Appendix A: Computation of the fitness score, S, for a given *chromosome* (set of SNPs)

We desire a fitness score, S, that is small if the *chromosome*'s d SNPs are unrelated to disease risk and large if they have a strong joint relationship to risk. For S, we use a quadratic form, akin to a paired Hotelling's T^2 statistic in structure. The vector components for the chromosome take one of five values (-2, -1, 0, 1, 2) based on case-minus-control differences in minor allele counts in each family. (We use "control" generically to mean complement for case-parents triads or unaffected sibling for disease-discordant sibling pairs.). Calculation of mean vectors and covariances is weighted to reflect each family's informativeness about a possible joint effect.

Weights and the Weighted Mean Vector

We incorporate family weights into S to improve detection of multi-SNP disease associations, allowing for the possibility that each SNP has a small marginal association with disease and that the combination of alleles associated with elevated risk may be uncommon. We reasoned that a family is more informative about risk when the case and control differ in allele count at multiple SNPs in the *chromosome*; therefore, we upweight families with multiple nonzero differences to improve identification of differential joint transmissions of that *chromosome*'s alleles (either major or minor) to the case. Loci where both case and control are heterozygous can also be somewhat informative, so they also contribute some to the weight.

Consider a *chromosome* including d SNPs. Let:

i index the family, $i \in \{1, 2, 3 \cdots, N\}$,

j index the SNPs in that *chromosome,* $j \in \{1, 2, 3 \cdots, d\}$,

$\boldsymbol{D_i}$ be the d-vector of minor allele counts for the case in family i,

$\boldsymbol{C_i}$ be the d-vector of minor allele counts for the control in family i,

$\boldsymbol{x_i}$ be the d-vector of differences between case and control allele counts: $\boldsymbol{x_i = D_i - C_i}$,

Using the following indicators,

$$\delta_{ij} = \begin{cases} 1 & \text{if } x_{ij} \neq 0 \\ 0 & \text{otherwise} \end{cases}$$

$$b_{ij} = \begin{cases} 1 & \text{if } D_{ij} = 1 \text{ and } C_{ij} = 1 \\ 0 & \text{otherwise} \end{cases}$$

we define the weight for the i^{th} family as:

$$w_i = \begin{cases} 0 & \text{if } \delta_{ij} = 0 \ \forall j \\ f\left(m_d \sum_j \delta_{ij} + m_1 \sum_j b_{ij} \right) & \text{otherwise} \end{cases}$$

where $f(x)$ is a function that raises a user-defined integer to the power of x and that defaults to $f(x) = 2^x$; and m_d and m_1 are user-defined tuning parameters with defaults $m_d = 2$ and $m_1 = 1$. With these weights, we construct a weighted mean case-control genotype difference vector across families as:

$$\overline{\boldsymbol{x}}_{\boldsymbol{w}}^{*} = \frac{\sum_i w_i \boldsymbol{x_i}}{w} \text{ where } w = \sum_i w_i \, .$$

Intuitively, if a SNP-set functions epistatically, its alleles should be jointly carried by cases more frequently than by their matched control. Thus, the vector $\overline{\boldsymbol{x}}_{\boldsymbol{w}}^{*}$ should tend to be longer for epistatic SNP-sets and, geometrically, should also tend to point into a particular orthant defined by the component-specific signs, depending on the joint effect on risk.

Data Driven Adaptive Recoding of SNPs showing a Recessive Mode of Inheritance

The computation of $\overline{\boldsymbol{x}}_{\boldsymbol{w}}^{*}$ treats one copy versus two copies of the variant allele as equivalent to zero copies versus one copy and treats zero versus two copies as a bigger difference. This computation ignores a possibly recessive mode of inheritance, where two copies of an allele might be required to confer increased disease risk. Intuitively, if an overwhelming excess of cases who jointly carry risk alleles at every locus carry two copies for a particular SNP, one can reasonably guess that that SNP should instead be coded as if recessive. We proceed in two steps: (1) nominating risk alleles and (2) assessing evidence for whether they act recessively.

Note that $\overline{\boldsymbol{x}}_{\boldsymbol{w}}^{*}$, via its component signs, indicates which allele was over-transmitted to cases for each SNP in the *chromosome*. With our initial minor allele coding, a positive-valued component of $\overline{\boldsymbol{x}}_{\boldsymbol{w}}^{*}$ for a given SNP implicates the minor allele as conferring risk, whereas a negative value implicates the

major ('wild type') allele. We refer to the implicated alleles as "provisional risk alleles," shortened here to "risk alleles" for convenience. We define an indicator for cases who carry one or more copies of the risk allele at every locus of that chromosome as:

$$r_{Di} = \begin{cases} 1 & \text{if the case in the } i^{th} \text{ family carries at least one risk allele for all } d \text{ SNPs} \\ 0 & \text{otherwise} \end{cases}$$

Similarly for the controls, we define:

$$r_{Ci} = \begin{cases} 1 & \text{if the control in the } i^{th} \text{ family carries at least one risk allele for all } d \text{ SNPs} \\ 0 & \text{otherwise} \end{cases}$$

And finally, we define an indicator variable for whether family i is informative:

$$I_{Wi} = \begin{cases} 1 & \text{if the } i^{th} \text{ family weight} > 0 \\ 0 & \text{otherwise} \end{cases}$$

We first restrict attention to cases with both $r_{Di} = 1$ and $\mathrm{I}_{Wi} = 1$. Let n_D denote the number of these cases: $n_D = \sum_i r_{Di} I_{Wi}$. For the j^{th} SNP in the *chromosome*, we compute the proportion of these cases that carry two copies of that SNP's risk allele, $\hat{p}_{Dj}$. Then, we restrict attention to controls with both $r_{Ci} = 1$ and $\mathrm{I}_{Wi} = 1$, similarly letting $n_C = \sum_i r_{Ci} I_{Wi}$, and compute an analogous proportion, $\hat{p}_{Cj}$.

Next, we examine whether $\hat{p}_{Dj}$ is large enough to warrant recoding the j^{th} SNP. We begin by computing a test statistic, $\xi_{1j} = \frac{\hat{p}_{Dj} - \tilde{p}}{\sqrt{\{\tilde{p}(1-\tilde{p})/n_D\}}}$, where $\tilde{p}$ is an analyst-specified reference proportion, which we set to 0.75 as default. If ξ_{1j} is large, recessive coding may be appropriate. If, however, the j^{th} SNP is common and does not follow a recessive risk model, both $\hat{p}_{Dj}$ and ξ_{1j} may still be large. To assess this possibility, we compute $n_D\hat{p}_{Dj}$, $n_D(1-\hat{p}_{Dj})$, $n_C\hat{p}_{Cj}$, and $n_C(1-\hat{p}_{Cj})$. If all of these expected counts are at least 5, we further compare $\hat{p}_{Dj}$ to $\hat{p}_{Cj}$ by computing a second statistic, $\xi_{2j} = \frac{\hat{p}_{Dj} - \hat{p}_{Cj}}{\sqrt{\left\{\bar{p}_j(1-\bar{p}_j)\left(\frac{1}{n_D}+\frac{1}{n_C}\right)\right\}}}$, where $\bar{p}_j = \frac{n_D\hat{p}_{Dj} + n_C\hat{p}_{Cj}}{n_D+n_C}$. If $\min(\xi_{1j}, \xi_{2j})$ exceeds a reference threshold (defaulting to 1.64), we recode the j^{th} SNP as recessive. Alternately, if the condition on expected counts is not satisfied, we recode if ξ_{1j} exceeds the reference threshold. In effect, we recode the SNP if we are at least 95% confident (using a one-sided confidence interval) that $\hat{p}_{Dj}$ exceeds a high

reference threshold, and, where possible, also 95% confident that the case proportion $\hat{p}_{Dj}$ exceeds the control proportion $\hat{p}_{Cj}$.

If a SNP is declared to follow a recessive mode of inheritance within a particular *chromosome*, we proceed by recomputing the family weights and $\overline{\boldsymbol{x}}_{\boldsymbol{w}}^{*}$. Specifically, in computing the difference sign vectors, $\boldsymbol{x_i}$, for a recessive locus, we require that either the case or matched control carry two copies of the risk allele for a difference at SNP j to be counted. Unlike the initial count coding approach, these differences may only take one of three values $\in \{-1, 0, 1\}$. Likewise, the indicator b_{ij}, corresponding to whether the case and complement are both heterozygous at SNP j, is set to zero when computing the family weights for that *chromosome*.

Re-coding is undertaken once per *chromosome* per generation and does not propagate to other *chromosomes*; that is, a SNP can be coded as recessive in some *chromosomes* and not in others, depending on the other SNPs in the *chromosome*. Similarly, if a SNP is re-coded in a *chromosome* for one generation, that SNP will be re-evaluated if the *chromosome* propagates to the next generation. While this strategy may slow down the algorithm some, we are concerned that a blanket re-coding across *chromosomes* and generations would lead to poor performance.

Computation of a Shrinkage Factor for the Weighted Mean Vector

After coding each SNP in the *chromosome* as recessive or not, we calculate a shrinkage factor, q, to apply in re-calculating the weighted mean vector. The shrinkage factor serves as a check that our weighting approach successfully identifies provisional risk genotypes that are jointly carried by cases more often than controls. We base it on the idea that, provided that the provisional risk genotypes truly reflect underlying risk, a high proportion among those who carry a provisional risk genotype at all d loci should be cases compared to controls. In principle, q can range from 0 to 1. It is designed to shrink $\overline{\boldsymbol{x}}_{\boldsymbol{w}}$ towards the zero-vector when cases make up a small proportion of the total cases plus controls who carry all d risk genotype(s). Specifically, we identify cases and controls who carry the provisional risk genotype (*i.e.*, 2 copies if recessive, 1 or 2 copies if not) at all d loci in the

chromosome in families where only the case or only the control carries the risk genotype(s) at every locus.

For cases, slightly modifying previously defined notation to now accommodate recessive SNPs, let

$$r_{Di} = \begin{cases} 1 & \text{if the case in the } i^{th} \text{family carries a risk genotype for all } d \text{ SNPs} \\ 0 & \text{otherwise} \end{cases}$$

Analogously, for controls, let

$$r_{Ci} = \begin{cases} 1 & \text{if the control in the } i^{th} \text{ family carries a risk genotype for all } d \text{ SNPs} \\ 0 & \text{otherwise} \end{cases}$$

Further define an indicator variable, I_{ri},:

$$I_{ri} = \begin{cases} 1 & \text{only the case or only the control in the } i^{th} \text{family carries a risk genotype for all } d \text{ SNPs} \\ 0 & \text{otherwise} \end{cases}$$

We compute the shrinkage factor, q, as:

$$q = \frac{\sum_i I_{ri} r_{Di}}{\sum_i I_{ri} r_{Di} + \sum_i I_{ri} r_{Ci}}$$

If $q \leq 0.5$, indicating at least as many controls as cases carry the risk genotypes, we automatically reset q to a very small positive value, 10^{-10} . We do not allow $q = 0$ because the fitness score, as defined below, must be positive. We finally use q to shrink the weighted mean vector:

$$\bar{\boldsymbol{x}}_{\boldsymbol{w}} = q\bar{\boldsymbol{x}}_{\boldsymbol{w}}^{*}$$

Computation of the Fitness Score

Using $\bar{\boldsymbol{x}}_{\boldsymbol{w}}$, we define a covariance matrix: $\widehat{\boldsymbol{\Sigma}} = \frac{\sum_i w_i (\boldsymbol{x_i} - \bar{\boldsymbol{x}}_{\boldsymbol{w}})(\boldsymbol{x_i} - \bar{\boldsymbol{x}}_{\boldsymbol{w}})^T}{w}$ where we assign elements $\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{p,q}} = 0$ if SNPs p and q are not in linkage. We assume SNPs located on different biological chromosomes are not in linkage, but the GADGETS software allows analysts to flexibly assign pairs of SNPs to have zero covariance. Using $\bar{\boldsymbol{x}}_{\boldsymbol{w}}$ and $\widehat{\boldsymbol{\Sigma}}$, we construct the fitness score: $S = w\bar{x}_w^T \hat{\Sigma}^{-1} \bar{x}_w$. If $\widehat{\boldsymbol{\Sigma}}$ is not invertible, we instead use the pseudoinverse. Because fitness scores are often very large, the software reports fitness scores divided by 1000 to improve readability.

Appendix B. Imposing crossover and mutation.

A tuning parameter determines the proportion of *chromosomes* passed from the current generation to the next that are subjected to crossover; the default is 80%. Crossover requires two distinct *chromosomes* (a *chromosome* cannot be crossed with a duplicate of itself), so the number selected for crossover must be even. In this setting "crossover" refers to the swapping of some subset of SNPs between two *chromosomes*. Let p_s be the number of *chromosomes* in the population and recall that one *chromosome* with the highest fitness is passed unchanged. If 80% of $p_s - 1$ is odd, we choose the next higher integer. For that subset, we randomly partition the *chromosomes* into pairs. We execute **crossover** with the following steps.

1. Suppose *chromosome 1* and *chromosome 2* are assigned to crossover, and *chromosome 1* has a higher fitness score than *chromosome 2*. We identify any SNPs contained in both and remove them from consideration to avoid the possibility of a new *chromosome* containing duplicate SNPs. The remaining SNPs are each either in *chromosome 1* or in *chromosome 2*. Suppose each *chromosome* has k such SNPs. If the *chromosomes* originally had no SNPs in common, then $k = d$, the *chromosome* size. In this case, to avoid potentially exchanging two full *chromosomes*, we reset $k = d - 1$. We then randomly sample an integer, $n_{cross} \in \{1, \ldots, k\}$ as the number of SNPs that will be crossed over.

2. Given n_{cross} and the SNPs eligible for crossover in those two chromosomes, we evaluate the contributions of each to the fitness of their current chromosomes using the statistic $t_j = \frac{|\overline{x}_{wj}|}{\hat{\sigma}_j}$, where $\overline{x}_{wj}$ is the element of the weighted mean vector corresponding to SNP j and $\hat{\sigma}_j$ is the square root of the j^{th} diagonal element of $\widehat{\boldsymbol{\Sigma}}$ ($\overline{\boldsymbol{x}}_{\boldsymbol{w}}$ and $\widehat{\boldsymbol{\Sigma}}$ are as defined in the main text). We regard t_j as indicative of a SNP's contribution to a *chromosome's* fitness score, with higher values signaling higher contributions.

3. With t_j for each of the eligible SNPs in each *chromosome*, we exchange SNPs between *chromosomes*. Recalling that *chromosome 1* has a higher fitness score than *chromosome 2*, we

begin by exchanging the eligible SNP with the lowest t_j on *chromosome 1* and the eligible SNP with the highest t_j on *chromosome 2*, which should tend to improve the fitness of the higher scorer (although improvement is not guaranteed). We continue through all n_{cross} eligible SNPs in sequence, replacing the SNP with the next lower t_j in the higher fitness *chromosome* by the SNP with the next higher t_j in the lower fitness *chromosome*.

The remaining 20% of *chromosomes* not crossed over are subjected to mutation. By default, SNPs inserted as mutations are sampled independently from the pool of input SNPs, with probability proportional to the $\sqrt{\chi^2}$ statistics from likelihood ratio tests of their marginal effects, as estimated by conditioning on the set of transmitted and untransmitted genotypes (20). We choose SNPs in this way to reflect an assumption that the marginal association provides some information about the likelihood a SNP could be a member of a true risk set. Alternatively, analysts could manually specify the SNP sampling probabilities as a way to incorporate subject matter expert opinion or prior biological information. Mutation proceeds as follows.

1. Suppose there are n_{total} total SNPs in the input data. At each new generation, we take a sample of size n_{total} with replacement from the input SNPs, where sampling probabilities are proportional to the square roots of the marginal association χ^2 statistics. SNPs in this pool are eligible to be inserted into mutated chromosomes for the current generation. SNPs with a higher sampling probability may occur multiple times in the pool. This step avoids repeated sampling without replacement with non-uniform probabilities from the input SNPs, thereby substantially speeding up computation while retaining the benefit of favoring SNPS with larger marginal effects.
2. For a given *chromosome*, we randomly sample an integer, $n_m \in \{1, \ldots, d\}$, and choose to mutate n_m of the *chromosome*'s SNPs.
3. We identify the SNP with the lowest t_j in the *chromosome* and replace it with a sampled SNP from the eligible pool generated in step 1 (prohibiting duplicate SNPs on the same *chromosome*). We mutate each SNP with the next smaller t_j sequentially until completing n_m mutations.

Appendix C: Application of the genetic algorithm:

Initialization:

1. We begin by pre-processing the input autosomal genetic data. For case-parents data, we combine all the parents' genetic data to identify the minor allele for each SNP. For affected/unaffected sibling pairs, we combine the siblings' genetic data to identify the minor alleles. We then re-code all SNPs such that we count copies of the minor allele. For case-parents data, we then compute each SNP's minor allele count in the complement, defined as mother count + father count – case count.

2. For each SNP in the input data, we estimate the minor allele frequency (MAF) based on the combined parental genotypes or the combined sibling pair genotypes and remove SNPs with MAFs below a pre-specified threshold. This threshold is a tuning parameter set to 0 (no filtering) by default.

3. We estimate SNP-specific marginal associations with disease status under a log-additive risk model, conditioning on the set of transmitted and untransmitted genotypes (20).

Island Model:

Any genetic algorithm requires a mechanism to generate a diverse set of *chromosomes* that enable the algorithm to effectively explore the solution space and avoid premature convergence. We implement a technique known as an island model (21). A genetic algorithm using an island model, instead of evolving a single population with a large number of *chromosomes*, simultaneously evolves many subpopulations, or islands, each with a smaller number of *chromosomes*. These islands evolve independently for many generations, with migration of top scoring *chromosomes* permitted among small clusters of islands at intervals of a predetermined number of generations. Because the islands evolve largely independently with minimal migration, the island model enables a diverse set of potential solutions and can take advantage of distributed computing resources to reduce run-times.

Once all islands have converged, we aggregate the final evolved populations to identify a final set of top *chromosomes*. We implement this island-model approach as follows:

1. We randomly generate 200 *chromosomes* for each island. For *chromosomes* containing fewer than five SNPs, we use 1000 islands; to accommodate the larger search spaces for *chromosomes* with five SNPs, we use 1500 islands; and we use 2000 islands for *chromosomes* with six SNPs.

2. For each island, that initial set of *chromosomes* is created by sampling SNPs at random (with equal probability) without replacement from a large collection of input SNPs. Users must specify the number of *chromosomes* and the number of SNPs per *chromosome*. By default, a given SNP can appear in at most one *chromosome* in each initial island subpopulation, but the same SNP can appear in multiple islands. If the input data has too few SNPs to accommodate this restriction (e.g., we have 10,000 input SNPs and want 4,000 *chromosomes* with three SNPs each), then SNPs are instead randomly sampled with replacement from the input data, allowing the same SNP to appear in more than one *chromosome*.

3. Islands are randomly partitioned into distinct clusters, each containing four islands. Islands in different clusters evolve completely independently, allowing use of distributed computing to simultaneously evolve many island clusters and significantly speed computation.

4. Within each island cluster, each island subpopulation independently evolves over 50 generations as described below in the section **Iteration Over Generations**. After the 50th generation, we determine whether stopping criteria have been satisfied.

5. If stopping criteria are not satisfied, migration occurs among islands in the cluster. For each island, the *chromosomes* with the 20 highest and the 20 lowest fitness scores in the current subpopulation are identified and the lowest scoring *chromosomes* are removed. The top 20 *chromosomes* are copied and the copies migrate to the neighboring island (island one migrates to island two,…, island four migrates to island one).

6. This 50-generation cycle continues until stopping criteria or a specified maximum number of generations, defaulting to 500, is reached. The number of islands, population size per island, number of islands per cluster, and number of *chromosomes* that migrate between islands are all tunable parameters.

Iteration Over Generations:

Let p_s be the subpopulation size (number of *chromosomes* per island per generation).

1. The fitness score is computed for each *chromosome* in the subpopulation.

2. The top scoring *chromosome* is identified. If there is a tie, one *chromosome* is arbitrarily selected. One copy of the top scoring *chromosome* is automatically propagated unchanged to the next generation to guarantee that the top fitness score will not decrease from generation to generation.

3. The unique *chromosomes* in the subpopulation, including the top scorer, are identified (i.e., any duplicates are purged). A sample of $p_s - 1$ of these is chosen with replacement and probability proportional to their fitness scores. These sampled *chromosomes* will serve as the 'parents' of the next generation. Specifically, we subject the 'parents' to crossover and mutation as described in Appendix B and propagate the resulting 'child' *chromosomes* to the subsequent generation.

4. We check stopping criteria at 50-generation intervals. That is, we determine whether the top scoring *chromosome* has changed over the last 50 generations, independently for each island in a given cluster. If the top-scorer has not changed for any island, we stop iteration for all islands in the cluster. Note the top scoring *chromosome* does not need to be the same across the islands in the cluster. Otherwise, the algorithm continues for 500 generations.

At termination, we save the top scoring *chromosome* from the final generation population of each island and combine them into a final overall list. The number of distinct *chromosomes* in the overall list is typically substantially smaller than the total number saved because many *chromosomes* are identified in multiple islands.

Appendix D: Quantifying Evidence for Epistasis

We examine whether a chromosome's fitness score is driven by marginal rather than synergistic effects of its component SNPs as follows. We begin by computing the fitness score for the *chromosome*, S, as specified in the main text. Then, to generate a no-epistasis null distribution of fitness scores, we execute the following permutation procedure. To begin, suppose none of the d SNPs are in linkage disequilibrium (which can be analyst defined). Let:

$\boldsymbol{I}$ be a N-vector of the family indices in the observed data

$\boldsymbol{M_j}$ be a N-vector of case minor allele counts for the j^{th} SNP

$\boldsymbol{U_j}$ be a N-vector of control minor allele counts for the j^{th} SNP

We create a permuted index vector for the j^{th} SNP, $\boldsymbol{I_{pj}}$, by randomly sampling N integers without replacement from $\boldsymbol{I}$. Next, we use $\boldsymbol{I_{pj}}$ to re-order the genotypes in $\boldsymbol{M_j}$ and $\boldsymbol{U_j}$. Let:

$\boldsymbol{M_{pj}}$ be $\boldsymbol{M_j}$ with genotypes in the order specified by $\boldsymbol{I_{pj}}$

$\boldsymbol{U_{pj}}$ be $\boldsymbol{U_j}$ with genotypes in the order specified by $\boldsymbol{I_{pj}}$

Note this operation in effect permutes family labels, rather than disease status.

We conduct this procedure separately for each of the d SNPs in the chromosome. Finally, we concatenate $\boldsymbol{M_{p1}}$,…, $\boldsymbol{M_{pd}}$ into a N by d matrix of pseudo-family case genotypes, $\boldsymbol{M_p}$, and, we similarly concatenate $\boldsymbol{U_{p1}}$,…, $\boldsymbol{U_{pd}}$ into a N by d matrix of pseudo-family control genotypes, $\boldsymbol{U_p}$. These genotype matrices preserve the marginal effects for each individual SNP, but any epistatic effects should be destroyed. Based on the genotypes in $\boldsymbol{M_p}$ and $\boldsymbol{U_p}$, we compute a fitness score, S_p. We repeat this entire procedure 10,000 times to generate a null distribution of fitness scores that we compare to the observed fitness score, S. If any of the d SNPs are in linkage, we proceed similarly, except we use the same $\boldsymbol{I_{pj}}$ for each set of linked SNPs.

Appendix E: Software Settings for Comparisons to Competitors

We used TrioFS as implemented in the Trio R package, version 3.28.0, available through Bioconductor (https://www.bioconductor.org/packages/release/bioc/html/trio.html). We used the MDR-PDT software, version 2.0.1.21, available at https://ritchielab.org/software/mdr-download. The EPISFA-LD method is not available as a standalone software package, but R scripts implementing the method are available at https://github.com/doublexism/episfa/blob/master/Simulation/functions.R. We used the version of this file available on May 14, 2021.

Each method requires a number of user-specified tuning parameters. We used default software arguments with the following exceptions. First, although not generally required for running GADGETS or TrioFS, for simplicity in carrying out comparisons we presumed omniscience by correctly specifying the risk-set size for GADGETS, MDR-PDT, and TrioFS. That is, we specifically searched for 3-SNP interactions for scenario 2 and 4-SNP interactions for scenario 5. We note that TrioFS requires specifying the maximum SNP-set size, but can dynamically return smaller sets. EPISFA-LD does not a require a user specified risk-set size and can return sets of any size.

For GADGETS in this application, because we used a limited number of candidate SNPs, we also used fewer islands. For scenario 2, we used 100 islands for 500 candidate SNPs and 20 islands for smaller numbers of candidate SNPs. For scenario 5, we used 300 islands for 500 candidate SNPs and 60 islands otherwise. TrioFS requires specification of the number of algorithm iterations and has documentation suggesting a number in the hundreds of thousands. For scenario 2, we used 500,000 iterations for 500 candidate SNPs and 100,000 iterations otherwise. For scenario 5, we used 1,500,000 iterations for 500 candidate SNPs and 300,000 iterations otherwise. We did not compute p-values for GADGETS or MDR-PDT and therefore did not execute permutations for either method. We used the ‘episfa’ function in the

authors' github R script to run EPISFA-LD with the tuning parameters specified in function 'episfa_sim'. Specifically, we set argument 'nfolds' to 10, 'recursion' to 5, 'criteria' to 'ebic', and used the matrix of complement pseudo-sibling genotypes for argument 'contrast'.

Each method was run on a single processor to assess relative performance with comparable computing resources. We note, however, that GADGETS can simultaneously use multiple processors via distributed computing to dramatically improve run times compared to single processor use. TrioFS lacks this capability. MDR-PDT can make use of multiple threads but only to re-run the method on permuted datasets, not for a single run on the original study data. Because TrioFS and GADGETS both use stochastic search approaches, their run-times largely reflect choices regarding tuning parameters controlling convergence. Because MDR-PDT searches exhaustively, its run-times reflect the size of the search space. We did not carry out analyses for MDR-PDT applied to 500 candidate SNPs because the runs on smaller SNP sets conservatively suggest run-times that would exceed one-month.

Table S1. Simulation scenarios

	Scenario 1	Scenario 2
SNPs in SNP-set 1 rs (SNP number)	rs6537495, rs7098516, rs4910793, rs10501820 (960, 1656, 2625, 4169)	rs7090929, rs12421071, rs17031482 (656, 4688, 6886)
SNPs in SNP-set 2 rs (SNP number)	rs1731422, rs4237892, rs7985535, rs1487251 (5877, 6743, 7979, 8646)	rs2065089, rs7911843, rs1994548, rs10863137, rs953130 (111, 2009, 3132, 6600, 8001)
SNP frequency in the original data	SNP-set 1: 0.060 0.058 0.065 0.065 SNP-set 2: 0.061 0.064 0.059 0.062	0.052 0.036 0.038 0.110 0.112 0.114 0.116 0.113
SNP genetic model (dominant/recessive D/R)	SNP-set 1: D-D-D-D SNP-set 2: D-D-D-D	D-D-D-D D-D-D-D
Risk with neither SNP-set	1.66/1000	1.66/1000
Risk with SNP-set 1	401/1000	119.2/1000
Risk with SNP-set 2	401/1000	197.8/1000
Risk with both SNP-sets	401/1000	952.6/1000
Cases with SNP-set 1 [a]	33, 28, 35, 38, 46	30, 32, 36, 32, 39
Controls with SNP-set 1 [a]	0, 0, 0, 0, 0	1, 0, 0, 0, 1
Cases with SNP-set 2 [a]	36, 37, 31, 45, 33	38, 44, 43, 52, 40
Controls with SNP-set 2 [a]	0, 0, 0, 0, 0	0, 0, 0, 0, 0

[a] Separate entries separated by commas correspond to different replicates of the same scenario.

	Scenario 3	Scenario 4	Scenario 5
SNPs in SNP-set 1 rs (SNP number)	rs10508738, rs17565737, rs1473938, rs7124944 (715, 1743, 2562,4105)	rs6537495 rs10748546 rs7117223 rs10501820 (960,1729,2704,4169)	rs6537495 rs10748546 rs7117223 rs10501820 (960,1729,2624, 4169)
SNPs in SNP-set 2 rs (SNP number)	rs16915128, rs1005890, rs10492405 (5429, 6717, 7937)(three singleton SNPs)	rs1731422,rs4761726,rs7985535, rs359334 (5877,6709,7979,8658)	rs1731422,rs4761726,rs7985535, rs359334 (5877,6709,7979,8658)
SNP frequency in the original data	0.099 0.099 0.099 0.100 0.098 0.098 0.099	0.060 0.278 0.265 0.065 0.061 0.276 0.059 0.279	0.060 0.278 0.612 0.065 0.061 0.276 0.059 0.279
SNP genetic model (dominant/recessive D/R)	D-D-D-D D, D, D	D-R-R-D D-R-D-R	D-R-R-D D-R-D-R
Risk with neither SNP-set	1.66/1000	0.8/1000	0.8/1000
Risk with SNP-set 1	401/1000	354/1000	52/1000
Risk with SNP-set 2	4.96/1000 (one singleton SNP)	401/1000	401/1000
Risk with both SNP-sets	668/1000 (SNP-set 1 & all three singleton SNPs)	998/1000	980/1000
Cases with SNP-set 1	48, 56, 42, 56, 50	35, 38, 36, 50, 32	36, 45, 49, 41
Controls with SNP-set 1	1, 0, 1, 0, 2	0, 0, 0, 1, 0	1, 0, 2, 0
Cases with SNP-set 2	NA	31, 37, 25, 34, 33	49, 31, 36, 38
Controls with SNP-set 2	NA	0, 0, 0, 0, 0	0, 0, 0, 0

Table S2. Marginal log relative risk (standard error) for SNPs in simulated risk-related SNP-sets. Estimates are from conditional logistic regression using a log additive model.

Replicate	SNP-set 1 SNPs	SNP-set 2 SNPs
Simulation 1		
1	0.23 (0.1), 0.12 (0.1), 0.41 (0.1), 0.36 (0.1)	0.16 (0.1), 0.40 (0.1), 0.59 (0.1), 0.17 (0.1)
2	0.36 (0.1), 0.09 (0.1), 0.27 (0.1), 0.24 (0.1)	0.27 (0.1), 0.35 (0.1), 0.11 (0.1), 0.15 (0.1)
3	0.14 (0.1), 0.42 (0.1), 0.38 (0.1), 0.15 (0.1)	0.17 (0.1), 0.17 (0.1), 0.02 (0.1), 0.31 (0.1)
4	0.35 (0.1), 0.35 (0.1), 0.43 (0.1), 0.17 (0.1)	0.33 (0.1), 0.21 (0.1), 0.22 (0.1), 0.10 (0.1)
5	0.20 (0.1), 0.44 (0.1), 0.29 (0.1), 0.33 (0.1)	0.14 (0.1), 0.35 (0.1), 0.36 (0.1), 0.26 (0.1)
Simulation 2		
1	0.33 (0.1), 0.36 (0.2), 0.24 (0.2)	0.31 (0.1), 0.20 (0.1), 0.20 (0.1), 0.08 (0.1), 0.14 (0.1)
2	0.18 (0.1), 0.24 (0.2), 0.45 (0.2)	0.17 (0.1), 0.09 (0.1), 0.40 (0.1), 0.07 (0.1), 0.06 (0.1)
3	0.36 (0.1), 0.36 (0.2), 0.17 (0.1)	0.10 (0.1), 0.16 (0.1), 0.15 (0.1), 0.21 (0.1), 0.23 (0.1)
4	0.30 (0.1), 0.12 (0.2), 0.61 (0.2)	0.20 (0.1), 0.23 (0.1), 0.20 (0.1), 0.34 (0.1), 0.24 (0.1)
5	0.43 (0.1), 0.10 (0.2), 0.63 (0.2)	0.25 (0.1), 0.08 (0.1), 0.19 (0.1), 0.18 (0.1), 0.15 (0.1)
Simulation 3		
1	0.07 (0.1), 0.25 (0.1), 0.44 (0.1), 0.12 (0.1)	0.27 (0.1), 0.37 (0.1), 0.36 (0.1)
2	-0.04 (0.1), 0.39 (0.1), 0.31 (0.1), 0.38 (0.1)	0.47 (0.1), 0.20 (0.1), 0.43 (0.1)
3	0.23 (0.1), 0.08 (0.1), 0.15 (0.1), 0.16 (0.1)	0.36 (0.1), 0.21 (0.1), 0.14 (0.1)
4	0.19 (0.1), 0.02 (0.1), 0.26 (0.1), 0.18 (0.1)	0.24 (0.1), 0.09 (0.1), 0.37 (0.1)
5	0.04 (0.1), 0.11 (0.1), 0.34 (0.1), 0.20 (0.1)	0.18 (0.1), 0.30 (0.1), 0.15 (0.1)
Simulation 4		
1	0.16 (0.1), 0.09 (0.1), 0.14 (0.1), 0.23 (0.1)	0.13 (0.1), 0.05 (0.1), 0.36 (0.1), 0.02 (0.1)
2	0.33 (0.1), 0.09 (0.1), 0.08 (0.1), 0.47 (0.1)	0.24 (0.1), 0.27 (0.1), 0.23 (0.1), 0.11 (0.1)
3	0.30 (0.1), 0.00 (0.1), 0.09 (0.1), 0.35 (0.1)	-0.06 (0.1), 0.00 (0.1), 0.16 (0.1), -0.01 (0.1)
4	0.31 (0.1), 0.06 (0.1), 0.07 (0.1), 0.41 (0.1)	0.24 (0.1), 0.04 (0.1), 0.43 (0.1), 0.17 (0.1)
5	0.23 (0.1), 0.11 (0.1), 0.11 (0.1), 0.24 (0.1)	0.45 (0.1), 0.16 (0.1), 0.36 (0.1), 0.01 (0.1)
Simulation 5		
1	0.15 (0.1), 0.08 (0.1), 0.08 (0.1), 0.20 (0.1)	0.16 (0.1), 0.21 (0.1), 0.32 (0.1), 0.11 (0.1)
2	0.17 (0.1), 0.11 (0.1), 0.03 (0.1), 0.34 (0.1)	0.34 (0.1), 0.03 (0.1), 0.13 (0.1), 0.16 (0.1)
3	0.46 (0.1), -0.06 (0.1), 0.07 (0.1), 0.22 (0.1)	0.34 (0.1), 0.09 (0.1), 0.39 (0.1), 0.16 (0.1)
4	0.29 (0.1), 0.18 (0.1), 0.03 (0.1), 0.28 (0.1)	0.15 (0.1), -0.04 (0.1), 0.08 (0.1), 0.02 (0.1)

Table S3. Simulation 1 recovery of risk-related SNP-sets directly from GADGETS *chromosomes*: entry is the rank (1 = highest) by fitness score of the first *chromosome* containing the number of risk set SNPs specified by the column. NF indicates that the highest ranked *chromosome* to meet the conditions did not appear among the number of unique *chromosomes* reported by GADGETS.

	Number of SNPs from SNP-set 1				Number of SNPs from SNP-set 2			
	≥ 1	≥ 2	≥ 3	4	≥ 1	≥ 2	≥ 3	4
Replicate 1								
d=2	NF	NF	-	-	1	1	-	-
d=3	3	3	3	-	1	1	1	-
d=4	2	2	2	2	1	1	1	1
d=5	17	17	17	17	1	1	1	1
d=6	251	251	251	251	1	1	1	1
Replicate 2								
d=2	NF	NF	-	-	NF	NF	-	-
d=3	2	2	2	-	1	1	1	-
d=4	17	NF	NF	NF	1	1	1	1
d=5	11	11	11	11	1	1	1	1
d=6	37	37	37	37	1	1	1	1
Replicate 3								
d=2	2	2	-	-	NF	NF	-	-
d=3	1	1	1	-	NF	NF	NF	-
d=4	1	1	1	1	NF	NF	NF	NF
d=5	1	1	1	1	NF	NF	NF	NF
d=6	1	1	1	1	176	NF	NF	NF
Replicate 4								
d=2	1	1	-	-	2	2	-	-
d=3	2	2	2	-	1	1	1	-
d=4	1	1	1	1	2	2	2	2
d=5	1	1	1	1	3	3	3	3
d=6	1	1	1	1	30	30	30	30
Replicate 5								
d=2	1	1	-	-	5	5	-	-
d=3	1	1	1	-	6	6	6	-
d=4	1	1	1	1	10	10	10	10
d=5	1	1	1	1	34	34	34	34
d=6	1	1	1	1	213	213	213	213

Table S4. Simulation 2 recovery of risk-related SNP-sets directly from GADGETS *chromosomes*: entry is the rank (1 = highest) by fitness score of the first *chromosome* containing the number of risk set SNPs specified by the column. NF indicates that the highest ranked *chromosome* to meet the conditions did not appear among the number of unique *chromosomes* reported by GADGETS.

	Number of SNPs from SNP-set 1			Number of SNPs from SNP-set 2				
	≥ 1	≥ 2	3	≥ 1	≥ 2	≥ 3	≥ 4	5
Replicate 1								
d=2	1	1	-	3	3	-	-	-
d=3	1	1	1	2	2	2	-	-
d=4	1	1	1	4	4	4	4	-
d=5	1	1	1	3	3	3	3	3
d=6	1	1	1	5	5	5	5	5
Replicate 2								
d=2	1	1	-	3	NF	-	-	-
d=3	1	1	1	9	NF	NF	-	-
d=4	1	1	1	7	28	NF	NF	-
d=5	1	1	1	50	50	50	50	50
d=6	1	1	1	74	74	74	74	74
Replicate 3								
d=2	1	1	-	NF	NF	-	-	-
d=3	1	1	1	NF	NF	NF	-	-
d=4	1	1	1	NF	NF	NF	NF	-
d=5	1	1	1	61	61	61	61	61
d=6	1	1	1	126	126	126	126	126
Replicate 4								
d=2	1	1	-	NF	NF	-	-	-
d=3	1	1	1	2	2	2	-	-
d=4	4	4	4	1	1	1	1	-
d=5	13	13	13	1	1	1	1	1
d=6	20	20	20	1	1	1	1	1
Replicate 5								
d=2	2	2	-	NF	NF	-	-	-
d=3	1	1	1	NF	NF	NF	-	-
d=4	1	1	1	NF	NF	NF	NF	-
d=5	1	1	1	NF	NF	NF	NF	NF
d=6	1	1	1	NF	NF	NF	NF	NF

Table S5. Simulation 3 recovery of risk-related SNP-sets directly from GADGETS *chromosomes*: entry is the rank (1 = highest) by fitness score of the first *chromosome* containing the number of risk set SNPs specified by the column. NF indicates that the highest ranked *chromosome* to meet the conditions did not appear among the number of unique *chromosomes* reported by GADGETS.

	Number of SNPs from SNP-set 1				Singleton 1	Singleton 2	Singleton 3
	≥ 1	≥ 2	≥ 3	4			
Replicate 1							
d=2	1	NF	-	-	NF	NF	4
d=3	1	1	1	-	NF	NF	9
d=4	1	1	1	7	NF	64	13
d=5	1	1	1	2	NF	223	56
d=6	1	1	1	1	302	212	121
Replicate 2							
d=2	1	1	-	-	2	NF	NF
d=3	1	1	1	-	6	NF	22
d=4	1	1	1	1	13	96	31
d=5	1	1	1	1	54	200	68
d=6	1	1	1	1	144	191	151
Replicate 3							
d=2	NF	NF	-	-	NF	NF	NF
d=3	NF	NF	NF	-	27	NF	NF
d=4	NF	NF	NF	NF	114	NF	NF
d=5	NF	NF	NF	NF	5	424	NF
d=6	780	NF	NF	NF	23	257	NF
Replicate 4							
d=2	NF	NF	-	-	NF	NF	6
d=3	NF	NF	NF	-	NF	NF	2
d=4	154	NF	NF	NF	NF	NF	1
d=5	363	363	NF	NF	NF	NF	1
d=6	153	153	399	NF	NF	NF	1
Replicate 5							
d=2	NF	NF	-	-	NF	NF	NF
d=3	1	1	1	-	NF	NF	NF
d=4	1	1	1	1	NF	71	NF
d=5	1	1	1	1	NF	144	NF
d=6	1	1	1	1	NF	23	NF

Table S6. Simulation 4 recovery of risk-related SNP-sets directly from GADGETS *chromosomes*: entry is the rank (1 = highest) by fitness score of the first *chromosome* containing the number of risk set SNPs specified by the column. NF indicates that the highest ranked c*hromosome* to meet the conditions did not appear among the number of unique *chromosomes* reported by GADGETS.

	Number of SNPs from SNP-set 1				Number of SNPs from SNP-set 2			
	≥ 1	≥ 2	≥ 3	4	≥ 1	≥ 2	≥ 3	4
Replicate 1								
d=2	NF	NF	-	-	NF	NF	-	-
d=3	NF	NF	NF	-	1	NF	NF	-
d=4	NF	NF	NF	NF	1	NF	NF	NF
d=5	NF	NF	NF	NF	1	1	1	1
d=6	NF	NF	NF	NF	1	1	1	1
Replicate 2								
d=2	1	1	-	-	8	NF	-	-
d=3	2	2	4	-	1	1	1	-
d=4	2	2	2	2	1	1	1	1
d=5	1	1	1	1	2	2	2	2
d=6	1	1	1	1	20	20	20	20
Replicate 3								
d=2	1	1	-	-	NF	NF	-	-
d=3	1	1	1	-	NF	NF	NF	-
d=4	1	1	1	NF	NF	NF	NF	NF
d=5	1	1	1	NF	NF	NF	NF	NF
d=6	1	1	1	NF	NF	NF	NF	NF
Replicate 4								
d=2	2	2	-	-	1	1	-	-
d=3	1	1	1	-	3	3	3	-
d=4	1	1	1	1	2	2	2	2
d=5	1	1	1	1	14	14	14	14
d=6	1	1	1	1	62	62	62	62
Replicate 5								
d=2	NF	NF	-	-	1	1	-	-
d=3	65	NF	NF	-	1	1	1	-
d=4	NF	NF	NF	NF	1	1	1	1
d=5	NF	NF	NF	NF	1	1	1	1
d=6	200	NF	NF	NF	1	1	1	1

Table S7. Simulation 5 recovery of risk-related SNP-sets directly from GADGETS *chromosomes:* entry is the rank (1 = highest) by fitness score of the first *chromosome* containing the number of risk set SNPs specified by the column. NF indicates that the highest ranked *chromosome* to meet the conditions did not appear among the number of unique *chromosomes* reported by GADGETS.

	Number of SNPs from SNP-set 1				Number of SNPs from SNP-set 2			
	≥ 1	≥ 2	≥ 3	4	≥ 1	≥ 2	≥ 3	4
Replicate 1								
d=2	NF	NF	-	-	7	7	-	-
d=3	NF	NF	NF	-	1	1	1	-
d=4	NF	NF	NF	NF	1	1	1	1
d=5	6	6	6	NF	1	1	1	1
d=6	36	36	36	NF	1	1	1	1
Replicate 2								
d=2	4	4	-	-	NF	NF	-	-
d=3	1	1	1	-	NF	NF	NF	-
d=4	1	1	1	NF	4	4	4	NF
d=5	1	1	1	NF	7	7	7	7
d=6	1	1	1	23	5	5	5	5
Replicate 3								
d=2	4	4	-	-	NF	NF	-	-
d=3	1	1	1	-	2	2	2	-
d=4	4	4	4	NF	1	1	1	1
d=5	13	13	13	NF	1	1	1	1
d=6	40	40	40	96	1	1	1	1
Replicate 4								
d=2	1	1	-	-	NF	NF	-	-
d=3	1	1	1	-	NF	NF	NF	-
d=4	1	1	1	5	NF	NF	NF	NF
d=5	1	1	1	13	119	NF	NF	NF
d=6	4	4	4	4	1	1	1	1

Table S8. P-values based on permutation, both for a global test that combines *chromosome* sizes (d) 2-6 and tests for respective specific *chromosome* sizes. These are based on the observed data set and 100 permuted data sets. The first column specifies the maximal number of top *chromosomes* that could be used to construct the test. The next five columns report the number of top *chromosomes* that were used in practice. The maximal number exceeds the number used when GADGETS returns fewer *chromosomes* than the maximal number specified for the observed data or any permute.

Top Chromosomes (*k*) Specified	*k* Used per *Chromosome* Size (*d*)					Global Test P	Tests Based on Specific *Chromosome* Sizes				
	2	3	4	5	6		2	3	4	5	6
Simulation 1, Replicate 2											
10	3	10	10	10	10	0.02	0.41	0.13	0.02	0.01	0.01
30	3	10	30	30	30	0.02	0.41	0.13	0.15	0.01	0.01
50	3	10	50	50	50	0.02	0.41	0.13	0.19	0.01	0.01
Simulation 2, Replicate 3											
10	1	6	10	10	10	0.01	0.31	0.02	0.01	0.01	0.01
30	1	6	30	30	30	0.01	0.31	0.02	0.01	0.01	0.01
50	1	6	47	50	50	0.01	0.31	0.02	0.01	0.01	0.01
Simulation 3, Replicate 1											
10	4	10	10	10	10	0.01	0.76	0.17	0.01	0.01	0.02
30	4	18	30	30	30	0.01	0.76	0.20	0.03	0.01	0.02
50	4	18	50	50	50	0.02	0.76	0.20	0.05	0.01	0.02
Simulation 4, Replicate 2											
10	2	8	10	10	10	0.01	0.05	0.01	0.01	0.01	0.01
30	2	8	30	30	30	0.01	0.05	0.01	0.01	0.01	0.01
50	2	8	50	50	50	0.01	0.05	0.01	0.01	0.01	0.01
Simulation 5, Replicate 2											
10	2	10	10	10	10	0.01	0.08	0.01	0.01	0.01	0.01
30	2	12	30	30	30	0.01	0.08	0.01	0.01	0.01	0.01
50	2	12	50	50	50	0.01	0.08	0.01	0.01	0.01	0.01

Table S9. Epistasis h-values for the top ranked *chromosome* for each *chromosome* size (*d*) from a data set representing each scenario considered.

Simulation(Replicate)	*d*=2	*d*=3	*d*=4	*d*=5	*d*=6
1(2)	0.0179**	0.0001	0.0001	0.0001	0.0001
2(3)	0.0002	0.0001	0.0001	0.0001	0.0001
3(1)	0.0033	0.0014	0.0003	0.0001	0.0001
4(2)	0.0001	0.0001	0.0001	0.0001	0.0001
5(2)	--*	0.0001	0.0001	0.0001	0.0001

*The epistasis h-value could not be computed because all SNPs were located on the same biological chromosome and considered to be in linkage.
**No SNPs from a risk-related SNP-set were contained in the top ranked *chromosome*.

Table S10. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 2 among 347 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 889 families from Asian populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a single distinct *chromosome* of size 2. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association ($p = 0.01$). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*		RSID		Relative Risk			h**
SNP1	SNP2	SNP1	SNP2	SNP1	SNP2	Joint	
ABCA4(1)	IRF6(1)	rs560426	rs2013162	1.4	1.2	1.5	--

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

**-- indicates SNP sets where the epistasis h-value could not be computed because all SNPs were located on the same biological chromosome.

Table S11. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 3 among 347 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 889 families from Asian populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 3 distinct *chromosomes* of size 3. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association ($p = 0.01$). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*			RSID			Relative Risk				h**
SNP1	SNP2	SNP3	SNP1	SNP2	SNP3	SNP1	SNP2	SNP3	Joint	
ABCA4(1)	ATP2B4(1)	IRF6(1)	rs560426	rs4951357	rs2013162	1.4	1.1	1.2	1.7	--
ABCA4(1)	IRF6(1)	GRID2(4)	rs560426	rs2013162	rs12506428	1.4	1.2	1.2	1.8	0.2032
ABCA4(1)	IRF6(1)	LOC102724968(20)	rs560426	rs2013162	rs13041247	1.4	1.2	1.2	1.8	0.1701

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

**-- indicates SNP sets where the epistasis h-value could not be computed because all SNPs are located on the same biological chromosome.

Table S12. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 4 among 347 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 889 families from an Asian population. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 7 distinct *chromosomes* of size 4. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association ($p = 0.01$). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*				RSID				Relative Risk					h**
SNP1	SNP2	SNP3	SNP4	SNP1	SNP2	SNP3	SNP4	SNP1	SNP2	SNP3	SNP4	Joint	
ABCA4(1)	IRF6(1)	GRID2(4)	20:40652989	rs560426	rs2013162	rs12506428	rs6102085	1.4	1.2	1.2	1.2	2.1	0.0579
ABCA4(1)	ATP2B4(1)	IRF6(1)	17:9016313	rs560426	rs4951357	rs2013162	rs9788972	1.4	1.1	1.2	1.4	2.7	0.0318
ABCA4(1)	ATP2B4(1)	IRF6(1)	GRID2(4)	rs560426	rs4951357	rs2013162	rs12506428	1.4	1.1	1.2	1.2	1.9	0.1697
ABCA4(1)	IRF6(1)	GRID2(4)	20:40652989	rs952499	rs2013162	rs12506428	rs6102085	1.2	1.2	1.2	1.2	1.9	0.0060
ABCA4(1)	IRF6(1)	GRID2(4)	NTN1(17)	rs952499	rs2013162	rs12506428	rs9915089	1.2	1.2	1.2	1.6	2.7	0.0054
ABCA4(1)	ATP2B4(1)	IRF6(1)	20:40652989	rs560426	rs4951357	rs2013162	rs6102085	1.4	1.1	1.2	1.2	1.9	0.4819
ABCA4(1)	ATP2B4(1)	IRF6(1)	1:209814702	rs560426	rs4951357	rs2013162	rs10863790	1.4	1.1	1.2	1.1	1.8	--

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

**-- indicates SNP sets where the epistasis h-value could not be computed because all SNPs were located on the same biological chromosome.

Table S13. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 5 among 347 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 889 families from an Asian population. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 24 distinct *chromosomes* of size 5. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association ($p = 0.01$). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*					RSID					Relative Risk						h
SNP1	SNP2	SNP3	SNP4	SNP5	SNP1	SNP2	SNP3	SNP4	SNP5	SNP1	SNP2	SNP3	SNP4	SNP5	Joint	
ABCA4(1)	IRF6(1)	GRID2(4)	17:9016313	20:40652989	rs952499	rs2013162	rs12506428	rs9788972	rs6102085	1.2	1.2	1.2	1.4	1.2	3.2	0.0004
ABCA4(1)	ATP2B4(1)	IRF6(1)	GRID2(4)	17:9016313	rs560426	rs4951357	rs2013162	rs12506428	rs9788972	1.4	1.1	1.2	1.2	1.4	3.2	0.0103
ABCA4(1)	ATP2B4(1)	IRF6(1)	17:9016313	LOC102724968 (20)	rs560426	rs4951357	rs2013162	rs9788972	rs13041247	1.4	1.1	1.2	1.4	1.2	3.5	0.0021
ABCA4(1)	ATP2B4(1)	IRF6(1)	GRID2(4)	17:9016313	rs952499	rs4951357	rs2013162	rs12506428	rs9788972	1.2	1.1	1.2	1.2	1.4	2.9	0.0015
ABCA4(1)	ATP2B4(1)	IRF6(1)	1:209814702	GRID2(4)	rs560426	rs4951357	rs2013162	rs10863790	rs12506428	1.4	1.1	1.2	1.1	1.2	2.1	0.1399
ABCA4(1)	ATP2B4(1)	IRF6(1)	17:9016313	LOC102724968 (20)	rs560426	rs4951357	rs2013162	rs9788972	rs11696257	1.4	1.1	1.2	1.4	1.2	3.5	0.0032
ABCA4(1)	IRF6(1)	C3orf52(3)	3:194959271	LOC102724968 (20)	rs560426	rs2073485	rs16859207	rs711993	rs6102074	1.4	1.2	1.6	1.3	1.3	5.2	0.0008
ABCA4(1)	ATP2B4(1)	IRF6(1)	GRID2(4)	20:40652989	rs560426	rs4951357	rs2013162	rs12506428	rs6102085	1.4	1.1	1.2	1.2	1.2	2.5	0.1131
ABCA4(1)	SYT14(1)	C3orf52(3)	3:194959271	LOC102724968 (20)	rs560426	rs11119388	rs16859207	rs711993	rs6065259	1.4	1.1	1.6	1.3	1.2	5.0	0.0001
ABCA4(1)	IRF6(1)	GRID2(4)	17:9017282	20:40652989	rs952499	rs2013162	rs12506428	rs4791330	rs6102085	1.2	1.2	1.2	1.3	1.2	2.6	0.0012

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Table S14. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 6 among 347 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 889 families from Asian populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 71 distinct *chromosomes* of size 6. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association (p = 0.01). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*						RSID						Relative Risk							h
SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	Joint	
ABCA4(1)	ABCA4(1)	ATP2B4(1)	IRF6(1)	4:125640770	NTN1(17)	rs560426	rs2297636	rs4951357	rs2013162	rs13140903	rs9915089	1.4	1.1	1.1	1.2	1.3	1.6	7.7	0.0052
ABCA4(1)	ATP2B4(1)	IRF6(1)	1:209814702	GRID2(4)	17:9016313	rs952499	rs4951357	rs2013162	rs10863790	rs12506428	rs9788972	1.2	1.1	1.2	1.1	1.2	1.4	3.2	0.0024
ABCA4(1)	ABCA4(1)	ATP2B4(1)	IRF6(1)	IRF6(1)	NTN1(17)	rs560426	rs2297636	rs4951357	rs2073485	rs2013162	rs9915089	1.4	1.1	1.1	1.2	1.2	1.6	4.6	0.0079
ABCA4(1)	ABCA4(1)	ATP2B4(1)	IRF6(1)	NTN1(17)	LOC102724968(20)	rs560426	rs2297636	rs4951357	rs2013162	rs9915089	rs13041247	1.4	1.1	1.1	1.2	1.6	1.2	6.9	0.0012
ABCA4(1)	ATP2B4(1)	IRF6(1)	1:209814702	GRID2(4)	17:9016313	rs560426	rs4951357	rs2013162	rs10863790	rs12506428	rs9788972	1.4	1.1	1.2	1.1	1.2	1.4	3.4	0.0100
ABCA4(1)	IRF6(1)	SHTN1(10)	17:9017282	18:31580789	20:40652989	rs560426	rs2013162	rs7078160	rs4791330	rs1616887	rs6102085	1.4	1.2	1.2	1.3	1.2	1.2	4.8	0.0014
ABCA4(1)	1:209814702	SYT14(1)	C3orf52(3)	3:194959271	LOC102724968(20)	rs560426	rs10863790	rs11119388	rs16859207	rs711993	rs6102074	1.4	1.1	1.1	1.6	1.3	1.3	6.4	0.0004
ABCA4(1)	ABCA4(1)	IRF6(1)	GRID2(4)	17:9016313	20:40652989	rs560426	rs952499	rs2013162	rs12506428	rs9788972	rs6102085	1.4	1.2	1.2	1.2	1.4	1.2	3.8	0.0007
ABCA4(1)	ATP2B4(1)	IRF6(1)	IRF6(1)	1:209814702	GRID2(4)	rs560426	rs4951357	rs2073485	rs2013162	rs10863790	rs12506428	1.4	1.1	1.2	1.2	1.1	1.2	2.2	0.1036
ABCA4(1)	IRF6(1)	SYT14(1)	C3orf52(3)	3:194959271	LOC102724968(20)	rs560426	rs2073485	rs11119388	rs16859207	rs711993	rs6102074	1.4	1.2	1.1	1.6	1.3	1.3	6.7	0.0002

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Table S15. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 2 among 395 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 668 families from European populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a single distinct *chromosome* of size 2. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association (p = 0.01). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*		RSID		Relative Risk			h
SNP1	SNP2	SNP1	SNP2	SNP1	SNP2	Joint	
8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs987525	rs5765956	1.9	1.2	2.0	0.2651

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Table S16. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 3 among 395 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 668 families from European populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 3 distinct *chromosomes* of size 3. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association ($p = 0.01$). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*			RSID			Relative Risk				h
SNP1	SNP2	SNP3	SNP1	SNP2	SNP3	SNP1	SNP2	SNP3	Joint	
ABCA4(1)	UNC5C(4)	8:128933908	rs560426	rs4254782	rs987525	1.2	1.2	1.9	2.2	0.0040
ABCA4(1)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs987525	rs5765956	1.2	1.9	1.2	2.4	0.0067
PAX7(1)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs6659735	rs987525	rs5765956	1.2	1.9	1.2	2.2	0.0520

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Table S17. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 4 among 395 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 668 families from European populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 18 distinct *chromosomes* of size 4. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association ($p = 0.01$). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*				RSID				Relative Risk					h
SNP1	SNP2	SNP3	SNP4	SNP1	SNP2	SNP3	SNP4	SNP1	SNP2	SNP3	SNP4	Joint	
ABCA4(1)	UNC5C(4)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs4254782	rs987525	rs5765956	1.2	1.2	1.9	1.2	2.7	0.0004
ABCA4(1)	UNC5C(4)	8:128933908	NTN1(17)	rs560426	rs4254782	rs987525	rs8069536	1.2	1.2	1.9	1.6	4.7	0.0009
ABCA4(1)	3:89485227	8:128933908	NTN1(17)	rs560426	rs7632427	rs987525	rs8069536	1.2	1.1	1.9	1.6	5.6	0.0002
1:18613886	ABCA4(1)	UNC5C(4)	8:128933908	rs4920522	rs560426	rs4254782	rs987525	1.2	1.2	1.2	1.9	2.7	0.0016
1:18613886	ABCA4(1)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs4920522	rs560426	rs987525	rs5765956	1.2	1.2	1.9	1.2	2.9	0.0048
1:18625618	ABCA4(1)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs17352100	rs560426	rs987525	rs5765956	1.2	1.2	1.9	1.2	3.0	0.0019
ABCA4(1)	8:128914415	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs12542837	rs987525	rs5765956	1.2	1.5	1.9	1.2	2.5	0.0027
ABCA4(1)	8:128933908	NTN1(17)	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs987525	rs8069536	rs5765956	1.2	1.9	1.6	1.2	5.3	0.0011
1:18625618	ABCA4(1)	UNC5C(4)	8:128933908	rs17352100	rs560426	rs4254782	rs987525	1.2	1.2	1.2	1.9	2.6	0.0006
ABCA4(1)	8:128903514	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs1519847	rs987525	rs5765956	1.2	1.5	1.9	1.2	2.5	0.0044

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Table S18. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 5 among 395 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 668 families from European populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 59 distinct *chromosomes* of size 5. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association (p = 0.01). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*					RSID					Relative Risk						h
SNP1	SNP2	SNP3	SNP4	SNP5	SNP1	SNP2	SNP3	SNP4	SNP5	SNP1	SNP2	SNP3	SNP4	SNP5	Joint	
ABCA4(1)	3:89485227	UNC5C(4)	8:128933908	NTN1(17)	rs560426	rs7632427	rs4254782	rs987525	rs8069536	1.2	1.1	1.2	1.9	1.6	7.6	0.0001
1:18613886	ABCA4(1)	UNC5C(4)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs4920522	rs560426	rs4254782	rs987525	rs5765956	1.2	1.2	1.2	1.9	1.2	3.6	0.0001
PAX7(1)	ABCA4(1)	UNC5C(4)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs766325	rs560426	rs4254782	rs987525	rs5765956	1.2	1.2	1.2	1.9	1.2	3.3	0.0001
ABCA4(1)	3:89485227	8:128914415	8:128933908	NTN1(17)	rs560426	rs7632427	rs12542837	rs987525	rs8069536	1.2	1.1	1.5	1.9	1.6	6.5	0.0001
1:18625618	ABCA4(1)	UNC5C(4)	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs17352100	rs560426	rs4254782	rs987525	rs5765956	1.2	1.2	1.2	1.9	1.2	3.4	0.0003
ABCA4(1)	UNC5C(4)	8:128933908	NTN1(17)	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs4254782	rs987525	rs8069536	rs5765956	1.2	1.2	1.9	1.6	1.2	6.3	0.0002
ABCA4(1)	3:89485227	8:128903514	8:128933908	NTN1(17)	rs560426	rs7632427	rs1519847	rs987525	rs8069536	1.2	1.1	1.5	1.9	1.6	6.5	0.0002
ABCA4(1)	3:89485227	8:128933908	8:128935636	NTN1(17)	rs560426	rs7632427	rs987525	rs12548036	rs8069536	1.2	1.1	1.9	1.5	1.6	6.5	0.0001
ABCA4(1)	3:89485227	8:128907554	8:128933908	NTN1(17)	rs560426	rs7632427	rs1519841	rs987525	rs8069536	1.2	1.1	1.4	1.9	1.6	6.5	0.0001
ABCA4(1)	UNC5C(4)	8:128914415	8:128933908	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs4254782	rs12542837	rs987525	rs5765956	1.2	1.2	1.5	1.9	1.2	2.8	0.0004

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Table S19. Top scoring *chromosomes*, relative risks, and epistasis test h-values for *chromosome* size 6 among 395 candidate SNPs from a case-parent triad study of cleft lip (with or without cleft palate) in 668 families from European populations. Candidate SNPs were selected based on the strength of marginal disease associations or being located in the WNT signaling pathway, as described by Li et al. (2015). GADGETS returned a total of 161 distinct *chromosomes* of size 6. *Chromosomes* are sorted by fitness score in descending order. The global test of the omnibus null of no association across *chromosome* sizes 2-6 for these data indicated the presence of an association (p = 0.01). Marginal relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype over the number of complements with a risk-related genotype among pairs that did not inherit identical alleles (though some such pairs would have had identical risk genotypes based on the assigned dominant or recessive role for the minor allele). Joint relative risks were computed as the number of cases with a GADGETS nominated risk-related genotype at each locus in the *chromosome* over the number of complements with a risk-related genotype at each locus, where each count was weighted by the GADGETS family weights. When no complements carried the nominated risk genotype, a fraction with the weighted number of cases carrying the risk genotype over zero is reported. Epistasis h-values calculated on GADGETS-selected SNP-sets will tend to be low under a no-epistasis null; one would need to test the identified set of SNPs in independent validation data to properly control type I error.

Gene(Chromosome)*						RSID						Relative Risk							h
SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	Joint	
ABCA4(1)	3:89485227	UNC5C(4)	8:128914415	8:128933908	NTN1(17)	rs560426	rs7632427	rs4254782	rs12542837	rs987525	rs8069536	1.2	1.1	1.2	1.5	1.9	1.6	9.4	0.0001
ABCA4(1)	3:89485227	UNC5C(4)	8:128903514	8:128933908	NTN1(17)	rs560426	rs7632427	rs4254782	rs1519847	rs987525	rs8069536	1.2	1.1	1.2	1.5	1.9	1.6	9.4	0.0001
ABCA4(1)	3:89485227	UNC5C(4)	8:128907554	8:128933908	NTN1(17)	rs560426	rs7632427	rs4254782	rs1519841	rs987525	rs8069536	1.2	1.1	1.2	1.4	1.9	1.6	9.4	0.0001
ABCA4(1)	3:89485227	UNC5C(4)	8:128933908	8:128935636	NTN1(17)	rs560426	rs7632427	rs4254782	rs987525	rs12548036	rs8069536	1.2	1.1	1.2	1.9	1.5	1.6	9.4	0.0001
ABCA4(1)	WNT9A(1)	3:89485227	8:128914415	8:128933908	NTN1(17)	rs560426	rs10127943	rs7632427	rs12542837	rs987525	rs8069536	1.2	0.9	1.1	1.5	1.9	1.6	13.5	0.0001
ABCA4(1)	3:13775872	3:55429452	8:128933908	NTN1(17)	ARHGAP8/PRR5-ARHGAP8(22)	rs560426	rs12485574	rs1822811	rs987525	rs8069536	rs5765956	1.2	1.1	1.1	1.9	1.6	1.2	563/0	0.0001
ABCA4(1)	WNT9A(1)	3:89485227	8:128903514	8:128933908	NTN1(17)	rs560426	rs10127943	rs7632427	rs1519847	rs987525	rs8069536	1.2	0.9	1.1	1.5	1.9	1.6	13.5	0.0001
ABCA4(1)	WNT9A(1)	3:89485227	8:128907554	8:128933908	NTN1(17)	rs560426	rs10127943	rs7632427	rs1519841	rs987525	rs8069536	1.2	0.9	1.1	1.4	1.9	1.6	13.5	0.0001
ABCA4(1)	3:89485227	8:128907554	8:128914415	8:128933908	NTN1(17)	rs560426	rs7632427	rs1519841	rs12542837	rs987525	rs8069536	1.2	1.1	1.4	1.5	1.9	1.6	7.2	0.0001
ABCA4(1)	3:89485227	8:128914415	8:128933908	8:128935636	NTN1(17)	rs560426	rs7632427	rs12542837	rs987525	rs12548036	rs8069536	1.2	1.1	1.5	1.9	1.5	1.6	7.2	0.0003

*Genes were annotated based on the dbSNP database from NCBI, build 38, using the rsnps R package (version 0.4.0). For SNPs located in intergenic regions, SNP chromosome:position is reported.

Figure S1. Network plot for simulation scenario 2, replicate 3. *Chromosomes* were filtered for inclusion using global permutations. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate pairs of SNPs located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

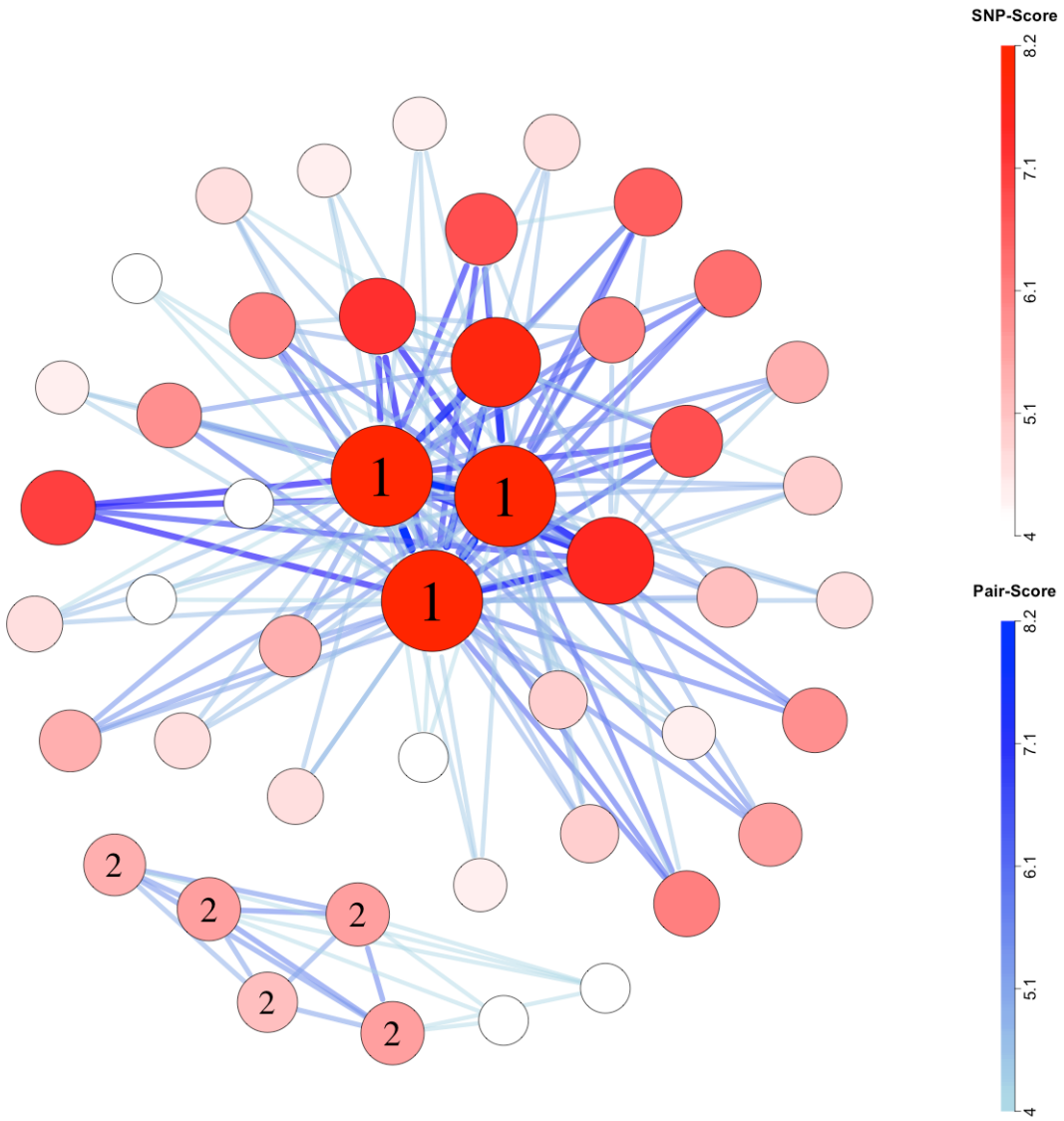

Figure S2. Network plot for simulation scenario 3, replicate 1. *Chromosomes* were filtered for inclusion using global permutations. SNP label '1' indicates membership in epistatic risk set 1. No SNPs from risk set 2 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate pairs of SNPs located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

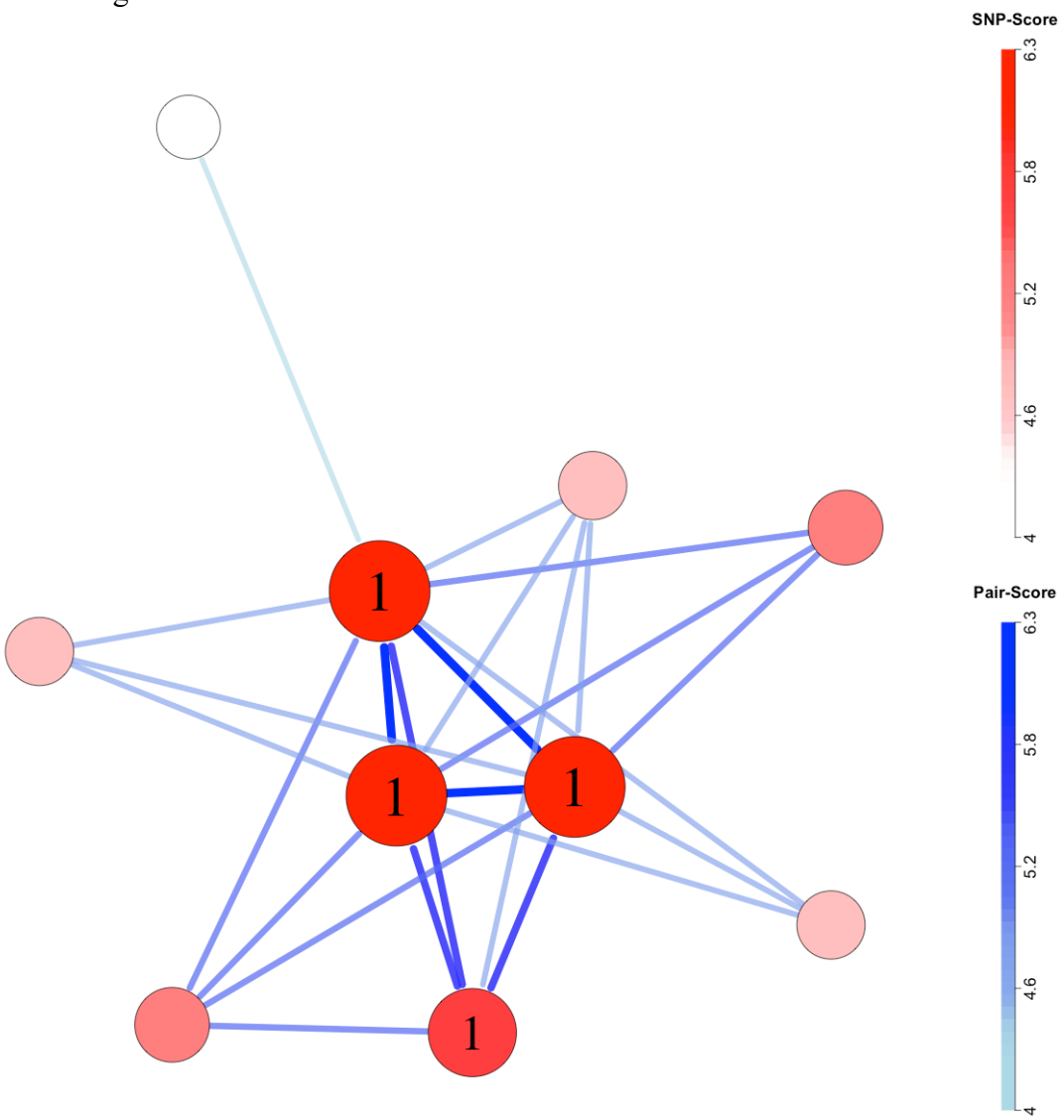

Figure S3. Network plot for simulation scenario 4, replicate 2. *Chromosomes* were filtered for inclusion using global permutations. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate pairs of SNPs located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

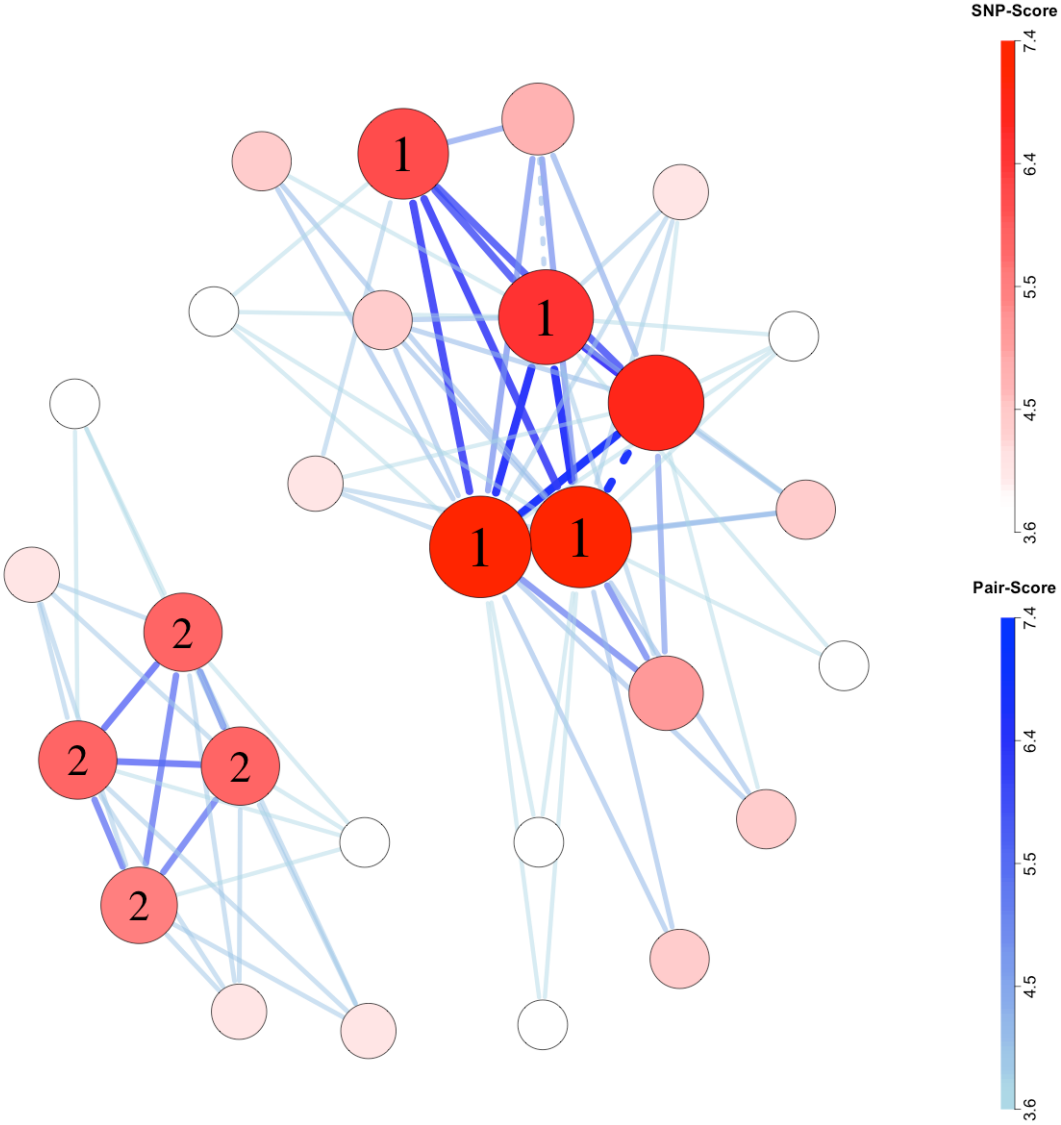

Figure S4. Network plot for simulation scenario 5, replicate 2. *Chromosomes* were filtered for inclusion using global permutations. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Unlabeled SNPs are not risk-related. Dashed connections indicate pairs of SNPs located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

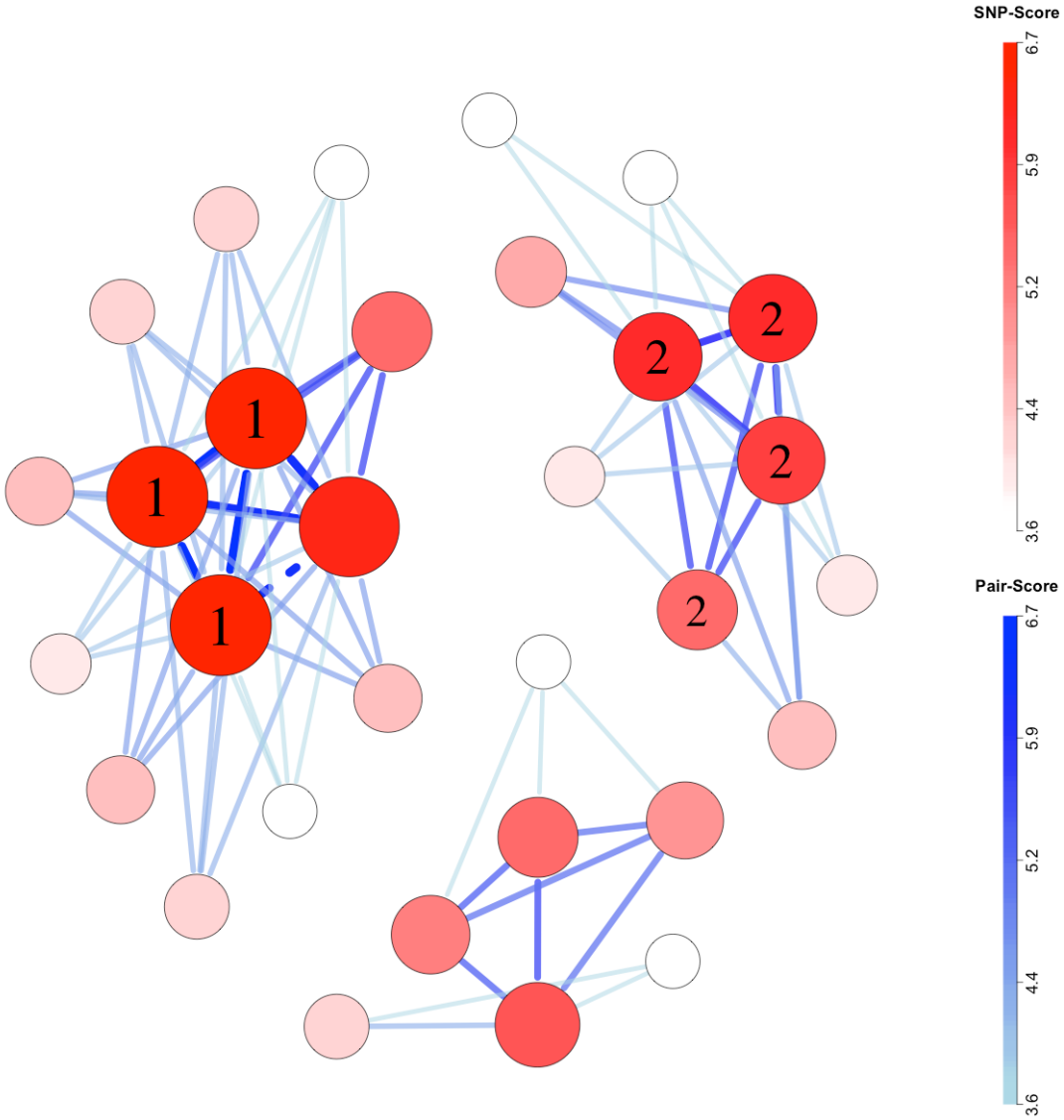

Figure S5. Network plot for simulation scenario 1, replicate 1. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

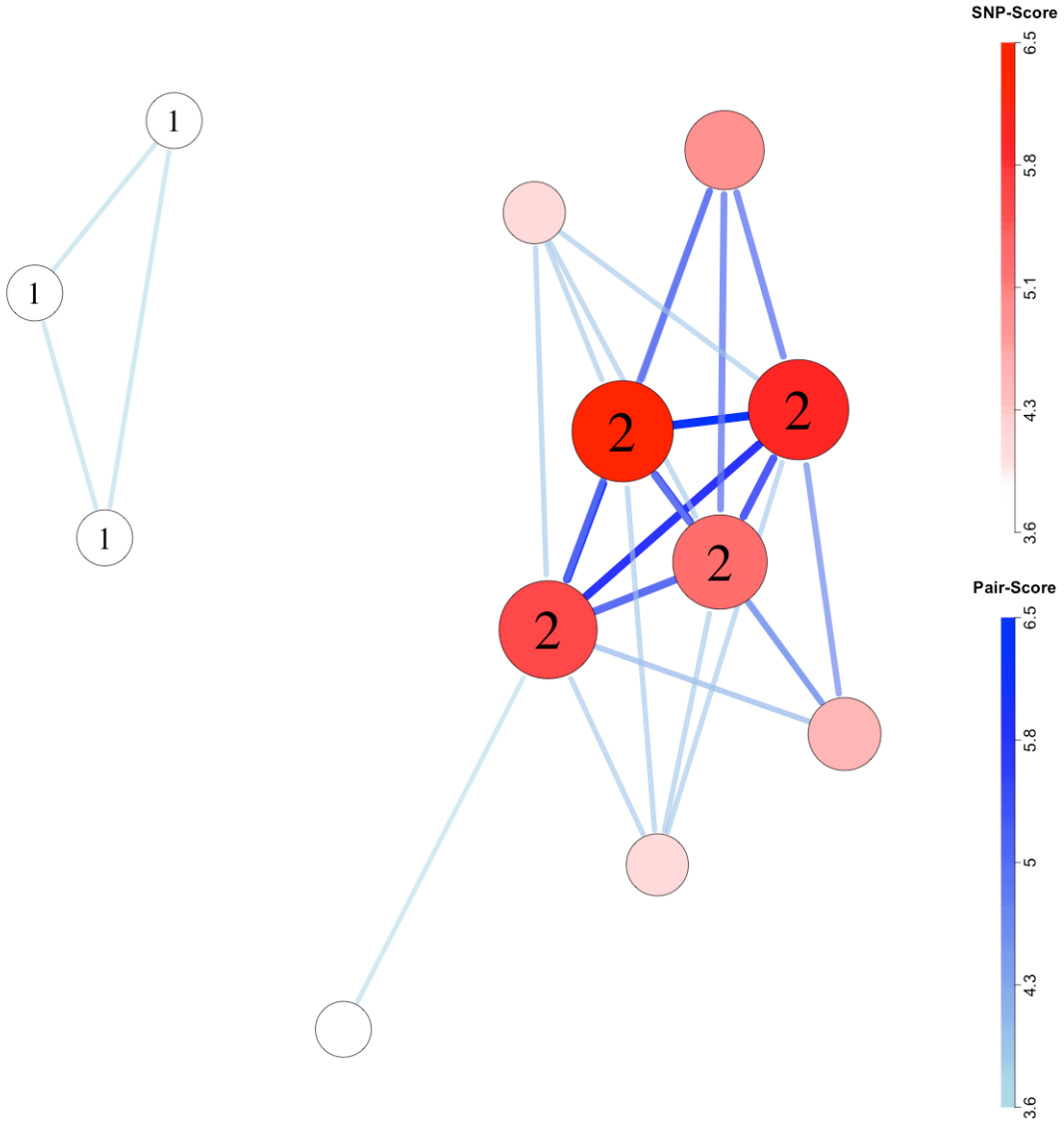

Figure S6. Network plot for simulation scenario 1, replicate 3. Global permutations were not available to filter *chromosomes*. SNP label '1' indicates membership in epistatic risk set 1. No SNPs from epistatic risk set 2 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

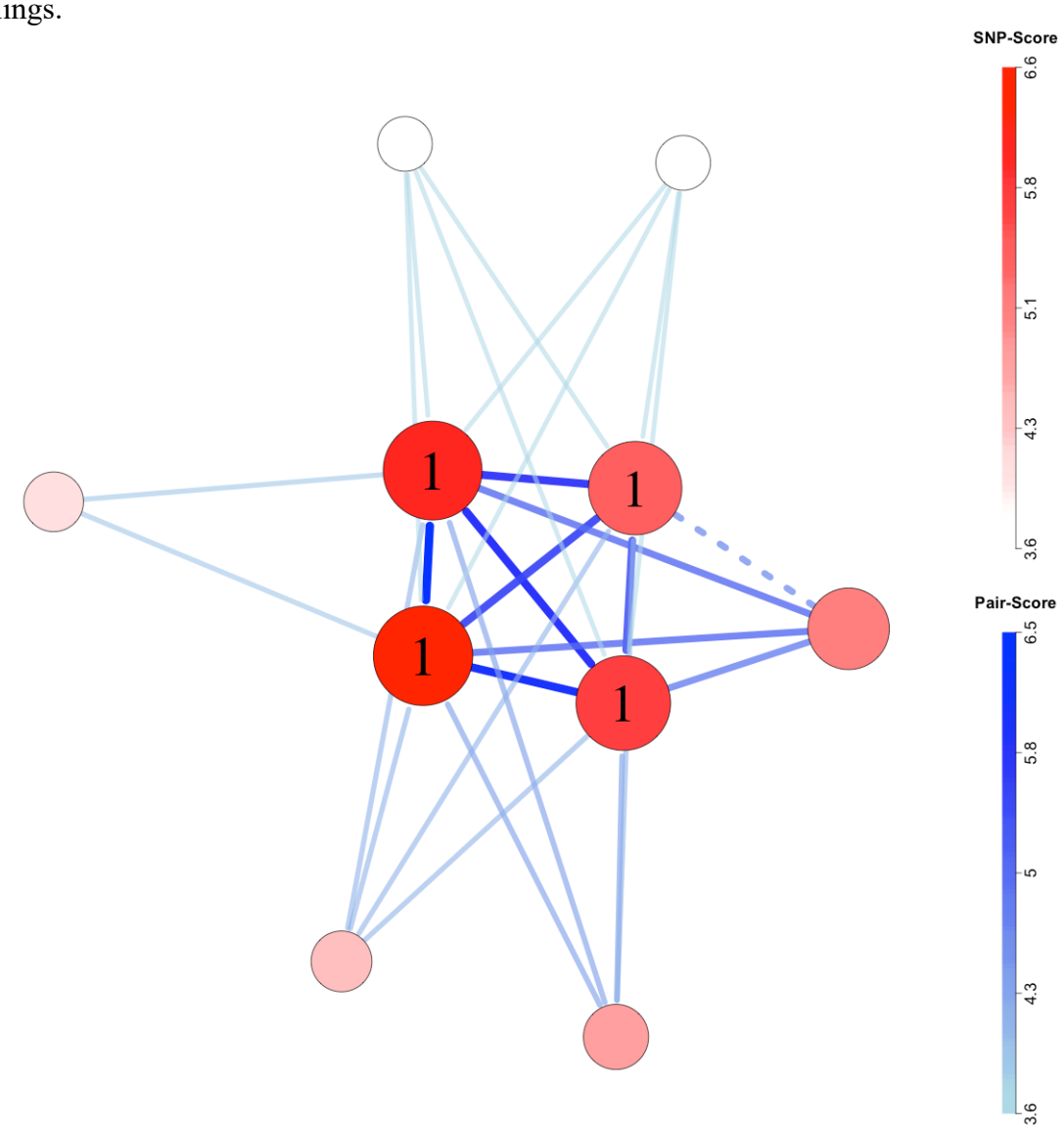

Figure S7. Network plot for simulation scenario 1, replicate 4. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

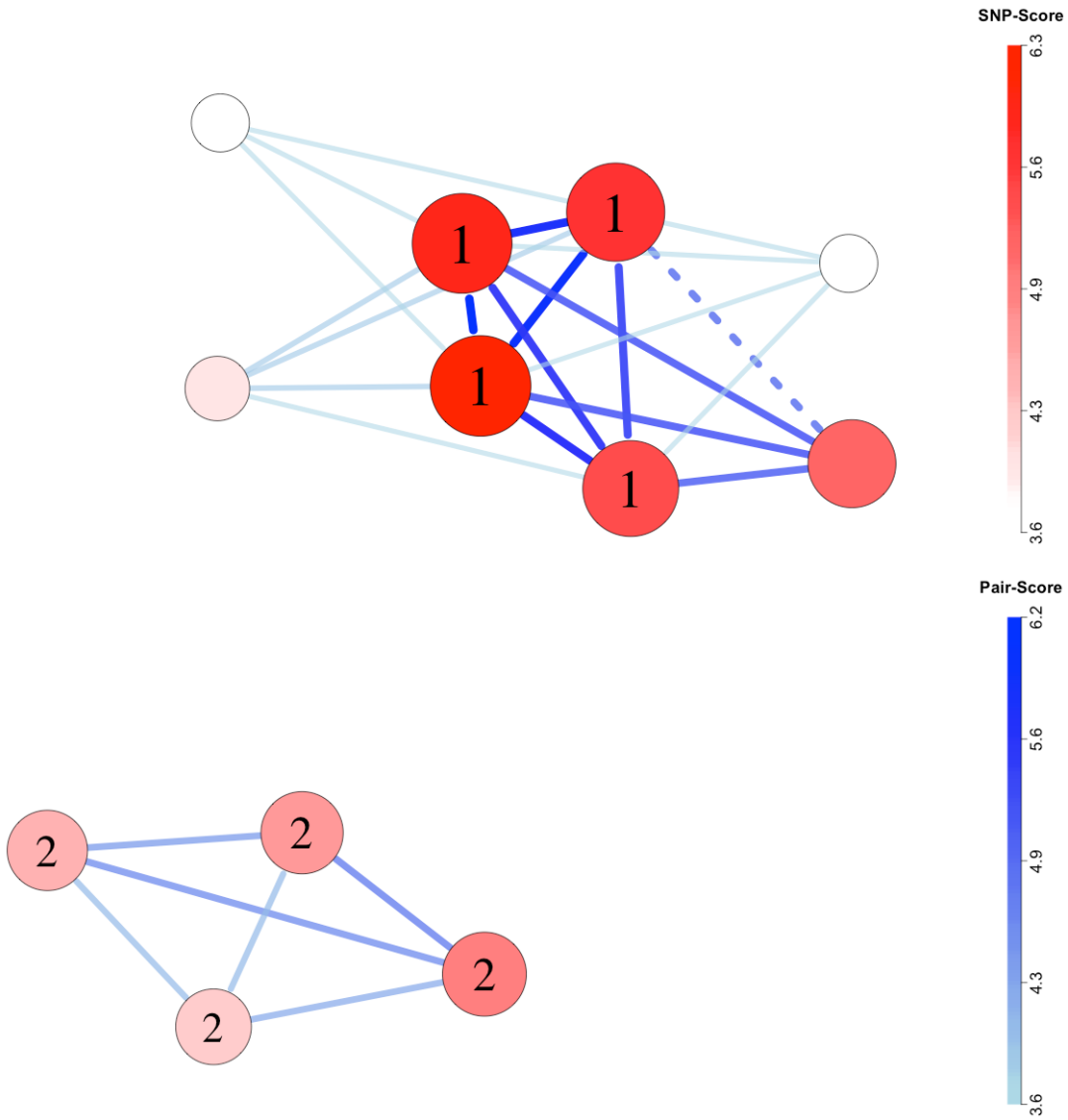

Figure S8. Network plot for simulation scenario 1, replicate 5. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

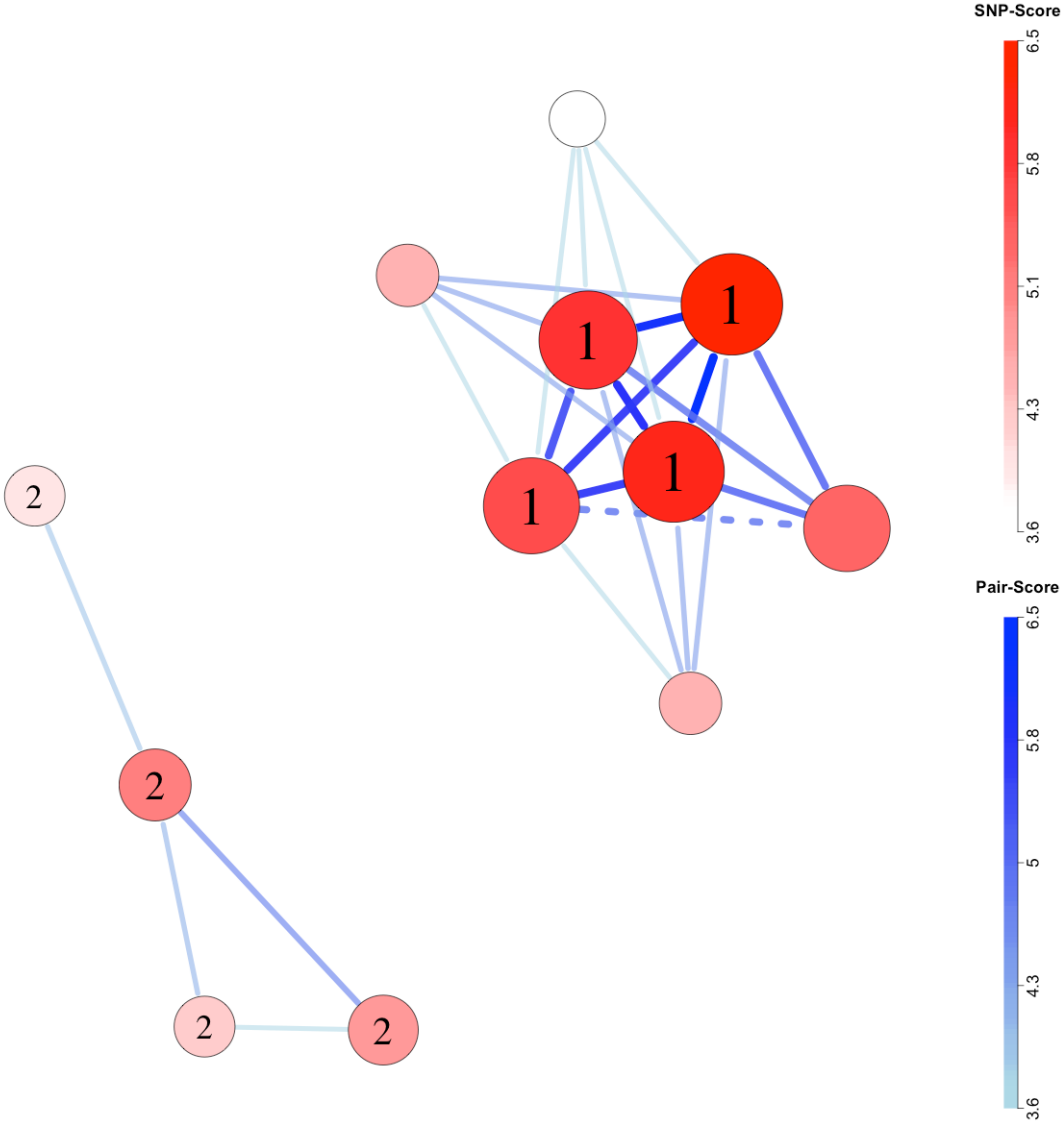

Figure S9. Network plot for simulation scenario 2, replicate 1. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

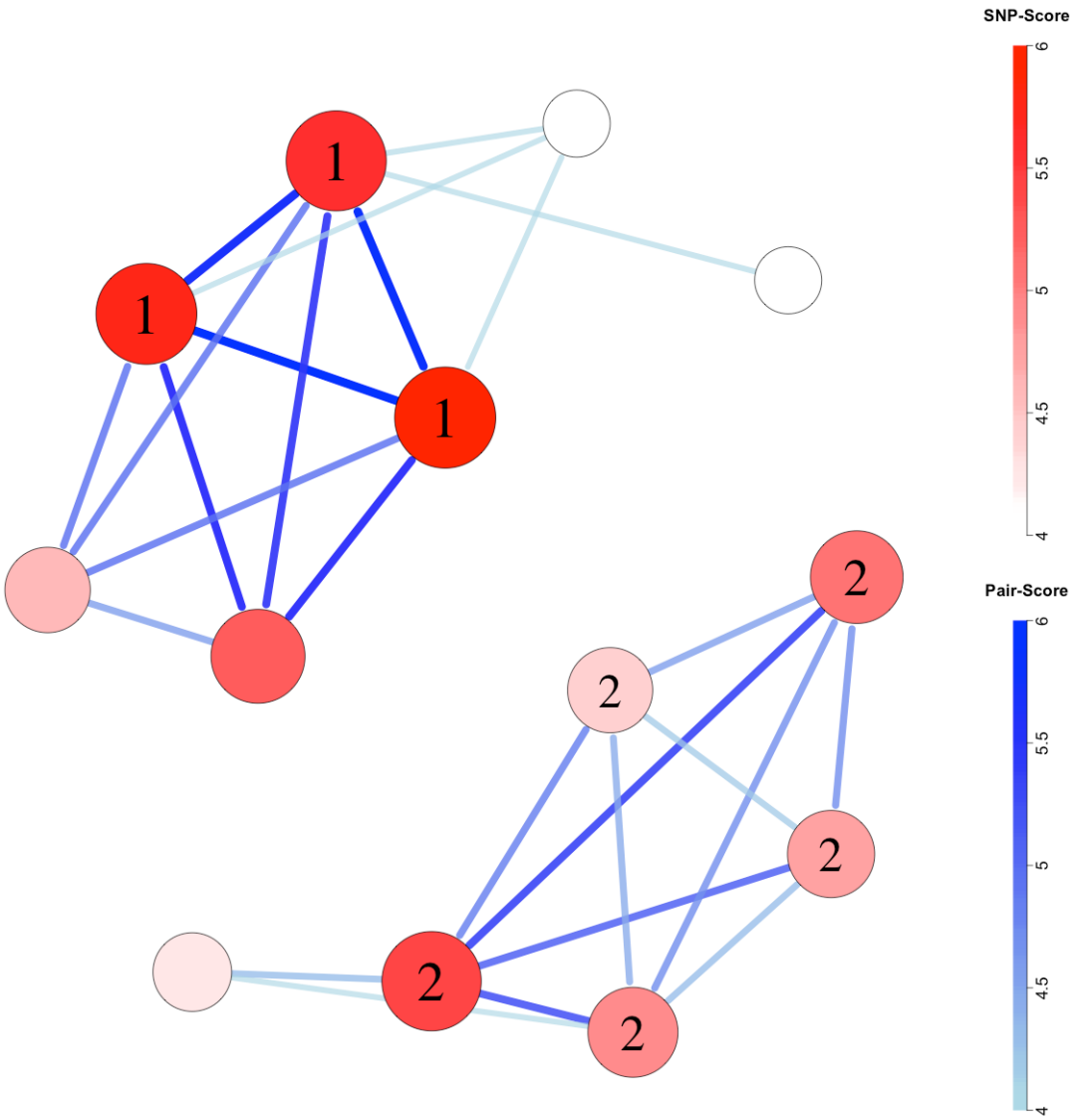

Figure S10. Network plot for simulation scenario 2, replicate 2. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

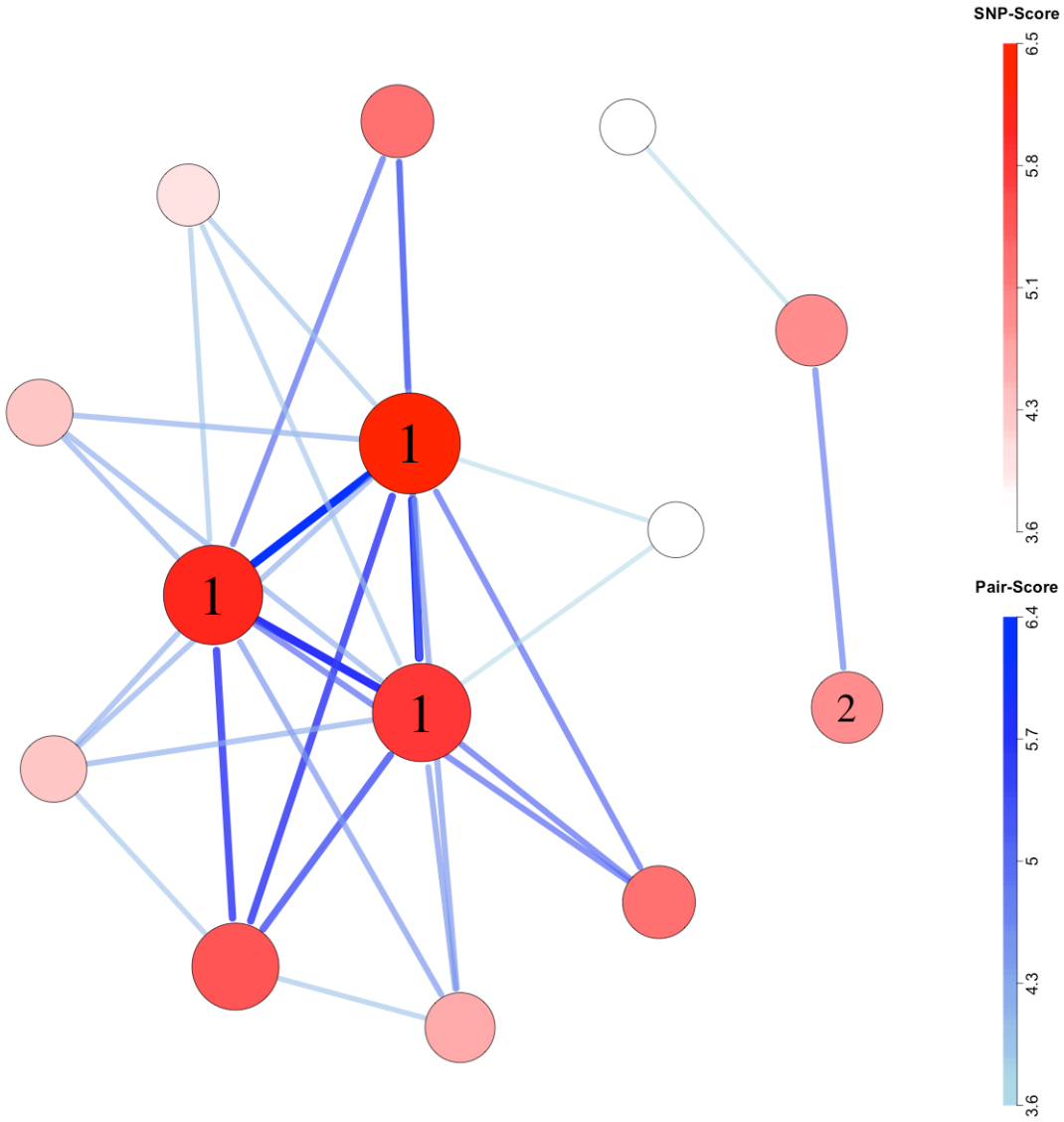

Figure S11. Network plot for simulation scenario 2, replicate 4. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

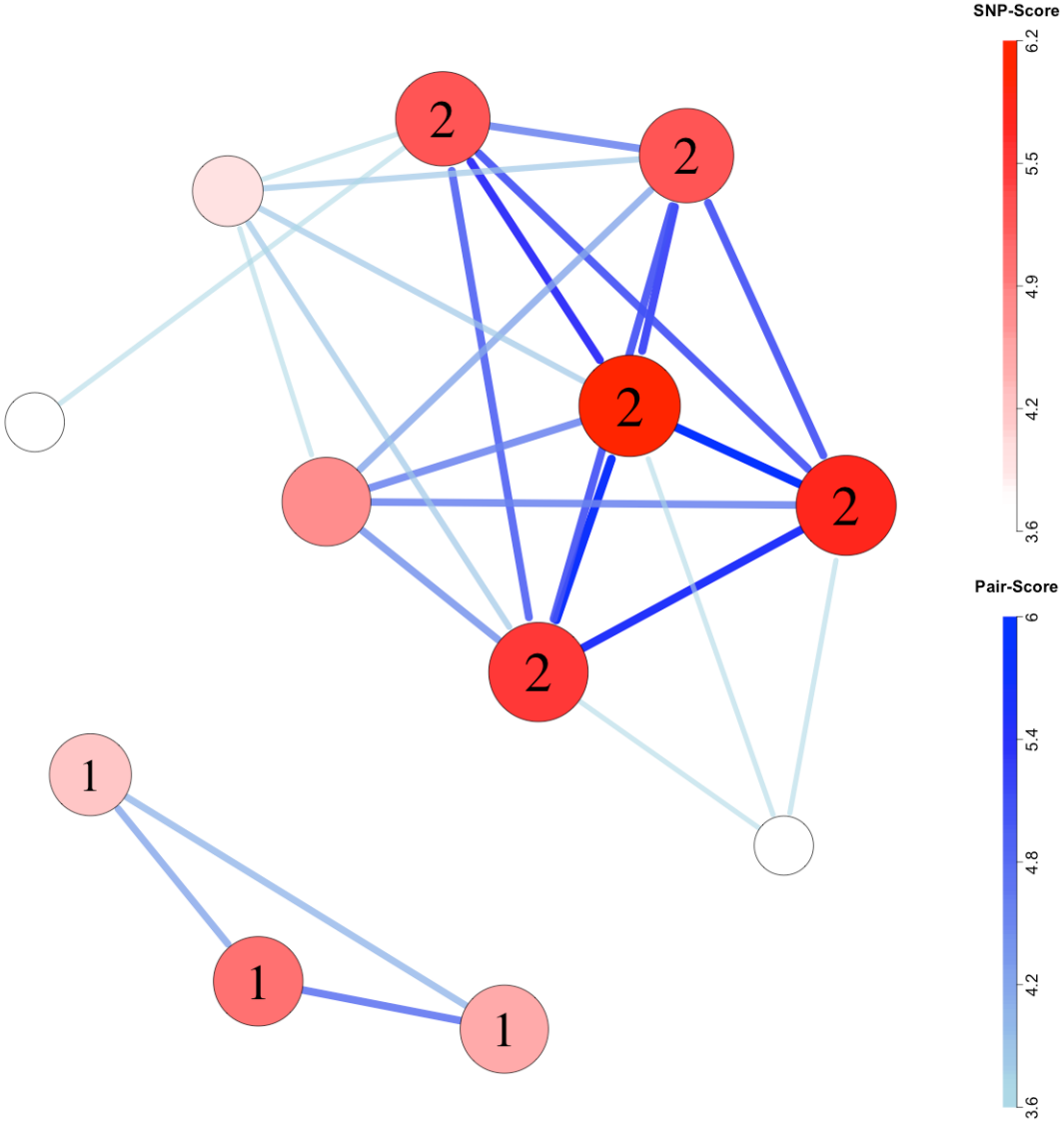

Figure S12. Network plot for simulation scenario 2, replicate 5. Global permutations were not available to filter *chromosomes*. SNP label '1' indicates membership in epistatic risk set 1. No SNPs from epistatic risk set 2 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

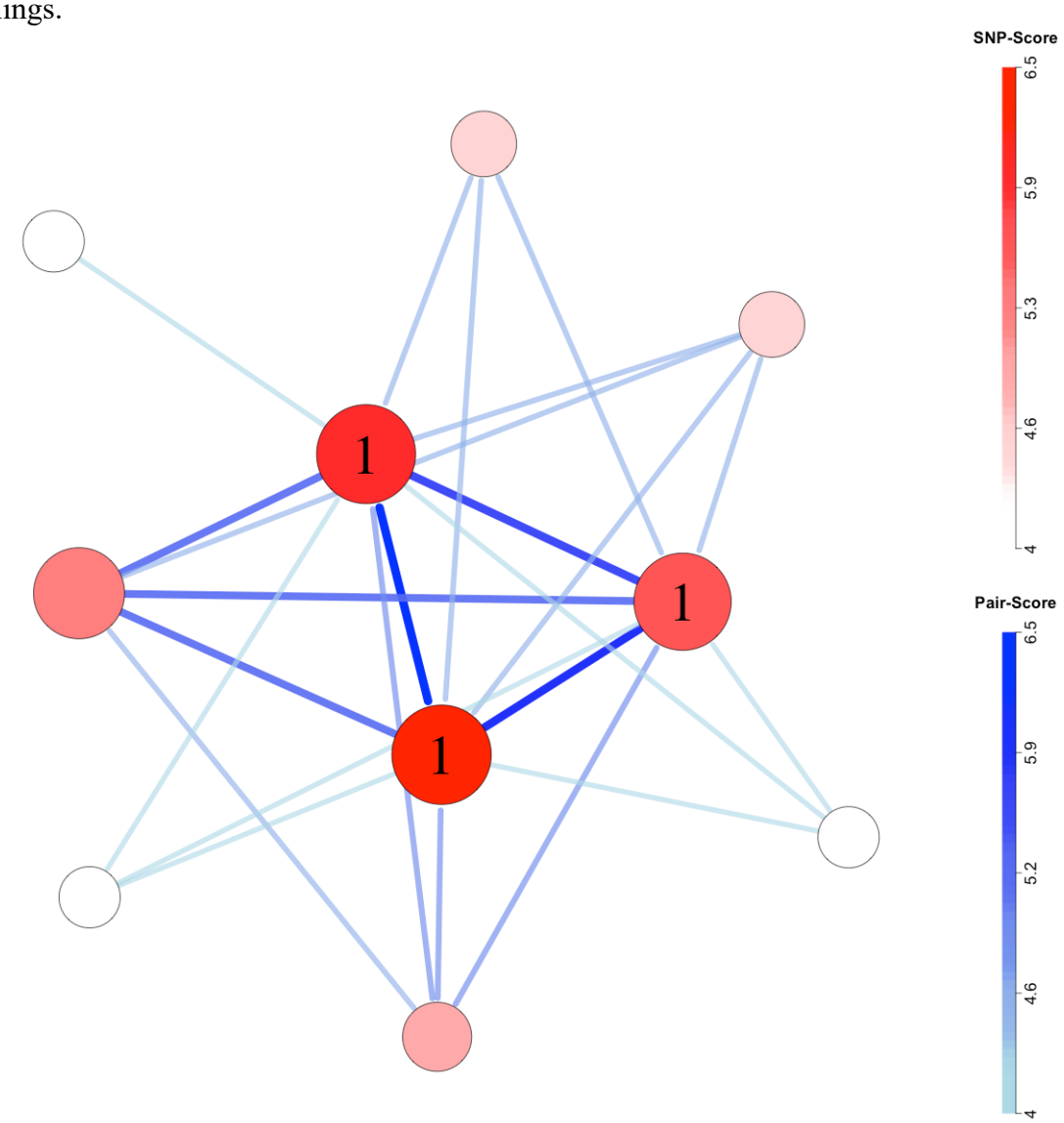

Figure S13. Network plot for simulation scenario 3, replicate 2. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

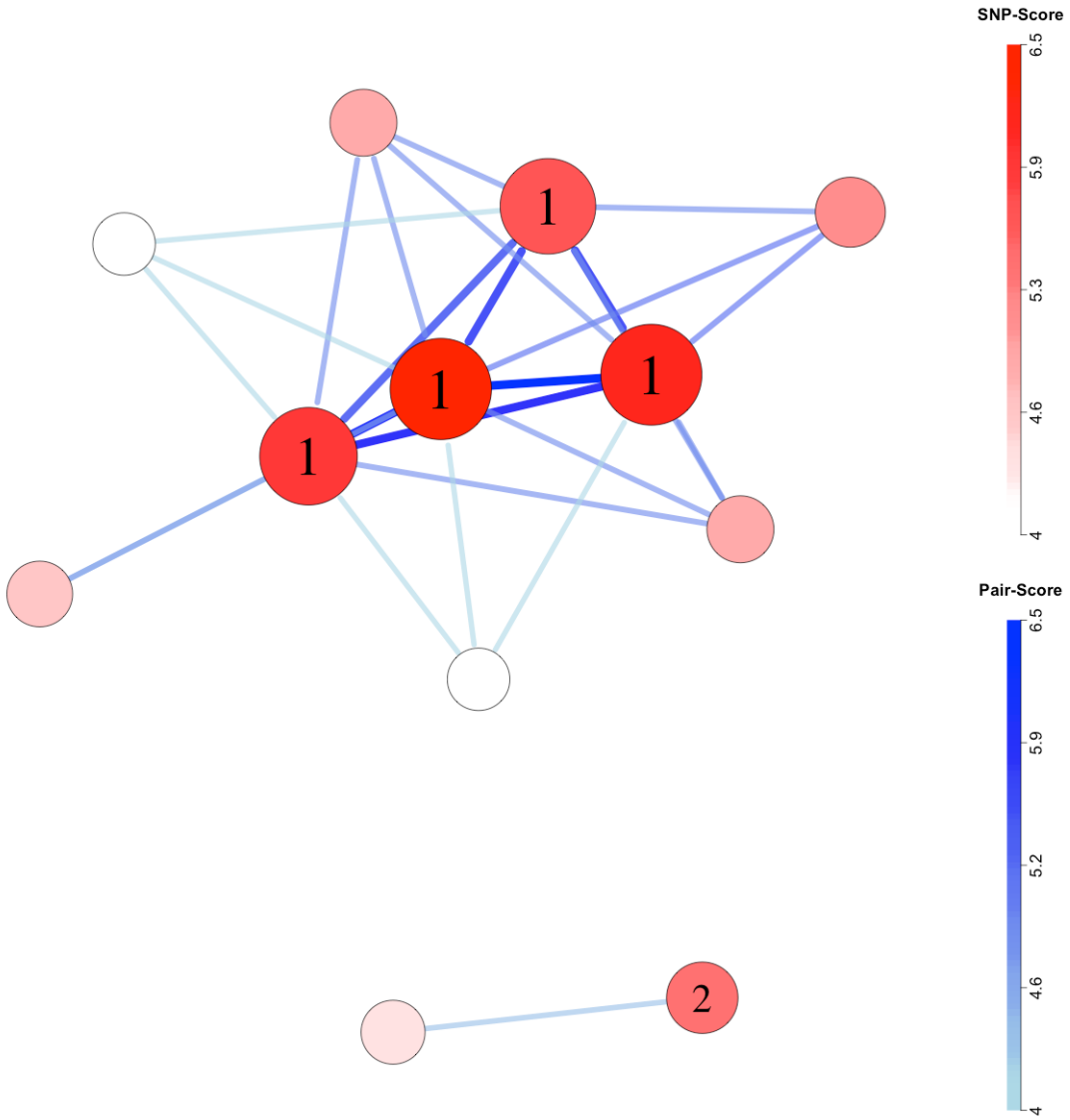

Figure S14. Network plot for simulation scenario 3, replicate 3. Global permutations were not available to filter *chromosomes*. No simulated risk-related SNPs were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

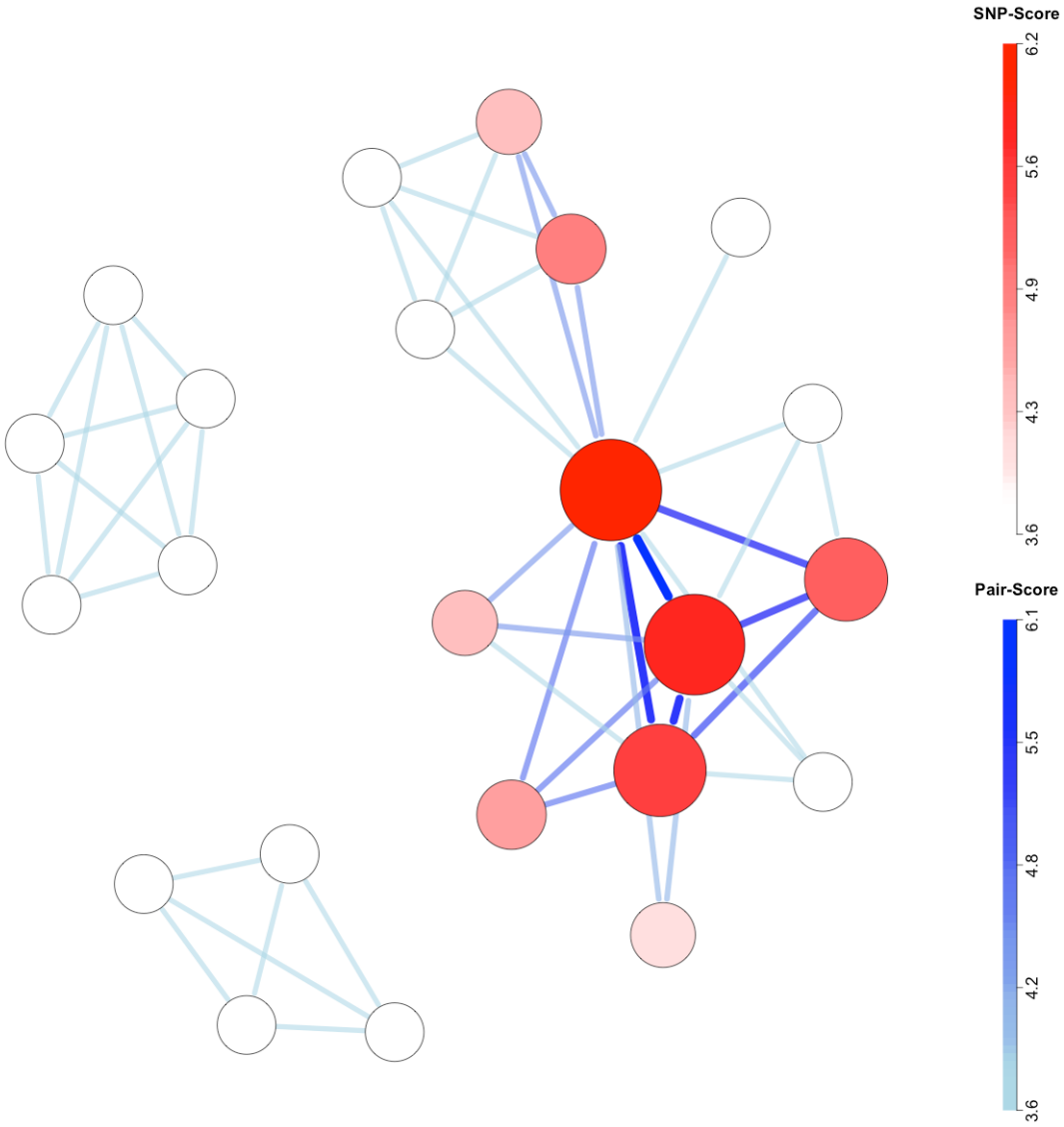

Figure S15. Network plot for simulation scenario 3, replicate 4. Global permutations were not available to filter *chromosomes*. SNP label '2' indicates membership in risk set 2. No SNPs from epistatic risk set 1 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

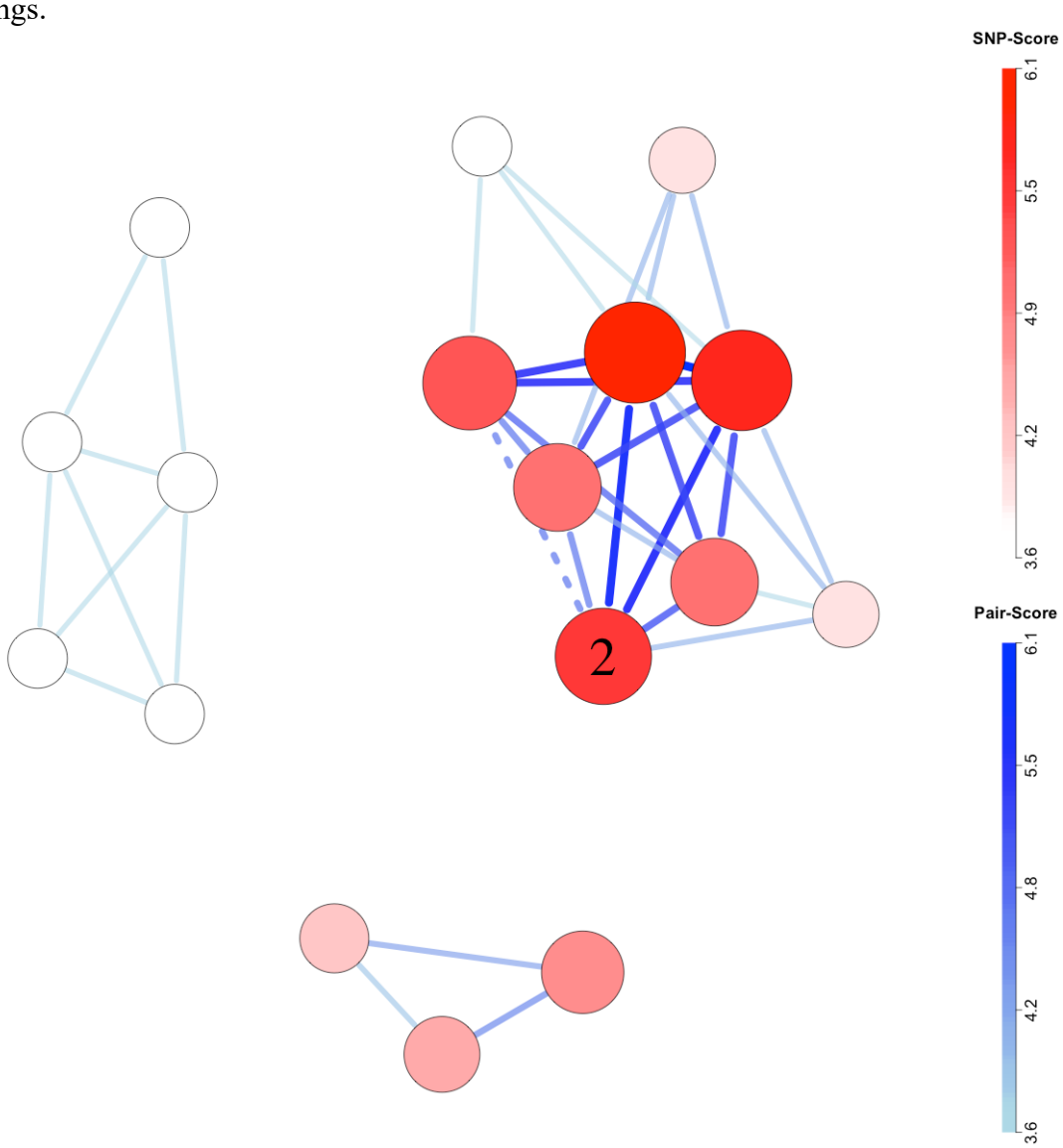

Figure S16. Network plot for simulation scenario 3, replicate 5. Global permutations were not available to filter *chromosomes*. SNP label '1' indicates membership in epistatic risk set 1. No SNPs from risk set 2 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

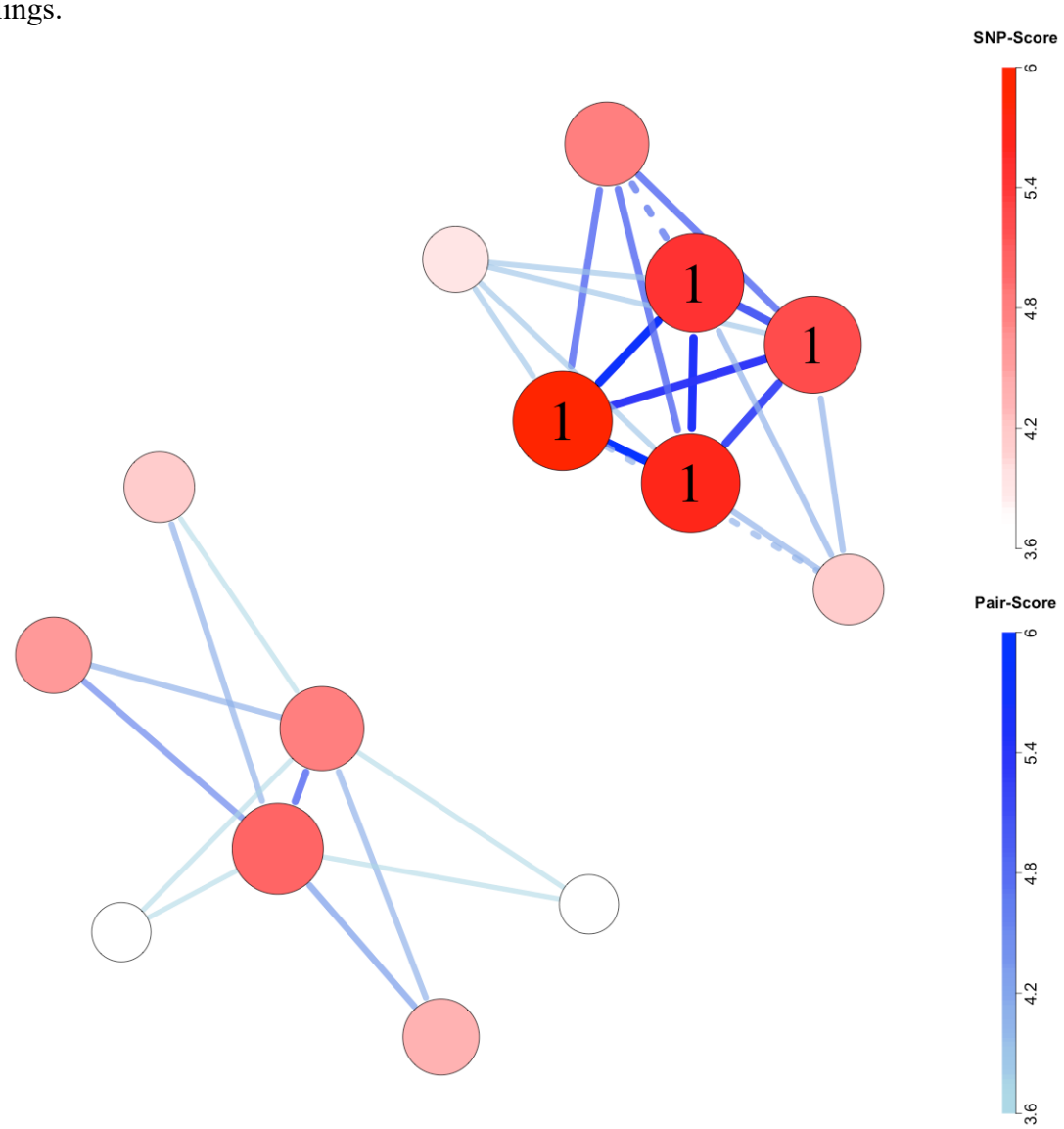

Figure S17. Network plot for simulation scenario 4, replicate 1. Global permutations were not available to filter *chromosomes*. SNP label '2' indicates membership in epistatic risk set 2. No SNPs from epistatic risk set 1 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

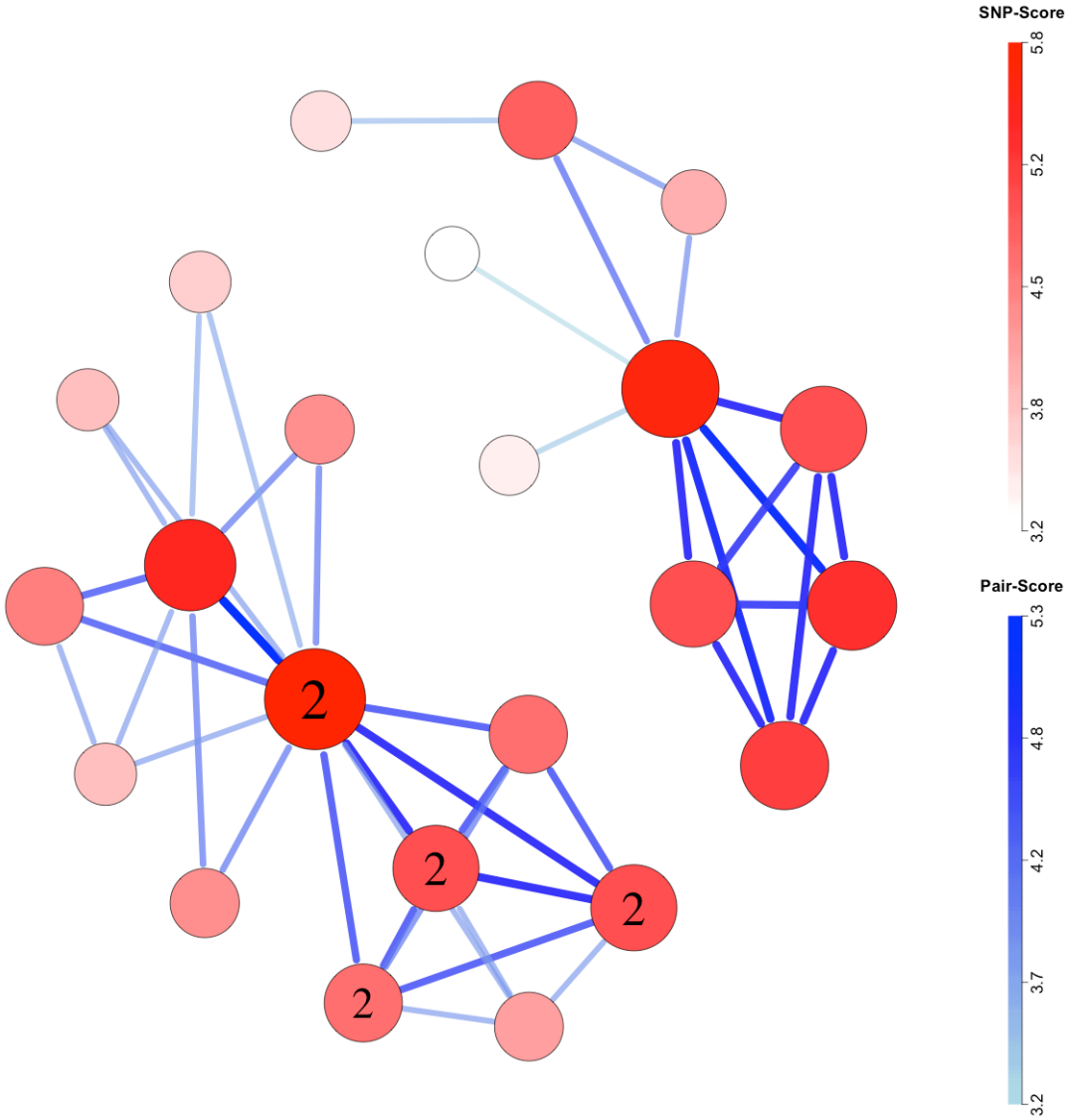

Figure S18. Network plot for simulation scenario 4, replicate 3. Global permutations were not available to filter *chromosomes*. SNP label '1' indicates membership in epistatic risk set 1. No SNPs from epistatic risk set 2 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

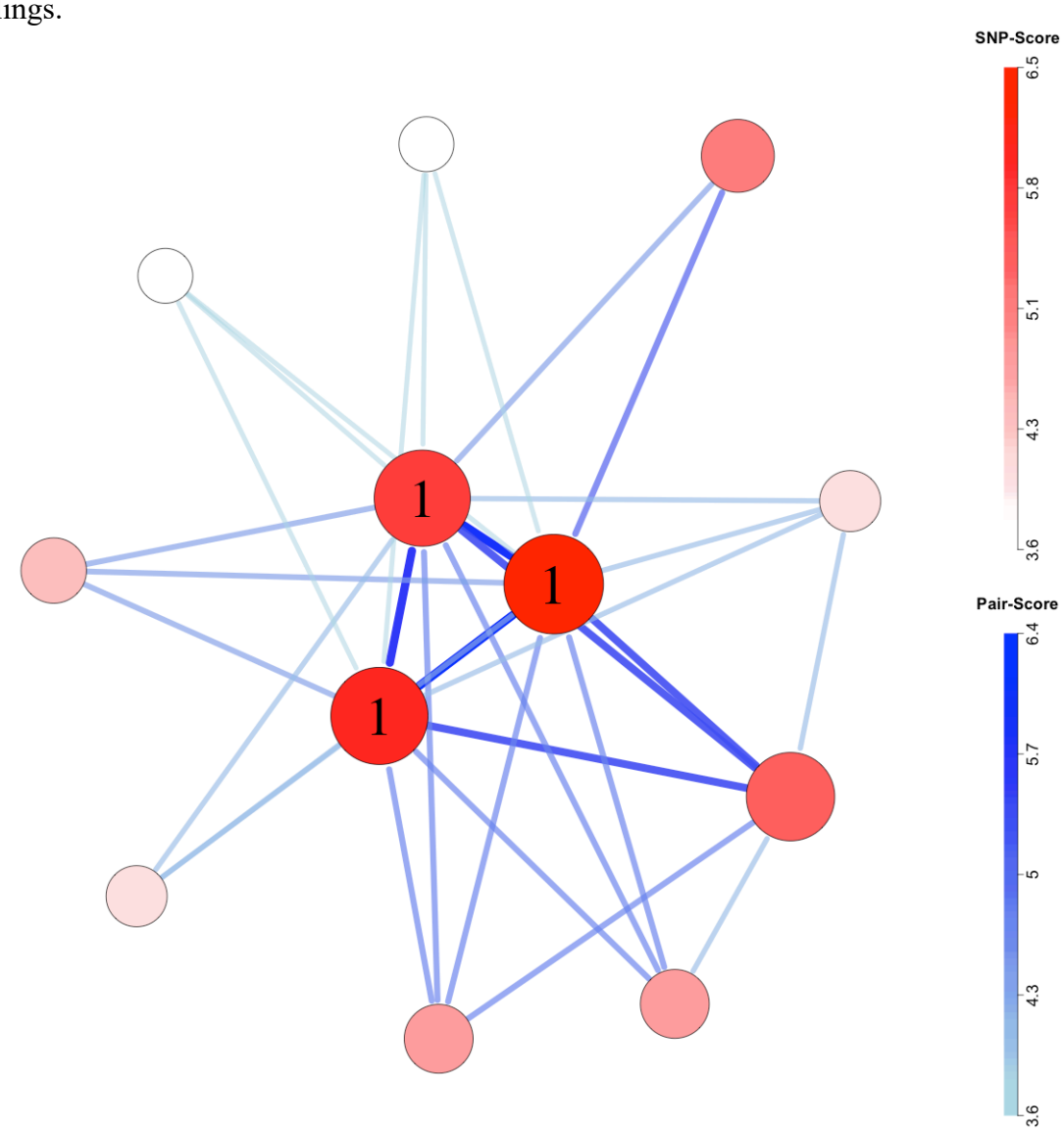

Figure S19. Network plot for simulation scenario 4, replicate 4. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

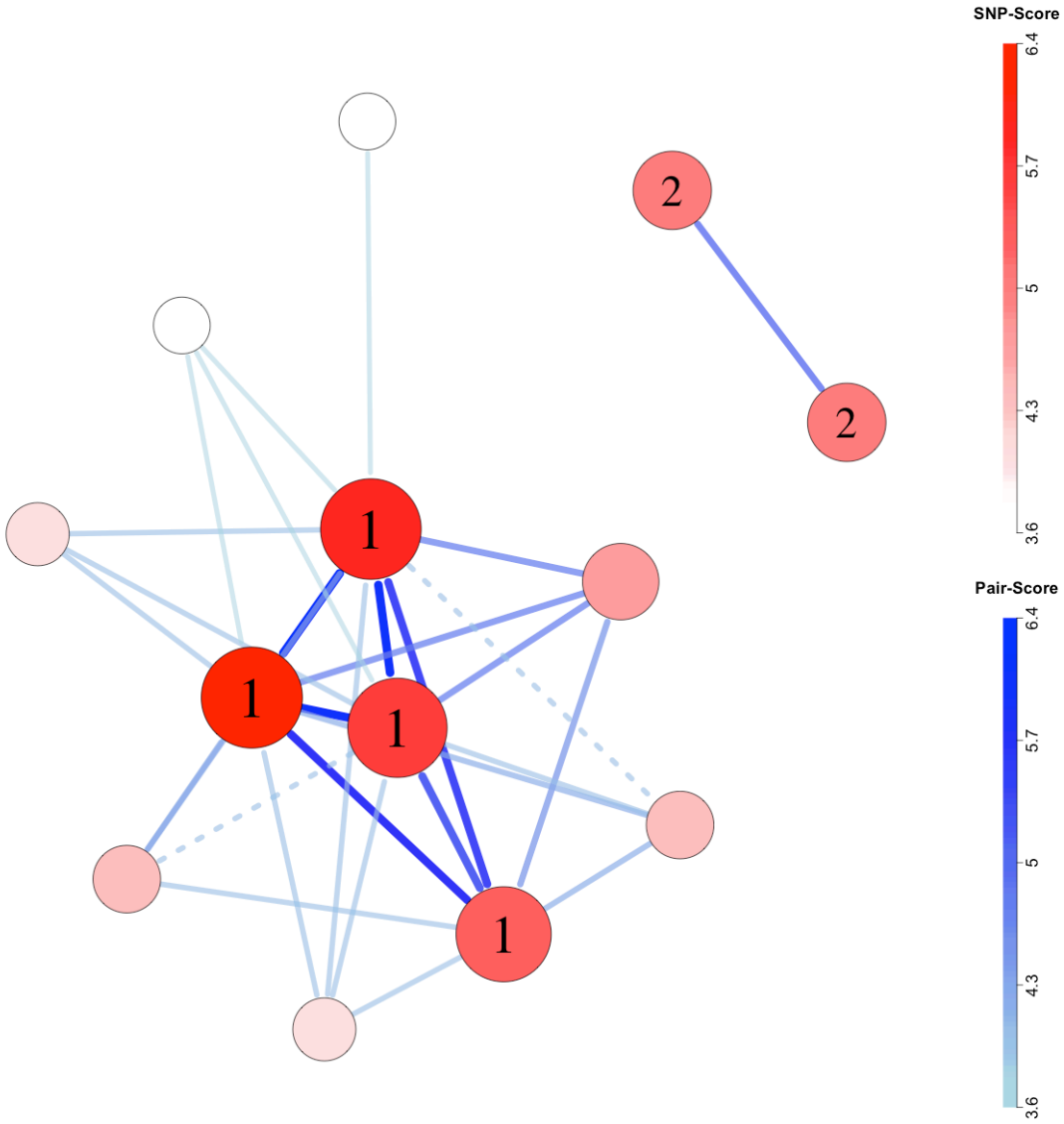

Figure S20. Network plot for simulation scenario 4, replicate 5. Global permutations were not available to filter *chromosomes*. SNP label '2' indicates membership in epistatic risk set 2. No SNPs from epistatic risk set 1 were identified. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

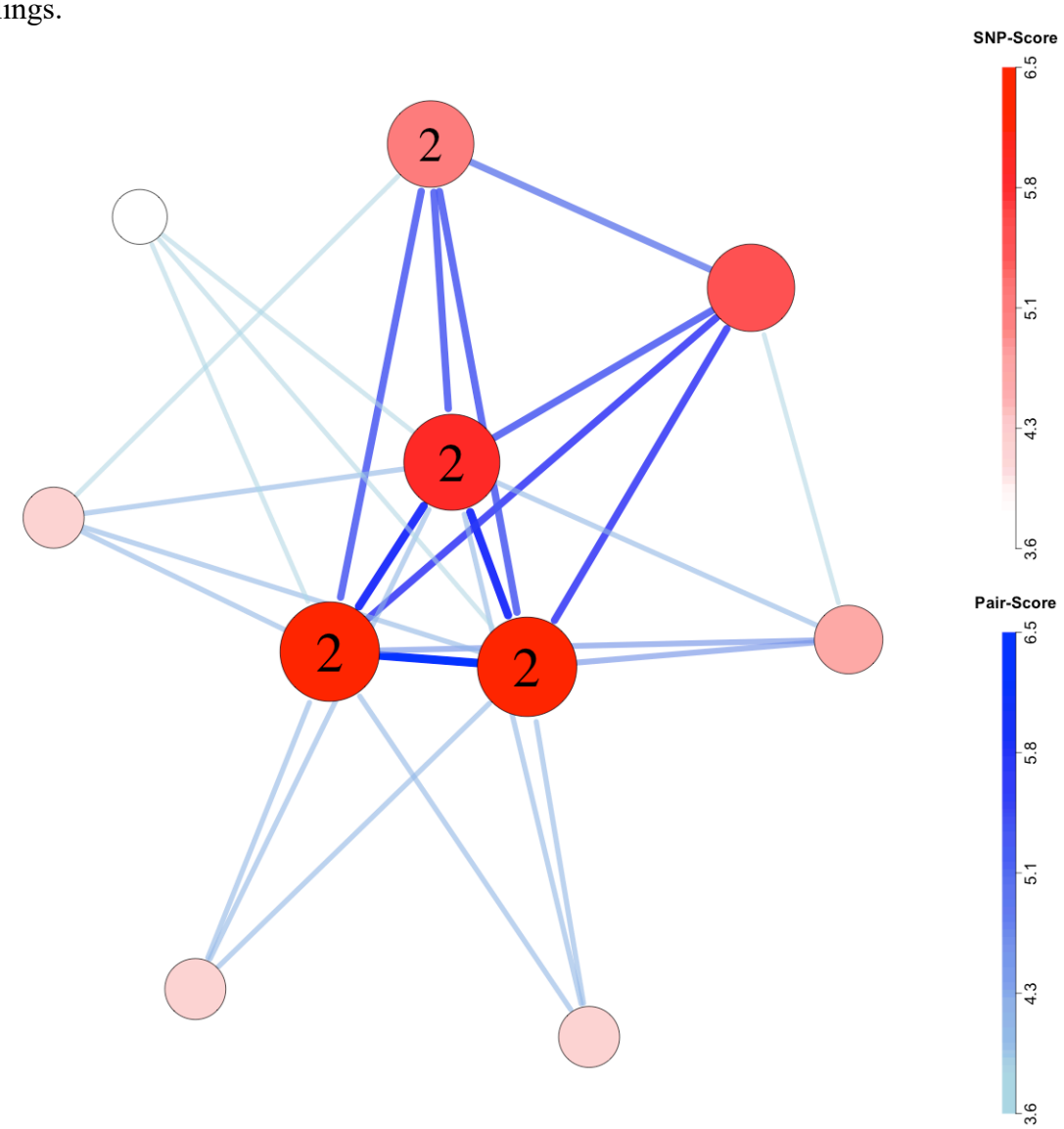

Figure S21. Network plot for simulation scenario 5, replicate 1. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

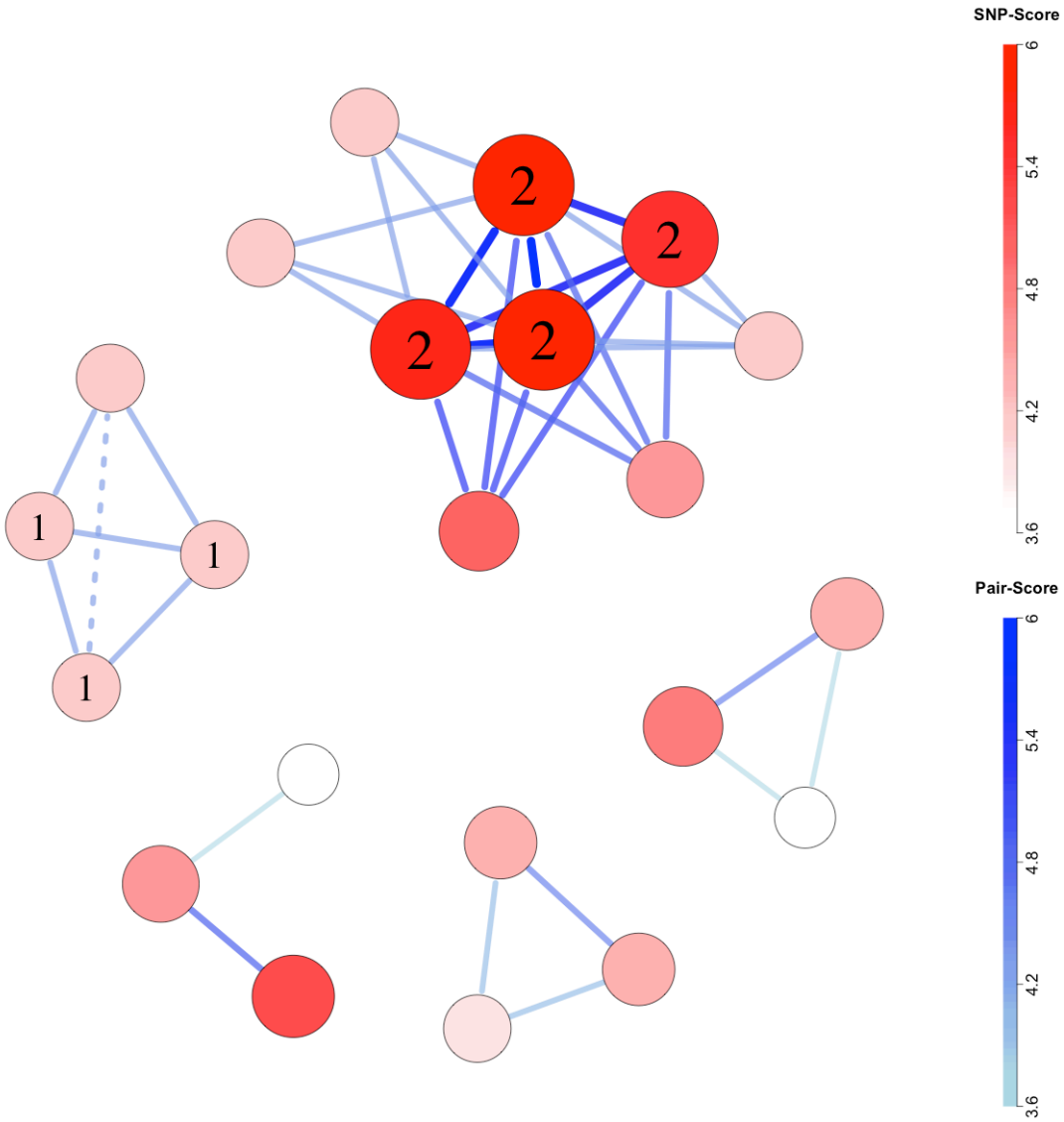

Figure S22. Network plot for simulation scenario 5, replicate 3. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.

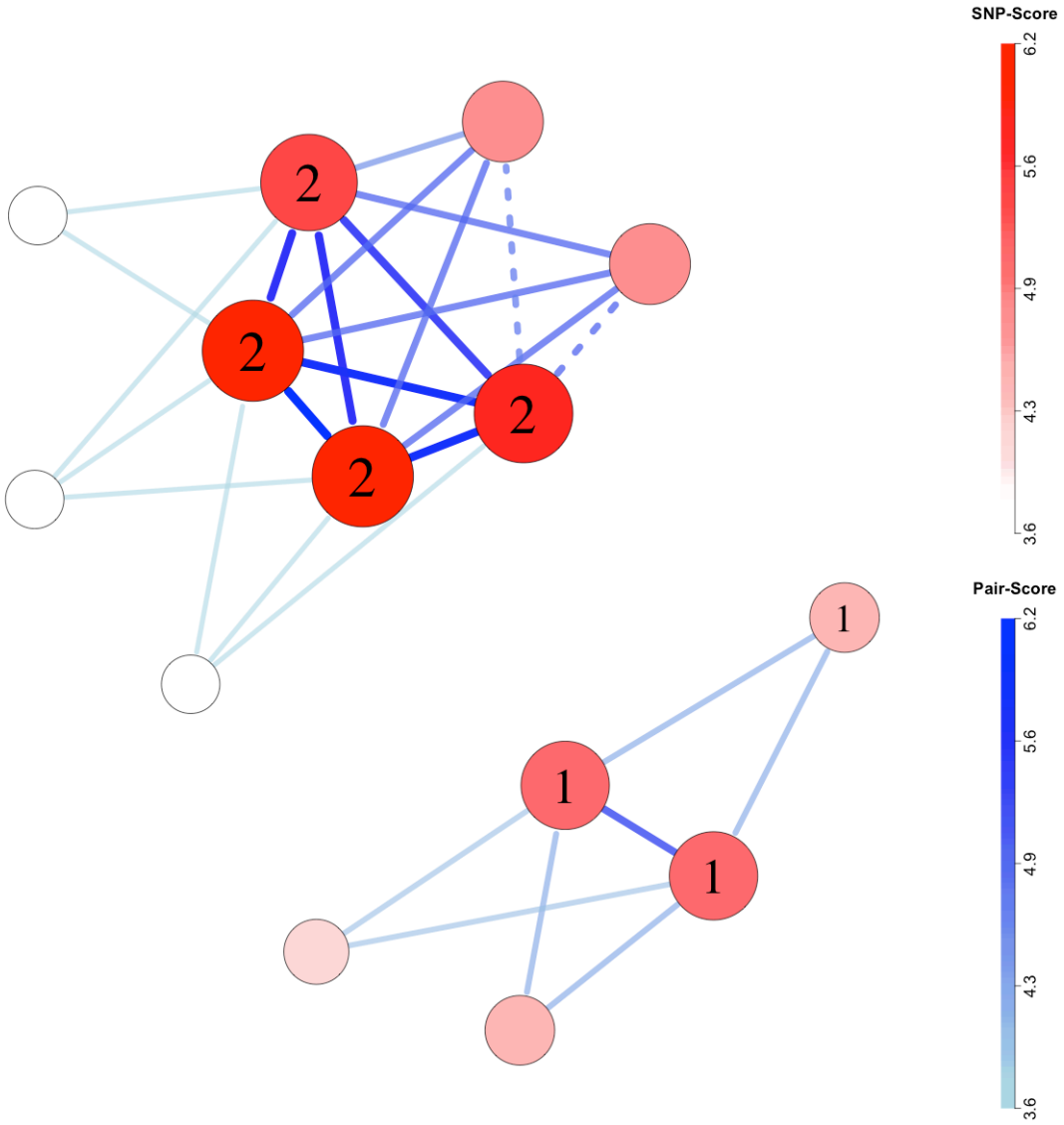

Figure S23. Network plot for simulation scenario 5, replicate 4. Global permutations were not available to filter *chromosomes*. SNP labels '1' and '2' indicate membership in epistatic risk sets 1 and 2, respectively. Larger, darker nodes and thicker, darker edges correspond to larger SNP and SNP-pair scores. Dashed connections indicate SNPs are located on the same biological chromosome with pairwise R^2 of at least 0.1 in complement pseudo-siblings.