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The Use of Machine Learning and Phonetic Endophenotypes to Discover Genetic Variants Associated with Speech Sound Disorder

Jason Lilley, Erin Crowgey, and H. Timothy Bunnell

Nemours Biomedical Research, Wilmington, DE, USA
jason.lilley@nemours.org, erin.crowgey@nemours.org, tim.bunnell@nemours.org

Abstract

Thirty-four (34) children with reported speech sound disorders (SSD) were recruited for a prior study, as well as 31 of their siblings, many of whom also showed SSD. Using data-clustering techniques, we assigned each child to one or more endophenotypes defined by the number and type of speech errors made on the GFTA-2. The genetic samples of 53 of the participants underwent whole exome sequencing. Variant alleles were detected, filtered, and annotated from the sequences, and the data were filtered using quality checks, annotations, and phenotypes. We then used Random Forest classification to search for associations between variants and endophenotypes. In this preliminary report, we highlight one promising association with a common variant of COMT, a dopamine metabolizer in the brain.

Index Terms: speech acquisition, speech delay, speech sound disorder, endophenotypes, whole exome sequencing, random forest, catechol-O-methyltransferase, COMT

1. Introduction

Speech sound disorder (SSD) is characterized by a difficulty with producing the sounds of one's native language in comparison to one's age-matched peers [1-3]. SSD in young children is a very common problem, at rates estimated between 4% and 16% depending on age [1, 3-6]. There are high rates of co-occurring problems with language, reading, learning, and social interactions, so intervention is needed for most [7, 8]. While most cases are resolved within a few years, others persist, and some may be early markers of more serious or specific syndromes such as dyslexia or specific language impairment [6, 9].

Twin and family studies have indicated that SSD has a strong genetic component (see [1] for review), but to date few studies have examined the genetic basis of SSD in particular, as opposed to related language conditions like dyslexia and childhood apraxia of speech (CAS) [2, 10], particularly using next-generation sequencing data. A common strategy of SSD studies has been to target genes and loci previously linked to other language disorders [2]. As an example, studies linking neurochemical signaling genes to vocabulary and grammar skills [11, 12], language impairment, and reading disorders [13] led to other studies of these genes in relation to SSD [14, 15]. They found associations with several genes, particularly DRD2, which encodes a dopamine receptor.

Technological advances in next-generation sequencing have made whole exome sequencing (WES) of large numbers of study participants feasible and affordable only recently. For example, [16] purports to be the first WES study of CAS. One problem is determining how to locate promising genes out of hundreds of thousands of alternatives provided by WES. Machine learning techniques such as Random Forests [17] are often used for genetic data [18], but it is still necessary to pre-filter the data, which may exclude genes of interest.

The approach taken in this study attempts to alleviate that problem through the use of multiple, distinct measures of affectedness. We first examine the distinct patterns of behaviors in our study populations and use them to define subpopulations, based on the distinct phonemes that they show difficulty with. We then use random forests on WES data to look for associations of genes with each subpopulation. The pre-filtering of variants is tuned to the particular measure, allowing multiple chances to find an associated variant. This also makes it unnecessary to adopt a single arbitrary definition for what is believed to be a heterogeneous disorder [1].

The underlying hypothesis is that distinct genotypes may underlie distinct manifestations of SSD associated with different phonetic classes. This is similar to the common concept of an *endophenotype* [19, 20], an objectively defined, measurable behavior used as a proxy for one or multiple cognitive phenotypes. Endophenotype measures are often used in speech studies, such as nonword repetition [21], phonological awareness tests [15], and the test used in our study, the Goldman-Fristoe Test of Articulation ([22], used in e.g. [1, 15]). Here we extend the concept a bit to the use of phonetic classes as distinct measures.

2. Data

This is a retrospective study, using data and genetic samples collected in a prior grant and reported previously (e.g., [23, 24]).

2.1. Participants

Sibling pairs (and one triplet) from 34 families were recruited for the original study, with the principal requirement being that at least one sibling must have been diagnosed with SSD. Four participants were later dropped due to unusable audio recordings, bringing the total to 65. Participant ages ranged from 5;1 to 10;1.

Saliva samples were taken from each participant for the purpose of DNA sequencing. The samples were stored at a temperature of about -80° until the time of sequencing.

2.2. Procedure

The second edition of the Goldman-Fristoe Test of Articulation (GFTA) is described as "a systematic means of assessing an individual's articulation of the consonant sounds of Standard American English" [22, pg. 1]. The Sound-in-Words portion of the GFTA involves the elicitation of 53 common words, out of which 77 target sounds (single consonants or clusters) are scored as correct or incorrect.

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Although it was not developed as a measure of SSD in particular, the test produces a Standard Score that is normalized per the child's age and gender. This score can thus serve as a useful initial estimate of the child's degree of SSD.

An experienced speech-language pathologist administered the GFTA to each participant, whose responses were recorded. The target sounds were each scored independently by two judges, who subsequently discussed the sounds they disagreed on until consensus was reached. The Raw Scores (total errors) were converted to Standard Scores and to percentile ranks (the percent of peers who made more errors) using the conversion tables published with the test, indexed by age and gender.

3. Analysis

3.1. DNA sequencing, annotation and filtration

For the present study, which began more than 10 years after the saliva samples were collected, we began by running concentration and quality checks on the samples. We determined that the samples of 53 of the participants were of sufficient concentration and quality for WES. DNA was extracted and exons were captured using Whole Exome Agilent SureSelect XT V5. Libraries were sequenced via Illumina HiSeq by Children's Hospital of Philadelphia. Fastq files are analyzed by fastqc, and further processed following GATK's Best Practices (bwa, picard, samtools[25-27]). Variant mutations were detected with Haplotyper [28], and annotated via ClinEff. After filtering for quality, this procedure produced a final list of 163,655 variants with associated genotypes.

3.2. Clustering of target sound error data

The scores of all 65 participants on the 77 GFTA-2 target sounds were used as the basis for defining phonetic endophenotypes as follows. The 65-by-77 matrix of error judgments (coded as "0" for correct and "1" for incorrect) was used to calculate a distance between each pair of target sounds, using an asymmetric binary distance metric. These distances were then used to cluster the GFTA targets and visualize the relationships among the common error types.

Figure 1 is one visualization of the distances, as computed by t-SNE [29]. As evident in the figure, the errors tend to cluster around particular phonemes and manner classes. In contrast, what we do not see much is clustering based on voicing, place of articulation, or position within the word, for example.

In particular, five groups of sounds stand out in Figure 1 (circled): 1) rhotic /r/ sounds (in both singletons and consonant clusters), 2) lateral /l/ sounds (particularly in clusters, but the singleton tokens are also plotted nearby), 3) alveolar fricatives /s, z/ (including clusters), 4) the interdental fricatives /θ, ð/, and 5) a larger cluster in the middle consisting of the remaining fricatives /ʃ, v/ as well as the affricates /ʧ, ʤ/. This last cluster is admittedly more diffuse and less homogenous, but clearly forms its own cluster, distinct from the other two groups of fricatives, as was confirmed by follow-up analyses involving only the set of fricatives and affricates.

A sixth cluster, consisting of only nasal sounds, is also visible in Figure 1, but this cluster is based on the errors of a single participant, the only one who had multiple nasal errors. Similarly, the participants had very few errors on singleton stop sounds, and so these sounds form several small clusters based on the idiosyncratic patterns of the few individuals who made those errors, rather than a single large cluster.

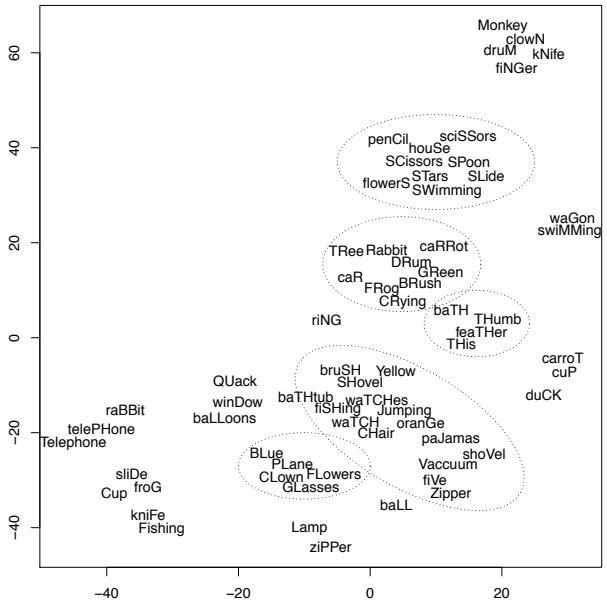

Figure 1: *Two-dimensional t-SNE visualization of relative error distances among GFTA targets (slightly adjusted to remove overlap). The particular target sound (or cluster) in each word is indicated by capital letters in conventional English spelling.*

3.3. Endophenotype class definitions and memberships

Based on these phonetic clusters, we defined five endophenotypes and classified each of the 53 participants whose DNA was sequenced as either having each phenotype or not. A participant was classified as having the phenotype if either (1) the number of errors of that type reached a threshold, or (2) a threshold fraction of all errors were of that type. This latter condition was added so as to include older participants who made relatively few errors but were still considered affected. The particular thresholds for inclusion differed among endophenotypes, and were determined by modeling the errors as bimodal distributions.

Table 1: *Number of DNA-sequenced participants in each class, based on errors on particular phones (listed) or on overall score.*

Class Name	Segments	# (out of 53)
Rhotic	/r/	25
Lateral	/l/	12
Alveolar	/s, z/	26
Interdental	/θ, ð/	19
OtherFric	/f, v, ʃ, ʧ, ʤ/	10
Overall	all	32

The definitions and number of members of each endophenotype are summarized in Table 1. Note that the memberships are not mutually exclusive. In addition, we defined an Overall class, based on total GFTA scores. Participants were classified as members of this class if their

Table 2: *Promising genetic variants linked to each endophenotype. MDA: Mean decrease in accuracy calculated by the RF algorithm after random permutation (see text). Rank: rank of variant on list when ordered by MDA.*

Class	MDA	Rank	rs#	Chr	Gene	Variant Type	Notes on gene/protein
Rhotic	.000501	7	11592585	10	JAKMIP3	missense	possible link to Alzheimer's
Alveolar	.000576	11	3751335	13	MTUS2	intron	linked to nervous system development
Interdental	.000932	3	71389065	16	TEKT5	in-frame insertion	high expression in fetal brain
Lateral	.000403	12	215976	12	CACNA1C	missense	linked to bipolar disorder
OtherFric	**.001683**	**1**	**4680**	**22**	**COMT**	**missense**	**neurotransmitter metabolizer**
Overall	.000939	1	778593	5	NDUFA2	5'-UTR region	associated with Leigh Syndrome

Standard Score was lower than 85 (one standard deviation) or lower than the 10th percentile for their age and gender.

3.4. Random Forests

Having assigned the participants into various classes, the next step is to find sets of genetic variants that are successful in predicting class memberships. To do this, we used the method of Random Forests (RF) [17]. This is a supervised classification technique that consists of thousands of classification trees, each trained on random subsamples of training cases and features. A test case is classified as the majority classification among all trees. One crucial characteristic of Random Forests is that it can also calculate the "importance" of each feature to the success of the overall forest. This is calculated as the mean decrease in accuracy (MDA) of the forest when the input values of the feature are randomly permuted.

We built separate RF classifiers to predict the memberships of each of the classes in Table 1, using the variant genotypes as the predictive features. To select the input features for each forest, we first removed all variants for which any participant's genotype was undetermined, leaving 104,214 variants. Next, we calculated the accuracy with which each variant alone could be used to predict each class. Finally, a threshold accuracy was determined for each class, and the set of features that reached the threshold was selected. The threshold was set so that the number of features selected was as close to 1000 as possible (between 500 and 2000).

The RF classifier for each class was then grown on all 53 participants with 50,000 trees using the selected variants. Since class memberships were imbalanced to various degrees, we restricted the random sampling process to select 50% of samples from each of the two subclasses (members and non-members) [30]. The number of features tested per split was set to the square root of the total feature number. The MDA of each feature was calculated from each forest, producing for each class an ordered list of the most "important" features for classification. We then investigated the variants at the top of each list for their biological importance and possible relevance to speech development.

4. Results

Because the selection of genetic variants for study did not exclude any on the basis of biological function, the majority of the most "important" variants on the lists were ones that coincidentally co-segregate with the class of interest, but appear to be biologically irrelevant. In most cases, the variants were in genes whose product proteins had no apparent connection to speech development. In other cases, the variations were synonymous (encoding the same amino acid) or found in introns, the noncoding parts of genes which have uncertain biological function.

Table 2 lists some of the more promising variants found for each endophenotype class. These were selected because their containing genes have previously been linked to nervous system development, or neurological conditions like bipolar disorder, though the connection to speech may be tenuous.

One variant on the lists is particularly promising. The variant with the largest MDA for the classification of the "OtherFric" endophenotype was rs4680, a missense variant in a gene on chromosome 22q11 that encodes a protein called catechol-O-methyltransferase (COMT), which metabolizes catecholamine neurotransmitters in the brain such as dopamine, epinephrine, and norepinephrine. The variant rs4680 alternation changes an amino acid from valine (Val) to methionine (Met), causing up to a 4-fold difference in activity level [31]. Dozens of papers have been published investigating associations of this polymorphism with various conditions [32]. Numerous studies have linked the Met allele to psychiatric disorders such as OCD, panic disorder, and major depression [33-35]. On the other hand, many papers link the Val allele to lower levels of performance on various kinds of cognitive tasks [36-38].

4.1. Post-hoc investigation of COMT

Table 3 shows how the COMT polymorphism segregates with the "OtherFric" endophenotype. If one classifies ValVal homozygotes as members of this class and the others as nonmembers, then the variant predicts the endophenotype with 86.7% accuracy. A Fisher's Exact Test for a difference in proportions among the classes gives a highly significant *p*-value of 0.0002017. The ValVal genotype also predicts membership in the Interdental class with 69.8% accuracy (p=.041), but fails to predict membership in the Overall class (56.6%) or the other endophenotypes.

Table 3: *COMT genotype vs OtherFric classification*

Membership	ValVal	MetVal	MetMet
OtherFric+	7	1	2
OtherFric-	4	29	10

The participants in the OtherFric class tended to make errors of other types as well. Table 4 lists the mean number of errors made in various phonetic classes. The ValVal homozygotes had higher mean error counts in almost every class of segment, including the class of all fricatives. ANOVA tests, however, failed to find a significant difference in any class except OtherFric.

Nevertheless, given the different numbers of errors in almost all phonetic classes, one would expect COMT

genotype to be associated with overall GFTA scores (Table 4, bottom). ANOVA tests of the association of genotype with either Raw or Standard scores fails to find significance (p=.125 and p=.101, respectively). However, if the genotype is reduced to a binary distinction between ValVal homozygotes versus Met carriers, then the ANOVA test does find a significant difference in Standard scores (p=.0324), and almost so for Raw scores as well (p=.0506).

Table 4: *Mean errors and scores by genotype.*

measure	ValVal	MetVal	MetMet	ANOVA p
Rhotics	4.91	2.93	3.08	.322
Laterals	2.00	1.17	1.17	.544
Stops/Nasals	1.09	0.73	1.17	.677
AlveolarFrics	4.45	2.73	3.25	.450
Interdentals	2.36	0.93	1.33	.0564
OtherFrics	**4.73**	**1.23**	**2.25**	**.0298**
all fricatives	9.73	4.6	6.33	.0997
Raw score	18.1	9.0	11.6	.125
Standard score	78.7	91.3	89.9	.101

A closer examination of the data revealed an important confound with sex: all 11 ValVal participants happen to be male, while 16 of 30 MetVal and 4 of 12 MetMet participants are female. When the females are removed from the analysis, then ValVal homozygotes are found to be significantly worse than Met carriers for both Raw and Standard scores (p=.0365 and p=.0376).

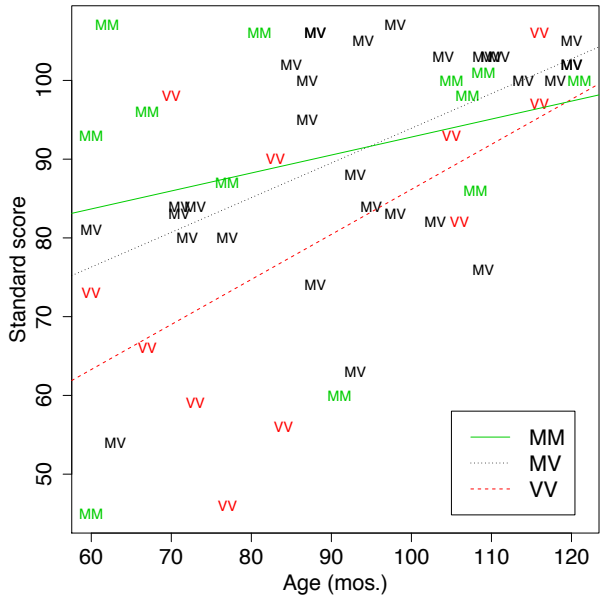

Figure 2: *Standard score versus age and COMT genotype, with regression lines for each genotype.*

There is also a substantial confound with age. As Figure 2 shows, the differences seen among genotypes from 5-7 years disappear at older ages, as most children show no signs of problems at 10 years old. Two-way ANOVAs including both age and genotype (VV versus Met carriers) find significant effects of both variables when predicting either Raw or Standard scores, although no significant interactions were found. The age effects are highly significant (p<0.001), while the effects of genotype are still marginally significant (Raw p=.0423 and Standard p=.0467). The genotype effect is stronger when the analysis is restricted to just males (Raw p=.0141 and Standard p=.0454).

5. Discussion

Although the cognitive effects of the COMT polymorphism have been extensively studied, to date there appear to be few studies of its association with language [39-41], or speech production in particular. Sugiura et al. [42] may be the first study to examine its effect on language development in young children. Using a standardized Japanese language exam, they found that young (ages 6-8) ValVal homozygotes performed significantly worse than Met carriers, but reach parity by age 10. Our data show the same trends and thus broadly support its conclusions. However, the Japanese test only measured general language ability (vocabulary, comprehension, writing) and did not include an articulation test. On the other hand, [11-15] found associations of neurochemical signaling genes – particularly DRD2, a dopamine receptor – with measures of SSD (including GFTA scores) and other language phenotypes, but their studies did not include COMT, a dopamine metabolizer. To our knowledge, this is the first study linking COMT polymorphism with speech sound development in particular.

Our results also support the approach of using endophenotypes defined by phonetic classes as an aid to discovering promising genetic variants. Although it is likely that COMT is linked to language development in general, and perhaps to overall performance on the GFTA – rather than on fricatives in particular – there was no association in our data between COMT genotype and general "affectedness" as defined by the Overall class. In fact, this variant was not included in the random forest for the Overall class because its accuracy with the Overall class (57%) did not meet the cutoff for inclusion (66%). Thus the link to COMT may not have been found without the examination of participant subpopulations. Note also that the variants were not pre-filtered for particular biological relevance, but rather included the whole exome. The fact that it nonetheless found a highly relevant gene may be taken as a promising sign of its effectiveness.

6. Conclusions

By breaking down the phenotype of SSD into endophenotypes based on phonetic sound classes, we were able to search WES data and successfully find a link to a gene that is likely to be relevant. In future work we will consider the possibility of defining endophenotypes based on still other types of data, such as acoustic measurements.

7. Acknowledgements

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8. References

[1] B.A. Lewis, L.D. Shriberg, L.A. Freebairn, et al., "The genetic basis of speech sound disorders: evidence from spoken and written language. *Journal of Speech, Language, and Hearing Research,* vol. 49, pp. 1294–1312, 2006.

[2] D.F. Newbury and A.P. Monaco, "Genetic advances in the study of speech and language disorders," *Neuron,* vol. 68, pp. 309–320, 2010.

[3] B.F. Pennington and D.V.M. Bishop, "Relations among speech, language, and reading disorders," *Annu Rev Psychol* vol. 60, pp. 283–306, 2009.

[4] National Institute on Deafness and Other Communication Disorders, "Strategic Plan Fiscal Year 2006-2008," 2005.

[5] American Speech-Language-Hearing Association (ASHA), "Schools Survey report: SLP caseload characteristics trends 1995-2010," 2010.

[6] L. D. Shriberg, J.B. Tomblin, and J. L. McSweeny, "Prevalence of speech delay in 6-year-old children and comorbidity with language impairment," *Journal of Speech, Language, and Hearing Research,* vol. 42, no. 6, pp. 1461-1481, 1999.

[7] J. A. Gierut, "Treatment efficacy: Functional phonological disorders in children," *Journal of Speech, Language, and Hearing Research,* vol. 41, no. 1, pp. S85-100, 1998.

[8] B. Dodd, A. Holm, Z. Hua et al., "English phonology: Acquisition and disorder," *Phonological development and disorders in children: A multilingual perspective,* Z. Hua and B. Dodd, eds., pp. 25-55. Tonawanda, NY: Multilingual Matters Ltd, 2006.

[9] L. D. Shriberg, J. Kwiatkowski, S. Best et al., "Characteristics of children with phonologic disorders of unknown origin," *J. Speech and Hearing Disorders*, vol. 51, no. 2, pp. 140-61, 1986.

[10] S.A. Graham and S.E. Fisher, "Decoding the genetics of speech and language," *Current Opinion in Neurobiology*, vol. 23, pp. 43-51, 2013.

[11] K.M. Beaver, M. Delisi, M.G. Vaughn, and J.P. Wright, "Association between the A1 allele of the DRD2 gene and reduced verbal abilities in adolescence and early adulthood," *J Neural Transm,* vol. 117, pp. 827 – 830, 2010.

[12] P.C. Wong, M. Ettinger, and J. Zheng, "Linguistic grammar learning and DRD2-TAQ-IA polymorphism," *PLoS One,* vol. 8, e64983, 2013.

[13] J.D. Eicher, N.R. Powers, K. Cho, et al, "Associations of prenatal nicotine exposure and the dopamine related genes ANKK1 and DRD2 to verbal language," *PLoS One*, vol. 8, e63762, 2013.

[14] C.M. Stein, B. Truitt, F. Deng, et al., "Association between AVPR1A, DRD2, and ASPM and endophenotypes of communication disorders." *Psychiatr Genet,* vol. 24, pp. 191–200, 2014.

[15] J. D. Eicher, C. M. Stein, F. Deng et al., "The DYX2 locus and neurochemical signaling genes contribute to speech sound disorder and related neurocognitive domains," *Genes, Brain and Behavior*, vol. 14, pp. 377-85, 2015.

[16] E.A. Worthey, G. Raca, J.J. Laffin, et al., "Whole-exome sequencing supports genetic heterogeneity in childhood apraxia of speech," *Journal of Neurodevelopmental Disorders*, vol. 5, no. 29, 2013.

[17] L. Breiman, "Random forests," *Machine Learning*, vol. 45, no. 1, pp. 5-32, 2001.

[18] F. Degenhardt, S. Seifert, and S. Szymczak, "Evaluation of variable selection methods for random forests and omics data sets," *Briefings in Bioinformatics,* pp. 1-12, 2017.

[19] I.I. Gottesman and J. Shields. *Schizophrenia and genetics: A twin study vantage point.* New York: Academic Press, 1972.

[20] I.I. Gottesman and T.D. Gould, "The endophenotype concept in psychiatry: Etymology and strategic intentions," *American Journal of Psychiatry,* vol. 160, pp. 636–645, 2003.

[21] S.E. Gathercole, "Nonword repetition and word learning: The nature of the relationship", Applied Psycholinguistics, vol. 27, pp. 513-543, 2006.

[22] R. Goldman and M. Fristoe, *Goldman-Fristoe Test of Articulation*, 2nd ed. Circle Pines, MN: American Guidance Service, 2000.

[23] H.T. Bunnell, N.C. Schanen, L.D. Vallino, et al., "Speech perception in children with speech sound disorder," *Proceedings of Interspeech 2007*, pp. 422-425, 2008.

[24] K. Nagao, M. Paullin, V. Livinsky, et al., "Speech production-perception relationships in children with speech delay," *Proceedings of InterSpeech 2012*, pp. 1127-1130, 2012.

[25] H. Li and R. Durbin, "Fast and accurate long-read alignment with Burrows-Wheeler Transform," *Bioinformatics,* vol. 26, no. 5, pp. 589-95, 2010.

[26] Picard [Online]. Available: http://broadinstitute.github.io/picard

[27] Samtools [Online]. Available: http://github.com/samtools

[28] M.A. DePristo, E. Banks, R. Poplin, et al., "A framework for variation discovery and genotyping using next-generation DNA sequencing data," *Nature Genetics*, vol. 43, pp. 491-98, 2011.

[29] L.J.P. van der Maaten and G. E. Hinton, "Visualizing high-dimensional data using t-SNE," *Journal of Machine Learning Research*, vol. 9, pp. 2579-2605, Nov. 2008.

[30] C. Chao, A. Liaw, and L. Breiman, "Using random forests to learn imbalanced data," Technical Report 666, Dept. of Statistics, Univ. California, Berkeley, CA, July 2004.

[31] H.M. Lachmann, D.F. Papolos, T. Saito, et al., "Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders," Pharmacogenetics, vol. 6, no. 3, pp. 243-50, 1996.

[32] A.V. Witte and A. Flöel, "Effects of COMT polymorphisms on brain function and behavior in health and disease," *Brain Res Bull.,* vol. 88, pp. 418–428, 2012.

[33] M. Karayiorgou, M. Altemus, B.L. Galke, et al., "Genotype determining low catechol-O-methyltransferase activity as a risk factor for obsessive-compulsive disorder," *Proc. Natl. Acad. Sci. U.S.A.,* vol. 94, pp. 4572–4575, 1997.

[34] K. Ohara, M. Nagai, and Y. Suzuki, "Low activity allele of catechol-O-methyltransferase gene and Japanese unipolar depression," *Neuroreport*, vol. 9, pp. 1305–1308, 1998.

[35] J.M. Woo, K.S. Yoon, Y.H. Choi, et al., "The association between panic disorder and the L/L genotype of catechol-O-methyltransferase," *J. Psychiatr. Res.,* vol. 38, pp. 365–370, 2004.

[36] M.F. Egan, T.E. Goldberg, B.S. Kolachana, et al., "Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia," *Proc. Natl. Acad. Sci. U.S.A.,* vol. 98, pp. 6917–6922, 2001.

[37] M.A. Enoch, J.F. Waheed, C.R. Harris, et al., "COMT Val158Met and cognition: main effects and interaction with educational attainment," *Genes Brain Behav.*, vol. 8, pp. 36–42, 2009. http://www.ncbi.nlm.nih.gov/pubmed/19076243.

[38] N. Raz, K.M. Rodrigue, K.M. Kennedy, and S. Land, "Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension," *Neuropsychology,* vol. 23, pp. 105–116, 2009.

[39] J.H. Barnett, J. Heron, S.M. Ring, et al., "Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children," *Am J Psychiatry,* vol. 164, pp. 142–149, 2007.

[40] D.P. Prata, A. Mechelli, C.H. Fu, et al., "Opposite effects of catechol-O-methyltransferase Val158Met on cortical function in healthy subjects and patients with schizophrenia," *Biol Psychiatry,* vol. 65, pp. 473–480, 2009.

[41] D. Gaysina, M.K. Xu, J.H. Barnett, et al., "The catechol-O-methyltransferase gene (COMT) and cognitive function from childhood through adolescence," *Biol Psychol*, vol. 92, pp. 359–364, 2013.

[42] L. Sugiura, T. Toyota, H. Matsuba-Kurita et al., "Age-dependent effects of catechol-o-methyltransferase (COMT) gene Val158Met polymorphism on language function in developing children," *Cerebral Cortex,* vol. 27, pp. 104-116, Jan. 2017.