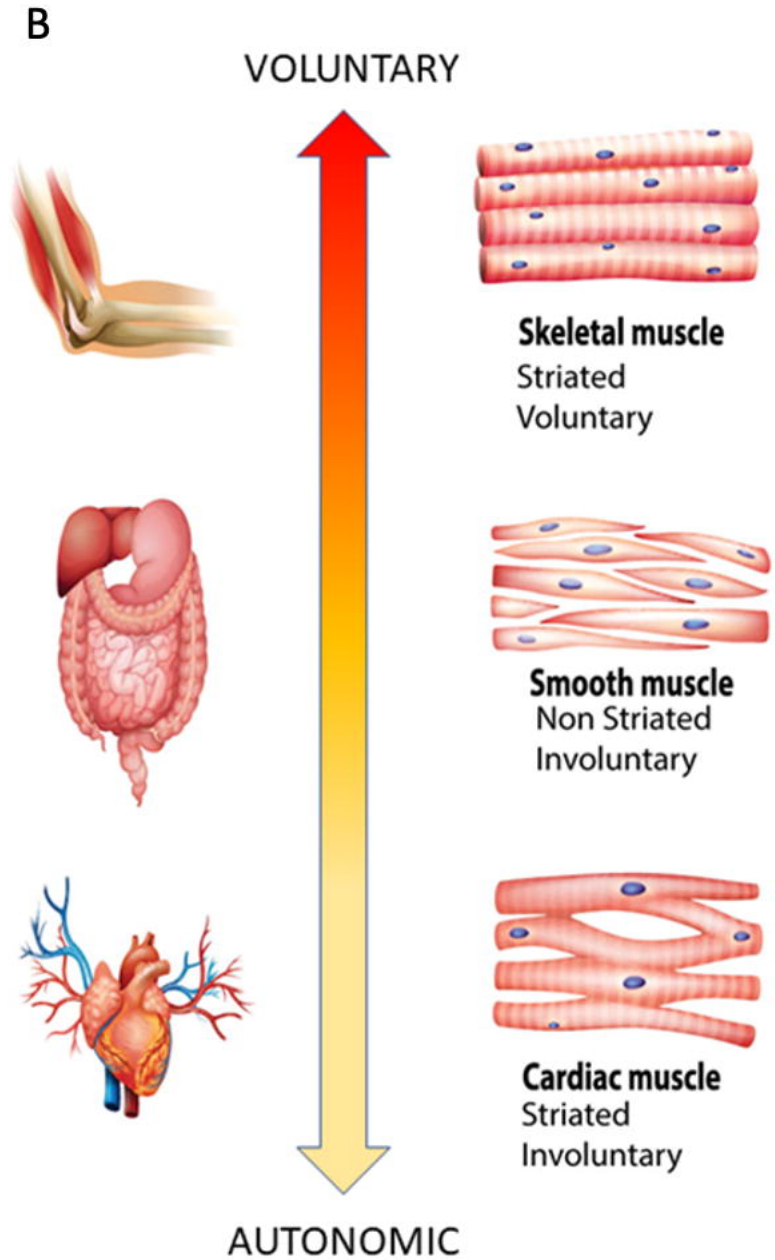
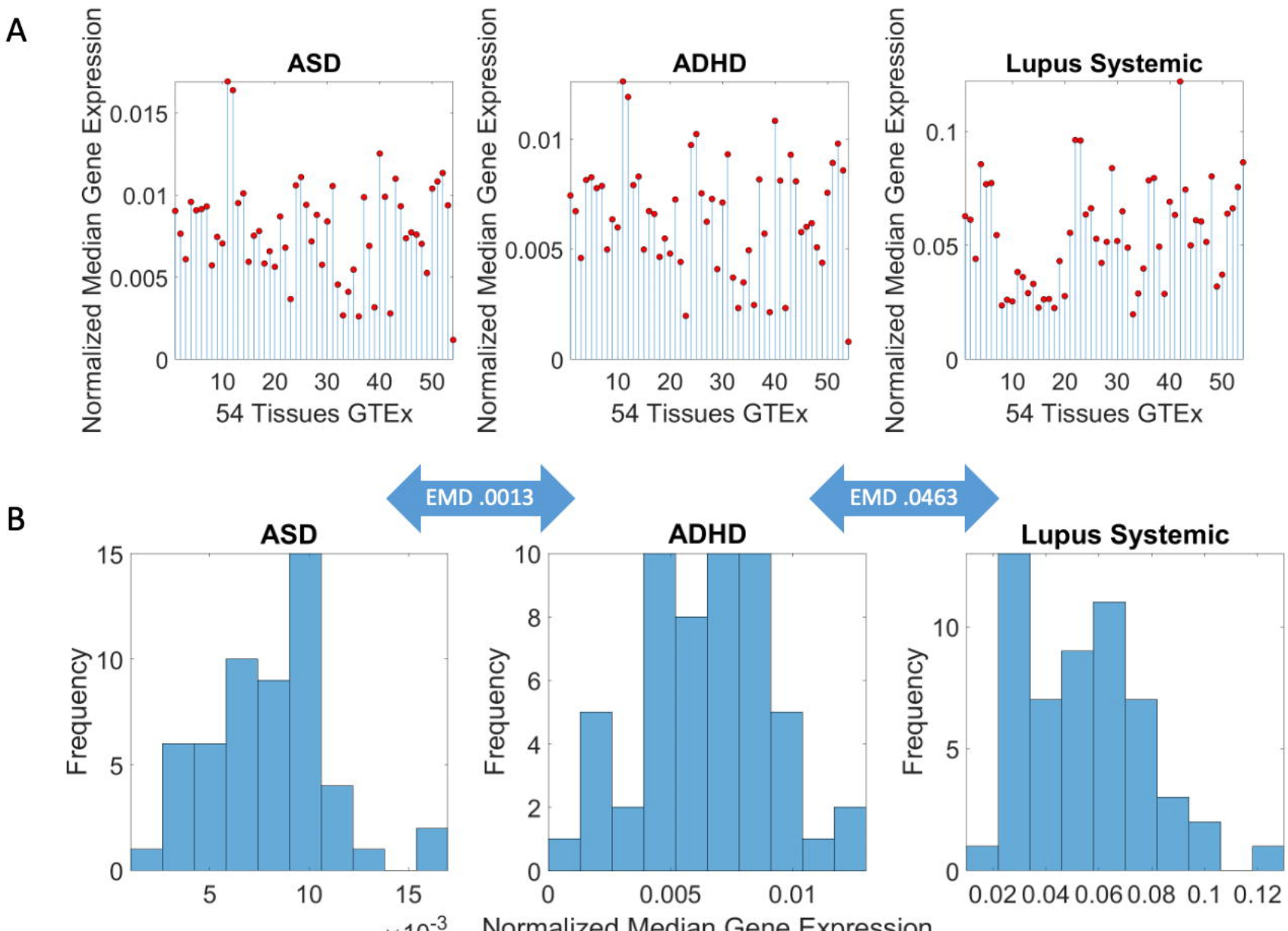
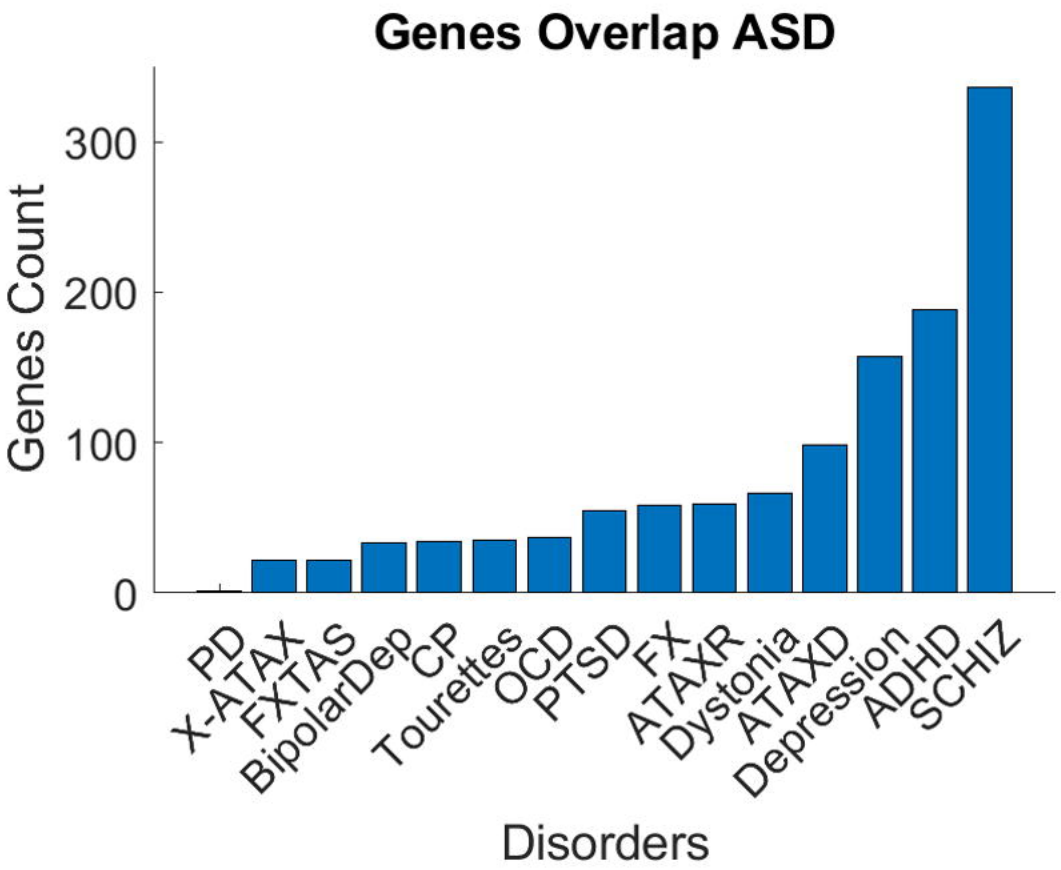
Cortex (205) / Frontal cortex (BA9) (175)
Anterior cingulate cortex (BA24) (147)
Caudate (basal ganglia) (194)
Nucleus accumbens (basal ganglia) (202)
Putamen (basal ganglia) (170)
Hypothalamus (170)
Amygdala (129)
Hippocampus (165)
Substantia nigra (114)
Cerebellum (209) / Cerebellar hemisphere (175)
Spinal cord (cervical c-1) (126)
Pituitary (237)
Lung (515)
Breast mammary tissue (396)
Pancreas (305)
Liver (208)
Adrenal gland (233)
Kidney cortex (73)
Kidney medulla (4)
Visceral omentum (469)
Small intestine terminal ileum (174)
Fallopian tube (8)
Ovary (167)
Uterus (129)
Not sun-exposed skin (suprapubic) (517)
Endocervix (10)
Ectocervix (9)
Vagina (141)
Sun-exposed skin (lower leg) (605)
Cultured fibroblasts (483)
Subcutaneous adipose (581)
Skeletal muscle (706)
Minor salivary gland (144)
Thyroid (574)
Aorta (387)
Atrial appendage (372)
Coronary artery (213)
Left ventricle (386)
Esophagus mucosa (497)
Esophagus muscularis (465)
Gastroesophageal junction (330)
Spleen (227)
Stomach (324)
Transverse colon (368)
Sigmoid colon (318)
Bladder (21)
Prostate (221)
Testis (322)
Whole blood (670)
EBV-transformed lymphocytes (147)
Tibial artery (584)
Tibial nerve (532)

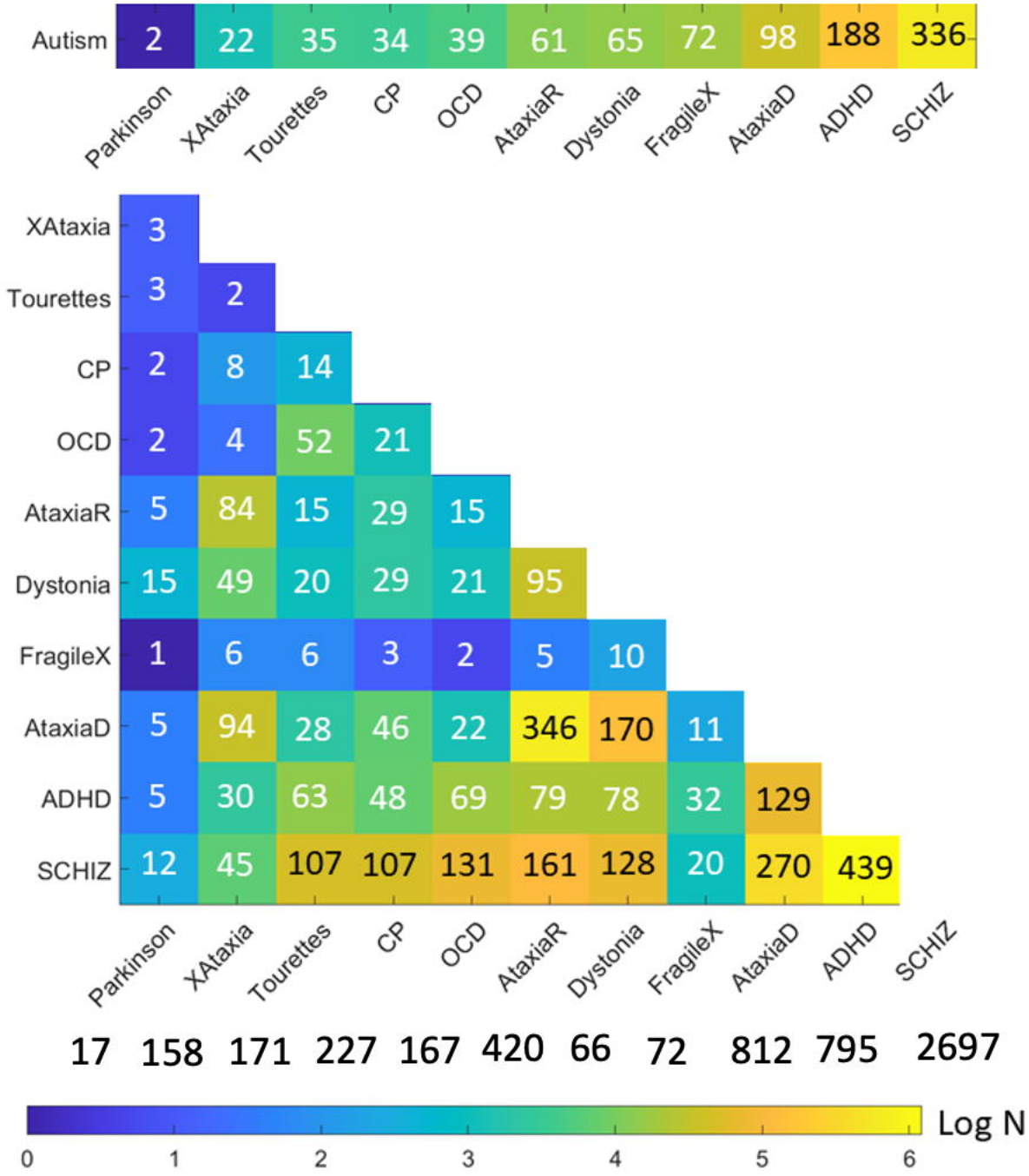

B
VOLUNTARY
Skeletal muscle
Striated
Voluntary
Smooth muscle
Non Striated
Involuntary
Cardiac muscle
Striated
Involuntary
AUTONOMIC


A
ASD
ADHD
Lupus Systemic
Normalized Median Gene Expression
54 Tissues GTEx
EMD .0013
EMD .0463
B
Frequency
Normalized Median Gene Expression
×10^-3

A


Genes Overlap ASD
Genes Count
300
200
100
0
PD
X-ATAX
FXTAS
BipolarDep
CP
Tourettes
OCD
PTSD
FX
ATAXR
Dystonia
ATAXD
Depression
ADHD
SCHIZ
Disorders

B


Autism 2 22 35 34 39 61 65 72 98 188 336
Parkinson XAtaxia Tourettes CP OCD AtaxiaR Dystonia FragileX AtaxiaD ADHD SCHIZ
XAtaxia 3
Tourettes 3 2
CP 2 8 14
OCD 2 4 52 21
AtaxiaR 5 84 15 29 15
Dystonia 15 49 20 29 21 95
FragileX 1 6 6 3 2 5 10
AtaxiaD 5 94 28 46 22 346 170 11
ADHD 5 30 63 48 69 79 78 32 129
SCHIZ 12 45 107 107 131 161 128 20 270 439
Parkinson XAtaxia Tourettes CP OCD AtaxiaR Dystonia FragileX AtaxiaD ADHD SCHIZ
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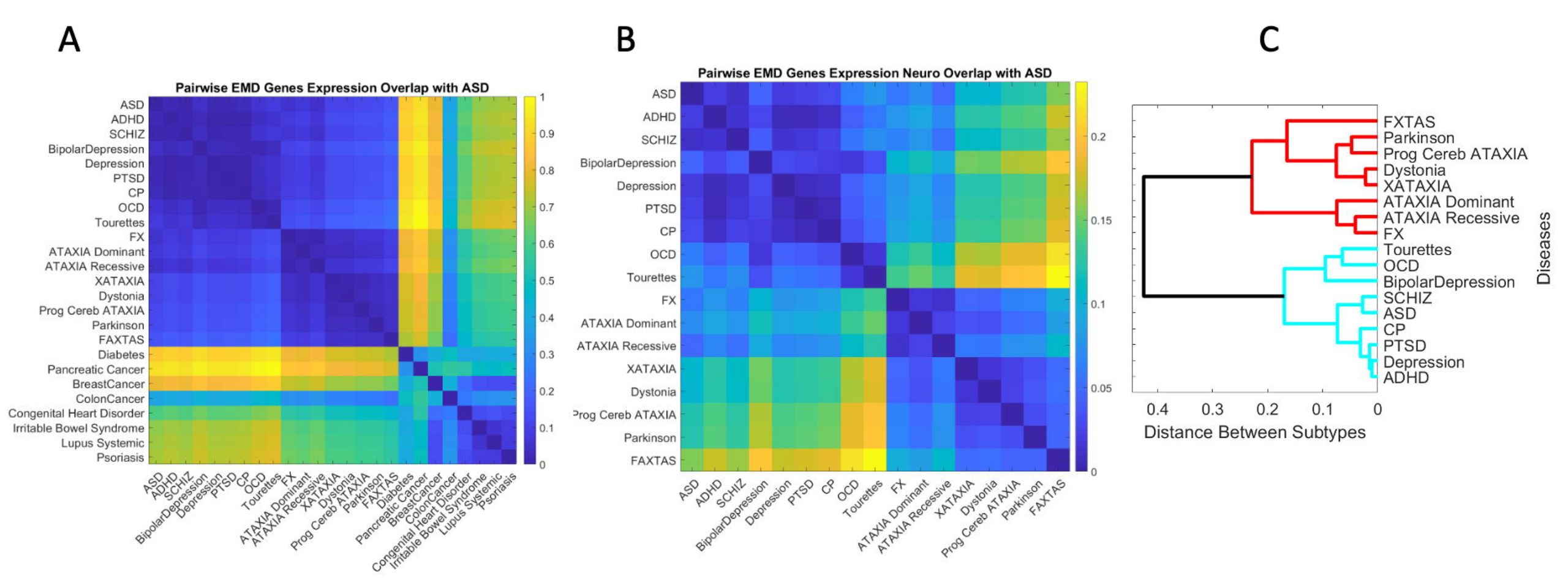
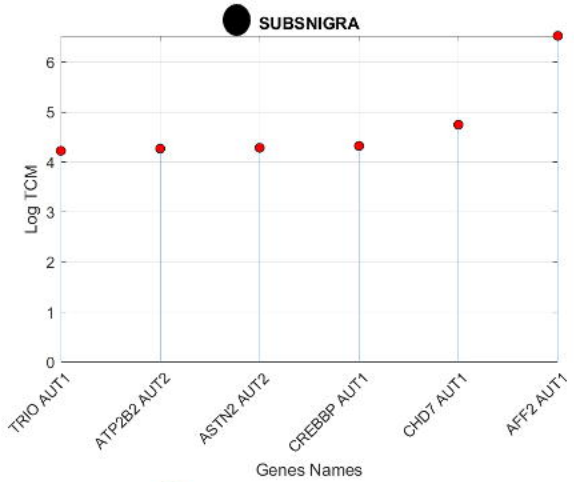

A
Pairwise EMD Genes Expression Overlap with ASD
ASD
ADHD
SCHIZ
BipolarDepression
Depression
PTSD
CP
OCD
Tourettes
FX
ATAXIA Dominant
ATAXIA Recessive
XATAXIA
Dystonia
Prog Cereb ATAXIA
Parkinson
FAXTAS
Diabetes
Pancreatic Cancer
BreastCancer
ColonCancer
Congenital Heart Disorder
Irritable Bowel Syndrome
Lupus Systemic
Psoriasis
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
B
Pairwise EMD Genes Expression Neuro Overlap with ASD
0.2
0.15
0.1
0.05
0
C
FXTAS
Parkinson
Prog Cereb ATAXIA
Dystonia
XATAXIA
ATAXIA Dominant
ATAXIA Recessive
FX
Tourettes
OCD
BipolarDepression
SCHIZ
ASD
CP
PTSD
Depression
ADHD
Diseases
0.4
0.3
0.2
0.1
0
Distance Between Subtypes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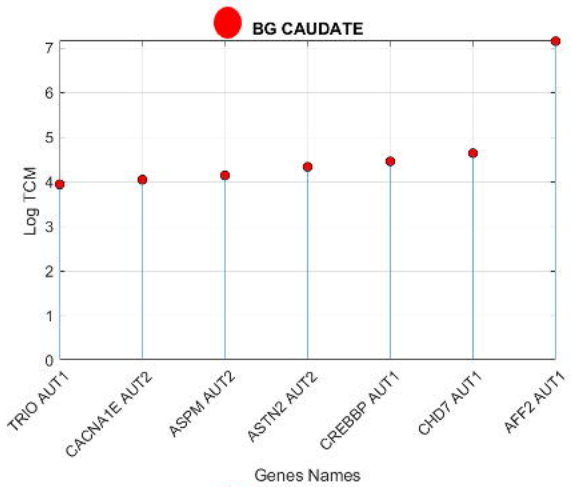
CREBBP AUT1
CHD7 AUT1
AFF2 AUT1
Genes Names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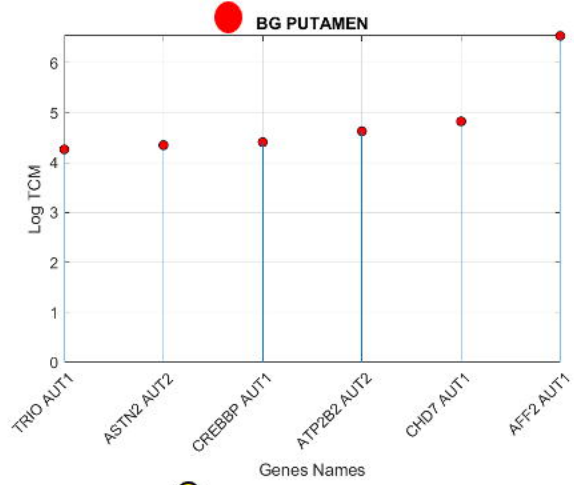
Genes Names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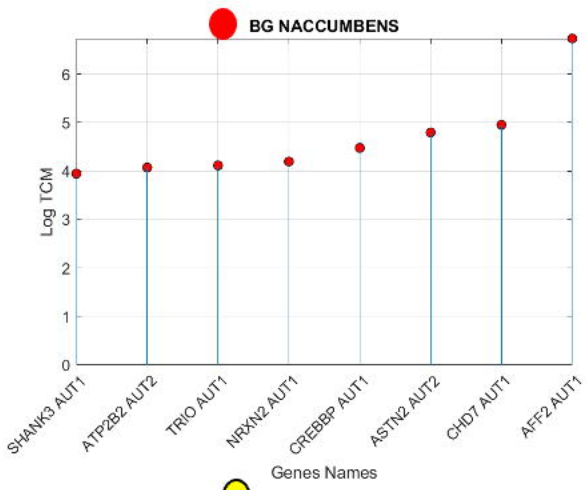
Genes Names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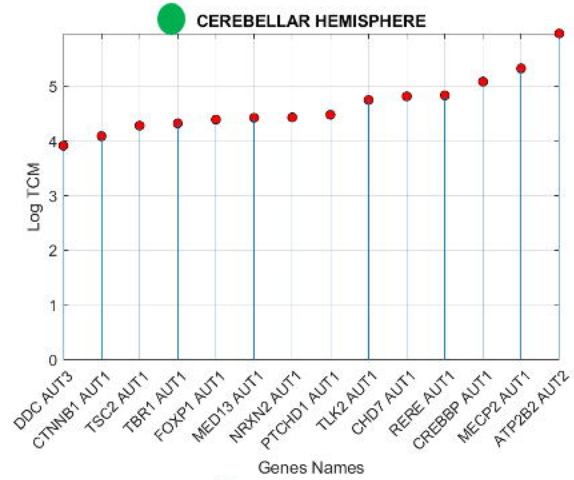
Genes Names


CEREBELLAR HEMISPHERE
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TBR1 AUT1
FOXP1 AUT1
MED13 AUT1
NRXN2 AUT1
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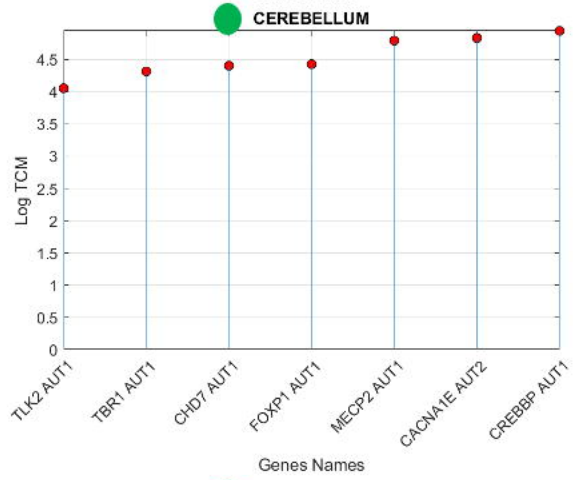
MECP2 AUT1
ATP2B2 AUT2
Genes Names


CEREBELLUM
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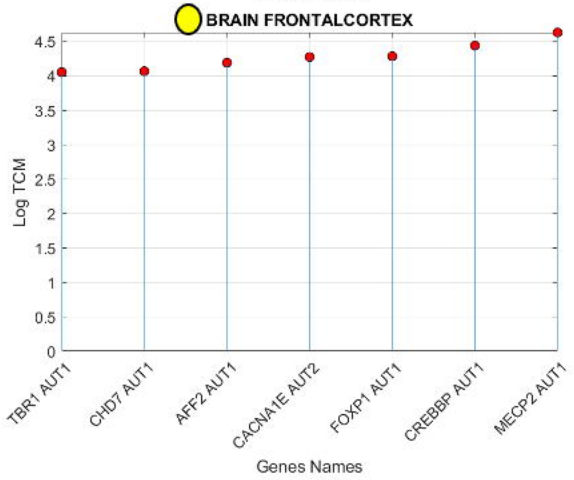
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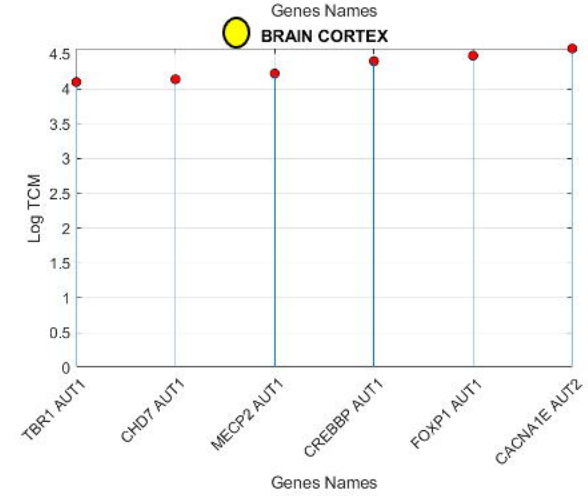
Genes Names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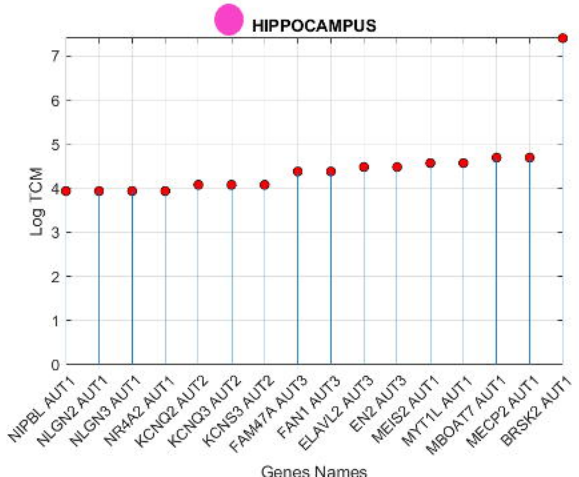
Genes Names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KCNQ3 AUT2
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FAM47A AUT3
FAN1 AUT3
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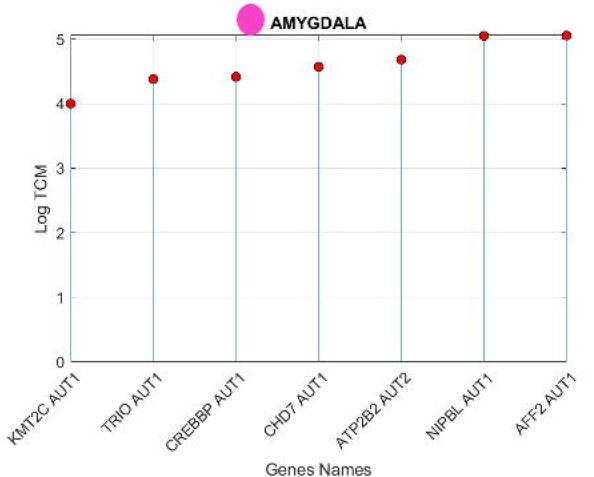
Genes Names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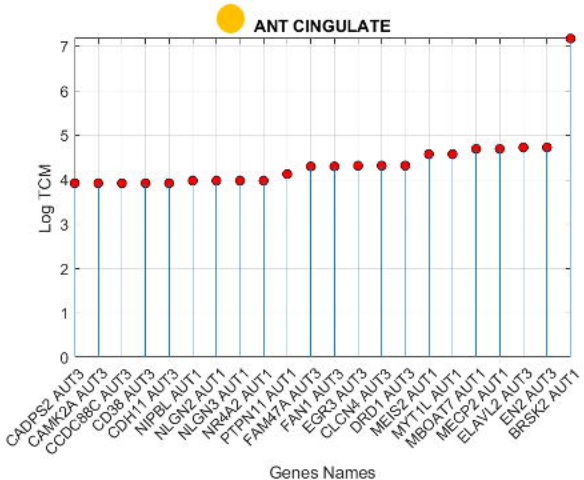
ANT CINGULATE
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CAMK2A AUT3
CCDC88C AUT3
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NLGN3 AUT1
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PTPN11 AUT1
FAM47A AUT3
FAN1 AUT3
EGR3 AUT3
CLCN4 AUT3
DRD1 AUT3
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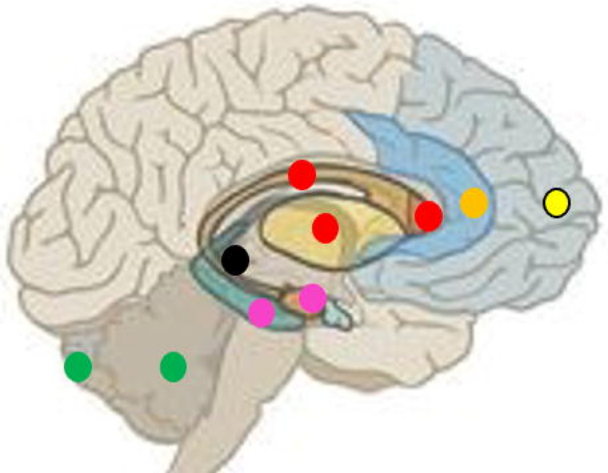
Genes Names



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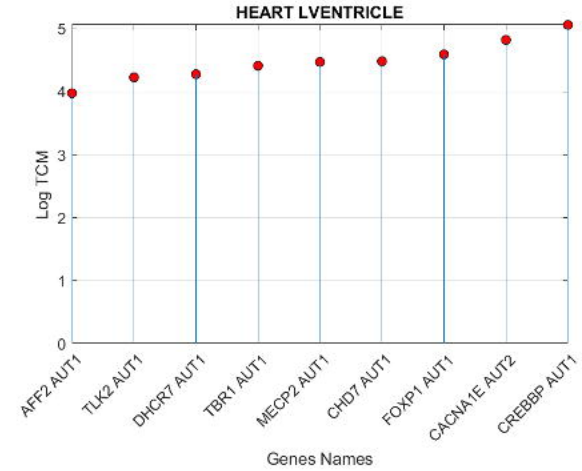
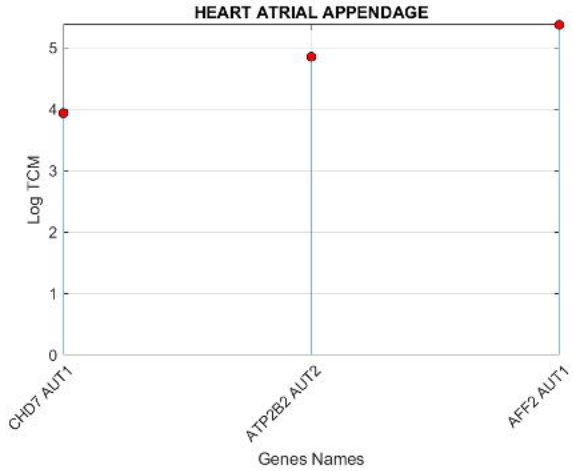
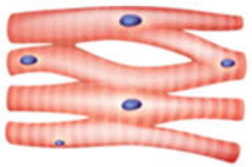
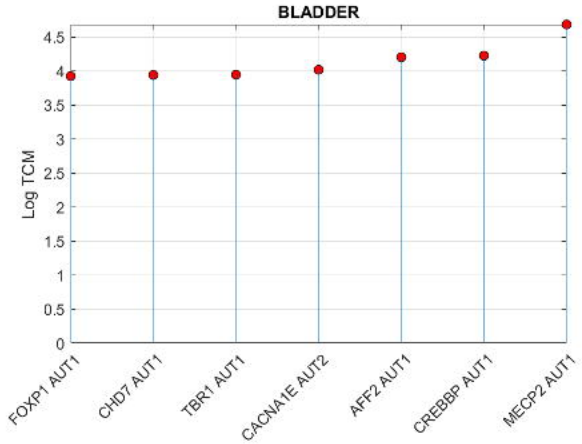
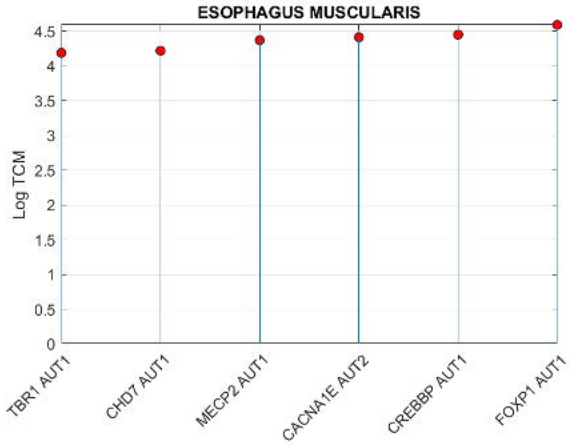


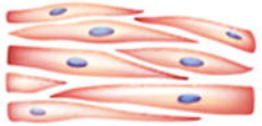




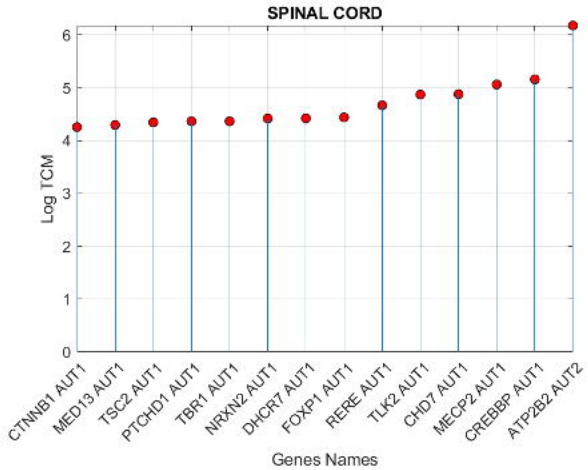
Cardiac muscle
Striated
Involuntary

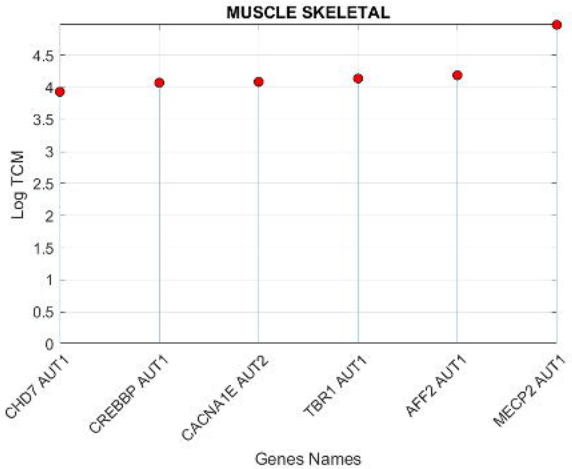


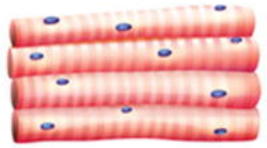




Smooth muscle
Non Striated
Involuntary

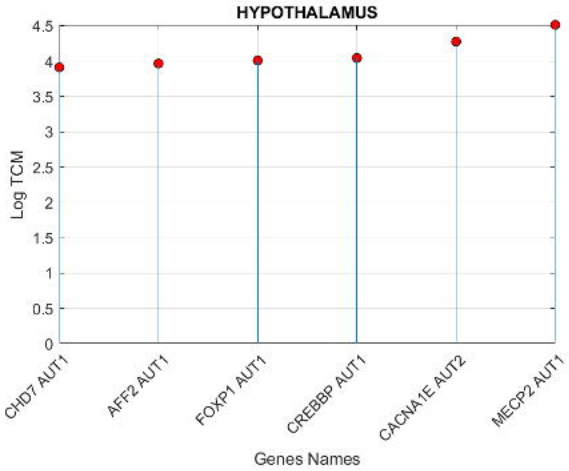


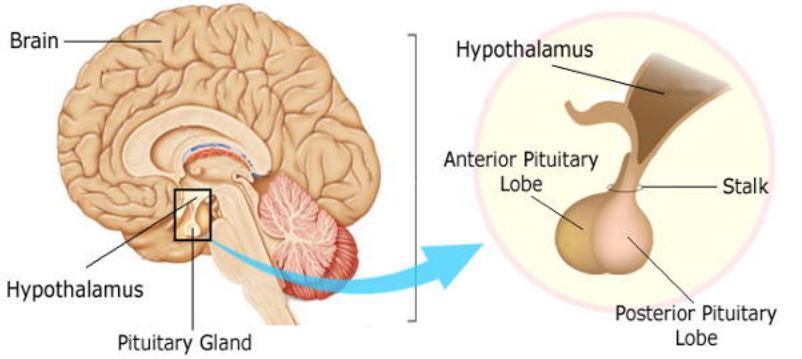
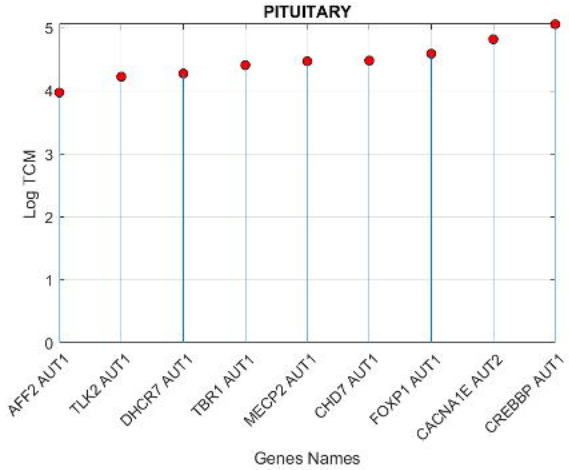




Skeletal muscle
Striated
Voluntary

B

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