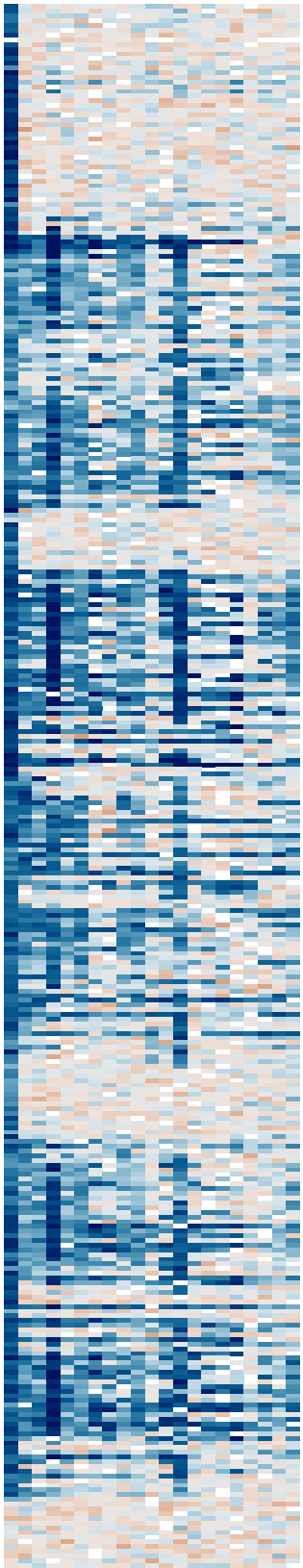
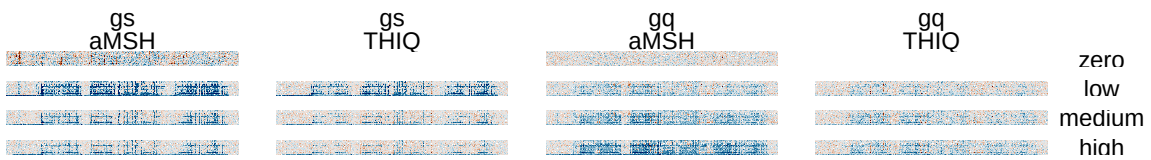
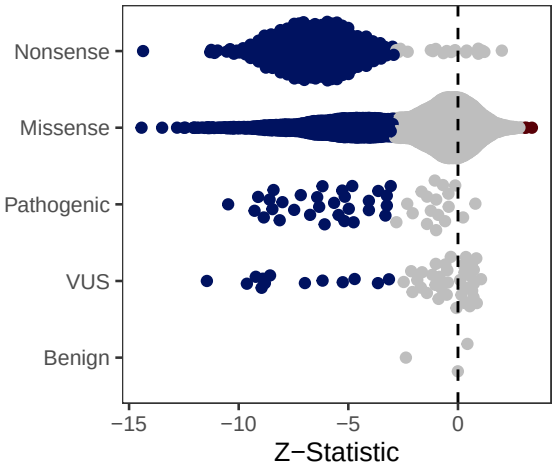
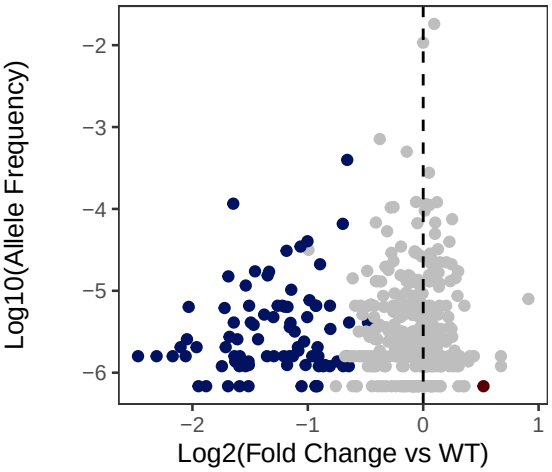
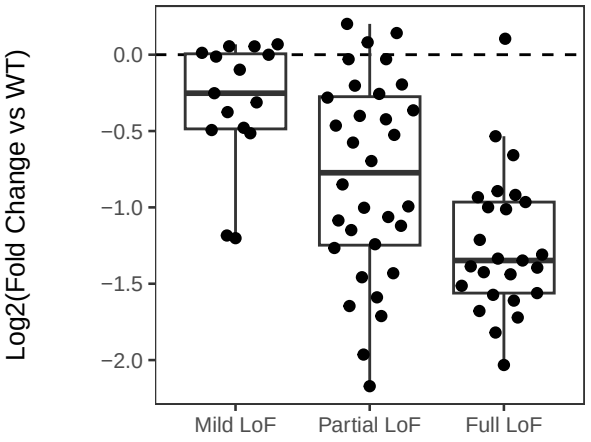
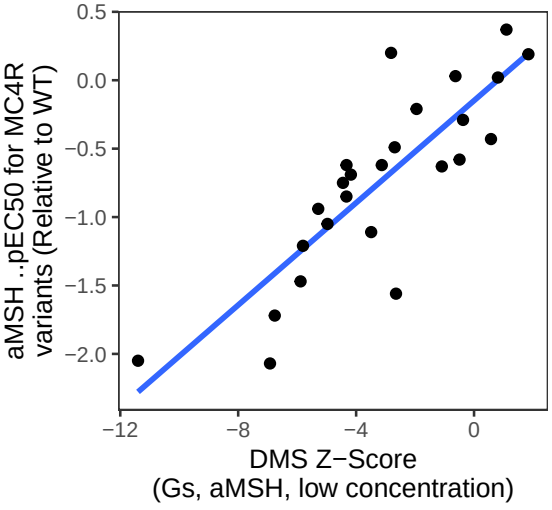


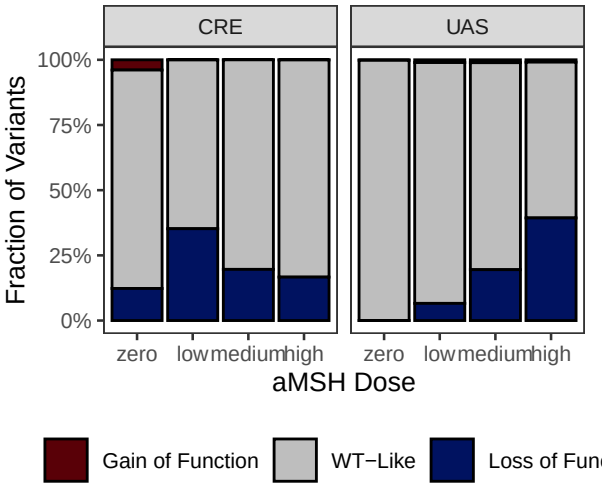

gs
aMSH
gs
THIQ
gq
aMSH
gq
THIQ
zero
low
medium
high


Nonsense
Missense
Pathogenic
VUS
Benign
−15
−10
−5
0
Z−Statistic


Log10(Allele Frequency)
−2
−3
−4
−5
−6
−2
−1
0
1
Log2(Fold Change vs WT)


Log2(Fold Change vs WT)
0.0
−0.5
−1.0
−1.5
−2.0
Mild LoF
Partial LoF
Full LoF


aMSH ..pEC50 for MC4R
variants (Relative to WT)
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−12
−8
−4
0
DMS Z−Score
(Gs, aMSH, low concentration)


CRE
UAS
Fraction of Variants
100%
75%
50%
25%
0%
zero
low
medium
high
aMSH Dose
Gain of Function
WT−Like
Loss of Func