Supplementary information S5 | Analytical methods for Table 3

We aimed to compare the yield of ‘ultra-rare’ nonsynonymous and splice site genetic variants in published sudden infant death syndrome (SIDS) cohorts to general population databases. We hypothesized a similarity of such genomic variation in genes associated with inherited cardiac conditions (ICCs) among SIDS cohorts and the general population.

Variants with a global minor allele frequency (MAF) of <0.00005 (1:20,000 alleles or 1 in 10,000 individuals)1 were considered as ‘ultra-rare’ using the Exome Aggregation Consortium (ExAC) browser (http://exac.broad institute.org). This contains whole-exome sequencing data from >60,706 unrelated individuals and was pulled on 12–13 January 2017.

Using PubMed, we searched the key phrases of “sudden infant death” and “gene”, “polymorphism”, or “mutation” and identified 21 population-based SIDS cohorts between 2000 and 2017. Studies based on definitions of SIDS contrary to current practices were excluded. We then undertook a comprehensive evaluation of all cohort studies (Supplementary Information Tables 1–4) that associate ICC-related genes with SIDS, which included mainly white individuals. We reanalysed all the gene variants published in these cohort studies, and filtered for nonsynonymous and splice site variants in ICC-related genes with a global MAF of <0.00005 in ExAC. The results were then aggregated per gene in Table 3. The yield of nonsynonymous and splice site variants in ICC genes with a MAF of <0.00005 in the same genes in ExAC are also presented in Table 3. Ultra-rare, nonsynonymous, and splice site variants in all SIDS cases were compared with ultra-rare, nonsynonymous, and splice site variants in ExAC exomes (all populations). A two-sample Chi-square test for equality of proportions with continuity equation was performed using the PASWw Statistics 18 software (SPSS Inc., USA). A two-sided P value of <0.001 was considered significant. The main limitations of the comparison are: differences in methods, platforms, and pipelines for calling variants in different cohort studies; inability to stratify formally for ethnicity; and the variable numerator size per gene tested.