Quality Control metrics of individual genetic variants in the Alzheimer's Disease Sequencing Project are associated with FAVOR annotations.

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Introduction

- The ADSP (Alzheimer's Disease Sequencing Project) released their 4th dataset consisting of **36,361 sequenced genomes, with 362 million variants.**
- The R4 dataset release also contains **variant level QC (Quality Control)** scores, along with composite **binary VFlags (5 in total) for each variant**, generated from the individual variant level QC scores.

FAVOR annotations

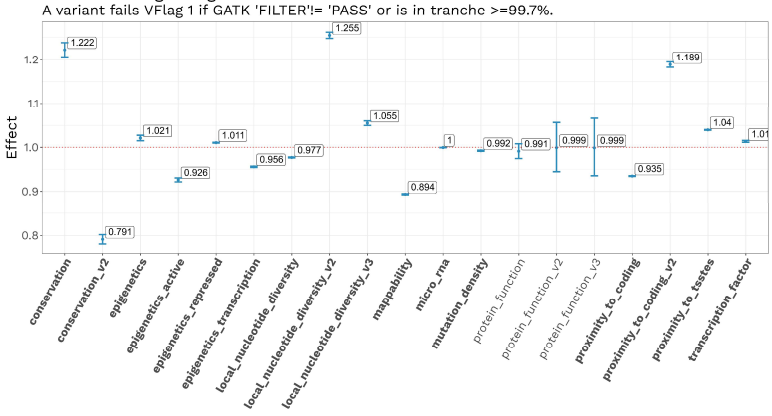
- FAVOR integrates data from multiple databases, including **CADD v1.5, GENCODE v31, Annovar, WGSA, ClinVar, ENCODE, SnpEff, 1000 Genome, TOPMed Bravo Freeze 8 and gnomAD v3.**
- FAVOR functional scores are divided into **17 groups**, along with **annotation Principal Components (aPCs)**, which are the first variant-specific PC calculated from each standardized individual annotation score within these 17 groups.

Annotations and QC metrics

- Approaches for statistical analysis of rare variants **increasingly rely on functional annotations** to weight association test statistics and increase statistical power.
- However, the **impact of variant quality** on these tests is largely unexplored.
- We performed **logistic regression analyses** on chromosomes **21 and 22** of the R4 dataset, with group **aPCs** as predictors, and **VFlags** as outcomes.

Predicted Effects of a change of one unit in the FAVOR aPCs on the odds of failing VFlag 1.

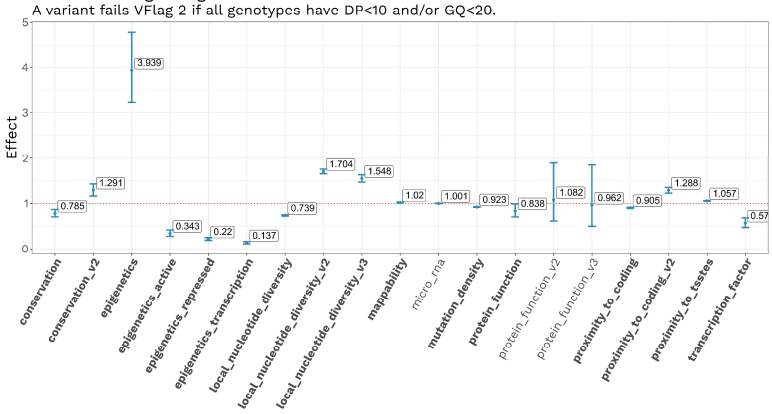
A variant fails VFlag 1 if GATK 'FILTER'!= 'PASS' or is in tranche >=99.7%.



Variants taken from Chromosomes 21 and 22 from the ADSP R4 data release.

Predicted Effects of a change of one unit in the FAVOR aPCs on the odds of failing VFlag 2.

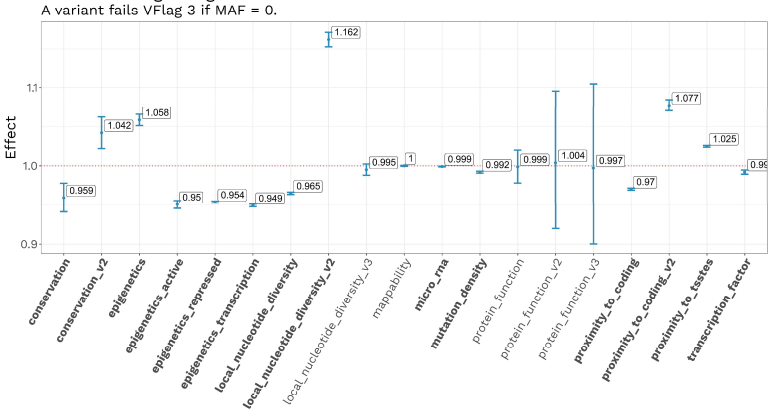
A variant fails VFlag 2 if all genotypes have DP<10 and/or GQ<20.



Variants taken from Chromosomes 21 and 22 from the ADSP R4 data release.

Predicted Effects of a change of one unit in the FAVOR aPCs on the odds of failing VFlag 3.

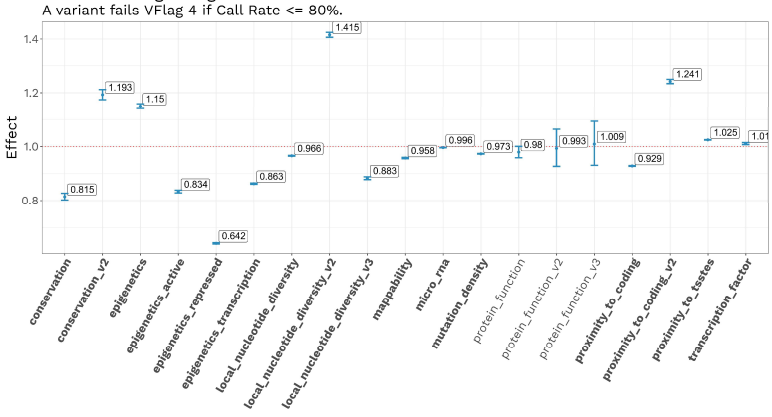
A variant fails VFlag 3 if MAF = 0.



Variants taken from Chromosomes 21 and 22 from the ADSP R4 data release.

Predicted Effects of a change of one unit in the FAVOR aPCs on the odds of failing VFlag 4.

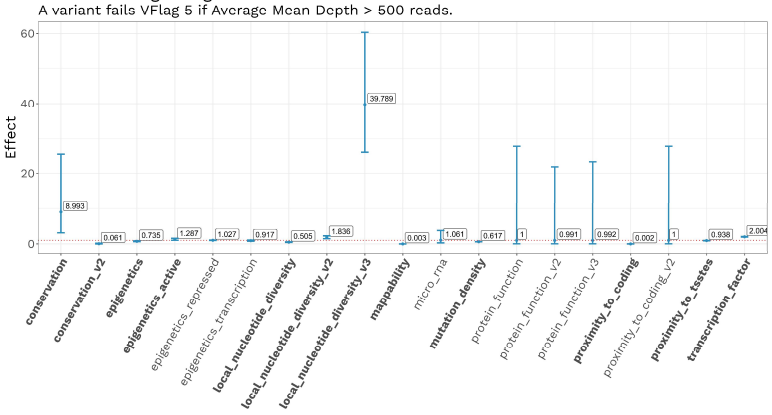
A variant fails VFlag 4 if Call Rate <= 80%.



Variants taken from Chromosomes 21 and 22 from the ADSP R4 data release.

Predicted Effects of a change of one unit in the FAVOR aPCs on the odds of failing VFlag 5.

A variant fails VFlag 5 if Average Mean Depth > 500 reads.



Variants taken from Chromosomes 21 and 22 from the ADSP R4 data release.

Results

- The aPCs were found to have a **statistically significant relationship with the odds of a variant failing the VFlags**, with some aPCs having different effects on different VFlags.
- For example, an increase in the aPC for the **"Epigenetics"** block by one unit for a variant increases the odds of failing VFlag 2 (All Genotypes have DP < 10 or GQ < 20) **by nearly four fold (95%CI=3.24 to 4.78, p < 10^-8)**, and the aPC for **"Local Nucleotide Diversity"** dramatically increases odds of failing VFlag 5 (Average Mean Depth > 500 reads) **by 40 fold (95%CI=26.22 to 60.36, p < 10^-8).**
- These relationships demonstrate the critical importance of variant quality filtering when using annotation weights in association testing.

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