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CALM1, CALM2, and CALM3 expression and translation efficiency provide insight into the severity of calmodulinopathy

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Background

- Missense variants in any of the calmodulin-encoding genes (*CALM1*, *CALM2*, and *CALM3*) cause calmodulinopathy, an ultra-rare disorder associated with ventricular arrhythmias and sudden cardiac death in childhood¹.
- Relative pathogenicity of identical mutations in *CALM1*, *CALM2*, and *CALM3* is unknown.

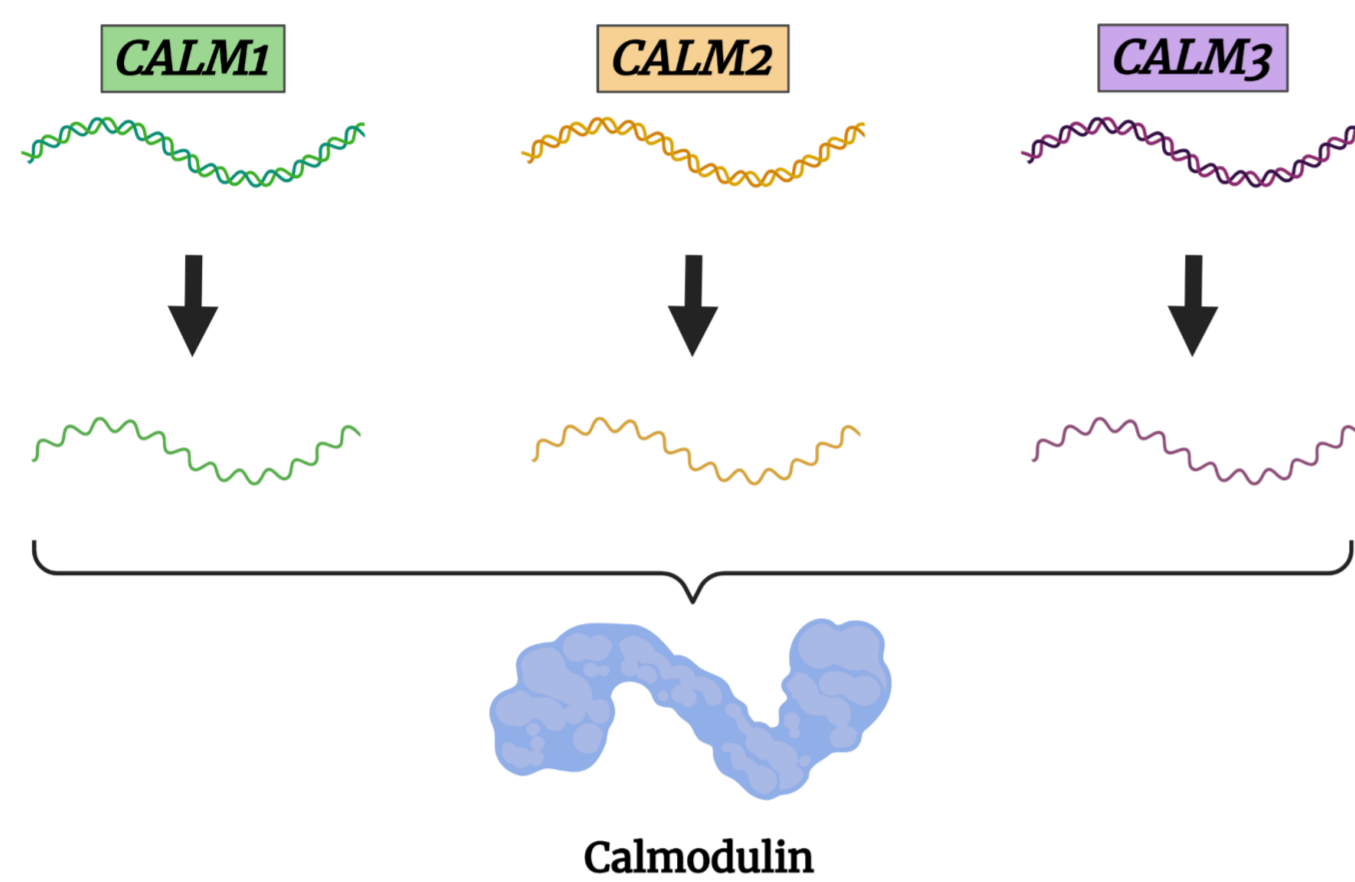


Fig. 1 | Genetic redundancy of *CALM1*, *CALM2*, and *CALM3*
CALM1, *CALM2*, and *CALM3* are genetically different but encodes an identical calmodulin protein.

Purpose of study

To decode the different pathogenicity among mutations in *CALM1*, *CALM2*, and *CALM3*.

Materials and Methods

- Clinical characteristics of missense mutation carriers was compared based on data from the 140 individuals in the International Calmodulinopathy Registry¹.
- Observed/expected ratios of mutations was obtained from the v4.1 release of the Genome Aggregation Database (gnomAD)².
- RNA sequencing data of 15,201 samples were obtained from 49 different non-diseased tissues from the Genotype-Expression Tissue (GTEx) project³. Relative gene expression was calculated as gene expression per gene compared to the total expression of *CALM1*, *CALM2*, and *CALM3*.
- Paired RNA sequencing and ribosome profiling data was obtained from a previous study of translational regulation in 80 human left ventricle samples⁴. We multiplied the median translational efficiency of *CALM1*, *CALM2*, and *CALM3* with the relative gene expression to estimate the translation per gene.

Results

- Cardiac events is most prevalent among *CALM1* (46/52, 89%) followed by *CALM2* (37/53, 70%) and *CALM3* (20/35, 57%) missense variant carriers.
- Observed/expected ratios of missense variants is lowest for *CALM1* (0.11) followed by *CALM2* (0.20) and *CALM3* (0.29).
- CALM3* was the least expressed gene in 39/49 tissues.
- The contribution to the total calmodulin amount in the left ventricle differed significantly among *CALM1*, *CALM2*, and *CALM3* ($p < 2 \times 10^{-16}$), with estimated contributions of 45% (range: 28%-72%), 44% (range: 24%-64%), and 11% (range: 4%-19%), respectively.

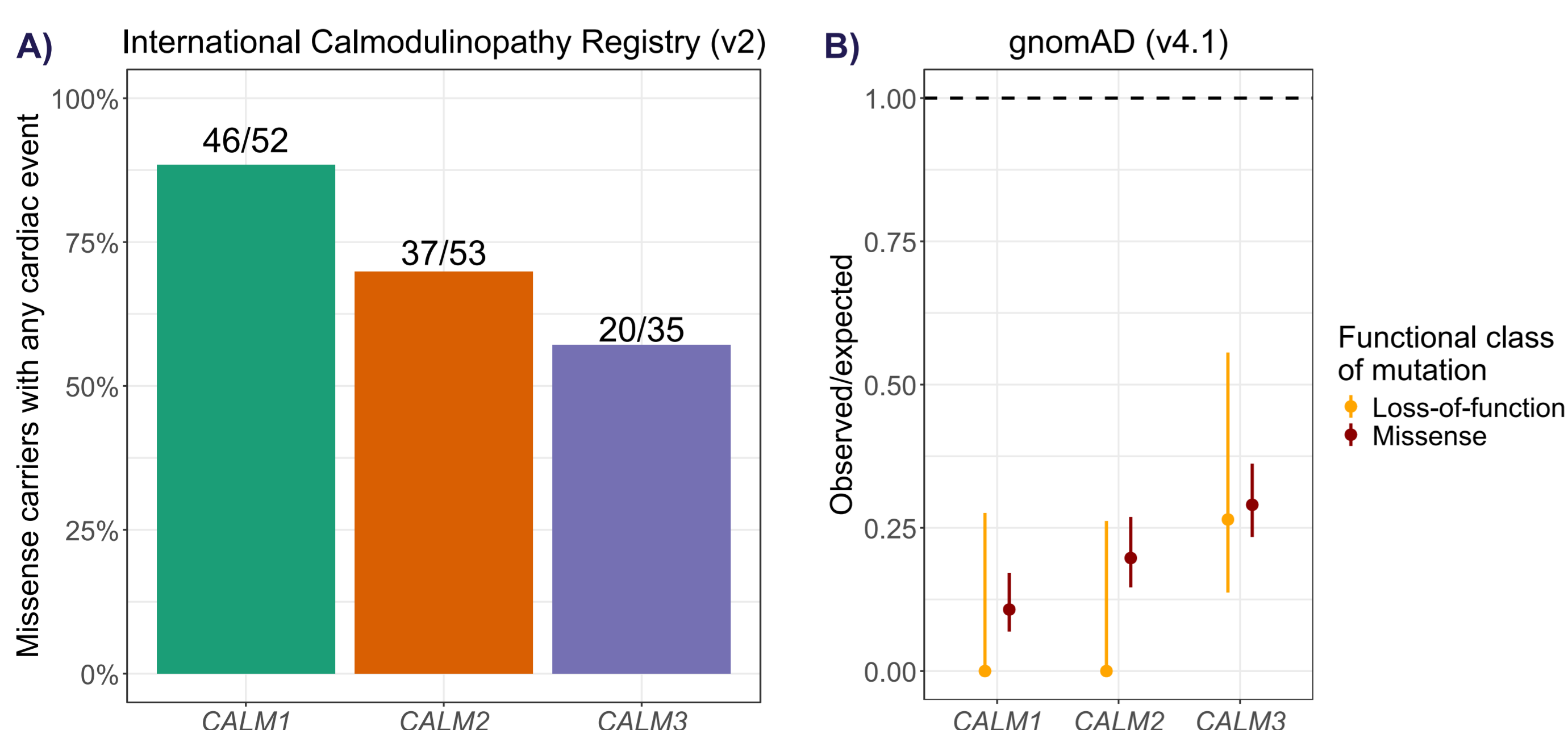


Fig. 2 | DNA variants in *CALM1*, *CALM2*, and *CALM3*
A) Percentage of missense variant carriers in *CALM1*, *CALM2*, and *CALM3* with cardiac events in the International Calmodulinopathy Registry. Cardiac events corresponds to any of arrhythmic syncope, aborted cardiac arrest, sudden cardiac death, or appropriate implantable cardioverter-defibrillator shocks. B) Observed-to-expected ratios in gnomAD together with 90% confidence intervals and categorized by functional class. The horizontal dashed line at observed-to-expected = 1 represents the expected number of variants under neutral selection.

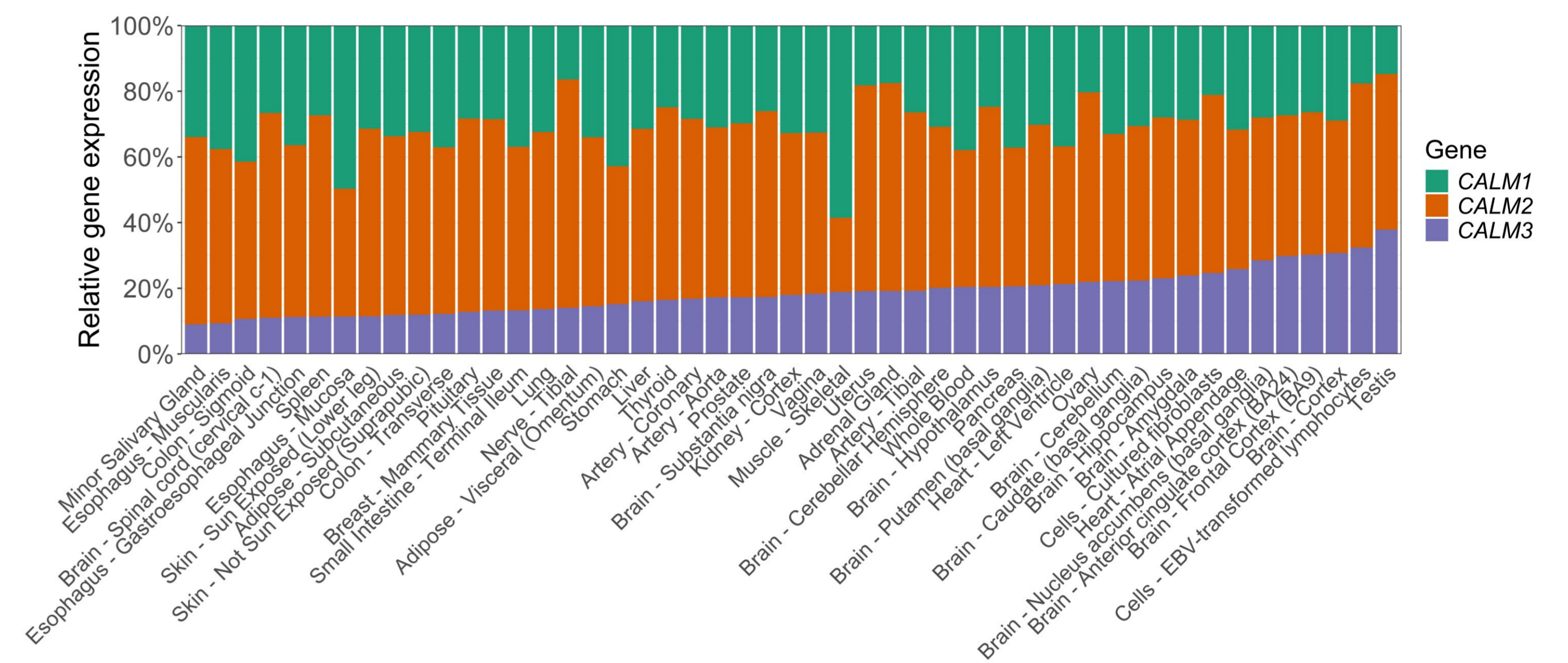


Fig. 3 | Relative expression of *CALM1*, *CALM2*, and *CALM3*
Percentage expressed of *CALM1*, *CALM2*, and *CALM3* per tissue among the 49 different tissues from the GTEx project. The tissues are arranged according to the mean relative gene expression of *CALM3*.

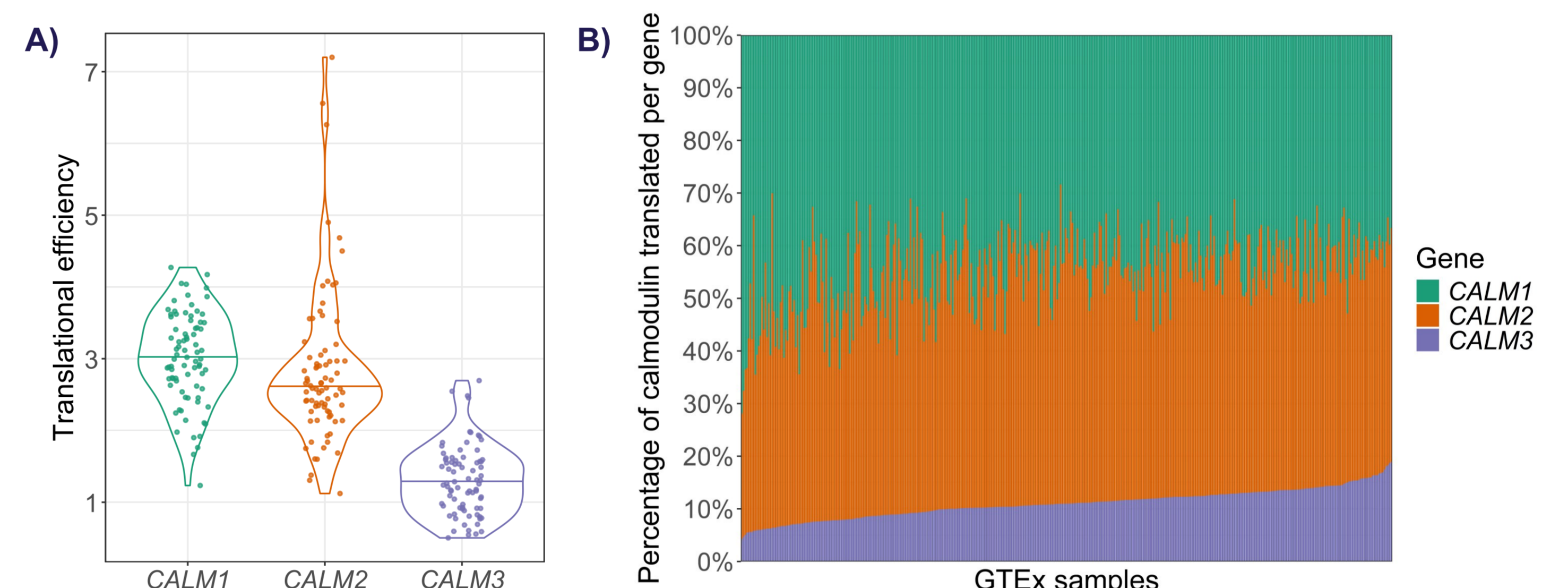


Fig. 4 | Estimated translation of *CALM1*, *CALM2*, and *CALM3* in left ventricle
A) Translational efficiency per individual among *CALM1*, *CALM2*, and *CALM3* in 80 left ventricle samples. The translational efficiency was significantly different using the Wilcoxon rank sum test for *CALM1* vs *CALM2* ($p = 2.53 \times 10^{-3}$), *CALM1* vs *CALM3* ($p = 2.79 \times 10^{-14}$), and for *CALM2* vs *CALM3* ($p = 5.51 \times 10^{-14}$). B) Estimated percentage of calmodulin translated per gene for left ventricle samples obtained from the GTEx project.

Discussion

- The contribution of *CALM1* and *CALM2* to the total calmodulin levels in the human heart is four-fold greater compared to *CALM3*, suggesting why missense variants in *CALM3* are associated with a less severe cardiac phenotype than those in *CALM1* and *CALM2*.
- Large variations in estimated translation per gene may explain variable expressivity in families affected by calmodulinopathy.

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Competing interests

We declare no competing interests.

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