Fall 2021 Lab Presentation

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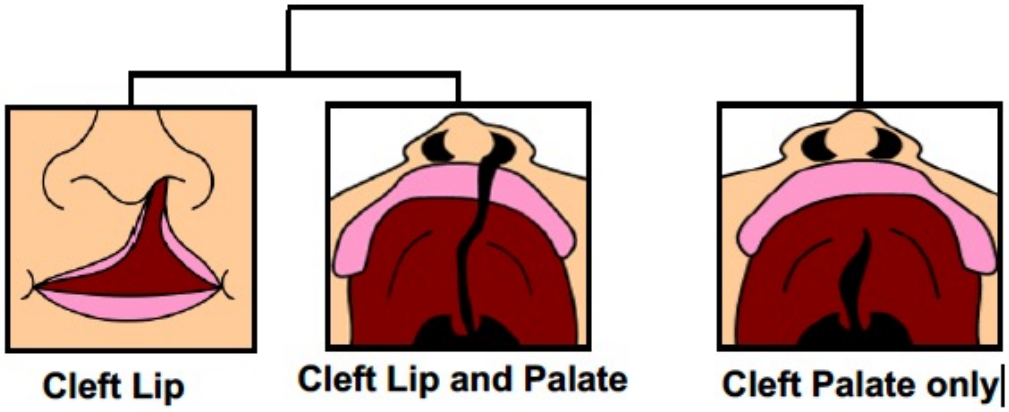
Background

- Orofacial clefts (OFCs) are the most common craniofacial malformation with an overall incidence of 1/1000 live births.
- Nonsyndromic OFCs are phenotypically and etiologically heterogenous.
- OFCs are generally classified into isolated cleft lip (CL), cleft lip with cleft palate (CLP), and isolated cleft palate (CP).



Background

- **Variant of uncertain significance (VUS):** This means that the test found a genetic change, but there is not enough known about the change to give a diagnosis.
- **Pathogenic variant**: A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder.

Data

Collected from **Gabriella Miller Kids First Pediatric Research Program**

837 trios in total

Europeans: 437

Taiwanese: 125

Colombian: 275

Controls: 302

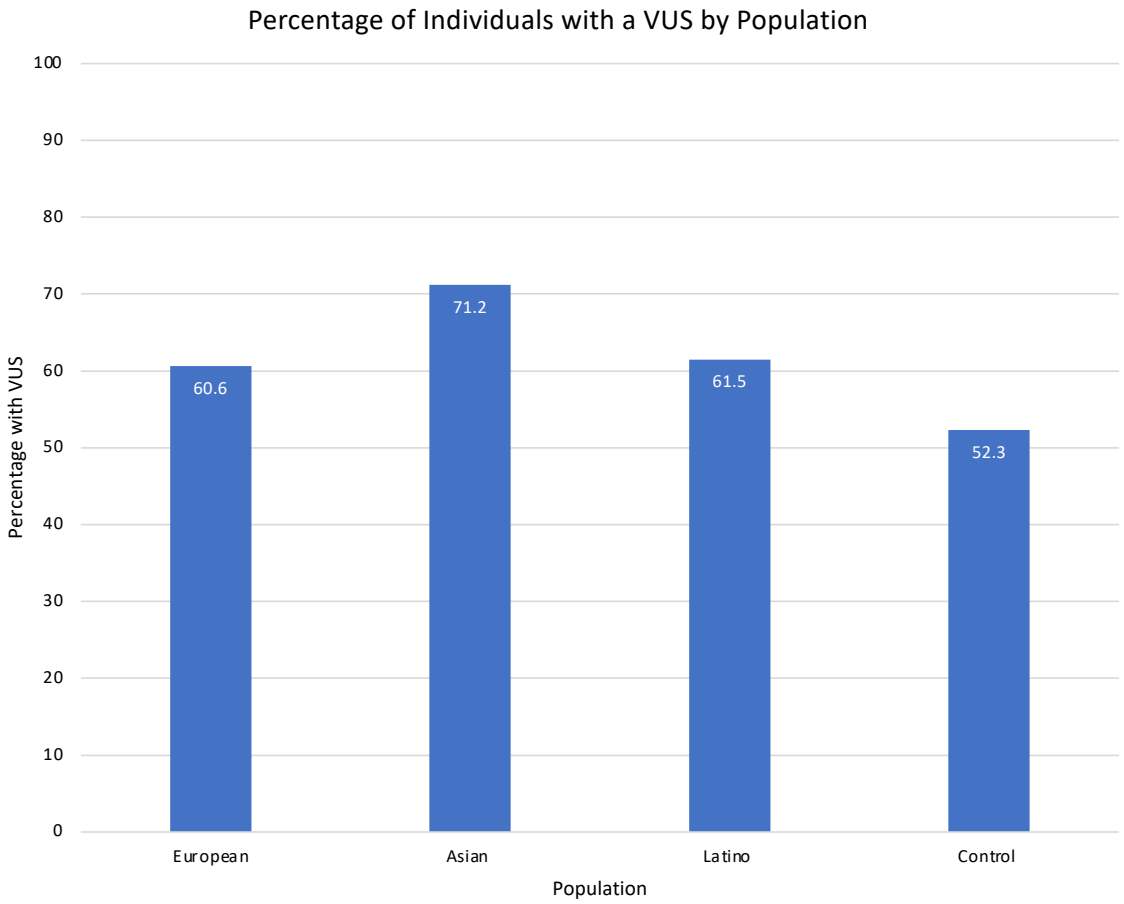
Purpose

IF THERE IS A SIGNIFICANT RELATIONSHIP BETWEEN VUS IN GENES WITH PATHOGENIC VARIANTS

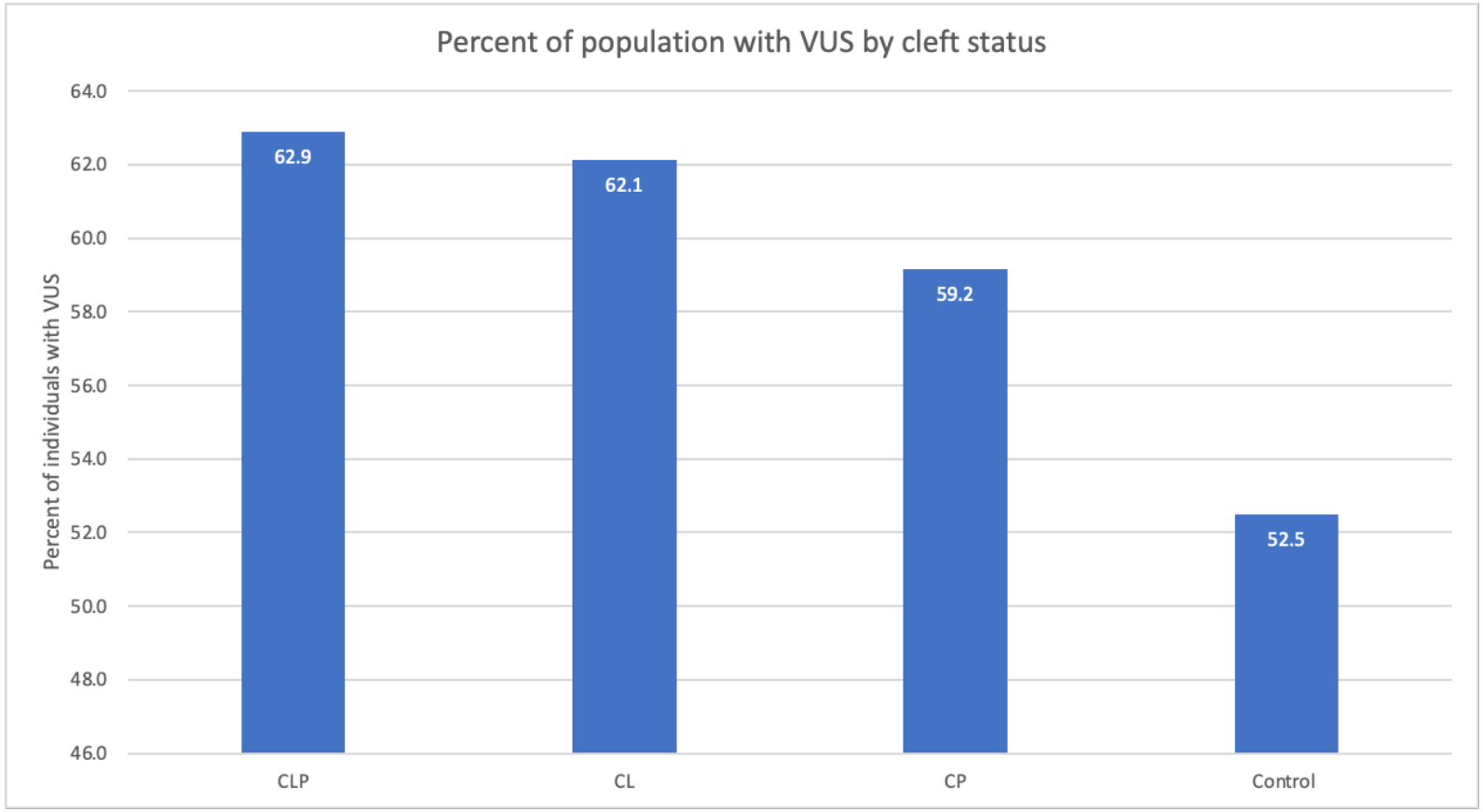
IF THERE IS A PATHOGENIC GENE THAT HAS A LOT OF VUS, MAYBE SOME OF THE VUS ARE ACTUALLY PATHOGENIC

Descriptive Statistics

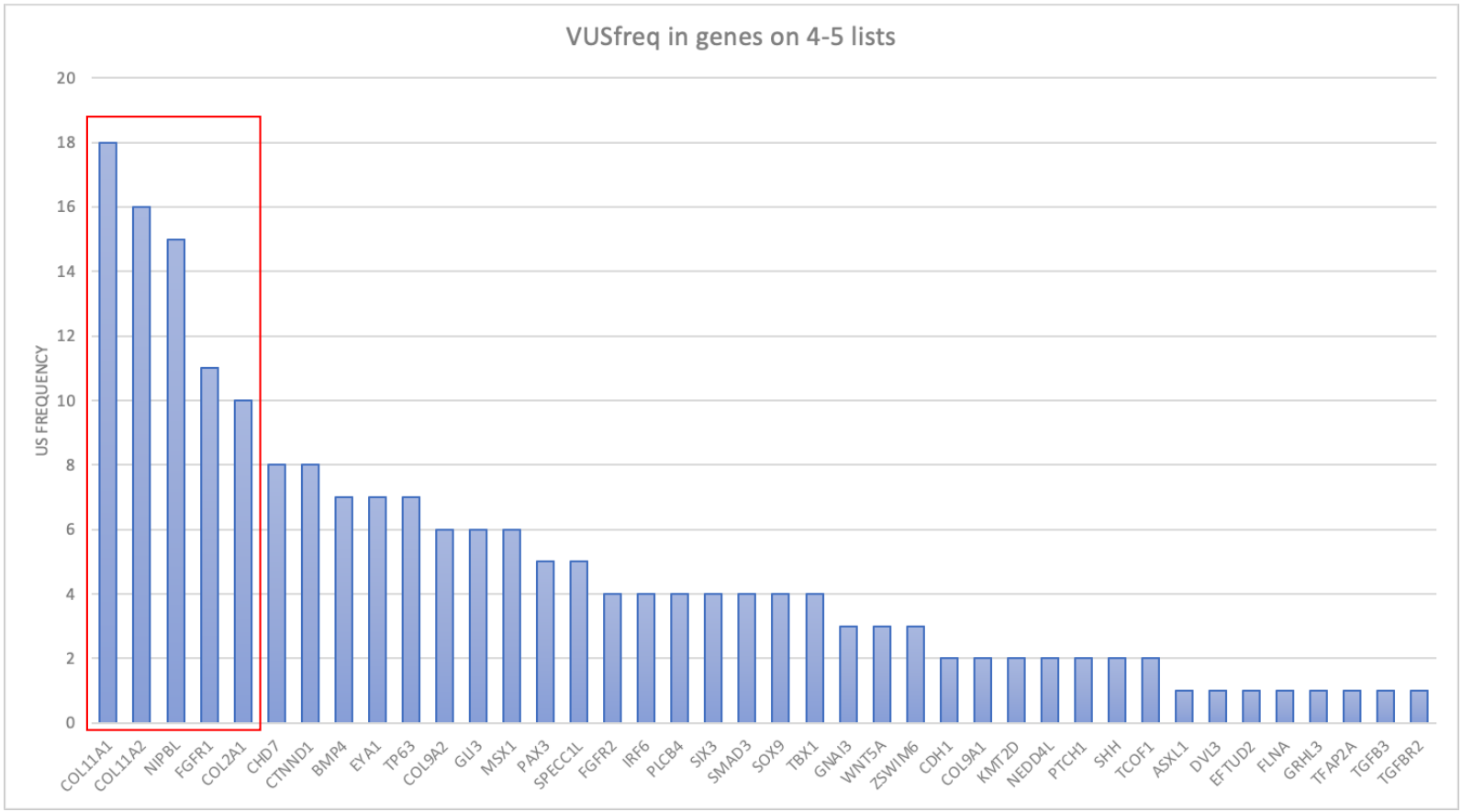
- 519 unique case ChildIDs
- 1040 VUS in 220 unique genes
- Percent of unique ChildIDs with a VUS by population



By Cleft Status

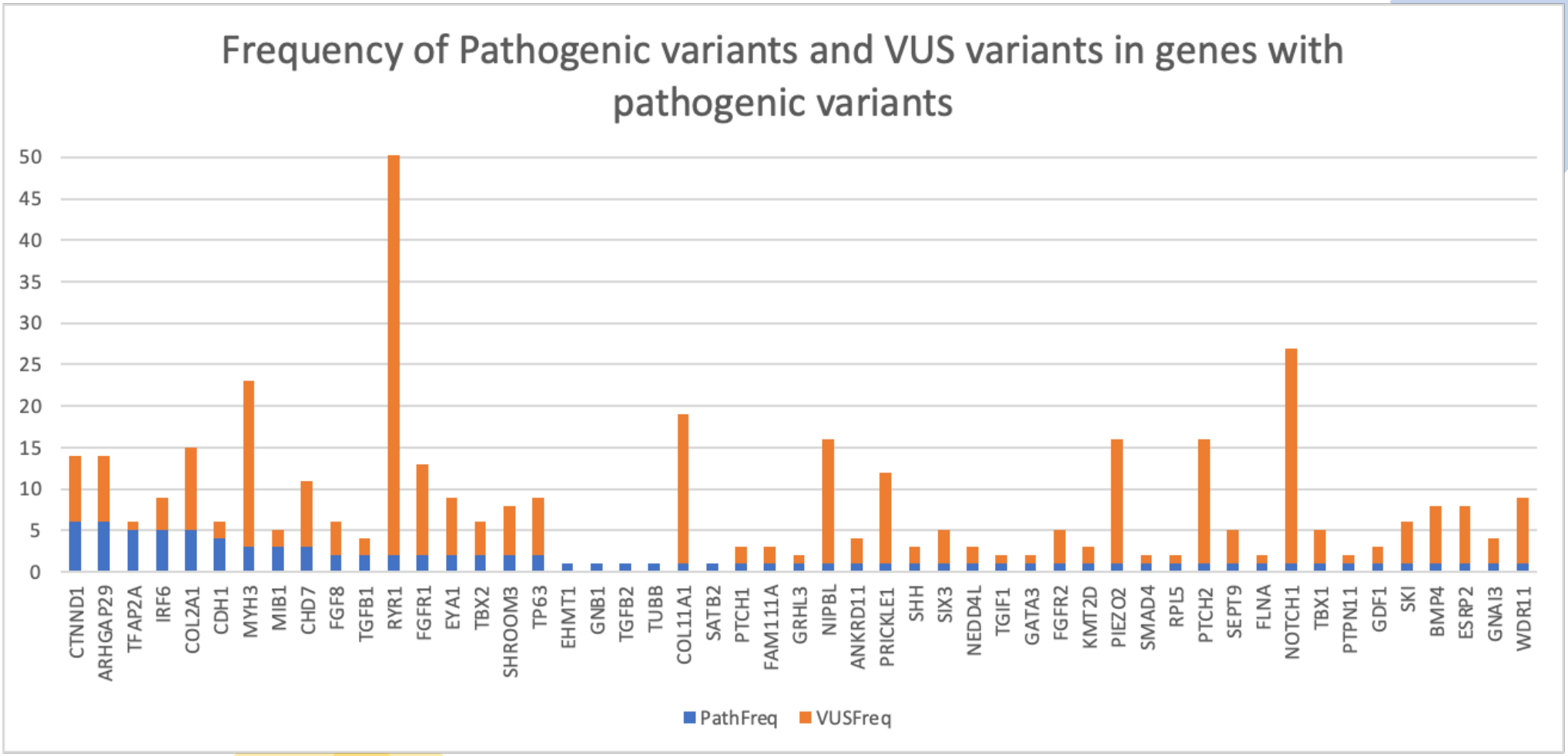


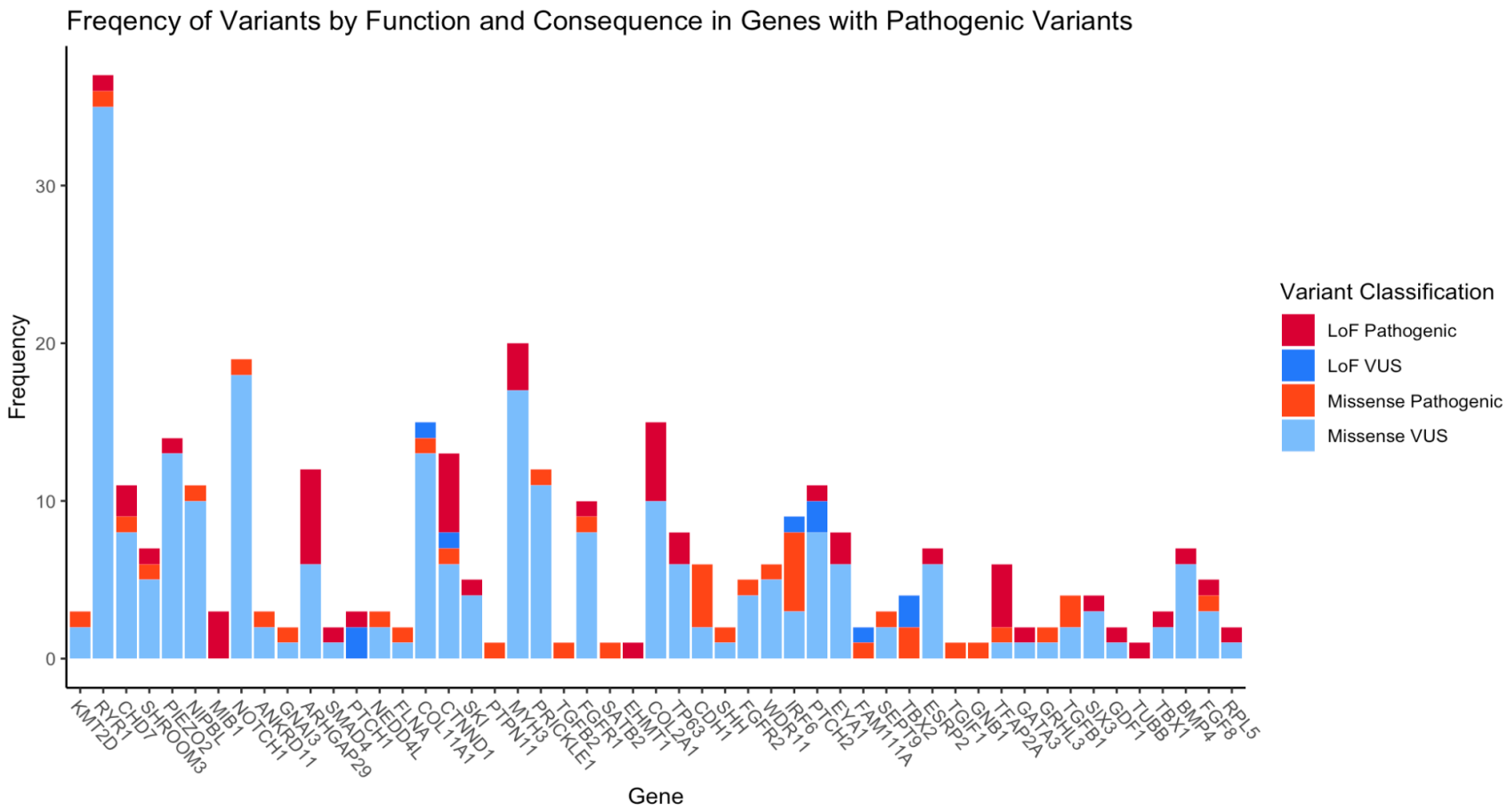
Genes on 4-5 Lists



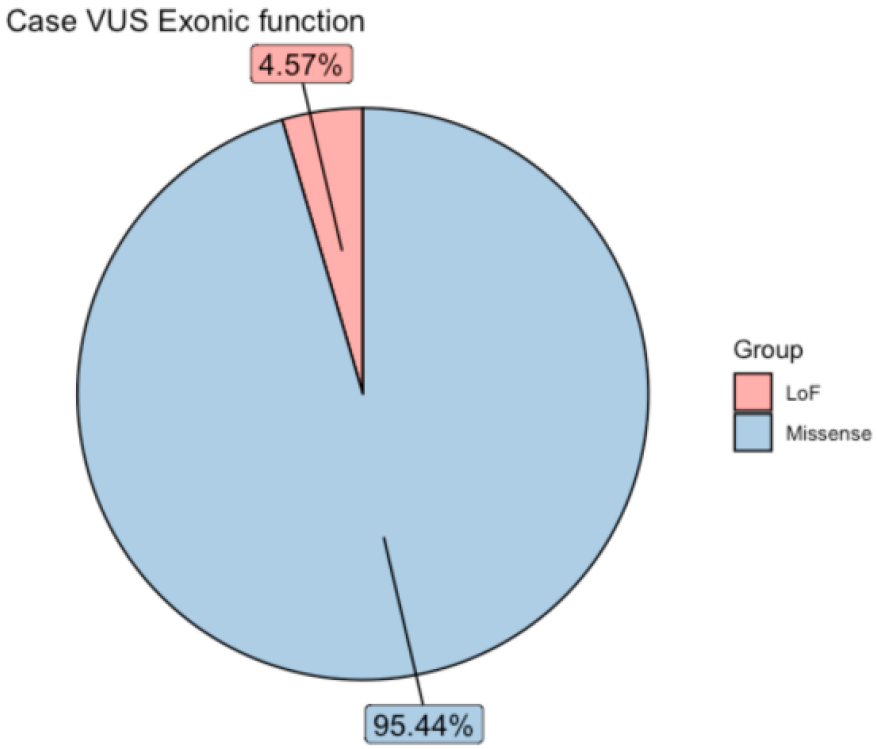
Chi squared and Fisher testing

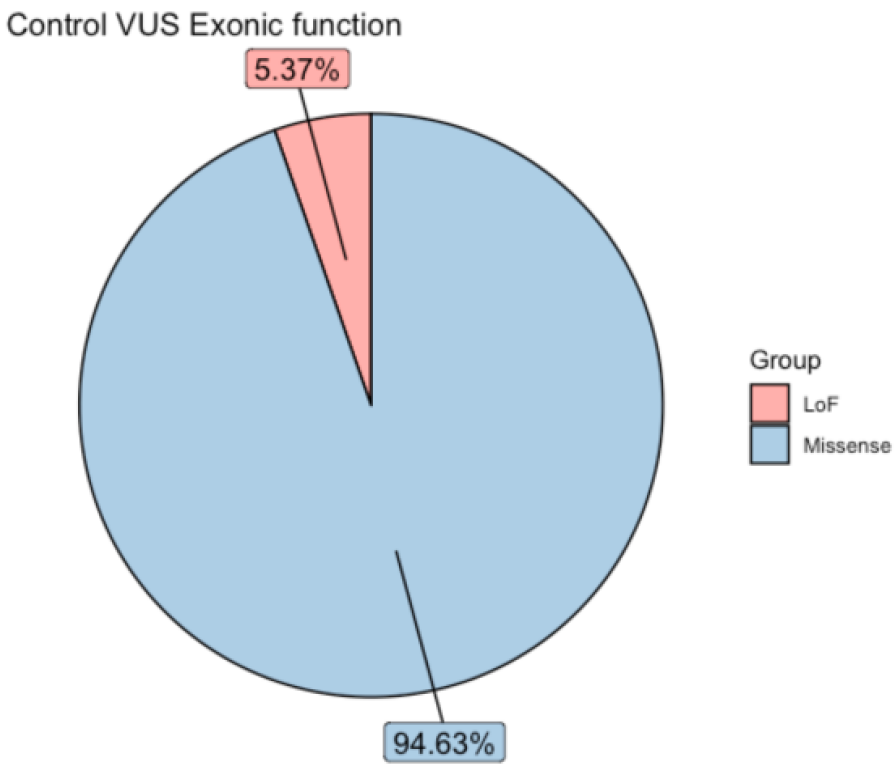
- By cleft status
  - CL vs control – p=0.0895
  - CLP vs control – p=0.006257**
  - CP vs control – p=0.311082
- By gene for top 5 genes with the most VUS
  - COL11A1, COL11A2, NIPBL, FGFR1, COL2A1
  - Test compared cases with VUS or pathogenic in cases vs. controls
  - None were statistically significant at a p=0.05


Frequency of Pathogenic variants and VUS variants in genes with pathogenic variants
50
45
40
35
30
25
20
15
10
5
0
CTNND1
ARHGAP29
TFAP2A
IRF6
COL2A1
CDH1
MYH3
MIB1
CHD7
FGF8
TGFB1
RYR1
FGFR1
EYA1
TBX2
SHROOM3
TP63
EHMT1
GNB1
TGFB2
TUBB
COL11A1
SATB2
PTCH1
FAM111A
GRHL3
NIPBL
ANKRD11
PRICKLE1
SHH
SIX3
NEDD4L
TGIF1
GATA3
FGFR2
KMT2D
PIEZO2
SMAD4
RPL5
PTCH2
SEPT9
FLNA
NOTCH1
TBX1
PTPN11
GDF1
SKI
BMP4
ESRP2
GNAI3
WDR11
PathFreq
VUSFreq

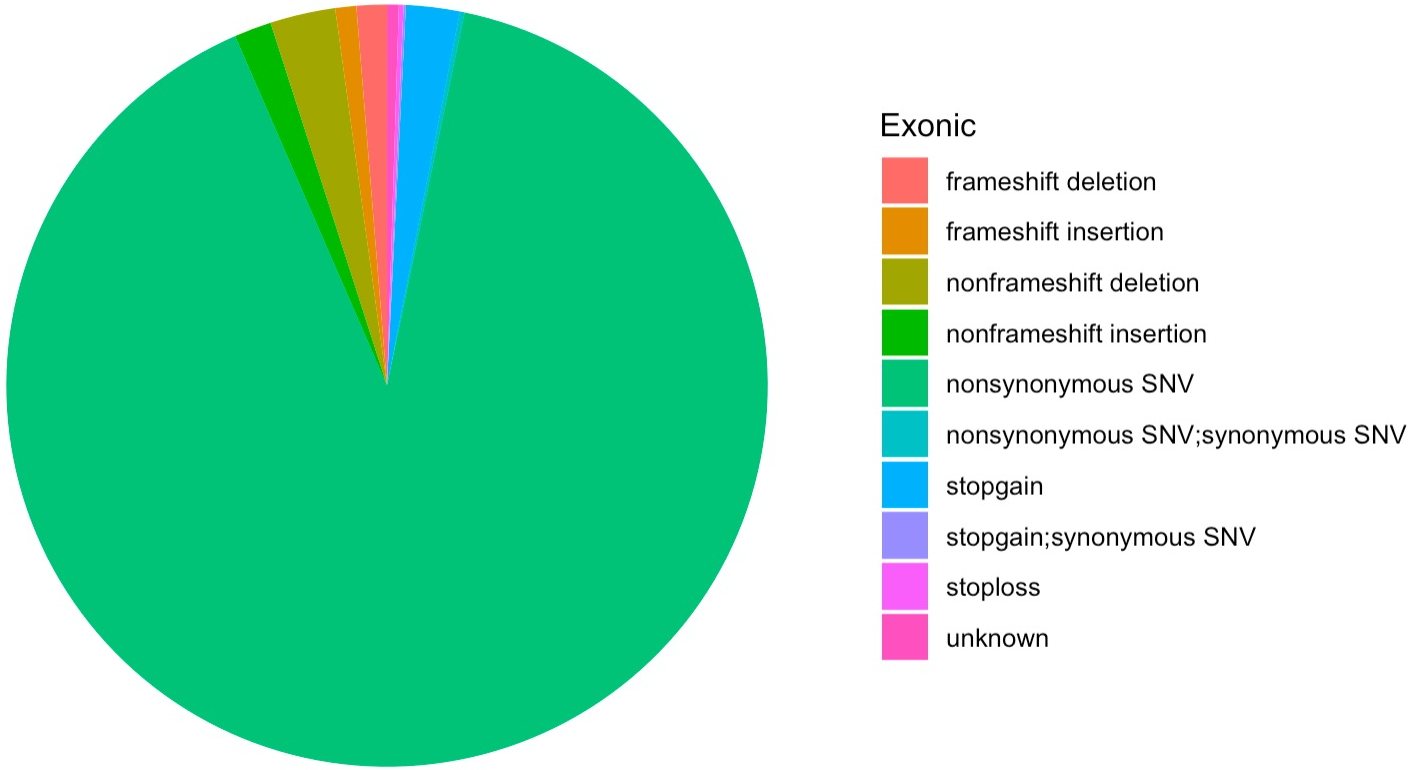

Freqency of Variants by Function and Consequence in Genes with Pathogenic Variants
Frequency
0
10
20
30
Gene
KMT2D
RYR1
CHD7
SHROOM3
PIEZO2
NIPBL
MIB1
NOTCH1
ANKRD11
GNAI3
ARHGAP29
SMAD4
PTCH1
NEDD4L
FLNA
COL11A1
CTNND1
SKI
PTPN11
MYH3
PRICKLE1
TGFB2
FGFR1
SATB2
EHMT1
COL2A1
TP63
CDH1
SHH
FGFR2
WDR11
IRF6
PTCH2
EYA1
FAM111A
SEPT9
TBX2
ESRP2
TGIF1
GNB1
TFAP2A
GATA3
GRHL3
TGFB1
SIX3
GDF1
TUBB
TBX1
BMP4
FGF8
RPL5
Variant Classification
LoF Pathogenic
LoF VUS
Missense Pathogenic
Missense VUS

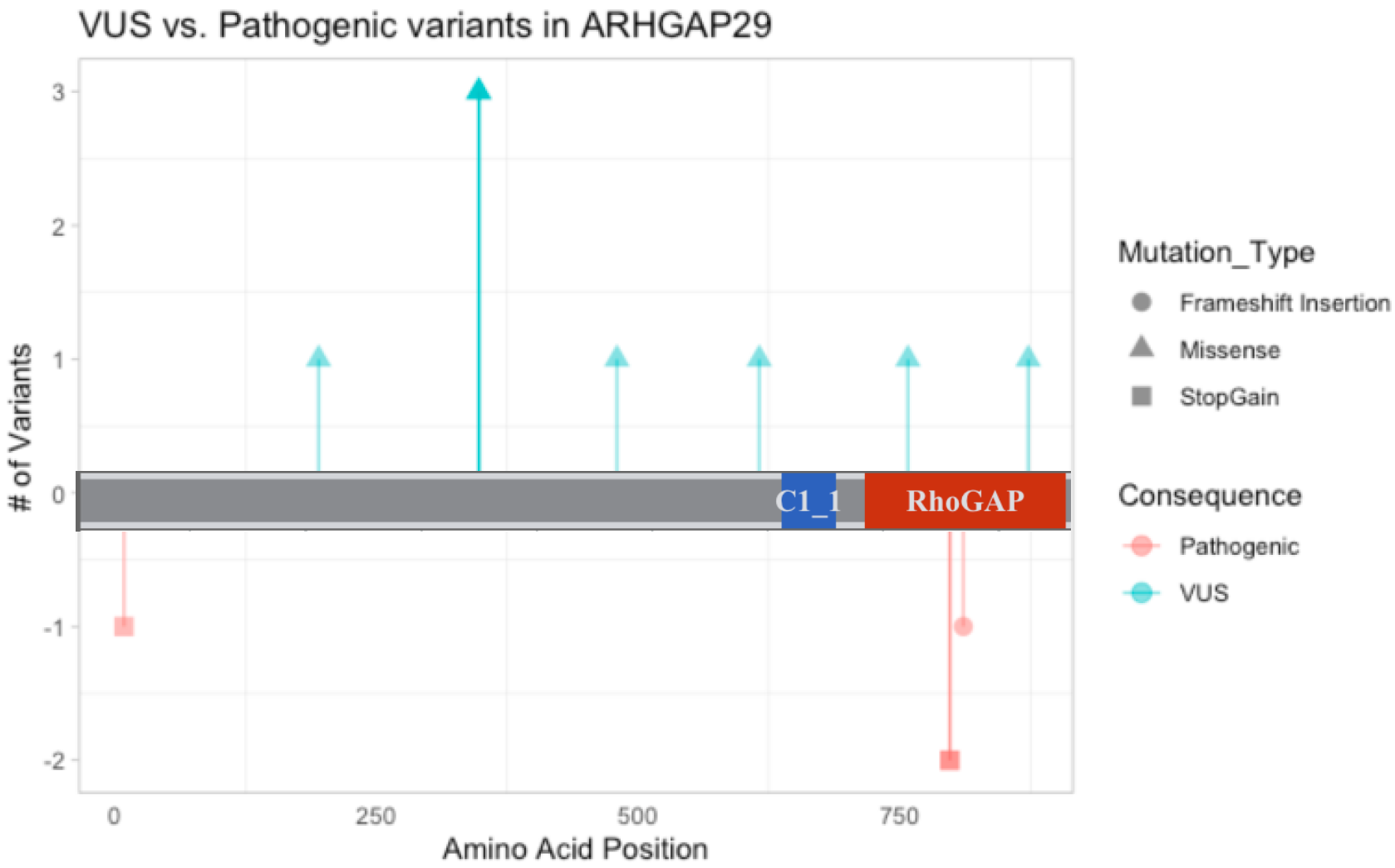
Cases vs. Controls by exonic function

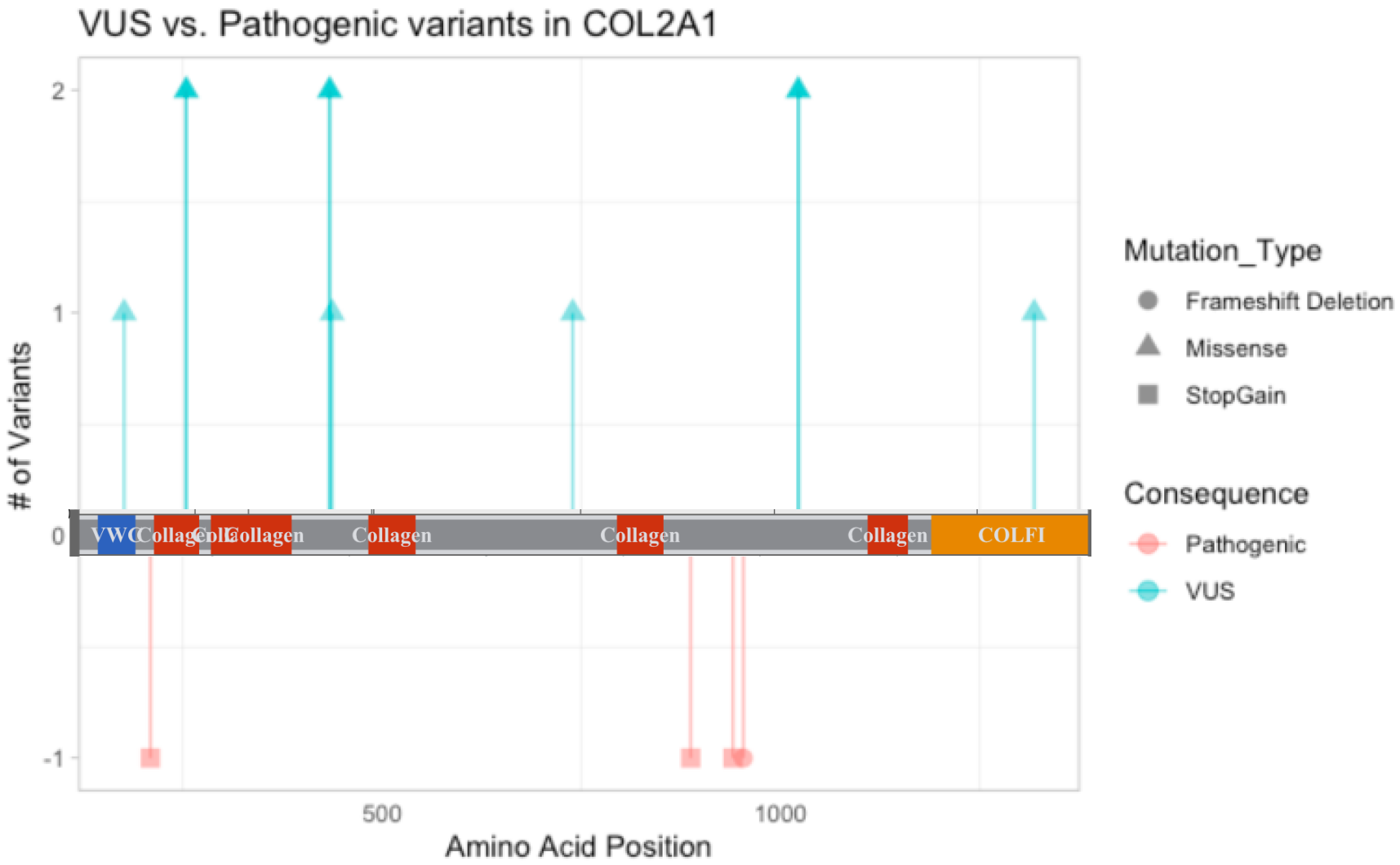


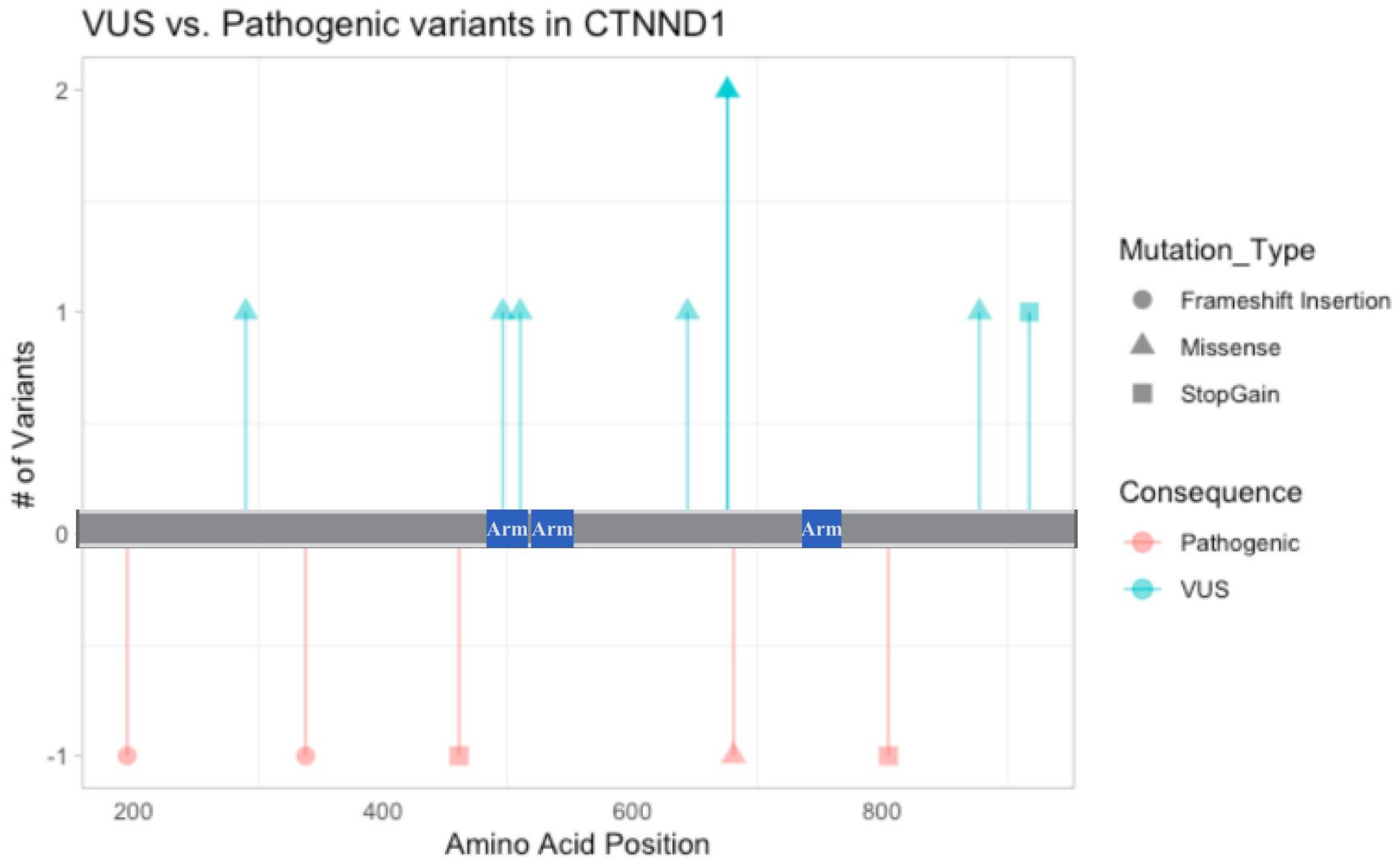


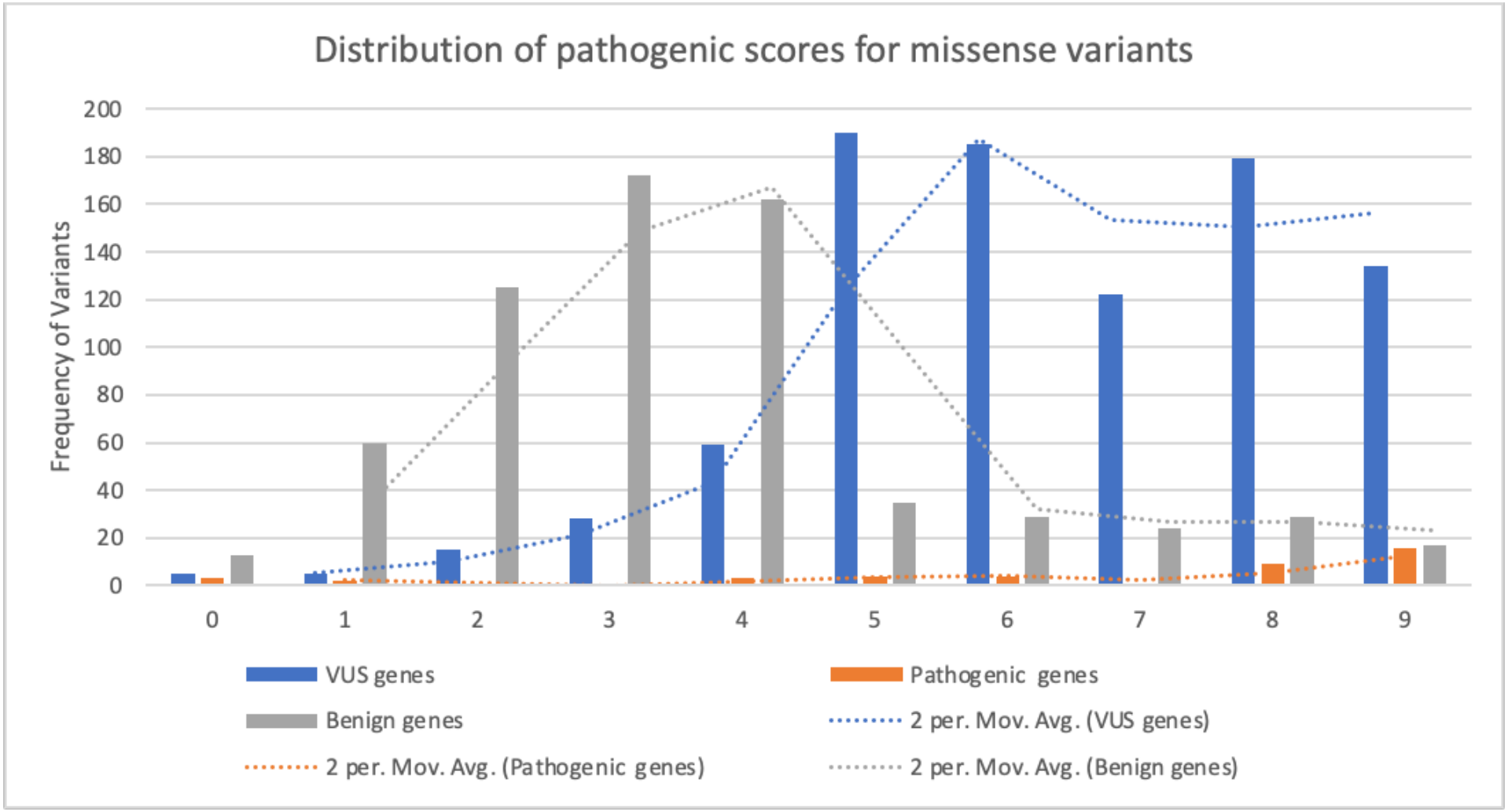
Further exonic function for VUS in cases

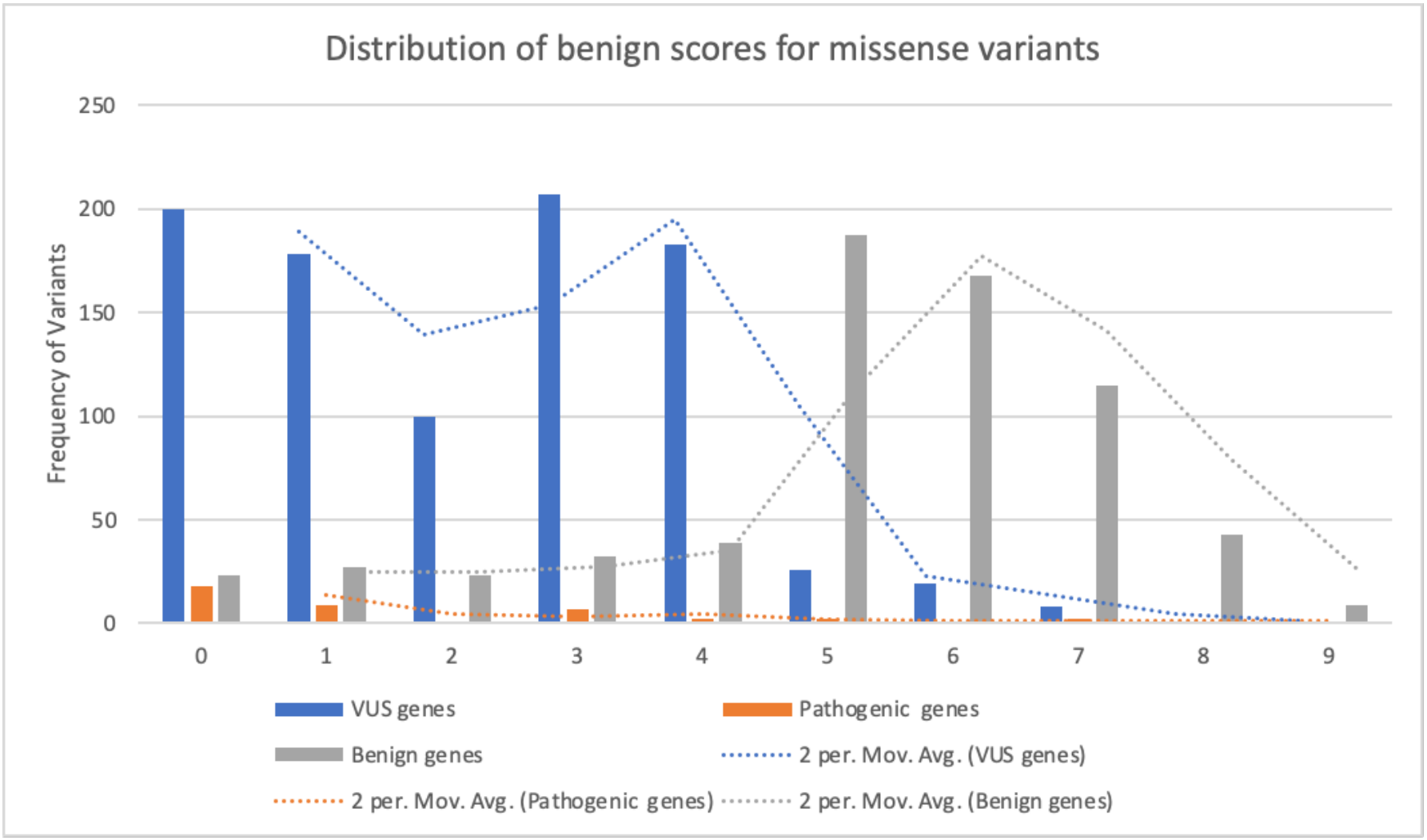



VUS vs. Pathogenic variants in ARHGAP29
# of Variants
3
2
1
0
-1
-2
0
250
500
750
Amino Acid Position
C1_1
RhoGAP
Mutation_Type
Frameshift Insertion
Missense
StopGain
Consequence
Pathogenic
VUS


VUS vs. Pathogenic variants in COL2A1
# of Variants
2
1
0
-1
VWC
Collagen
Collagen
Collagen
Collagen
Collagen
COLFI
500
1000
Amino Acid Position
Mutation_Type
Frameshift Deletion
Missense
StopGain
Consequence
Pathogenic
VUS


VUS vs. Pathogenic variants in CTNND1
# of Variants
2
1
0
-1
Arm
Arm
Arm
200
400
600
800
Amino Acid Position
Mutation_Type
Frameshift Insertion
Missense
StopGain
Consequence
Pathogenic
VUS


Distribution of pathogenic scores for missense variants
Frequency of Variants
200
180
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
VUS genes
Pathogenic genes
Benign genes
2 per. Mov. Avg. (VUS genes)
2 per. Mov. Avg. (Pathogenic genes)
2 per. Mov. Avg. (Benign genes)


Distribution of benign scores for missense variants
Frequency of Variants
250
200
150
100
50
0
0
1
2
3
4
5
6
7
8
9
VUS genes
Pathogenic genes
Benign genes
2 per. Mov. Avg. (VUS genes)
2 per. Mov. Avg. (Pathogenic genes)
2 per. Mov. Avg. (Benign genes)

Thank you!

Questions?