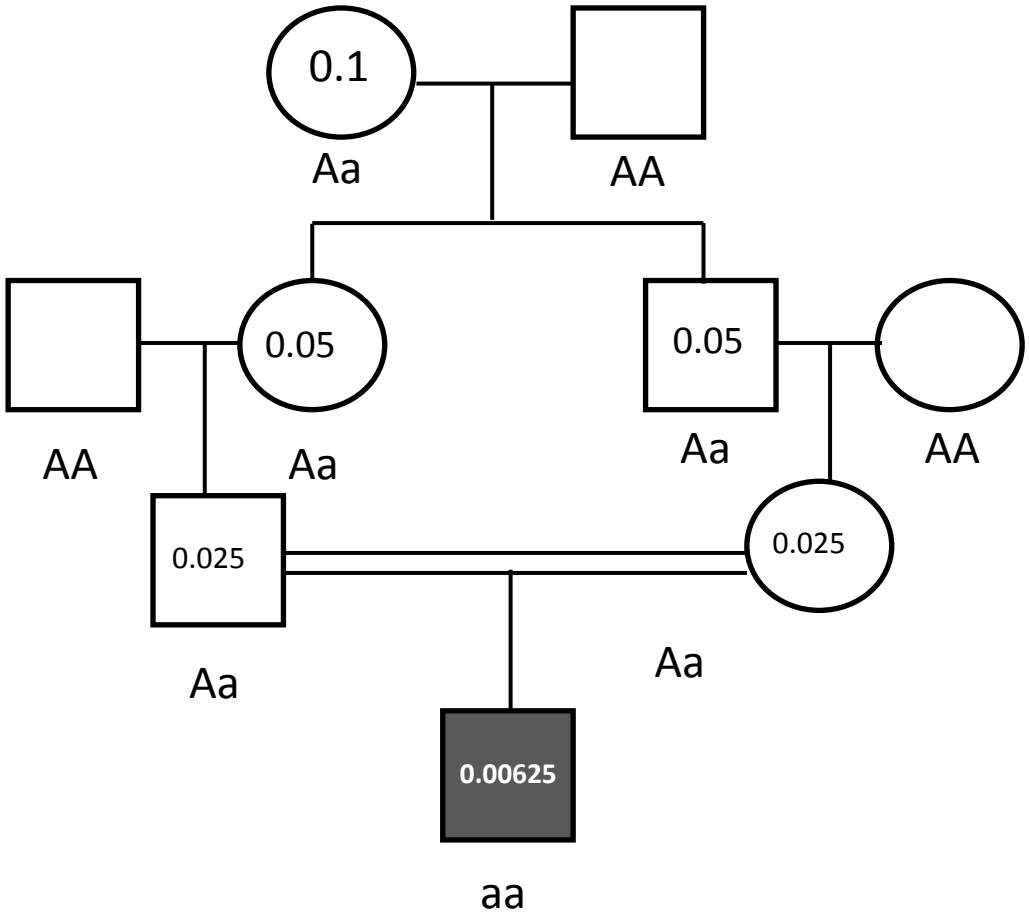
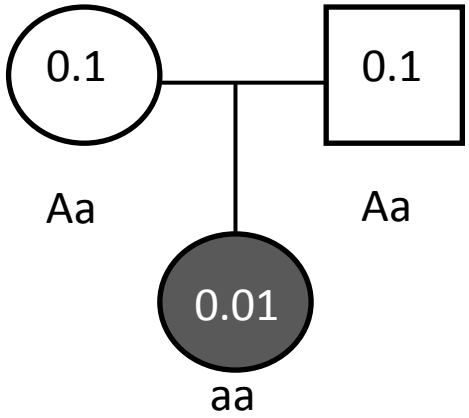
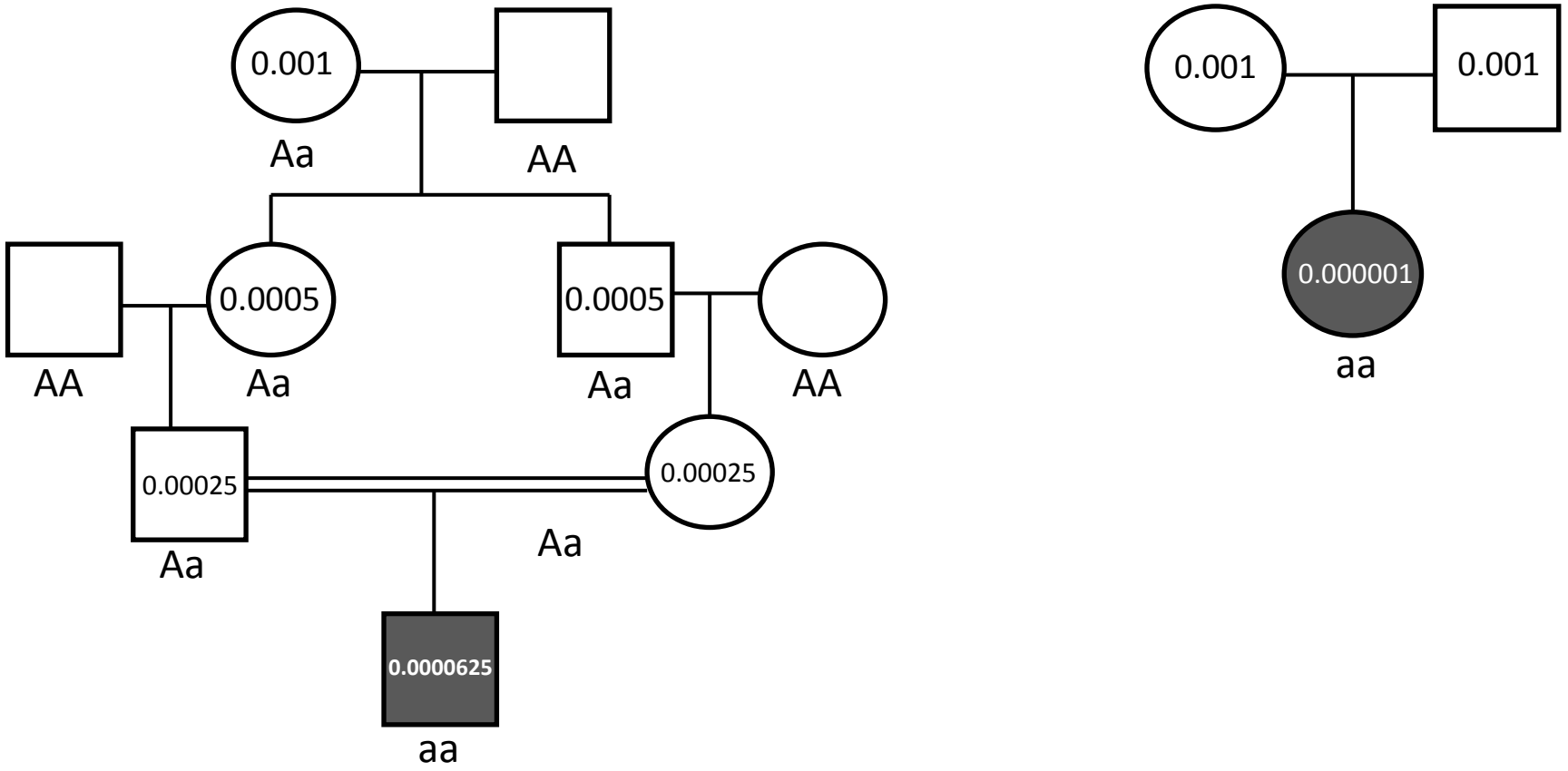
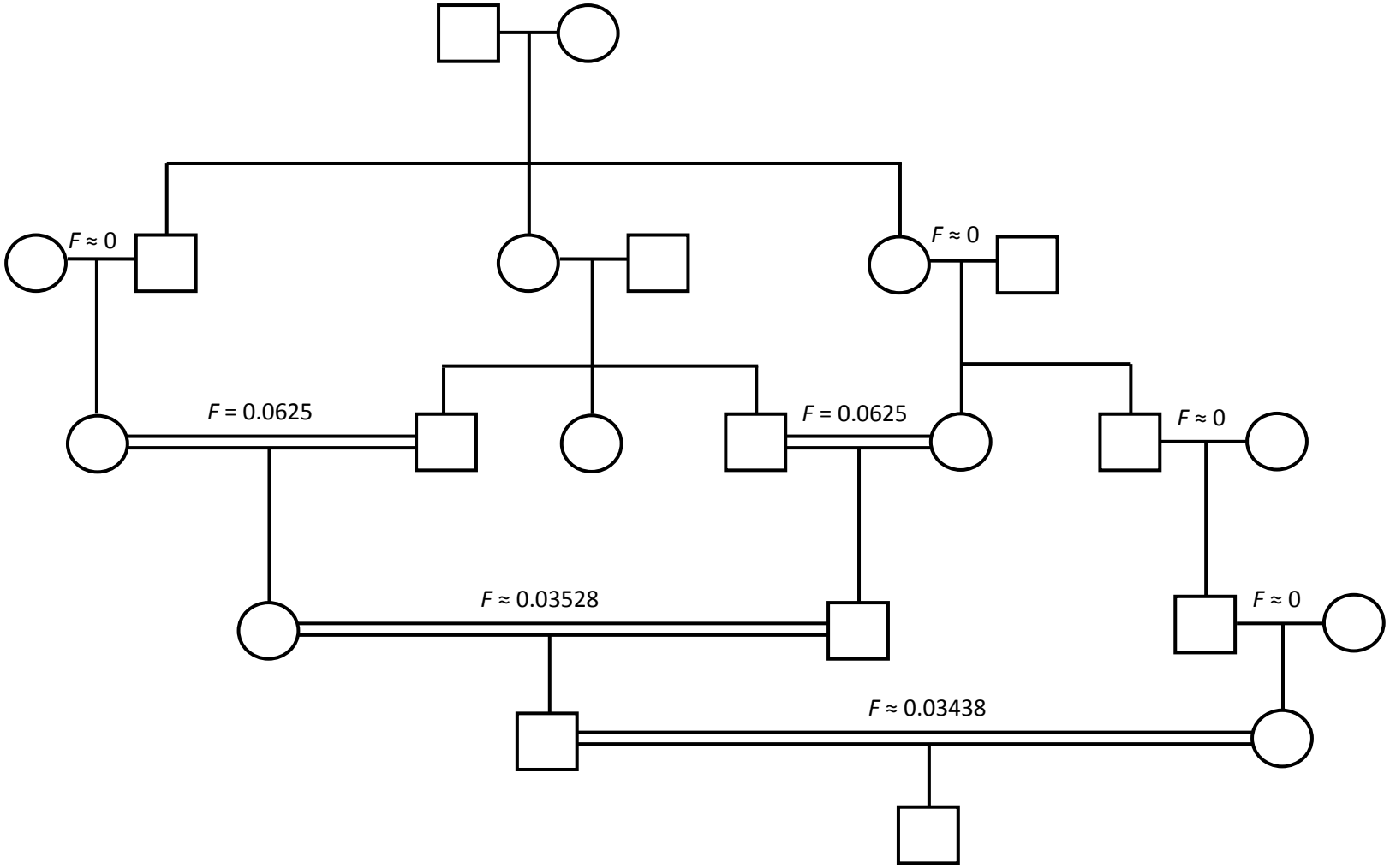


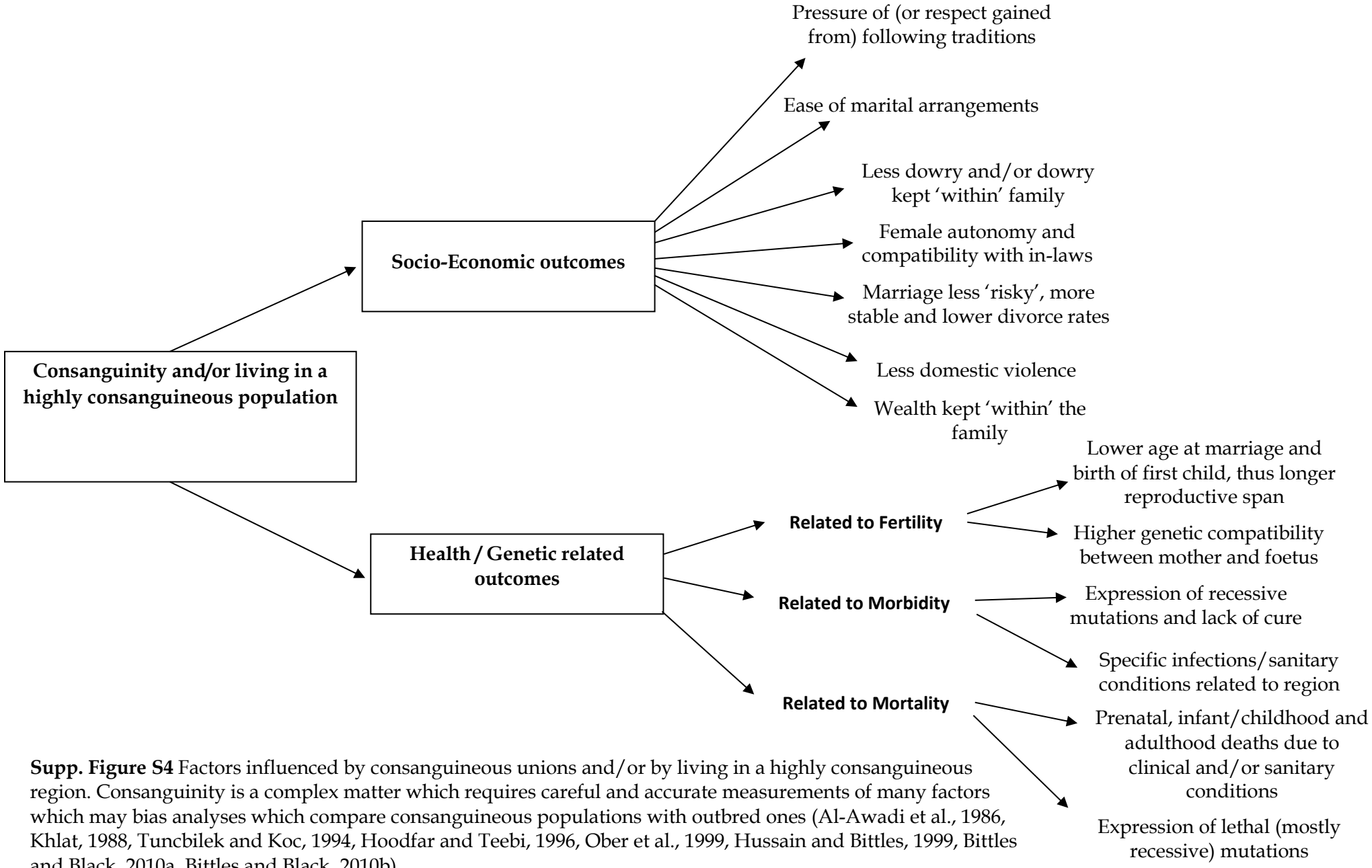

**Supp. Figure S1** Comparison between offspring of outbred individuals and first cousins using the example of an allele for which q = 0.1 (frequency of 1 in ten in a population) and there are three unrelated homozygotes (i.e. AA) who marry into the family. In this scenario, when an allele is very common in a population (e.g. 0.1 as in this case), it is much more likely to find a homozygote in the offspring of outbred individuals compared to the offspring of first cousins. This is because of the lower probability of the LoF mutation travelling down the generations to meet its counterpart in her great-grandchildren. Due to purifying selection, we would not expect mutations causing LoF to be close to this frequency (see Supp. Figure S2). A: wild-type allele. a: LoF allele.



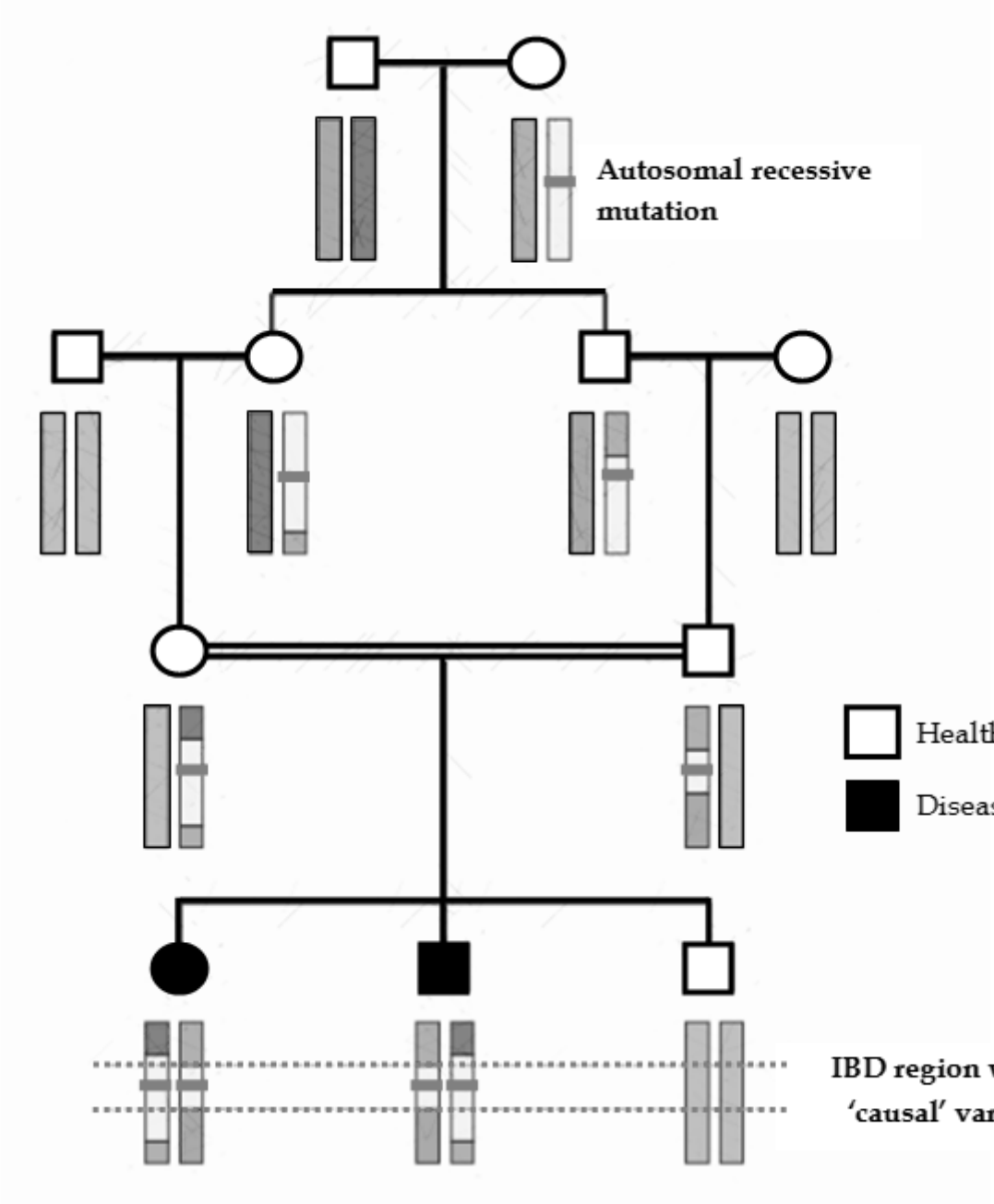

**Supp. Figure S2** Comparison between offspring of outbred individuals and first cousins using the example of an allele for which q = 0.001 (frequency of 1 in thousand in a population). The true effects of consanguinity is seen in this example as there is 62.5 fold increased probability of observing a homozygote in the offspring first cousins compared to offspring of outbred individuals – even if the LoF mutation has to travel down three generations to meet its counterpart. A: wild-type allele. a: LoF allele.




**Supp. Figure S3** Example of a complex pedigree with multiple consanguineous unions. These types of complex loops of intra-familial unions which persist for many generations can harbour very large *F* values (especially if multiple uncle-niece and double first cousin unions occur). For example, even though the last consanguineous union is between second cousins ($F_{expected}$ = 0.015625), the *F* value for their offspring is 0.03438 – which translates to approximately 120% higher autozygosity compared to standard second cousin offspring. This inflation in the *F* values could also happen in endogamous populations and/or tribes. Square: Male, Circle: Female, Double lines: Consanguineous unions.




**Supp. Figure S4** Factors influenced by consanguineous unions and/or by living in a highly consanguineous region. Consanguinity is a complex matter which requires careful and accurate measurements of many factors which may bias analyses which compare consanguineous populations with outbred ones (Al-Awadi et al., 1986, Khlat, 1988, Tuncbilek and Koc, 1994, Hoodfar and Teebi, 1996, Ober et al., 1999, Hussain and Bittles, 1999, Bittles and Black, 2010a, Bittles and Black, 2010b).




**Supp. Figure S5 Autozygosity mapping and Consanguinity** A recessive mutation which is inherited within an inbreeding family has the potential to be passed down the generations and be inherited in a homozygous state (due to IBD) in the offspring of the grandchildren (first cousins). Assuming familial data is available, following the autozygous regions in the generations will enable researchers to pinpoint where the causal variant is; or LRoHs can be detected. IBD: Identical by descent.

| Chromosome No | Potential stop-gains | Potential missense mutations | Potential missense variants predicted 'deleterious' by SIFT | Potential missense variants predicted 'deleterious' by Polyphen-2 | Potential missense variants predicted 'deleterious' by FATHMM | Potential stop-losses |
|---|---|---|---|---|---|---|
| **1** | 487480 | 8467065 | 3347260 | 3854115 | 1221832 | 62572 |
| **2** | 363376 | 6108312 | 2563015 | 2782135 | 995554 | 44020 |
| **3** | 283426 | 4849265 | 1874572 | 2198890 | 767750 | 42152 |
| **4** | 205941 | 3388227 | 1297317 | 1485985 | 473172 | 33151 |
| **5** | 219006 | 3738180 | 1553672 | 1759632 | 504748 | 25432 |
| **6** | 244104 | 4151134 | 1692057 | 1926158 | 572431 | 28653 |
| **7** | 220408 | 3847838 | 1564136 | 1695240 | 614793 | 28698 |
| **8** | 168650 | 2881145 | 1151638 | 1265275 | 418389 | 26880 |
| **9** | 189793 | 3370973 | 1333376 | 1524419 | 474573 | 24432 |
| **10** | 191621 | 3289834 | 1323421 | 1488356 | 468687 | 24363 |
| **11** | 262358 | 4850828 | 2001340 | 2210778 | 697377 | 33717 |
| **12** | 253130 | 4361643 | 1745694 | 2001575 | 757405 | 31582 |
| **13** | 87557 | 1448206 | 549045 | 679773 | 275827 | 9120 |
| **14** | 155852 | 2672365 | 1020606 | 1182304 | 342163 | 27263 |
| **15** | 155001 | 2686408 | 1169872 | 1298185 | 452945 | 8352 |
| **16** | 174677 | 3350511 | 1406819 | 1588250 | 512379 | 12994 |
| **17** | 242866 | 4510502 | 2010220 | 2158614 | 829781 | 19853 |
| **18** | 72225 | 1223623 | 504444 | 597802 | 164751 | 4140 |
| **19** | 274257 | 5160678 | 2450500 | 2416241 | 699383 | 19202 |
| **20** | 107404 | 1984320 | 811427 | 905090 | 298709 | 14196 |
| **21** | 49159 | 841258 | 331579 | 373539 | 121269 | 8331 |
| **22** | 92490 | 1785378 | 729532 | 802734 | 262976 | 11603 |
| **Total** | 4,500,781 | 78,967,693 | 32,431,542 | 36,195,090 | 11,926,894 | 540,706 |

**Supp. Table S1 Potential LoF mutations in the human genome** To calculate the potential number of missense, stop gain and stop loss mutations in the human genome, we downloaded the dbNSFP database (release 2.6) and parsed the functional annotations for all potential non-synonymous single nucleotide variants. Predictions for missense variants were obtained from SIFT, Polyphen-2 and FATHMM.