**Table S-23. Enrichment analysis (cardiac disease).**

| **Annotation** | **Match group** | **FastEpistasis / logistic regression** | | | | | **BOOST** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **N, total** | **N, rep. (%)** | **Enrich P** | **Min Int P** | **Thresh** | **N, total** | **N, rep.** | **Enrich P** | **Min Int P** | **Thresh** |
| Exonic | None | 3421 | 2.6 | 1.000 | A: 1.64E-11<br>R: 4.19E-09 | 1.12E-12 | 3919 | 5.5 | 1.000 | A: 6.54E-11<br>R: 4.51E-10 | 1.12E-12 |
| | Either | 33 | 0 | | A: 9.75E-11<br>R: N/A | 6.38E-11 | 47 | 4.3 | | A: 2.35E-09<br>R: 3.63E-08 | 6.38E-11 |
| | Both | 0 | 0 | | A: N/A<br>R: N/A | 1.45E-08 | 0 | 0 | | A: N/A<br>R: N/A | 1.45E-08 |
| Reg. 1,2, or 3 | None | 3209 | 2.6 | 0.852 | A: 1.64E-11<br>R: 4.19E-09 | 1.20E-12 | 3656 | 5.5 | 1.000 | A: 6.54E-11<br>R: 4.51E-10 | 1.20E-12 |
| | Either | 240 | 2.1 | | A: 2.12E-11<br>R: 7.65E-08 | 1.42E-11 | 308 | 5.2 | | A: 1.82E-10<br>R: 7.78E-09 | 1.42E-11 |
| | Both | 5 | 0 | | A: 4.56E-09<br>R: N/A | 6.73E-10 | 2 | 0 | | A: 2.40E-08<br>R: N/A | 6.73E-10 |
| Disease EQTL | None | 3425 | 2.5 | 0.528 | A: 1.64E-11<br>R: 4.19E-09 | 1.12E-12 | 3926 | 5.5 | 0.480 | A: 6.54E-11<br>R: 4.51E-10 | 1.12E-12 |
| | Either | 29 | 3.5 | | A: 3.67E-09<br>R: 2.40E-07 | 7.16E-11 | 40 | 7.5 | | A: 1.62E-09<br>R: 6.67E-09 | 7.16E-11 |
| | Both | 0 | 0 | | A: N/A<br>R: N/A | 1.83E-08 | 0 | 0 | | A: N/A<br>R: N/A | 1.83E-08 |
| Disease gene | None | 2837 | 2.8 | 0.084 | A: 1.64E-11<br>R: 4.19E-09 | 1.35E-12 | 3229 | 5.6 | 0.462 | A: 6.54E-11<br>R: 4.51E-10 | 1.35E-12 |
| | Either | 586 | 1.4 | | A: 2.19E-11<br>R: 1.81E-07 | 6.37E-12 | 691 | 4.9 | | A: 8.54E-11<br>R: 3.37E-09 | 6.37E-12 |
| | Both | 31 | 0 | | A: 9.72E-09<br>R: N/A | 1.20E-10 | 46 | 2.2 | | A: 2.75E-09<br>R: 7.20E-08 | 1.20E-10 |
| Any gene | None | 1088 | 3.4 | 0.067 | A: 1.64E-11<br>R: 1.36E-08 | 3.72E-12 | 1185 | 6.2 | 0.426 | A: 1.16E-10<br>R: 4.51E-10 | 3.72E-12 |
| | Either | 1668 | 2.3 | | A: 2.12E-11<br>R: 4.19E-09 | 2.23E-12 | 1973 | 5.1 | | A: 6.54E-11<br>R: 1.25E-09 | 2.23E-12 |
| | Both | 698 | 1.7 | | A: 9.75E-11<br>R: 4.97E-09 | 5.34E-12 | 808 | 5.5 | | A: 8.54E-11<br>R: 2.15E-09 | 5.34E-12 |
| Marginal | None | 3086 | 2.5 | 8.03E-05 | A: 1.64E-11<br>R: 4.19E-09 | 1.24E-12 | 3543 | 5.2 | 1.15E-04 | A: 6.54E-11<br>R: 4.51E-10 | 1.24E-12 |
| | Either | 353 | 2.0 | | A: 3.18E-10<br>R: 3.94E-08 | 1.08E-11 | 415 | 7.0 | | A: 3.37E-10<br>R: 2.15E-09 | 1.08E-11 |
| | Both | 15 | 20.0 * | | A: 1.29E-08<br>R: 1.09E-07 | 3.77E-10 | 8 | 37.5 | | A: 1.23E-08<br>R: 1.23E-08 | 3.77E-10 |

Followed-up interactions (interactions with $P<10^{-7}$ in either the FastEpistasis or BOOST analyses) were grouped by the number of SNPs that match a particular annotation category (**Match group**: none, either, or both SNPs matching). Annotation categories are described in the Supplemental Methods section. **N, total**: total number of interactions in each annotation match group. **N, rep (%)**: percentage of the total that were nominally replicated. **Enrich P**: enrichment test P-value (testing if there is a significant difference between percentages of nominally replicated interactions among the different annotation match groups; chi-square test or Fisher's exact test). **Min Int P**: among all interactions in the particular annotation match category, the P-value of the most significant interaction (A), and the P-value of the most significant nominally replicated interaction (R). **Thresh**: hypothetical significance threshold assuming that the search space was first trimmed to only include SNP pairs corresponding to the particular annotation match group. Green shading: enrichment P-value < 0.05. Cyan shading: a "Min Int P" value that is less than the respective "Thresh".

* The three interactions that were nominally replicated (among FastEpistasis-identified interactions where both SNPs were marginally significant; i.e., 20.0% of 15 in the table above) were the following: rs17018095 × rs2206426, rs10485227 × rs61352759, rs11768588 × rs11105883.