

**Supplementary Table 1.** Distribution of samples across countries and geographic regions, before filtering.

| <b>Geographic Region</b>   | <b>Country/<br/>Territory</b> | <b>Individuals</b> |
|----------------------------|-------------------------------|--------------------|
| <b>Arabian Peninsula</b>   | Kuwait                        | 45                 |
|                            | Oman                          | 19                 |
|                            | Qatar                         | 8                  |
|                            | Saudi Arabia                  | 184                |
|                            | UAE                           | 44                 |
|                            | Yemen                         | 8                  |
|                            | <b>Northeast Africa</b>       | Egypt              |
|                            | Libya                         | 59                 |
| <b>Northwest Africa</b>    | Algeria                       | 13                 |
|                            | Morocco                       | 96                 |
|                            | Tunisia                       | 4                  |
| <b>Persia and Pakistan</b> | Iran                          | 87                 |
|                            | Pakistan                      | 136                |
| <b>Syrian Desert</b>       | Iraq                          | 10                 |
|                            | Israel                        | 13                 |
|                            | Jordan                        | 40                 |
|                            | Lebanon                       | 5                  |
|                            | West Bank                     | 9                  |
|                            | Syria                         | 6                  |
| <b>Turkish Peninsula</b>   | Turkey                        | 249                |
| <b>Total</b>               |                               | 1649               |

**Supplementary Table2.** The majority of loss of function (LOF) variants are had allele frequency <.5%, and co-occurrence within a gene was rare. The functional class of predicted LOF variants, and the counts for three allele frequency bins (<.5%, .5%<x<2%, >2%) shown.

|                             | <.5%   |      | .5%<x<2% |      | >2%    |      | Total Variants | Genes |
|-----------------------------|--------|------|----------|------|--------|------|----------------|-------|
|                             | Indels | SNPs | Indels   | SNPs | Indels | SNPs |                |       |
| <b>Frameshift Deletion</b>  | 1426   | 0    | 276      | 0    | 279    | 0    | 1981           | 1670  |
| <b>Frameshift Insertion</b> | 762    | 0    | 319      | 0    | 461    | 0    | 1542           | 1338  |
| <b>Stopgain</b>             | 48     | 5129 | 7        | 795  | 8      | 306  | 6293           | 4648  |
| <b>Stoploss</b>             | 4      | 174  | 1        | 51   | 2      | 68   | 300            | 282   |
| <b>Exonic near-splice</b>   | 0      | 72   | 0        | 25   | 3      | 35   | 135            | 127   |
| <b>Splice Junction</b>      | 20     | 0    | 6        | 1    | 10     | 3    | 40             | 40    |

**Supplemental Table 4.** Number of predicted high-impact variants passing segregation filters and allele count filters. Four datasets were used as a healthy background to reduce the number of candidates: HSP – using only healthy members of HSP families, With GME – using the GME variome to estimate allele frequencies, With EA – using the EVS EA population, With AA – using the EVS AA population as background. 0,1,2,3 refer to the number of allele shares for that fraction of variants.

| Family      | Members | HSP only |      |      |      |       | With GME AF |      |      |      |       | With EA AF |      |      |      |       | With AA AF |      |      |      |       |
|-------------|---------|----------|------|------|------|-------|-------------|------|------|------|-------|------------|------|------|------|-------|------------|------|------|------|-------|
|             |         | 0        | 1    | 2    | 3    | total | 0           | 1    | 2    | 3    | total | 0          | 1    | 2    | 3    | total | 0          | 1    | 2    | 3    | total |
| 1242        | 1       | 51       | 23   | 29   | 14   | 117   | 9           | 1    | 3    | 0    | 13    | 22         | 1    | 4    | 0    | 27    | 17         | 1    | 3    | 0    | 21    |
| 1314        | 1       | 50       | 41   | 26   | 23   | 140   | 11          | 1    | 1    | 0    | 13    | 14         | 1    | 1    | 0    | 16    | 12         | 1    | 1    | 0    | 14    |
| 1549        | 1       | 74       | 30   | 23   | 16   | 143   | 12          | 3    | 3    | 1    | 19    | 33         | 3    | 3    | 1    | 40    | 29         | 2    | 2    | 1    | 34    |
| 1829        | 1       | 55       | 28   | 18   | 18   | 119   | 6           | 2    | 0    | 1    | 9     | 17         | 2    | 0    | 1    | 20    | 16         | 2    | 1    | 1    | 20    |
| 709         | 1       | 80       | 38   | 40   | 25   | 183   | 31          | 5    | 4    | 5    | 45    | 48         | 6    | 4    | 5    | 63    | 39         | 6    | 5    | 5    | 55    |
| 789         | 1       | 35       | 17   | 20   | 14   | 86    | 12          | 1    | 1    | 3    | 17    | 16         | 1    | 1    | 3    | 21    | 15         | 1    | 1    | 3    | 20    |
| 882         | 1       | 44       | 21   | 16   | 22   | 103   | 9           | 4    | 1    | 1    | 15    | 19         | 4    | 1    | 1    | 25    | 17         | 2    | 1    | 1    | 21    |
| <b>Mean</b> |         | 55.6     | 28.3 | 24.6 | 18.9 | 127   | 12.9        | 2.43 | 1.86 | 1.57 | 18.7  | 24.1       | 2.57 | 2    | 1.57 | 30.3  | 20.7       | 2.14 | 2    | 1.57 | 26.4  |
| 1098        | 2       | 19       | 10   | 9    | 12   | 50    | 2           | 1    | 0    | 0    | 3     | 3          | 1    | 0    | 0    | 4     | 5          | 1    | 0    | 0    | 6     |
| 1241        | 2       | 12       | 10   | 7    | 5    | 34    | 2           | 3    | 0    | 1    | 6     | 8          | 3    | 0    | 1    | 12    | 6          | 3    | 0    | 1    | 10    |
| 1290        | 2       | 19       | 12   | 3    | 10   | 44    | 1           | 0    | 0    | 1    | 2     | 3          | 0    | 0    | 1    | 4     | 1          | 0    | 0    | 1    | 2     |
| 1349        | 2       | 9        | 7    | 9    | 13   | 38    | 1           | 0    | 0    | 2    | 3     | 2          | 0    | 0    | 2    | 4     | 3          | 0    | 0    | 2    | 5     |
| 1526        | 2       | 18       | 8    | 7    | 3    | 36    | 9           | 1    | 0    | 1    | 11    | 15         | 1    | 0    | 1    | 17    | 8          | 1    | 0    | 1    | 10    |
| 1598        | 2       | 29       | 10   | 9    | 10   | 58    | 2           | 0    | 2    | 0    | 4     | 8          | 0    | 2    | 0    | 10    | 5          | 1    | 2    | 0    | 8     |
| 1611        | 2       | 45       | 19   | 22   | 13   | 99    | 13          | 2    | 5    | 1    | 21    | 23         | 2    | 5    | 2    | 32    | 15         | 2    | 6    | 2    | 25    |
| 1675        | 2       | 24       | 13   | 5    | 10   | 52    | 2           | 0    | 0    | 2    | 4     | 7          | 0    | 0    | 2    | 9     | 10         | 1    | 0    | 2    | 13    |
| 1800        | 2       | 21       | 4    | 4    | 7    | 36    | 5           | 1    | 0    | 1    | 7     | 7          | 1    | 0    | 1    | 9     | 9          | 1    | 0    | 1    | 11    |
| 659         | 2       | 36       | 17   | 10   | 14   | 77    | 11          | 2    | 1    | 2    | 16    | 19         | 2    | 1    | 2    | 24    | 15         | 4    | 1    | 2    | 22    |
| 738         | 2       | 9        | 5    | 13   | 9    | 36    | 1           | 0    | 1    | 1    | 3     | 5          | 1    | 1    | 1    | 8     | 5          | 0    | 1    | 1    | 7     |
| 787         | 2       | 6        | 4    | 4    | 3    | 17    | 1           | 0    | 0    | 1    | 2     | 1          | 0    | 0    | 1    | 2     | 1          | 0    | 0    | 1    | 2     |
| 803         | 2       | 13       | 5    | 7    | 6    | 31    | 3           | 0    | 0    | 0    | 3     | 4          | 0    | 0    | 0    | 4     | 2          | 0    | 0    | 0    | 2     |
| 910         | 2       | 32       | 20   | 14   | 14   | 80    | 9           | 1    | 3    | 1    | 14    | 16         | 2    | 3    | 1    | 22    | 8          | 3    | 3    | 1    | 15    |
| <b>Mean</b> |         | 20.1     | 9.71 | 8.14 | 9    | 47    | 4.57        | 0.57 | 0.71 | 1.14 | 7     | 8.43       | 0.86 | 0.71 | 1.14 | 11.1  | 7.14       | 1.29 | 0.71 | 1.14 | 10.3  |
| 786         | 3       | 11       | 5    | 3    | 3    | 22    | 4           | 1    | 0    | 0    | 5     | 4          | 1    | 0    | 0    | 5     | 5          | 1    | 0    | 0    | 6     |