Gene-Level Analysis of Missense Sensitivity in Neurodevelopmental Disorders

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Abstract

Neurodevelopmental disorders (NDDs) pose a growing medical challenge—collectively, they are a significant cause of paediatric hospitalisations and result in debilitating health issues. With the advent of large-scale sequencing technologies, our understanding of the genetic basis of NDDs has greatly advanced. Rare protein-coding variants, namely protein-truncating variants (PTVs) and missense variants, are associated with thousands of rare, neurodevelopmental conditions. Characterizing the functional impact of such variants—whether they exert pathogenicity via loss-of-function (LOF) or gain-of-function (GOF) effects—is crucial to understanding disease mechanism and therapeutic development. While predicting the functional impact of PTVs is relatively straightforward, predicting missense variant impact is extremely challenging and remains a major hurdle in translational efforts.

In this thesis, we use bioinformatics tools to evaluate missense sensitivity and functional impact in NDDs. At the gene-level, missense sensitivity refers to a gene's vulnerability to disruption by missense variation. Specifically, we aim to quantitatively define and apply missense sensitivity to understand variant impact. First, we develop a quantitative metric of missense sensitivity through computational modeling. Next, we compare the missense sensitivity metric to observed genomic and phenotypic data. Lastly, we apply missense sensitivity to characterize the functional and clinical impact of genetic variants. Using such data, we simultaneously compile a database of NDDs, disease-causing variants and their functional effects. Such insights, we hope, will fuel further efforts in identifying clinically relevant variants and allow for important translational efforts in the treatment of NDDs.

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1. Introduction

Rare disorders, defined as those affecting fewer than 1 in 2,000 individuals, are a significant cause of paediatric hospitalisations (Dodge et al., 2011; Yoon et al., 1997). They collectively present a population prevalence of 3.5 to 5.9% and account for 35% of deaths within the first year of life (Nguengang Wakap et al., 2019; Wright et al., 2018). There are an estimated 7,000 rare disorders, 80% of which are genetic (Amberger et al., 2009; Wright et al., 2018). As such, identifying the genetic etiologies of such diseases is critical, not only in advancing our knowledge of disease mechanisms but in developing effective therapies.

Genetic Architecture of Neurodevelopmental Disorders

Neurodevelopmental disorders (NDDs) are characterized by the impaired development of cognitive, emotional, and motor functions during childhood (Thapar et al., 2015). The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) categorizes learning disorders (involving reading, writing, and arithmetic), intellectual disability (ID), communication disorders, motor disorders, attention deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) as NDDs (American Psychiatric Association et al., 2013). Epilepsy, cerebral palsy (CP), global developmental delay (GDD), and schizophrenia are also included in this classification (McRae et al., 2017; Niemi et al., 2018; Thapar et al., 2015). Neurodevelopmental disorders are a broad category, encompassing a wide range of health issues, abilities, and needs—from those with rare, severe conditions that require full time care to those with above average IQs who lead independent lives. Table 1 provides a non-exhaustive list of NDDs and their population prevalence.

NDDs are highly heritable (Deng et al., 2012; Ronald & Hoekstra, 2011; Stromswold, 2001; Thapar et al., 1999), and, as such, genetic causes play an important role in the biological and clinical aspects of disease. Investigators use many approaches to explore the genetic architecture of such disorders. Research has shown that rare NDDs are often monogenic in their etiology (Niemi et al., 2018). Moreover, many mutation types have been associated with NDDs, such as chromosomal rearrangements, copy number variations (CSVs), small indels, and single nucleotide variants (SNVs) (Parenti et al., 2020). Such variations can either be inherited or newly arising, known as *de novo*; perhaps unsurprisingly, investigators have found that *de novo* variants comprise approximately 70% of genetic diagnoses in NDDs (Fitzgerald et al., 2014).

Moreover, many variant types, both coding and non-coding, are associated with NDDs. Table 2 provides a comprehensive list of coding variants. Such variants can exert distinct functional effects on the gene product, such as a protein's stability, catalytic activity, binding interactions and much more (Studer et al., 2013). A variant's functional consequence can be

Neurodevelopmental Disorder	Prevalence (%)
Lesch-Nyhan syndrome	0.0005
Lowe syndrome	0.0005
Rubinstein-Taybi syndrome	0.0008
Cornelia de Lange syndrome	0.0014
Cri du chat syndrome	0.0020
Galactosaemia	0.0020
Angelman syndrome	0.0040
Williams syndrome	0.0044
Marfan syndrome	0.0067
Prader-Willi syndrome	0.0067
Rett syndrome	0.0080
Phenylketonuria	0.0100
Duchenne muscular dystrophy	0.0143
Tuberous sclerosis	0.0167
Edwards' Syndrome (Trisomy 18)	0.0250
Velocardiofacial syndrome	0.0250
Neurofibromatosis type 1	0.0308
Turner syndrome	0.0400
XYY	0.0545
XXX	0.0550
Noonan syndrome	0.0571
Fragile X syndrome	0.0615
Klinefelter syndrome (XXY)	0.0860
Fetal alcohol syndrome	0.1000
Cerebral palsy	0.1500
Down syndrome (Trisomy 21)	0.1667
Tourette syndrome	0.5000
Autistic spectrum disorder	0.6500
Developmental dyscalculia	3.0000
Attention deficit hyperactivity disorder	5.0000
Intellectual disability	5.5000
Developmental dyslexia	6.0000
Developmental coordination disorder	6.5000
Specific language impairment	7.4000
Speech sound disorder	10.0000

Table 1. List of neurodevelopmental disorders by prevalence. Adapted from Bishop, 2010.

categorized into loss-of-function (LOF), resulting in partial or complete knockdown of protein activity, gain-of-function (GOF), resulting in enhanced or novel protein activity, or dominant negative (DN), in which the mutant protein interferes with wild-type protein activity. This thesis focuses specifically on protein-truncating variants (PTVs) and missense variants. PTVs

encompass variants that result in shortened or absent protein, including stop gained single-nucleotide variants (SNVs), frameshift insertions or deletions (indels), large structural variants, and splice-disrupting SNVs (Holbrook et al., 2004; Rivas et al., 2015). In almost all cases, PTVs result in a LOF effect, though in rare cases, they may result in a truncated protein. On the other hand, missense variants, which result in an amino acid change, have a far more complex functional landscape. Missense variants can have LOF, GOF, DN or benign effects—and missense variants within the same gene can result in drastically different effects and clinical outcomes.

Variant Type	Description
Synonymous variant	A sequence variant where there is no resulting change to the encoded amino acid
Splice acceptor variant	A splice variant that changes the 2-base region at the 3' end of an intron
Splice donor variant	A splice variant that changes the 2-base region at the 5' end of an intron
Stop gained	A sequence variant whereby at least one base of a codon is changed, resulting in a premature stop codon, leading to a shortened transcript
Frameshift variant	A sequence variant which causes a disruption of the translational reading frame, because the number of nucleotides inserted or deleted is not a multiple of three
Stop lost	A sequence variant where at least one base of the terminator codon (stop) is changed, resulting in an elongated transcript
Start lost	A codon variant that changes at least one base of the canonical start codon
Inframe insertion	An inframe non synonymous variant that inserts bases into in the coding sequence
Inframe deletion	An inframe nonsynonymous variant that deletes bases from the coding sequence
Missense variant	A sequence variant, that changes one or more bases, resulting in a different amino acid sequence but where the length is preserved
Start retained variant	A sequence variant where at least one base in the start codon is changed, but the start remains
Stop retained variant	A sequence variant where at least one base in the terminator codon is changed, but the terminator remains

Table 2. Types of coding variants. Adapted from the Variant Effect Predictor (McLaren et al., 2016).

The advent of sequencing technologies and bioinformatics tools has rapidly advanced the identification of genetic variants. However, linking genotype to phenotype in the case of missense variants is incredibly difficult and an ever more pressing issue. Various standards exist for classifying the clinical impact of mutations, including the American College of Medical Genetics and Genomics (ACMG) standard (Richards et al. 2015). The ACMG defines categories from "pathogenic" to "benign", along with the category of "variant of uncertain significance" (VUS). While the rate of variant identification has exponentially increased, so too has the number of VUSs. In ClinVar, a public database of gene-disease associations, VUS make

up over half of all entries for missense variants (Weile & Roth, 2018). Such uncertainties not only thwart translational efforts in disease and treatment characterization, but they also cause great anxiety amongst patients and their families. As such, future work is needed to further evaluate, understand and characterize the functional impact of missense variation in disease.

Missense Sensitivity

One approach in characterizing missense variation is to look at the gene-level—can we dissect the functional and clinical significance of variants based on a gene's "missense sensitivity"? As will be used in this paper, missense sensitivity refers to a gene's vulnerability to disruption by missense variation compared to other genes. We wondered whether a missense sensitivity metric, describing a gene's intolerance to missense variation, may provide further insights into the functional and clinical significance of observed missense variants.

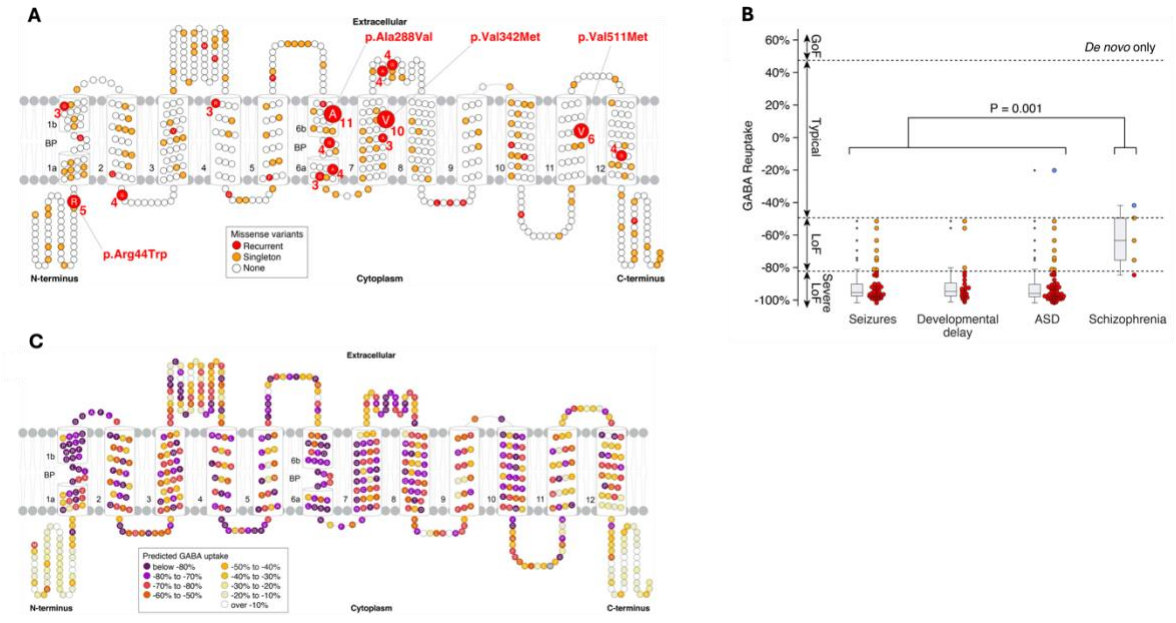

Figure 1. (A) Representation of GAT-1 organized by 12 transmembrane domains and linking or terminal chains. Observed missense variants are highlighted, with recurrent variants (red) and single variants (orange). **(B)** GABA uptake values for *de novo* variants according to the presence of seizures, developmental delay, autism spectrum disorder (ASD), or schizophrenia. **(C)** All 599 amino acids of GAT-1 colored by the mean predicted GABA uptake of all possible missense variants. Adapted from Silva et al., 2024.

Recent functional studies have demonstrated missense sensitivity in the context of NDDs. One such example is *SLC6A1,* which encodes the GAT-1 GABA transporter. Heterozygous variants in this gene are associated with seizures, developmental delay, and autism. Most affected individuals carry missense variants, many of which are recurrent *de novo* mutations (Figure 1A),

highly suggestive of a GOF or DN mechanism. The authors conducted functional analyses through an *in vitro* GABA uptake assay for 213 unique variants (Silva et al., 2024); surprisingly, *de novo* variants consistently resulted in decreased GABA uptake, pointing towards a LOF, as opposed to GOF or DN, mechanism (Figure 1B). By applying linear regression across multiple missense severity scores, the authors extrapolate functional data to all potential *SLC6A1* missense variants and find an abundance of residues that are sensitive to substitution (Figure 1C). They write that this "apparent missense sensitivity accounts for the clinically observed enrichment in *de novo* missense variation", but also points to the immense challenge in predicting the functional and clinical impact of such variants.

Thesis Outline

Predicting the impact of missense variants in NDDs can be critical to the discovery of disease mechanisms and the development of treatments. To this end, I quantify and investigate missense sensitivity to characterize functional and clinical effects. First, I apply bioinformatics tools to develop a quantitative metric of missense sensitivity across all protein-coding genes. Next, I evaluate missense sensitivity scores against observed functional and phenotypic data. Lastly, I apply the missense sensitivity score to tease apart variant functional impact in neurodevelopmental disorders. Through this process, I also generate a comprehensive database of genetic variants associated with NDDs, annotated with functional mechanisms and clinical correlates.

2. Methods

Transcripts

This project analyzed coding transcripts as defined by the Matched Annotation from the NCBI and EMBL-EBI (MANE) v1.3. (Morales et al., 2022). The GENCODE GRCh38 primary assembly version 46 was used as the reference genome (Frankish et al., 2023). The MANE set includes 19,190 transcripts; of these, 10 were excluded due to alternate contigs. As such, this study analyzed a total of 19,180 coding transcripts.

Variant Modeling

Single-nucleotide variant (SNV) modeling was performed using geneVarMaker (Sanders, 2024), a Python Package that outputs all possible SNVs in the UTR and CDS of a gene. Input files were prepared in Python using the MANE v1.3 transcript set and the GENCODE version 46 reference genome. In total, this resulted in over 250 million modeled SNVs.

Variant Annotation

SNVs were annotated using ANNOVAR, a software tool to functionally annotate genetic variants (Wang et al., 2010). ANNOVAR annotations include 54 pathogenicity prediction scores. We further annotated SNVs with AlphaMissense predicted pathogenicity scores for each available residue (a full list of predictors annotated can be found in Supplemental Table 1). We annotated functional consequences for ClinVar (Landrum et al., 2014) variants using the ClinVar Variant Summary (version released 2023-10-21 23:31:50).

Rare and *de novo* Variants from Developmental Cohorts

Case *de novo* mutations for analyses were obtained from studies of developmental disorders (DD) and autism spectrum disorder (ASD). Specifically, variant data was procured from the Deciphering Developmental Disorders (DDD) study (Wright et al., 2015) and Autism Sequencing Consortium (ASC) (Buxbaum et al., 2012). Control *de novo* mutations were obtained from neurotypical siblings.

ROC Analysis

To determine the optimal classification threshold of each pathogenicity prediction score (i.e. pathogenic or benign), we performed a Receiver Operating Characteristic (ROC) analysis. All modeled variants were filtered to those with a ClinVar functional annotation. Using the ClinVar annotations as our truth set, the ROC curve was used to identify a threshold that maximizes model performance for each prediction metric. The ROC calculation was implemented using the scikit-learn library in Python (Pedregosa et al., 2011). The optimal threshold was identified based on the criteria of maximizing the Youden's Index for a given metric.

Predicted & Observed Missense Ratio Calculations

After obtaining the optimal threshold for each prediction metric, we calculated the predicted missense ratio for each protein-coding gene as follows (where # *predicted pathogenic missense variants* was the number of missense variants above the calculated threshold):

$$Predicted\ Missense\ Ratio = \frac{\#\ predicted\ pathogenic\ missense\ variants}{\#\ total\ modeled\ missense\ variants}$$

For genes with NDD associations, clinically observed variants were isolated from the databases mentioned above and filtered based on consequence of "Missense" or "PTV." The observed missense and observed PTV ratios were calculated as follows:

$$Observed\ PTV\ Ratio = \frac{\#\ PTV\ variants\ associated\ with\ NDD}{\#\ total\ modeled\ PTV\ variants}$$

$$Observed\ Missense\ Ratio = \frac{\#\ missense\ variants\ associated\ with\ NDD}{\#\ total\ modeled\ missense\ variants}$$

Code

All analyses were completed using Python 3.9.7, unless otherwise stated. Data analysis was completed through Pandas and NumPy. All figures were generated using Matplolib and finalized in Illustrator, unless otherwise stated.

Data Availability

All data generated in this study is available through an Amazon Web Services (AWS) S3 bucket. The S3 bucket contains all raw output datasets and can be accessed upon request.
MANE dataset was downloaded from https://ftp.ncbi.nlm.nih.gov/pub/clinvar/tab_delimited/variant_summary.txt.gz.
GENCODE GRCh38 primary assembly was downloaded from https://ftp.ncbi.nlm.nih.gov/pub/clinvar/tab_delimited/variant_summary.txt.gz.
AlphaMissense scores were downloaded from https://github.com/google-deepmind/alphamissense.
ANNOVAR was accessed from https://www.openbioinformatics.org/annovar/annovar_download_form.php.
ClinVar data was downloaded from https://www.openbioinformatics.org/annovar/annovar_download_form.php.
Variants from developmental cohorts were accessed from internal lab repositories.

3. Developing a Metric of Missense Sensitivity

We first set out to develop a gene-level metric of missense sensitivity. To this end, we isolated all protein-coding genes from the Matched Annotation from the NCBI and EMBL-EBI (MANE) transcript set, which totaled 19,180 genes. For each gene sequence, we modeled all possible SNVs by mutating, base-by-base, a given reference allele to 3 alternate alleles (keeping the remaining reference sequence constant). All modeled SNVs were then annotated with variant-, gene-, and protein-level information using ANNOVAR. SNVs were filtered to isolate missense variants, which were further annotated with several pathogenicity predictors. Table 3 provides a list of the 39 predictors used in our analyses. Such scores rely on various approaches in predicting pathogenicity of missense variants, including evolutionary conservation (i.e. SIFT, MutationTaster, phyloP), protein structure and function (i.e. PROVEAN, AlphaMissense), or a combination the two (i.e. CAAD, Polyphen2, REVEL). Each metric uses distinct models and scales; as such, the distribution of missense variant scores across all tested genes varies significantly from metric to metric (Figure 2).

SIFT	SIFT4G	Polyphen2 HDIV	Polyphen2 HVAR	LRT
MutationTaster	MutationAssessor	FATHMM	PROVEAN	VEST4
MetaSVM	MetaLR	MetaRNN	M-CAP	REVEL
MutPred	MVP	MPC	PrimateAI	DEOGEN2
BayesDel AF	BayesDel no AF	ClinPred	LIST S2	CADD
DANN	Fathmm MKL	Fathmm XF	Eigen	Eigen PC
GenoCanyon	Integrated fitCons	LINSIGHT	GERP++NR	GERP++RS
phyloP100way vertebrate	phyloP30way mammalian	SiPhy 29way	AlphaMissense	

Table 3. Pathogenicity predictors used in analyses.

To quantify missense sensitivity at the gene-level, we calculated the ratio of predicted pathogenic missense variants to the total number of possible missense variants. This ratio, known as the predicted missense ratio, was calculated for each predictor across all coding genes. However, to calculate this ratio, we first needed to define the optimal pathogenicity threshold—the value which best segregates true pathogenic vs benign variants—for each predictor. While some predictors have pre-suggested thresholds, others do not. We therefore applied Receiver Operating Characteristic (ROC) analysis to define a consistent and

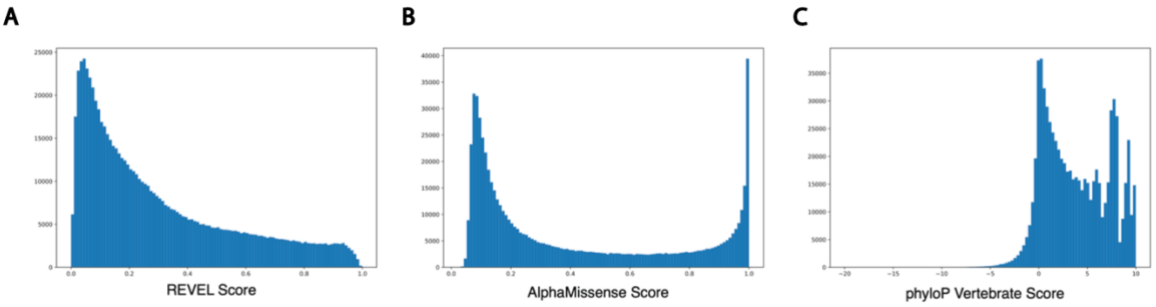

Figure 2. Distribution of pathogenicity prediction scores across modeled missense variants in all tested genes for **(A)** REVEL **(B)** AlphaMissense, and **(C)** phyloP Vertebrate. Due to dataset size, distributions were calculated using random sampling (every 100th variant across all tested genes).

robust method for thresholding. ROC analysis was performed using ClinVar's clinically observed annotations as our truth set. For each predictor, the area under the curve (AUC) was calculated, in addition to identifying the optimal threshold value (see Methods). Figure 3 presents the ROC curve and analysis for the AlphaMissense predictor; ROC analysis for all 39 metrics can be found in Supplemental Figure 1.

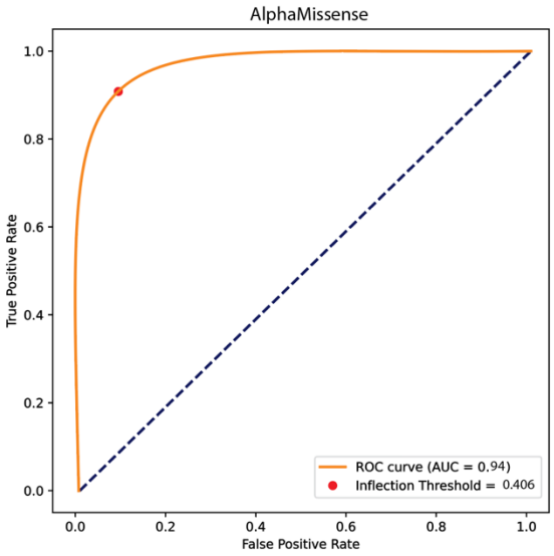

Figure 3. ROC analysis for AlphaMissense predictor. The optimal threshold point (red) was identified by maximizing the Youden's index.

Once the optimal threshold was identified for each predictor, we then calculated predicted missense ratios across all protein-coding genes. In essence, a higher predicted missense ratio corresponds to greater missense sensitivity—or a gene's increased vulnerability to disruption by missense variation. To determine the performance of each ratio, we plotted predicted missense ratios against the gnomAD loss-of-function observed/expected upper bound fraction (LOEUF) v4.0 score, a continuous metric demonstrating a gene's intolerance to loss-of-function variation. We applied linear regression to understand the relationship between

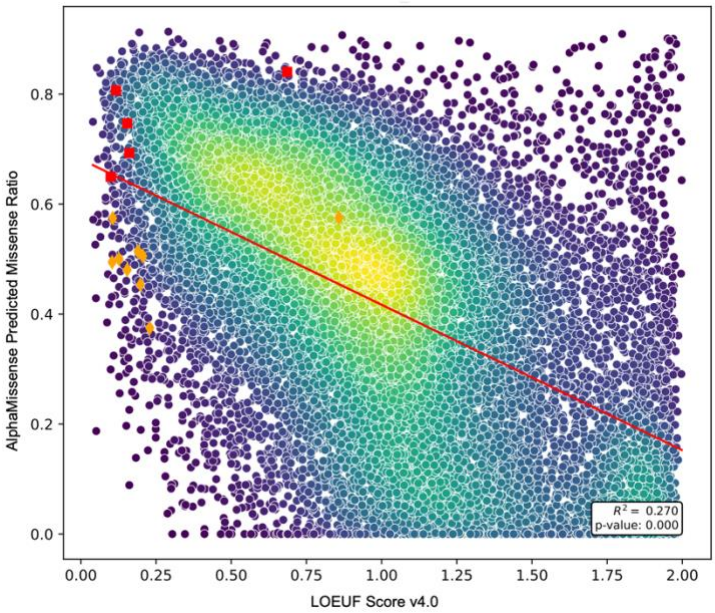

Figure 4. AlphaMissense predicted missense ratio scores versus gnomAD LOEUF scores (each point represents a gene). Linear regression analysis was performed (R^2 value shown). Missense-enriched genes (red) and PTV-enriched genes (orange) are presented.

each metric's predicted missense ratios and LOEUF scores. Moreover, we examined each model against 14 NDD-associated genes known to be either enriched in pathogenic missense variants (red) or pathogenic PTVs (orange). We expect missense-enriched genes to present with greater predicted missense ratio scores, relative to PTV-enriched genes. Figure 4 presents the linear regression analysis for the AlphaMissense predicted missense ratio scores; data for all 39 metrics can be found in Supplemental Figure 2.

In looking at all 39 metrics, we evaluated the metric's accuracy, the strength of the linear regression analysis (based on R^2 values), and its ability to segregate previously known missense-enriched vs PTV-enriched gene sets. A recent study independently assessed the performance of AlphaMissense against other predictors using experimental data from multiplexed assays of variant effect (MAVE) results; they conclude that AlphaMissense represents the current best-in-class predictor (Ljungdahl et al., 2023). Based on such data, and results from ROC analysis, we ultimately picked the AlphaMissense predicted missense ratio as our missense sensitivity metric. The missense sensitivity metric ranges from 0 to 1, with 0 indicating a gene to be missense tolerant and 1 indicating a gene to be missense sensitive.

4. Comparing Missense Sensitivity to Observed Phenotypic Data

We next sought to compare the missense sensitivity metric to observed functional data in the context of NDDs. Specifically, we isolated genes from the ASC and DDD dataset, which provides functional and clinical data of observed missense and PTV variants associated with

NDDs. We filtered for genes with greater than 20 annotated variants, resulting in a total of 136 genes in our final analyses. From this gene set, we calculated the observed missense ratio and observed PTV ratio for each gene; in doing so, we capture observed missense enrichment versus PTV enrichment. How does the missense sensitivity metric perform in accurately capturing the observed differences? As shown in Figure 5, genes in the missense-enriched set (lower right quadrant, with high observed missense ratio values and low observed PTV ratio values) presented with significantly higher missense sensitivity scores than the PTV-enriched set (upper left quadrant, with low observed missense ratio values and high observed PTV ratio values). We further quantified this difference (Figure 6) using a Wilcoxon rank-sum test; missense-enriched genes were indeed found to have greater (p-value < 0.0001) missense sensitivity scores relative to PTV-enriched genes.

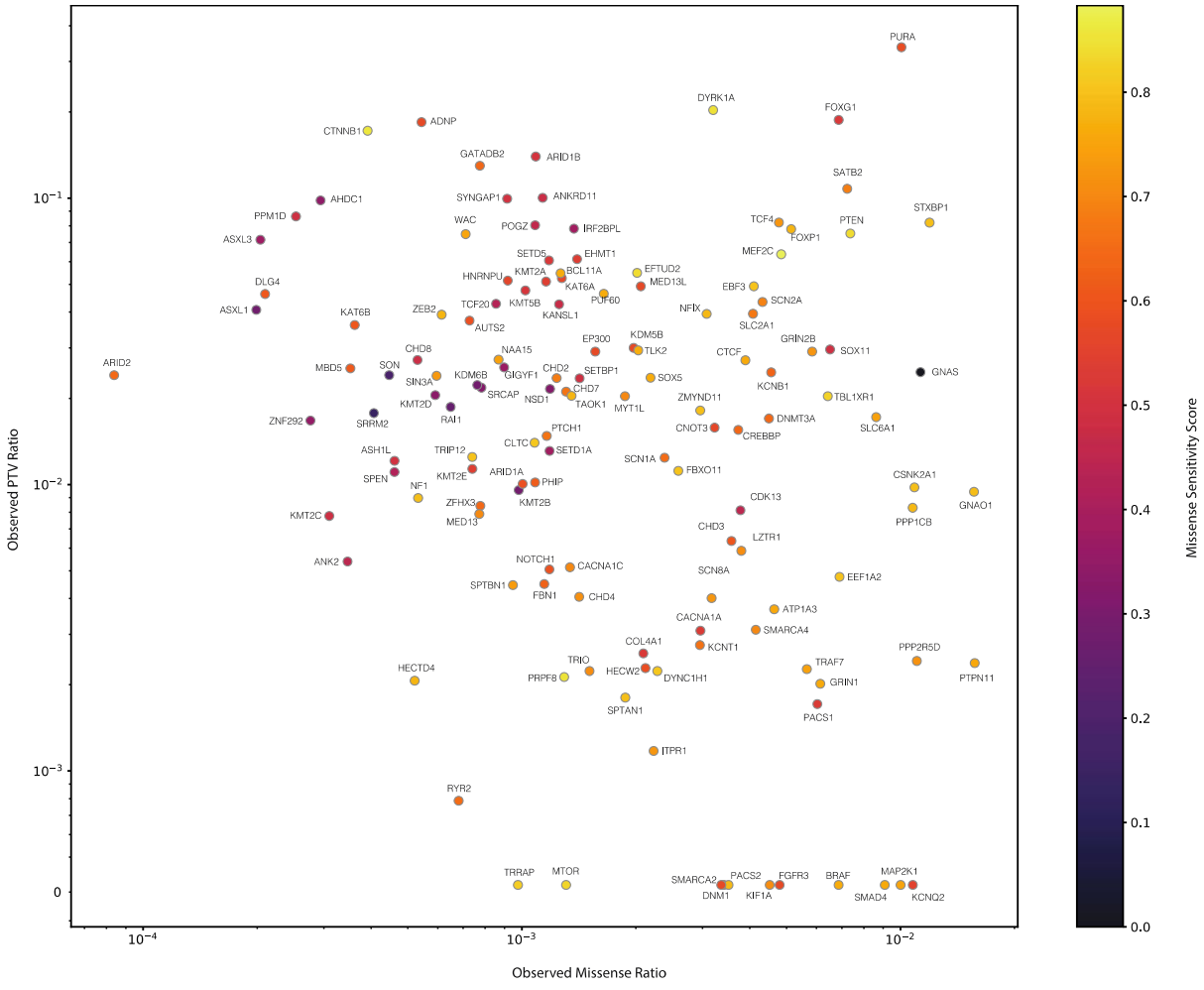

Figure 5. Plot demonstrating observed missense ratio values versus observed PTV ratio values (log-scaled). Genes are colored according to heatmap values, corresponding to missense sensitivity scores.

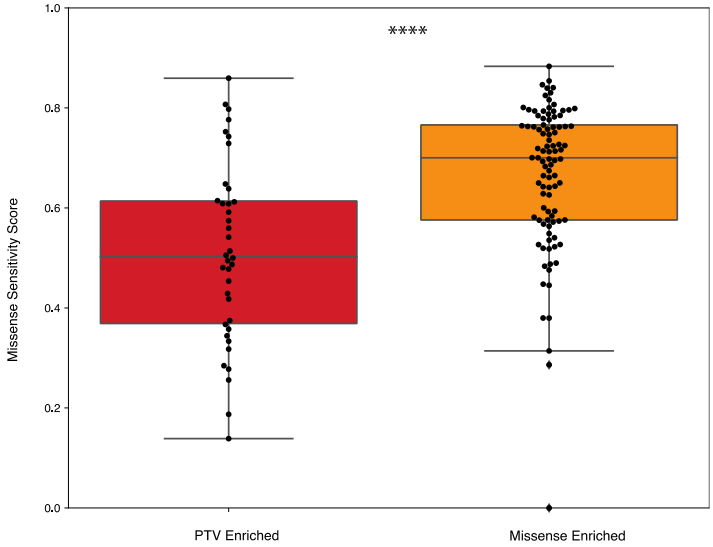

Figure 6. Box plot comparing missense sensitivity scores between genes clinically observed to be PTV-enriched (red) or missense-enriched (orange).

Further investigation of outlier genes reveals important insights. *CTNNB1*, which encodes for catenin beta-1, for example, has a high missense sensitivity score of 0.71; however, based on clinical annotations in neurodevelopmental disorders, *CTNNB1* appears to be PTV-enriched, not missense-enriched. Interestingly, *CTNNB1* has been extensively studied as an oncogene in cancer pathogenesis. Specifically, GOF missense mutations in exon 3 of β-catenin are specific for Wilms' tumors (Li et al., 2004). As such, while *CTNNB1* may be enriched for pathogenic PTVs in neurodevelopmental disorders, in the context of cancer, it appears to be enriched for pathogenic missense variants.

5. Applying Missense Sensitivity to Assess Functional Impact

We wanted to apply the missense sensitivity metric to characterize and delineate functional impact. Namely, we sought to understand how a gene's observed enrichment for PTVs or missense variants, alongside its predicted missense sensitivity, may explain the functional impact (LOF, GOF, DN) of its variants. To do this, I conducted a scoping literature search of the 136 genes used in the NDD analysis. For each gene, we examined variant annotations in Online Mendelian Inheritance in Man (OMIM); we further searched for all publications detailing variant functional data across PubMed. Based on the literature data, we classified whether clinically significant variants were shown to have LOF, GOF or DN effects in each gene. The full database detailing all genes, functional impact and associated publications can be found in the supplemental information.

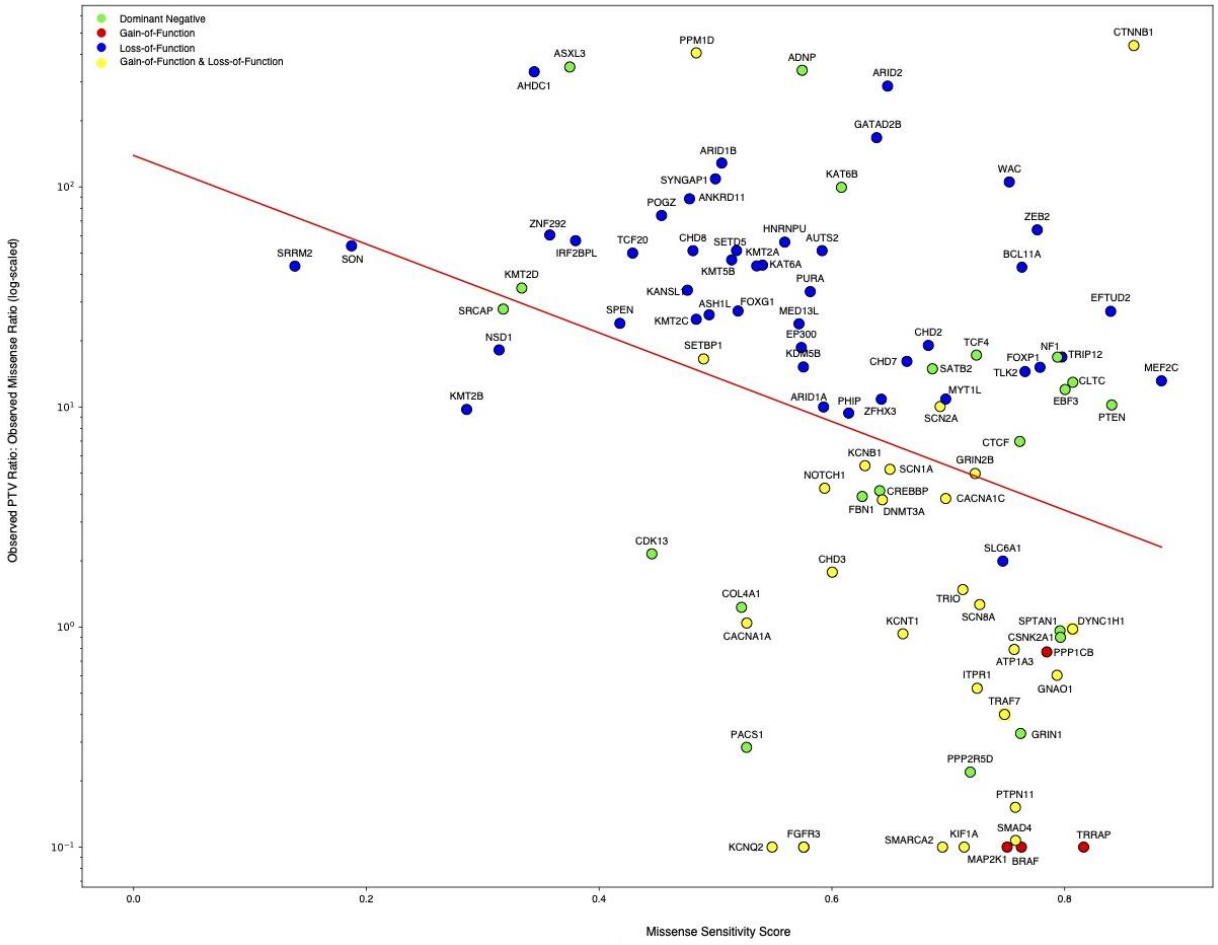

Figure 7. Plot presenting the missense sensitivity score against the observed PTV to observed missense ratio (log-scaled). Linear regression analysis was performed and shown in red. Genes symbols are shown and colored by the observed functional impact of genetic variants: GOF (red), LOF (blue), DN (green), or both LOF, GOF and/or DN (yellow.

Based on such classifications, we visualized the relationship between functional effects of genetic variants and missense sensitivity. Genes were placed into 4 categories based on whether clinically significant variants presented with 1) loss-of-function, 2) gain-of-function, 3) dominant negative, or 4) both LOF, GOF, and/or DN effects. Figure 7 presents the distribution of NDD-associated genes, where the x-axis is the missense sensitivity score, and the y-axis is the observed PTV to observed missense ratio. A high y-value corresponds to observed PTV-enrichment, whereas a low y-value corresponds to missense-enrichment.

As shown, there are three dominant gene sets present. The first gene set presents with low missense sensitivity scores and observed PTV enrichment; the majority of disease-causing variants in such genes have LOF effects. One clear outlier is *PPM1D,* which encodes for protein phosphatase 1D. In rare cases, PTVs may escape nonsense-mediated decay and result

in toxic truncated protein products; in the case of *PPM1D,* PTVs in exon 6 result in toxic GOF Wip1 expression and are associated with tumorigenesis (Kleiblova et al., 2013). The second gene set involves genes with high missense sensitivity scores and moderate missense enrichment; disease-causing variants in such genes primarily exert LOF or DN effects. This gene set includes the previously discussed *SLC6A1*, which, as demonstrated through functional studies, is vulnerable to loss of protein function due to missense variation. The third gene set includes genes with high missense sensitivity scores and observed missense enrichment; disease-causing variants in this population primarily exert GOF or a combination of GOF, LOF and DN effects.

6. Discussion

Missense variation is a significant cause of rare and severe neurodevelopmental disorders; with the advent of gene-therapy techniques, therapeutic opportunities for such disorders are greater than ever. However, realizing the therapeutic potential of a gene requires understanding the impact of disease-causing variants. While characterizing the functional mechanisms by which PTVs cause pathogenicity is relatively straightforward, characterizing the impact of missense variants remains incredibly challenging. As such, in this project, we aim to characterize, evaluate and catalogue missense sensitivity, functional effects and disease mechanisms.

We first developed a quantitative metric of missense sensitivity. To do this, we modeled all possible single-nucleotide variants across protein-coding genes in the MANE transcript set, totaling 19,180 genes. We then annotated modeled SNVs with various pathogenicity predictors. Using ROC analysis, we determined the optimal pathogenicity threshold for each predictor and applied such thresholding to calculate the predicted missense ratios across all genes. To validate the performance of each predicted missense ratio, we used a set of 14 genes with well-characterized PTV-enrichment or missense-enrichment. Using such data, as well as previous studies on predictor accuracy, we defined the missense sensitivity metric as the AlphaMissense predicted missense ratio.

Next, we compared the missense sensitivity score to clinically observed variants in NDDs. From the DDD and ASC datasets, we isolated 136 genes associated with neurodevelopmental conditions and identified the number of disease-causing missense variants and PTVs in each gene. Using such data, we calculated the observed missense and observed PTV ratios, which provide a measure of observed missense- and PTV-enrichment. In visualizing such data, we found that indeed genes known to be missense enriched had higher missense sensitivity scores. To further understand the role of missense sensitivity in functional impact, we conducted a scoping literature search to classify the impact of disease-causing variants—as loss-of-function,

gain-of-function, dominant negative, or both—in the 136-gene set. In doing so, we unearthed several interesting observations. Genes with high missense sensitivity scores and observed missense-enrichment were greatly enriched in gain-of-function effects. Conversely, genes with low missense sensitivity scores and observed PTV-enrichment were enriched for loss-of-function effects.

Through such efforts, we hope to advance current knowledge about the impact of missense variants in disease and provide a valuable resource for the identification of genetic targets.

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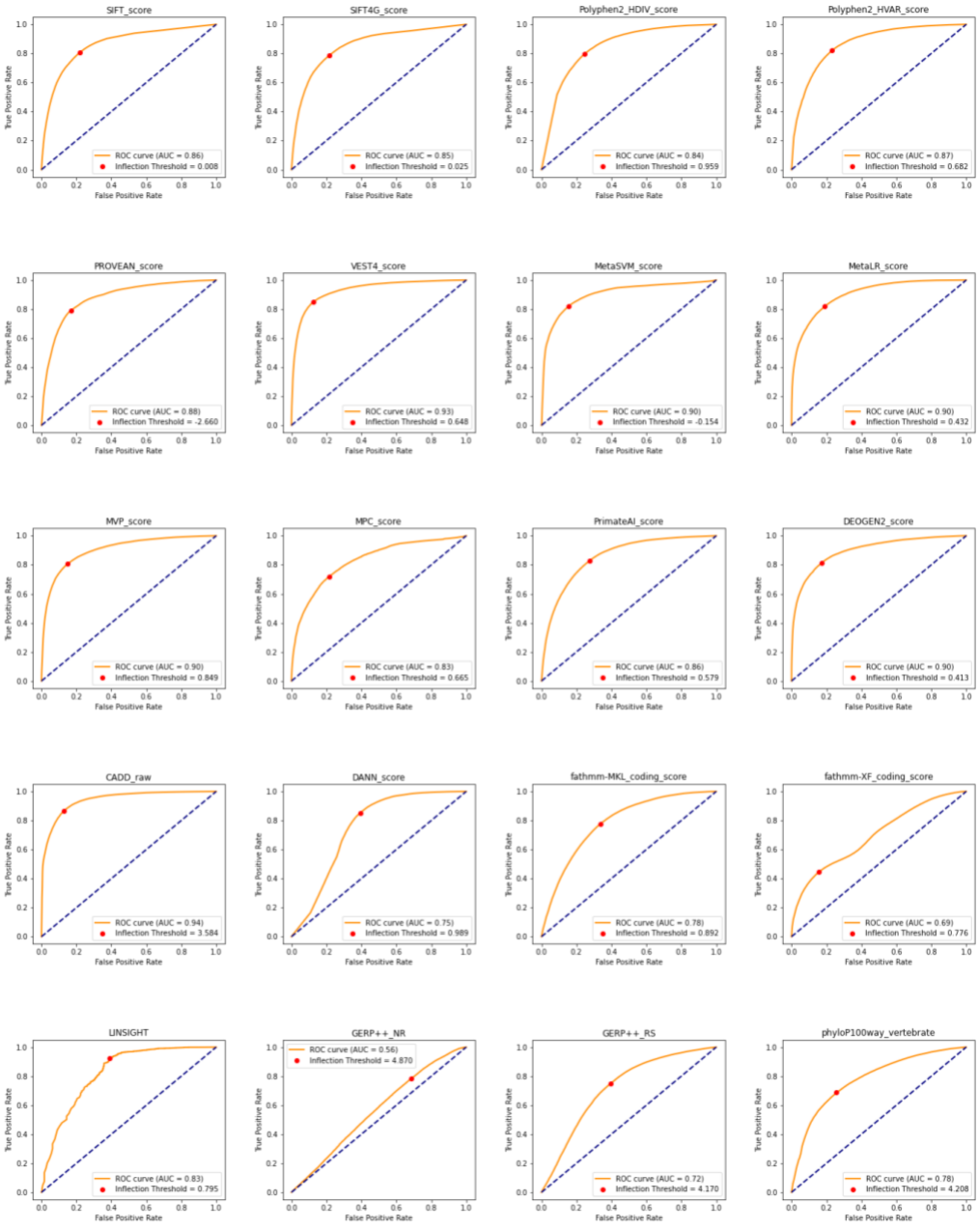
8. Supplemental Information

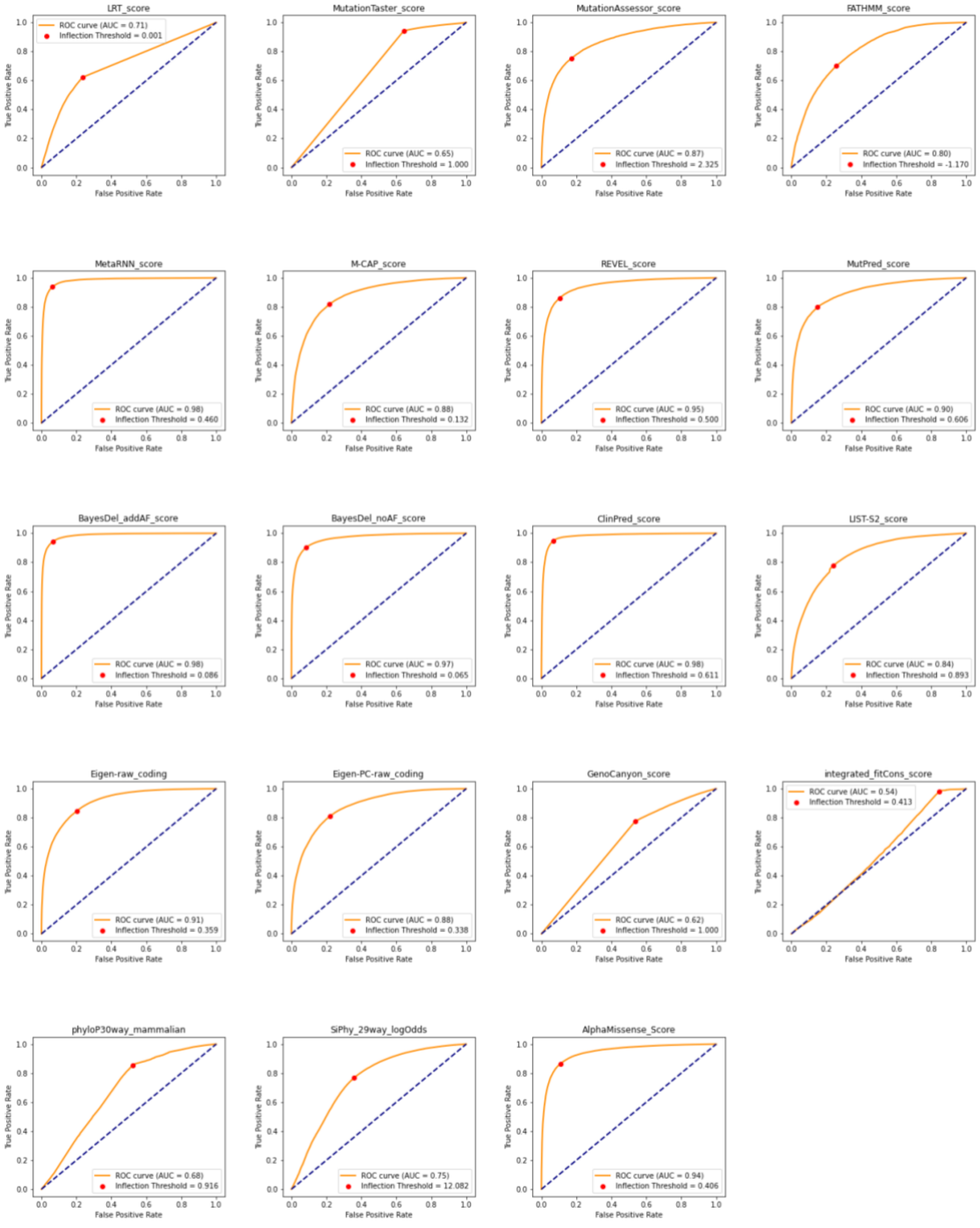
Supplemental Table 1. All pathogenicity predictors.

SIFT_score	SIFT_converted_rankscore	SIFT_pred	SIFT4G_score	SIFT4G_converted_rankscore
SIFT4G_pred	Polyphen2_HDIV_score	Polyphen2_HDIV_rankscore	Polyphen2_HDIV_pred	Polyphen2_HVAR_score
Polyphen2_HVAR_rankscore	Polyphen2_HVAR_pred	LRT_score	LRT_converted_rankscore	LRT_pred
MutationTaster_score	MutationTaster_converted_rankscore	MutationTaster_pred	MutationAssessor_score	MutationAssessor_rankscore
MutationAssessor_pred	FATHMM_score	FATHMM_converted_rankscore	FATHMM_pred	PROVEAN_score
PROVEAN_converted_rankscore	PROVEAN_pred	VEST4_score	VEST4_rankscore	MetaSVM_score
MetaSVM_rankscore	MetaSVM_pred	MetaLR_score	MetaLR_rankscore	MetaLR_pred
MetaRNN_score	MetaRNN_rankscore	MetaRNN_pred	M-CAP_score	M-CAP_rankscore
M-CAP_pred	REVEL_score	REVEL_rankscore	MutPred_score	MutPred_rankscore
MVP_score	MVP_rankscore	MPC_score	MPC_rankscore	PrimateAI_score
PrimateAI_rankscore	PrimateAI_pred	DEOGEN2_score	DEOGEN2_rankscore	DEOGEN2_pred
BayesDel_addAF_score	BayesDel_addAF_rankscore	BayesDel_addAF_pred	BayesDel_noAF_score	BayesDel_noAF_rankscore
BayesDel_noAF_pred	ClinPred_score	ClinPred_rankscore	ClinPred_pred	LIST-S2_score
LIST-S2_rankscore	LIST-S2_pred	Aloft_pred	Aloft_Confidence	CADD_raw
CADD_raw_rankscore	CADD_phred	DANN_score	DANN_rankscore	fathmm-MKL_coding_score
fathmm-MKL_coding_rankscore	fathmm-MKL_coding_pred	fathmm-XF_coding_score	fathmm-XF_coding_rankscore	fathmm-XF_coding_pred
Eigen-raw_coding	Eigen-raw_coding_rankscore	Eigen-PC-raw_coding	Eigen-PC-raw_coding_rankscore	GenoCanyon_score
GenoCanyon_rankscore	integrated_fitCons_score	integrated_fitCons_rankscore	integrated_confidence_value	LINSIGHT
LINSIGHT_rankscore	GERP++_NR	GERP++_RS	GERP++_RS_rankscore	phyloP100way_vertebrate
phyloP100way_vertebrate_rankscore	phyloP30way_mammalian	phyloP30way_mammalian_rankscore	phastCons100way_vertebrate	phastCons100way_vertebrate_rankscore

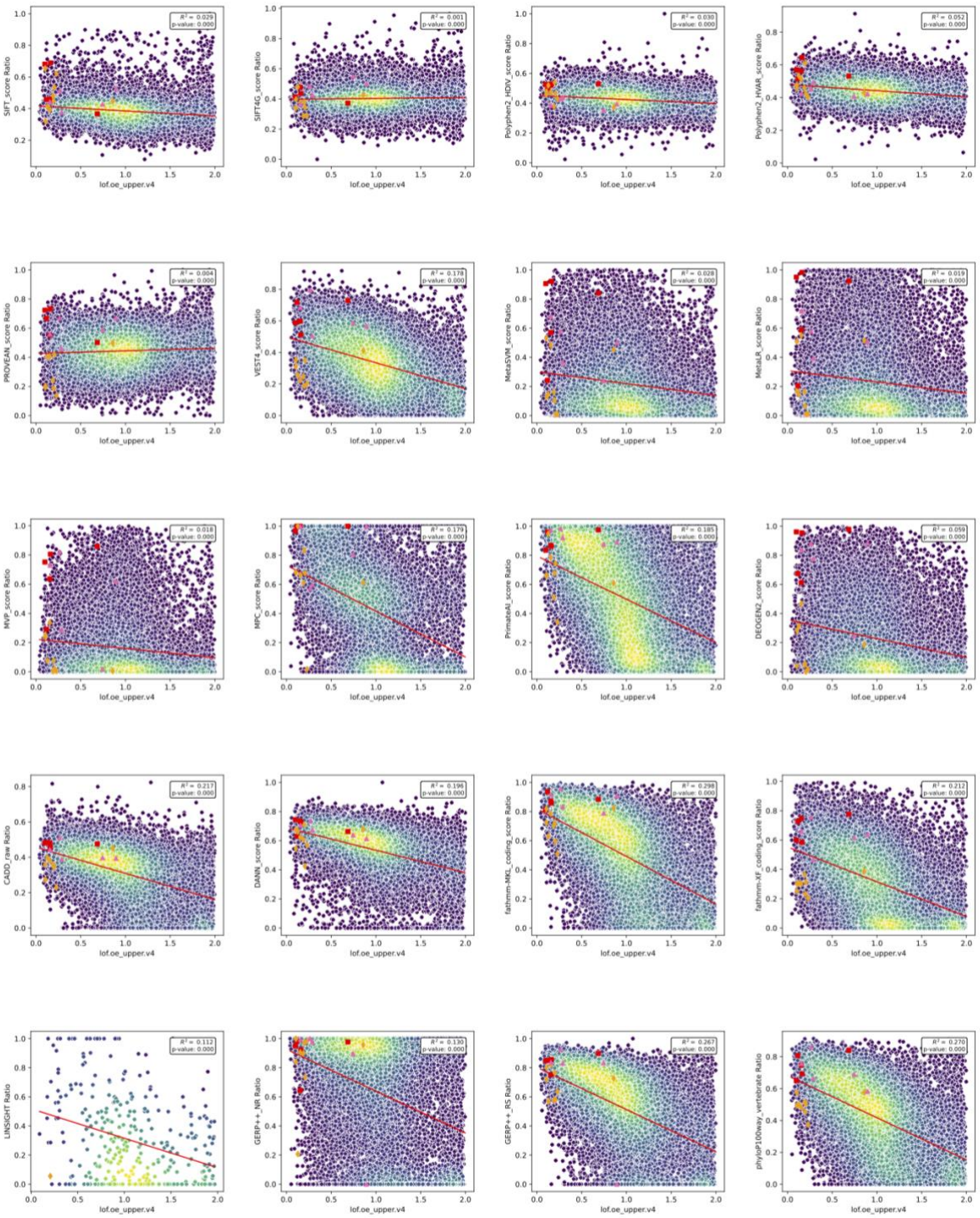
phastCons30way_mammalian	phastCons30way_mammalian_rankscore	SiPhy_29way_logOdds	SiPhy_29way_logOdds_rankscore	phyloP50way_mammalian_2020
AlphaMissense_Score	AlphaMissense_Interp			

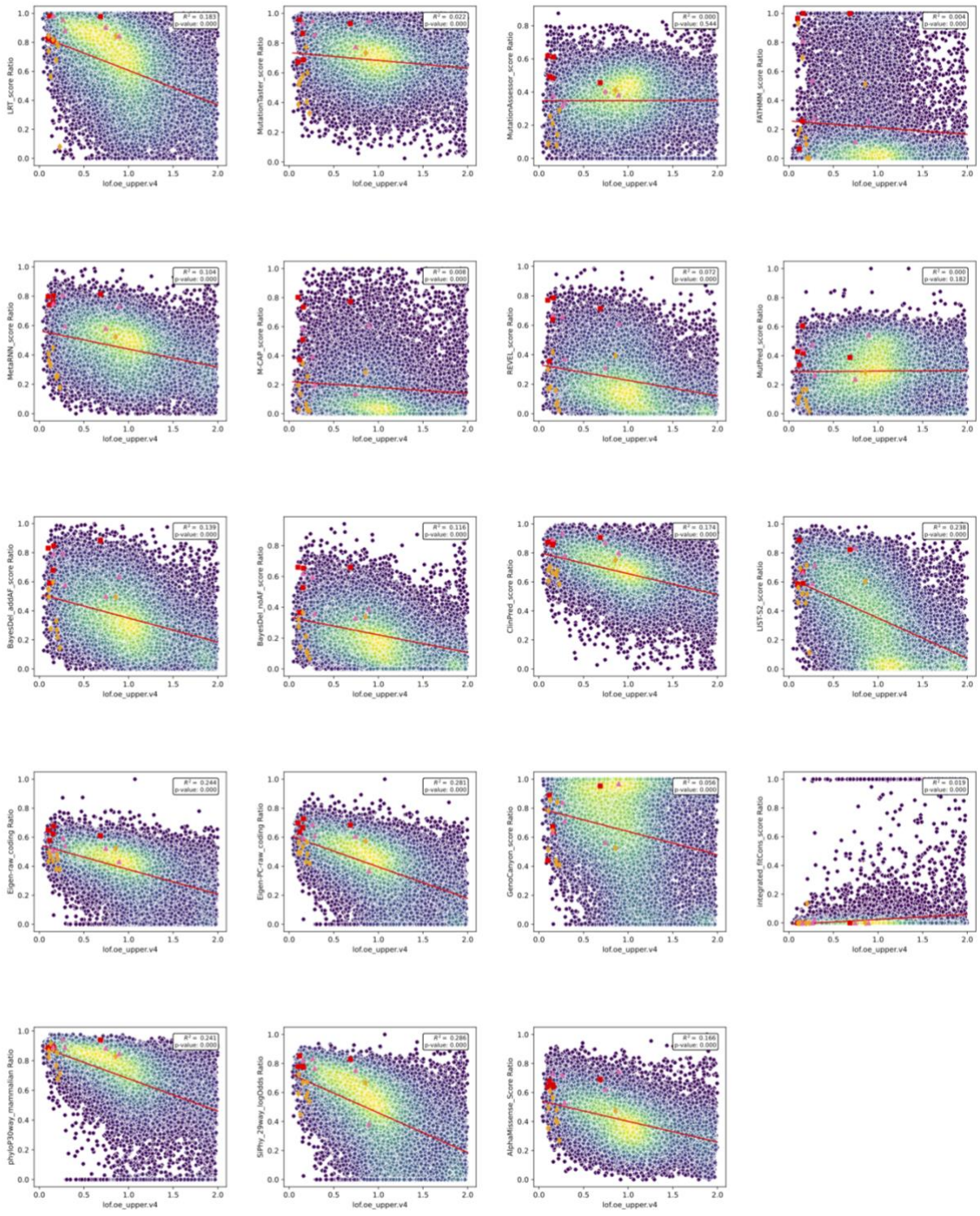
Supplemental Figure 1. ROC analysis of all predictors.




LRT_score
ROC curve (AUC = 0.71)
Inflection Threshold = 0.001
MutationTaster_score
ROC curve (AUC = 0.65)
Inflection Threshold = 1.000
MutationAssessor_score
ROC curve (AUC = 0.87)
Inflection Threshold = 2.325
FATHMM_score
ROC curve (AUC = 0.80)
Inflection Threshold = -1.170
MetaRNN_score
ROC curve (AUC = 0.98)
Inflection Threshold = 0.460
M-CAP_score
ROC curve (AUC = 0.88)
Inflection Threshold = 0.132
REVEL_score
ROC curve (AUC = 0.95)
Inflection Threshold = 0.500
MutPred_score
ROC curve (AUC = 0.90)
Inflection Threshold = 0.606
BayesDel_addAF_score
ROC curve (AUC = 0.98)
Inflection Threshold = 0.086
BayesDel_noAF_score
ROC curve (AUC = 0.97)
Inflection Threshold = 0.065
ClinPred_score
ROC curve (AUC = 0.98)
Inflection Threshold = 0.611
LIST-S2_score
ROC curve (AUC = 0.84)
Inflection Threshold = 0.893
Eigen-raw_coding
ROC curve (AUC = 0.91)
Inflection Threshold = 0.359
Eigen-PC-raw_coding
ROC curve (AUC = 0.88)
Inflection Threshold = 0.338
GenoCanyon_score
ROC curve (AUC = 0.62)
Inflection Threshold = 1.000
integrated_fitCons_score
ROC curve (AUC = 0.54)
Inflection Threshold = 0.413
phyloP30way_mammalian
ROC curve (AUC = 0.68)
Inflection Threshold = 0.916
SiPhy_29way_logOdds
ROC curve (AUC = 0.75)
Inflection Threshold = 12.082
AlphaMissense_Score
ROC curve (AUC = 0.94)
Inflection Threshold = 0.406
True Positive Rate
False Positive Rate

Supplemental Figure 2. All predicted missense ratio scores against gnomAD LOEUF.




LRT_score Ratio
MutationTaster_score Ratio
MutationAssessor_score Ratio
FATHMM_score Ratio
MetaRNN_score Ratio
M-CAP_score Ratio
REVEL_score Ratio
MutPred_score Ratio
BayesDel_addAF_score Ratio
BayesDel_noAF_score Ratio
ClinPred_score Ratio
LIST-S2_score Ratio
Eigen-raw_coding Ratio
Eigen-PC-raw_coding Ratio
GenoCanyon_score Ratio
integrated_fitCons_score Ratio
phyloP30way_mammalian Ratio
SiPhy_29way_logOdds Ratio
AlphaMissense_Score Ratio
lof.oe_upper.v4