The American Journal of Human Genetics, Volume *109*

Supplemental information

KnockoffTrio: A knockoff framework for the identification of putative causal variants in genome-wide association studies with trio design

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Supplemental Note 1: Exchangeability and FDR control in trio studies

We now formally define the exchangeability and FDR control in trio studies.

1 Notations

Let $\mathbf{P}_i$, a $4 \times p$ matrix, denote the parental haplotypes for the i-th trio:

$$\mathbf{P}_i = \begin{bmatrix} H_i^{f,1} \\ H_i^{f,2} \\ H_i^{m,1} \\ H_i^{m,2} \end{bmatrix}.$$

We assume that the genome has been divided into K contiguous regions of equal sizes, e.g., 200kb, and that no recombination occurs within each region. The indices of genetic variants in the k-th region are denoted as $\mathcal{T}_k$, and $t_k = |\mathcal{T}_k|$. We have $\cup_{k=1}^{K} \mathcal{T}_k = [p]$. Let $\mathbf{P}_{i,k}$, a $4 \times t_k$ matrix, denote the parental haplotypes in the k-th region.

Given the parental haplotypes, the offspring haplotypes within a region are a function of the parental haplotypes, either viewed as deterministic (observed) or random. As we have assumed no recombination events, the form of the function remains the same for all genetic variables in $\mathcal{T}_k$. A further observation is that this function is a linear form of $\mathbf{P}_{i,k}$. Therefore, it can be represented by $\mathbf{\Gamma}_{i,k}$, a 2×4 matrix. Now let $\mathbf{\Gamma}_i$ be a $2K \times 4K$ block diagonal matrix of $\mathbf{\Gamma}_{i,k}$'s

$$\mathbf{\Gamma}_i = \begin{bmatrix} \mathbf{\Gamma}_{i,1} & & \\ & \ddots & \\ & & \mathbf{\Gamma}_{i,K} \end{bmatrix},$$

and $\mathbf{P}_i^{\text{block}}$ be a $4K \times p$ block diagonal matrix of $\mathbf{P}_{i,k}$'s

$$\mathbf{P}_i^{\text{block}} = \begin{bmatrix} \mathbf{P}_{i,1} & & \\ & \ddots & \\ & & \mathbf{P}_{i,K} \end{bmatrix}.$$

Then, the offspring haplotypes can be represented as

$$\begin{bmatrix} X_i^f \\ X_i^m \end{bmatrix} = \mathbf{A}\mathbf{\Gamma}_i\mathbf{P}_i^{\text{block}},$$

where A is a $2 \times 2K$ matrix of 0's and 1's, with 1's at odd positions in the first row and at even positions in the second row.

2 Exchangeability for trios

We first construct the knockoff variables for parental haplotypes using the SCIT algorithms as described in the Methods section. Let $\tilde{\mathbf{P}}_i$, a $4 \times p$ matrix, denote the knockoff parental haplotypes for the i-th trio

$$\tilde{\mathbf{P}}_i = \begin{bmatrix} \tilde{H}_i^{f,1} \\ \tilde{H}_i^{f,2} \\ \tilde{H}_i^{m,1} \\ \tilde{H}_i^{m,2} \end{bmatrix}.$$

We also define $\tilde{\mathbf{P}}_i^{\text{block}}$ similarly. The knockoff offspring haplotypes are obtained by setting

$$\begin{bmatrix} \tilde{X}_i^f \\ \tilde{X}_i^m \end{bmatrix} = \mathbf{A}\mathbf{\Gamma}_i\tilde{\mathbf{P}}_i^{\text{block}},$$

where we assume the transmission patterns are the same for both the original and synthetic trios.

The exchangeability is defined at the matrix level. We say that $[\mathbf{P}_i, \tilde{\mathbf{P}}_i]$ satisfies the exchangeability condition if for any $\mathcal{S} \subset [p]$

$$[\mathbf{P}_i, \tilde{\mathbf{P}}_i] \overset{D}{=} [\mathbf{P}_i, \tilde{\mathbf{P}}_i]_{\text{swap}(\mathcal{S})}$$

where $[\mathbf{P}_i, \tilde{\mathbf{P}}_i]_{\text{swap}(\mathcal{S})}$ is obtained by swapping the j-th column of $\mathbf{P}_i$ and $\tilde{\mathbf{P}}_i$ for $j \in \mathcal{S}$. Note that if the exchangeability condition holds for $[\mathbf{P}_i, \tilde{\mathbf{P}}_i]$, then it also holds for $[\mathbf{P}_i^{\text{block}}, \tilde{\mathbf{P}}_i^{\text{block}}]$. Therefore,

$$\begin{bmatrix} X_i^f & \tilde{X}_i^f \\ X_i^m & \tilde{X}_i^m \end{bmatrix}_{\text{swap}(\mathcal{S})} = \mathbf{A}\mathbf{\Gamma}_i[\mathbf{P}_i^{\text{block}}, \tilde{\mathbf{P}}_i^{\text{block}}]_{\text{swap}(\mathcal{S})}.$$

This implies that, if we consider all haplotypes in a trio, the exchangeability holds in the sense that

$$\begin{bmatrix} \mathbf{P}_i & \tilde{\mathbf{P}}_i \\ X_i^f & \tilde{X}_i^f \\ X_i^m & \tilde{X}_i^m \end{bmatrix} \overset{D}{=} \begin{bmatrix} \mathbf{P}_i & \tilde{\mathbf{P}}_i \\ X_i^f & \tilde{X}_i^f \\ X_i^m & \tilde{X}_i^m \end{bmatrix}_{\text{swap}(\mathcal{S})}. \tag{1}$$

Here, we treat the transmission pattern $\mathbf{\Gamma}_i$ as given. In the case that we also consider the randomness of $\mathbf{\Gamma}_i$, the exchangeability can be understood as (1) holds conditional on $\mathbf{\Gamma}_i$.

As shown in Figure S1, the exchangeability property holds in simulations.

3 Exchangeability for trios with missing parents

If one of the parents is missing, a valid construction of knockoff variables can still be obtained by conceptually setting the knockoff variables for the missing parent to the original variables. Specifically, we can assume $H_i^{m,1}$ and $H_i^{m,2}$ are missing in $\mathbf{P}_i$. For the knockoff counterparts, we can then hypothetically set $\tilde{H}_i^{m,1} = H_i^{m,1}$, $\tilde{H}_i^{m,2} = H_i^{m,2}$, and consequently $\tilde{X}_i^m = X_i^m$, which is a trivial construction of knockoff variables. Therefore, the exchangeability condition (1) is still satisfied.

4 FDR control for trios

Our goal is to test the conditional null hypothesis

$$H_{0,g} : \boldsymbol{Y} \perp\!\!\!\perp \boldsymbol{G}_g | \boldsymbol{G}_{-g}$$

where $\boldsymbol{G} \in \{0,1,2\}^{3n \times p}$ is the matrix of trio genotypes and $g \subset [p]$ is a continuous block. For trios, the null hypothesis is essentially

$$H_{0,l} : \boldsymbol{Y} \perp\!\!\!\perp (\mathbf{X}_{gl}, \mathbf{P}_{gl}) | (\mathbf{X}_{-gl}, \mathbf{P}_{-gl}), l = 1, \ldots, L$$

where $\mathbf{X} \in \{0,1\}^{2n \times p}$ are the offspring haplotypes, $\mathbf{P} \in \{0,1\}^{4n \times p}$ are the parental haplotypes, and $g_1, \ldots, g_L \subset [p]$ are a collection of continuous blocks of p genetic variables. Let KnockoffTrio's feature importance statistic for a window be

$$W_l = w_l\left(\begin{bmatrix} \mathbf{P} & \tilde{\mathbf{P}} \\ \mathbf{X} & \tilde{\mathbf{X}} \end{bmatrix}, \boldsymbol{y} \right)$$

for some anti-symmetric function w_l. Because the p-values for calculating W_l's are obtained from marginal tests for each genetic variable in a window, we can see that for any $S \subset 1, \ldots, L$

$$w_l\left(\begin{bmatrix}\mathbf{P} & \tilde{\mathbf{P}} \\ \mathbf{X} & \tilde{\mathbf{X}}\end{bmatrix}_{\text{swap}(S)}, \boldsymbol{y}\right) = \begin{cases} w_l\left(\begin{bmatrix}\mathbf{P} & \tilde{\mathbf{P}} \\ \mathbf{X} & \tilde{\mathbf{X}}\end{bmatrix}, \boldsymbol{y}\right), & l \notin S, \\ -w_l\left(\begin{bmatrix}\mathbf{P} & \tilde{\mathbf{P}} \\ \mathbf{X} & \tilde{\mathbf{X}}\end{bmatrix}, \boldsymbol{y}\right), & l \in S \end{cases} \tag{2}$$

where $\begin{bmatrix}\mathbf{P} & \tilde{\mathbf{P}} \\ \mathbf{X} & \tilde{\mathbf{X}}\end{bmatrix}_{\text{swap}(S)}$ is defined by swapping original genetic variables in all windows $g_l, l \in S$ with their knockoffs. The flip-sign property (2) in combination with the exchangeability (1) leads to valid FDR control for trios. The proof is for single knockoff construction and can be easily generalized to the case of multiple knockoffs with similar arguments.

5 Protection against external confounders

Based on the exchangeability condition (1), when a hypothesis $H_{0,g}$ is rejected, at least one of the following two cases is true: (1) $X_g \not\perp\!\!\!\perp Y \mid (X_{-g}, \mathbf{P}_{-g})$; (2) $\mathbf{P}_g \not\perp\!\!\!\perp Y \mid (X_{-g}, \mathbf{P}_{-g})$. Under the definition of external confounders introduced in [1], the claim from case (1) is robust to external confounders, such as population stratification, while case (2) is not. While it is possible that the observed association between P_g and Y is due to population stratification, because the family-based association test (FBAT) is applied to calculate feature importance statistics in KnockoffTrio, the p-value for the original cohort can only be small when case (1) holds, and is expected to be relatively large for case (2). This feature leads to protection against external confounders: when a discovery is made by KnockoffTrio, the family-based association test helps distinguish case (1) from case (2), and the discovery is most likely due to the association of case (1).

As shown in Figure S2, KnockoffTrio controls the FDR in the presence of population stratification at a target FDR of 0.1 for both dichotomous and quantitative traits.

Supplemental Note 2: Empirical power and FDR in meta-analysis simulations

We adopted the same simulation settings as in the "Empirical power and FDR in single-locus simulations" Section except that in each replicate we partitioned the trios into two subcohorts of 5,000 trios each. We then applied KnockoffTrio to the two subcohorts respectively and used KnockoffTrio's meta-analysis procedure to combine the results from the two subcohorts. In Figure S3, we show the empirical power and FDR for KnockoffTrio's meta-analysis of the two subcohorts, compared to the corresponding mega-analysis of the combined cohort. KnockoffTrio's meta-analysis has comparable power to the mega-analysis (when $M = 10$) while preserving the FDR in all scenarios.

Supplemental Note 3: KnockoffScreen in trio studies

KnockoffScreen was designed for independent individuals in population-based studies. We investigated the power and FDR of KnockoffScreen in trio studies. Specifically, we used KnockoffScreen to generate knockoffs of trio data disregarding the family structure and treating family members as unrelated individuals. We adopted the same simulation settings as in the "Empirical power and FDR in single-locus simulations" Section. As shown in Figure S4, KnockoffScreen has inflated FDR when applied to trio data.

Supplemental Note 4: Analyses of AGP, SPARK, and SSC cohorts with digital twin test

We applied the digital twin test to the AGP, SPARK, and SSC cohorts. We applied the digital twin test only to those loci identified by KnockoffTrio because of its demanding computational cost and because many of those loci have independent literature support so we believe they are *bona fide* ASD loci. This focused analysis is also consistent with the analysis in the original digital twin manuscript [1]. The digital twin test was performed with default parameters, 10,000 permutations, and testing windows ranging from 1kb to 2Mb (1kb, 2kb, 5kb, 10kb, 20kb, 50kb, 100kb, 200kb, 500kb, 1Mb, and 2Mb) centered around the loci identified by KnockoffTrio. We present the results in Table S1. For the AGP cohort, the digital twin test identified *ARHGEF10* ($p = 0.045$, window size = 2Mb) at the $\alpha = 0.05$ level and found suggestive significance for *LMNTD1-RASSF8* ($p = 0.053$, window size = 5kb). For the SPARK cohort, the digital twin test identified *SLC22A23/PSMG4* ($p = 0.012$, window size = 1kb), *CHSY3-HINT1* ($p = 0.024$, window size = 1Mb), *BAG4* ($p = 0.040$, window size = 2Mb), and *CCNB1IP1-PARP2* ($p = 0.048$, window size = 500kb) at the $\alpha = 0.05$ level. For the SSC cohort, the digital twin test identified no loci at the $\alpha = 0.05$ level.

In Table S1, we show the results from the digital twin test in addition to KnockoffTrio. For the digital twin test, we show the most significant p-value and corresponding testing window size for a locus.

Supplemental Note 5: Analyses of AGP and SPARK cohorts with KnockoffGWAS

We applied KnockoffGWAS to the AGP and SPARK cohorts. We did not apply KnockoffGWAS to the SSC cohort because we estimated the runtime to be more than a month in addition to unpredictable queue waiting time on the clusters. We defined the ASD children as cases and non-ASD parents as controls (N case/control: AGP = 1266/2522 and SPARK = 10540/17989). Therefore, the cases in the case-control KnockoffGWAS are identical to the cases tested by the KnockoffTrio. We performed the analyses using the default parameters in KnockoffGWAS (number of references for each haplotype mosaic = 10, size of haplotype clusters between 1k and 10k, and 7 levels of knockoff filter resolution). In line with KnockoffGWAS, we also used RaPID [2] to generate identical-by-descent (IBD) segments longer than 3 cM for each cohort. For the AGP cohort, KnockoffGWAS identified no loci significant at FDR=0.5 at any level of resolution. For the SPARK cohort, KnockoffGWAS identified seven loci at FDR=0.3 at a resolution of 41 kb. However, these loci do not overlap with the loci identified by KnockoffTrio. Among these loci, we have found that several have some level of support on their potential association with ASD. Specifically, a *de novo* deleterious variant in *PLA2G4A* was identified in one female individual from the Faroe Islands with autism without intellectual disability [3]. Similarly, *de novo* mutations in *SLC12A2* were identified in six children with neurodevelopmental disorders [4]. No loci were significant at FDR=0.1 or 0.2 (Table S2).

Supplemental Note 6: KnockoffTrio is robust in the presence of phasing errors

We evaluate KnockoffTrio's performance in the presence of phasing errors. We first adopted the same simulation settings as in the "Empirical power and FDR in single-locus simulations" Section to generate haplotype and genotype data and then in each replicate we produced switch errors in the haplotype data. A switch error is defined as the switch of haplotypes at a heterozygous site. The switch error rate (SER) is estimated to be <0.1% for SHAPEIT when parental genotype data are available[5]. Therefore, we randomly selected 0.1% of all heterozygous sites in a replicate to produce switch errors in the haplotype data. We then analyzed the haplotype data with switch errors and the genotype data using KnockoffTrio. As shown in Figure S6, KnockoffTrio is robust to phasing errors particularly when multiple knockoffs were generated.

Supplemental Note 7: Power and FDR for KnockoffTrio in the presence of lowered linkage disequilibrium

The inflated FDR for M=1 in Figure 2 is partly caused by the strong correlation between causal and non-causal variants, and is especially apparent for dichotomous traits. As a comparison, we used the same simulation settings as in the Empirical power and FDR in single-locus simulations except that we applied hierarchical clustering such that variants from different clusters have correlation no greater than 0.6 instead of 0.7. As shown in Figure S7, a single knockoff no longer has inflated FDR when the correlation between variants is lowered.

Supplemental Figures

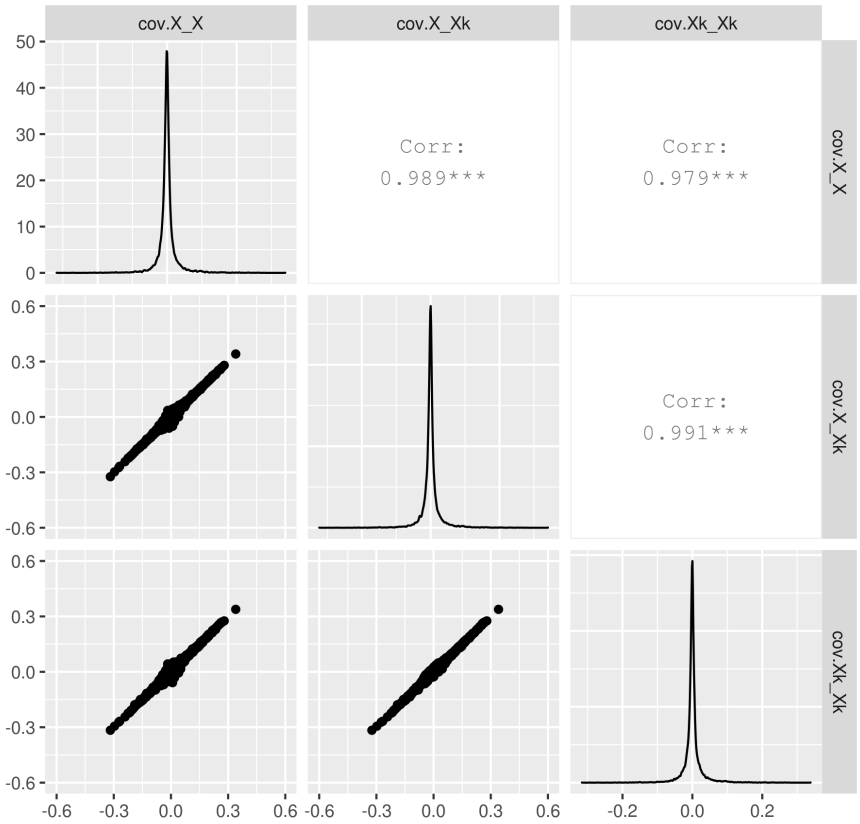

Figure S1: Empirical validation for exchangeability property in KnockoffTrio. To validate the exchangeability, we generated offspring knockoff genotypes (Xk) using the proposed algorithm and evaluated whether the second order (covariance between each pair of genetic variants) is exchangeable for common variants in the region. "Cov.X_X" is the covariance between each pair of original variants, "cov.Xk_Xk" is the covariance between each pair of knockoff variants, and "cov.X_Xk" is the covariance between each pair of original and knockoff variants.

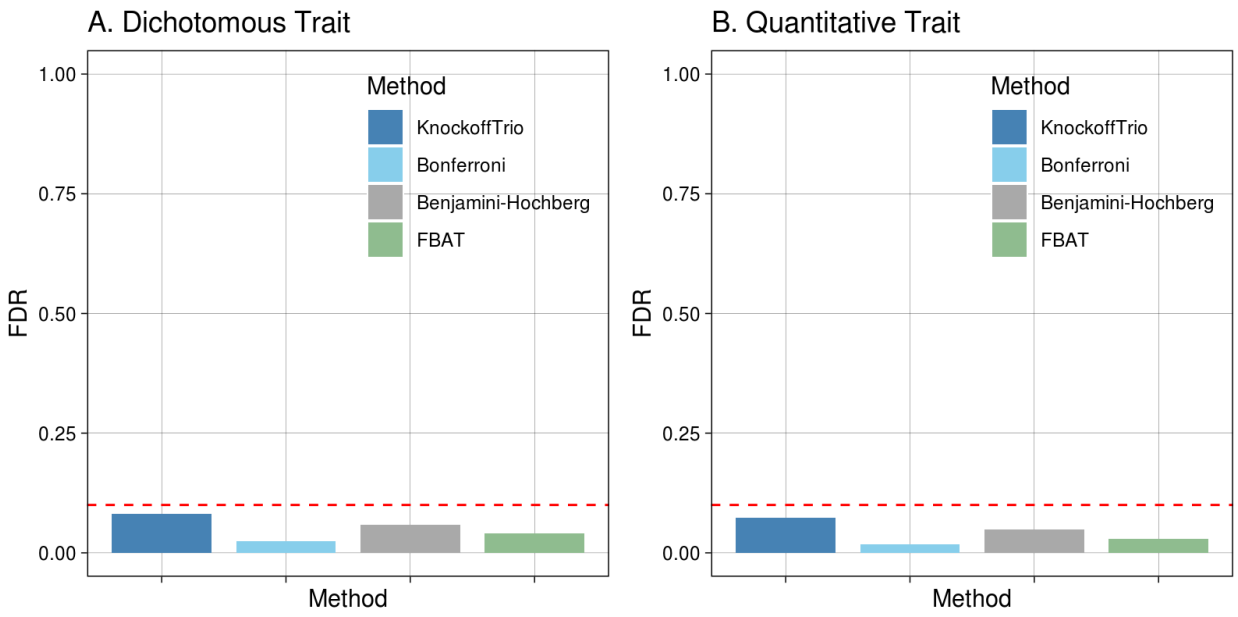

Figure S2: KnockoffTrio controls FDR in the presence of population stratification. The two panels show the FDR in the presence of population stratification for dichotomous and quantitative traits. A method's FDR is defined as the proportion of replicates where any window is detected among 500 replicates. The target FDR is 0.1.

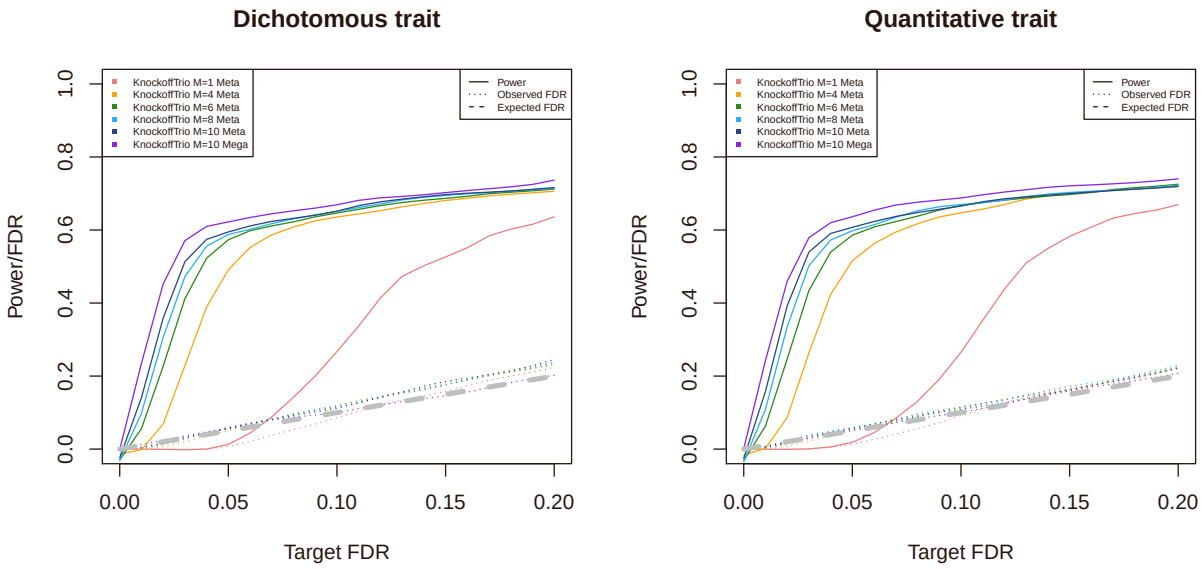

Figure S3: KnockoffTrio's power and FDR in meta-analysis. The two panels show the power and FDR for dichotomous and quantitative traits. We evaluate KnockoffTrio's power and FDR with a target FDR ranging from 0 to 0.2 and with different numbers of knockoffs. The solid lines indicate KnockoffTrio's power and the dotted lines indicate KnockoffTrio's observed FDR. The different colors indicate different numbers of knockoffs. The grey dashed line indicates the expected FDR.

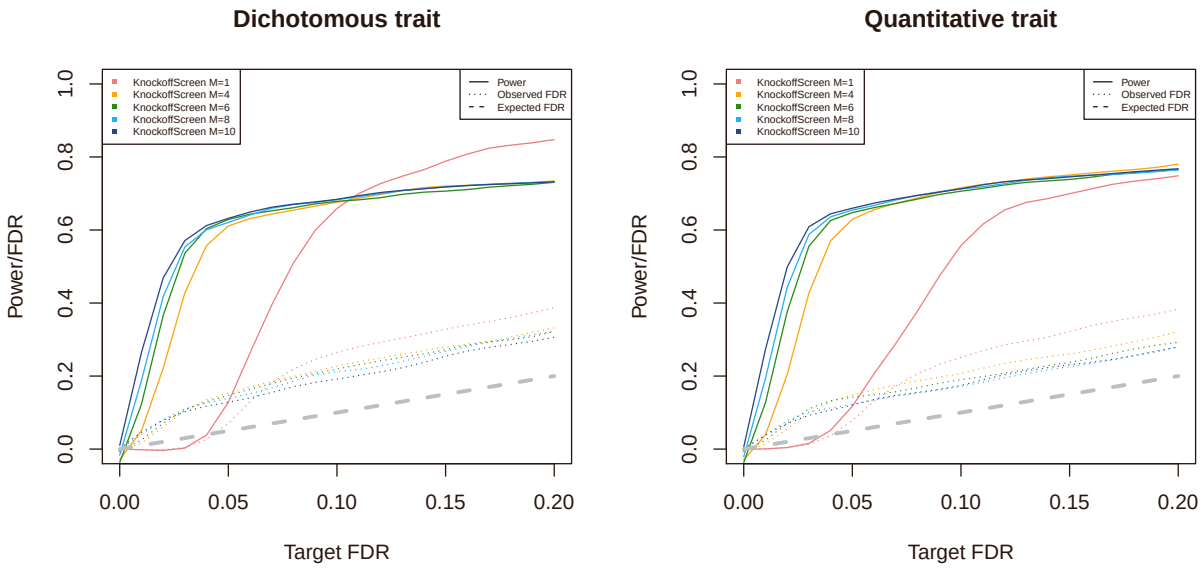

Figure S4: KnockoffScreen's power and FDR in single-locus simulations. The two panels show the power and FDR for dichotomous and quantitative traits. We evaluate KnockoffScreen's power and FDR with a target FDR ranging from 0 to 0.2 and with different numbers of knockoffs. The solid lines indicate KnockoffTrio's power and the dotted lines indicate KnockoffScreen's observed FDR. The different colors indicate different numbers of knockoffs. The grey dashed line indicates the expected FDR.

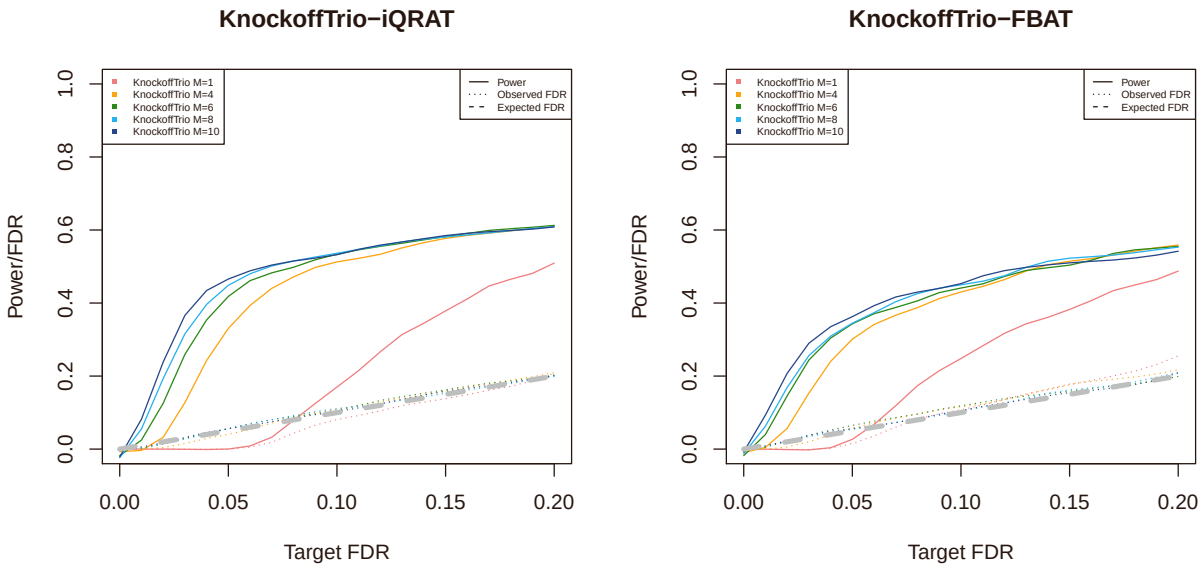

Figure S5: KnockoffTrio-iQRAT improves power in detecting complex associations. The two panels show the power and FDR for quantitative traits with Cauchy error terms using KnockoffTrio-iQRAT and KnockoffTrio-FBAT, respectively. We evaluate KnockoffTrio's power and FDR with a target FDR ranging from 0 to 0.2 and with different numbers of knockoffs. The solid lines indicate KnockoffTrio's power and the dotted lines indicate KnockoffTrio's observed FDR. The different colors indicate different numbers of knockoffs. The grey dashed line indicates the expected FDR.

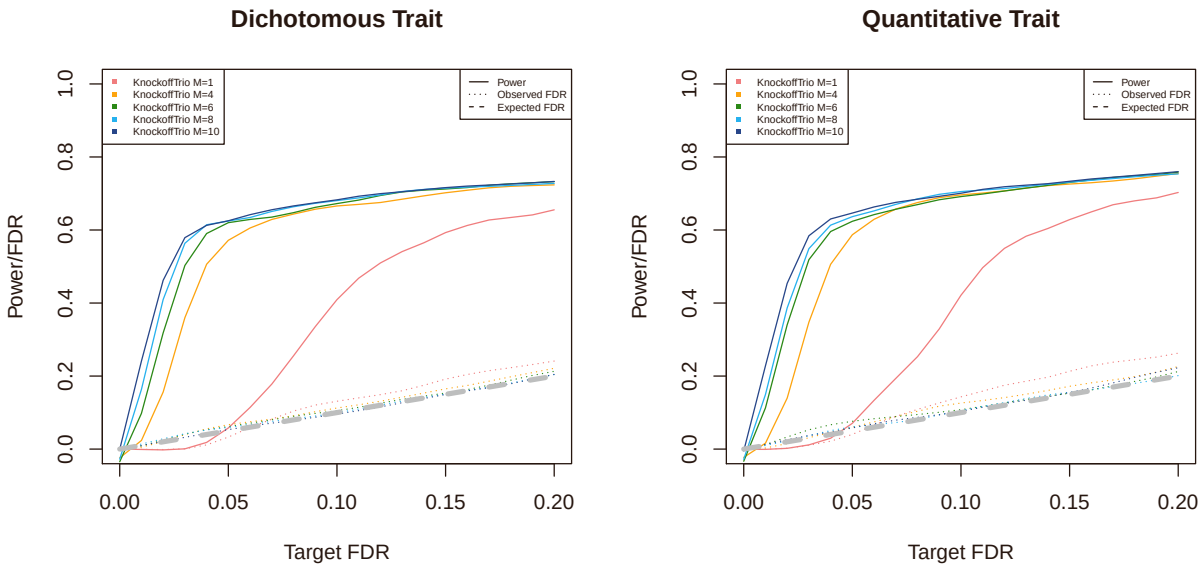

Figure S6: KnockoffTrio's power and FDR in the presence of phasing errors. The two panels show the power and FDR for dichotomous and quantitative traits. We evaluate KnockoffTrio's power and FDR with a target FDR ranging from 0 to 0.2 and with different numbers of knockoffs. The solid lines indicate KnockoffTrio's power and the dotted lines indicate KnockoffTrio's observed FDR. The different colors indicate different numbers of knockoffs. The grey dashed line indicates the expected FDR.

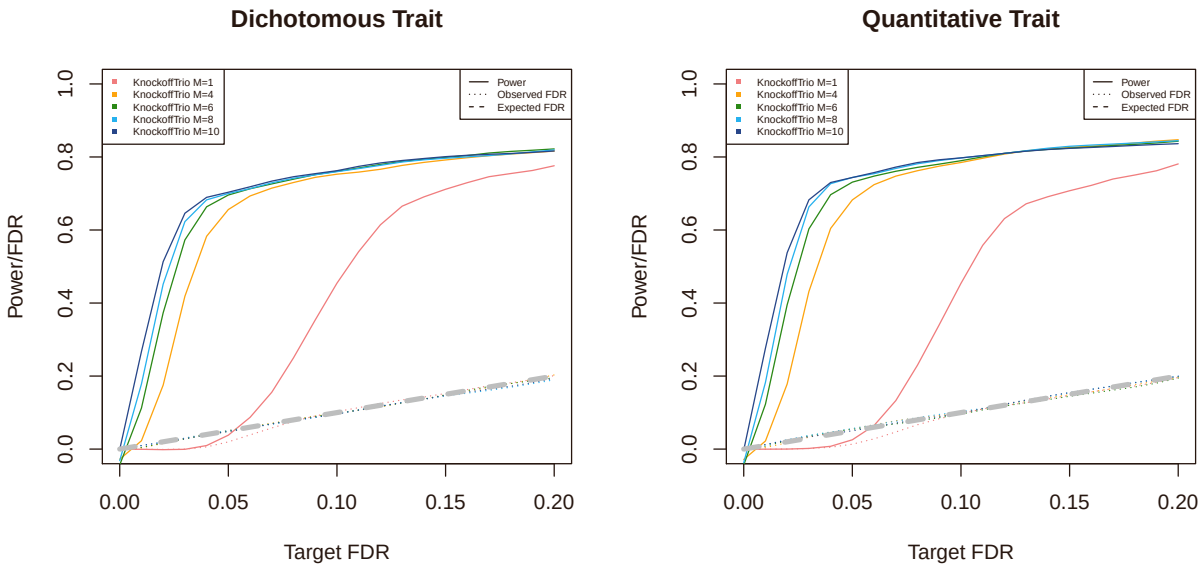

Figure S7: KnockoffTrio's power and FDR with reduced inter-cluster LD. The two panels show the power and FDR for dichotomous and quantitative traits. We evaluate KnockoffTrio's power and FDR with a target FDR ranging from 0 to 0.2 and with different numbers of knockoffs. The solid lines indicate KnockoffTrio's power and the dotted lines indicate KnockoffTrio's observed FDR. The different colors indicate different numbers of knockoffs. The grey dashed line indicates the expected FDR.

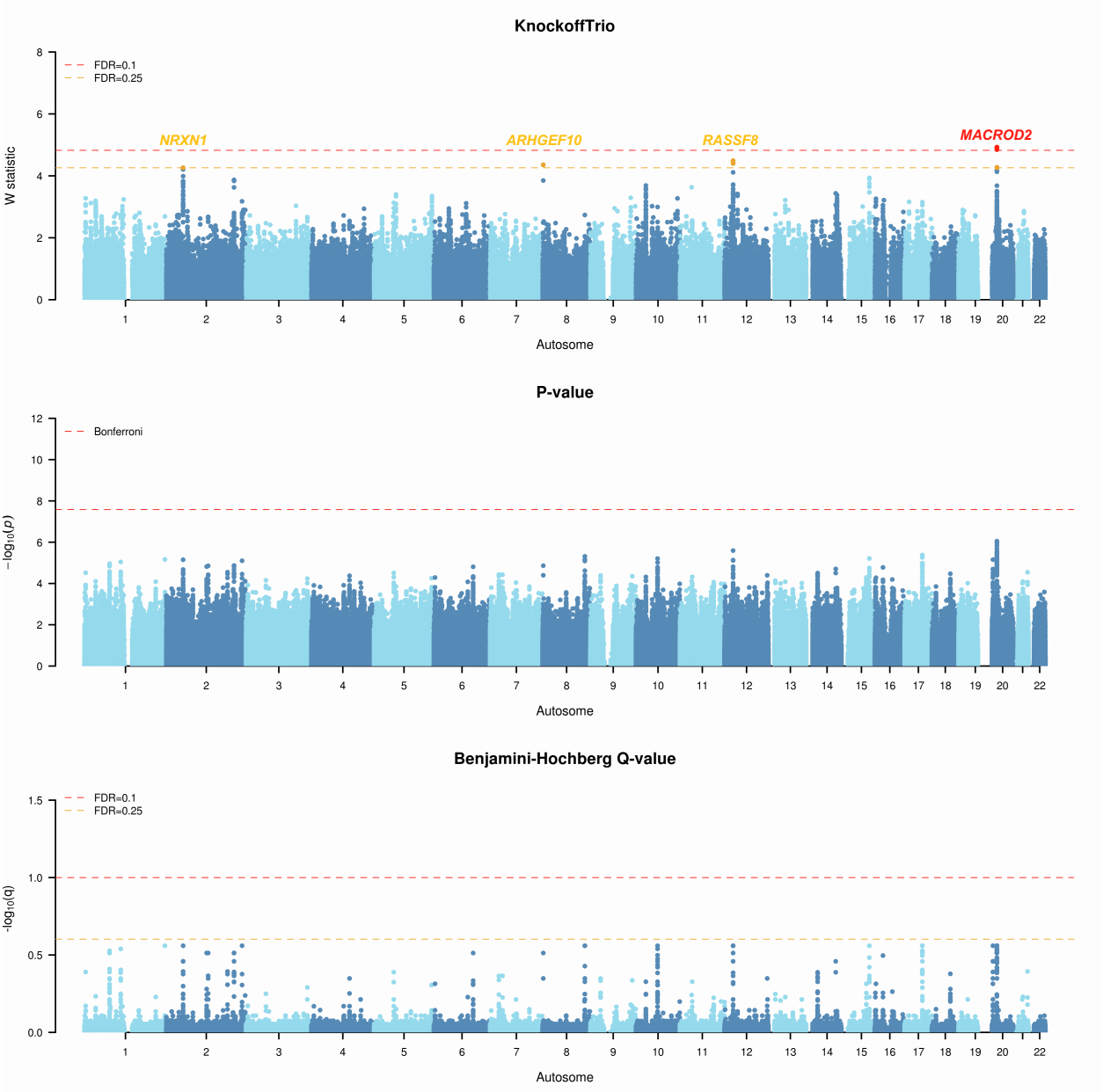

Figure S8: Replication of Autism Genome Project (AGP) KnockoffTrio results. Manhattan plots from KnockoffTrio analysis for the Autism Genome Project (AGP) with different random seeds in knockoff generation. The Manhattan plots of the W statistics from KnockoffTrio, the p-values from the conventional association tests with the Bonferroni correction for controlling the FWER, and the Q-values from the BH procedure for controlling the FDR. Different random seeds were used to generate knockoffs than in the main manuscript. The FDR target level for KnockoffTrio and the BH procedure is 0.1 or 0.25. Each locus is annotated with the closest gene name.

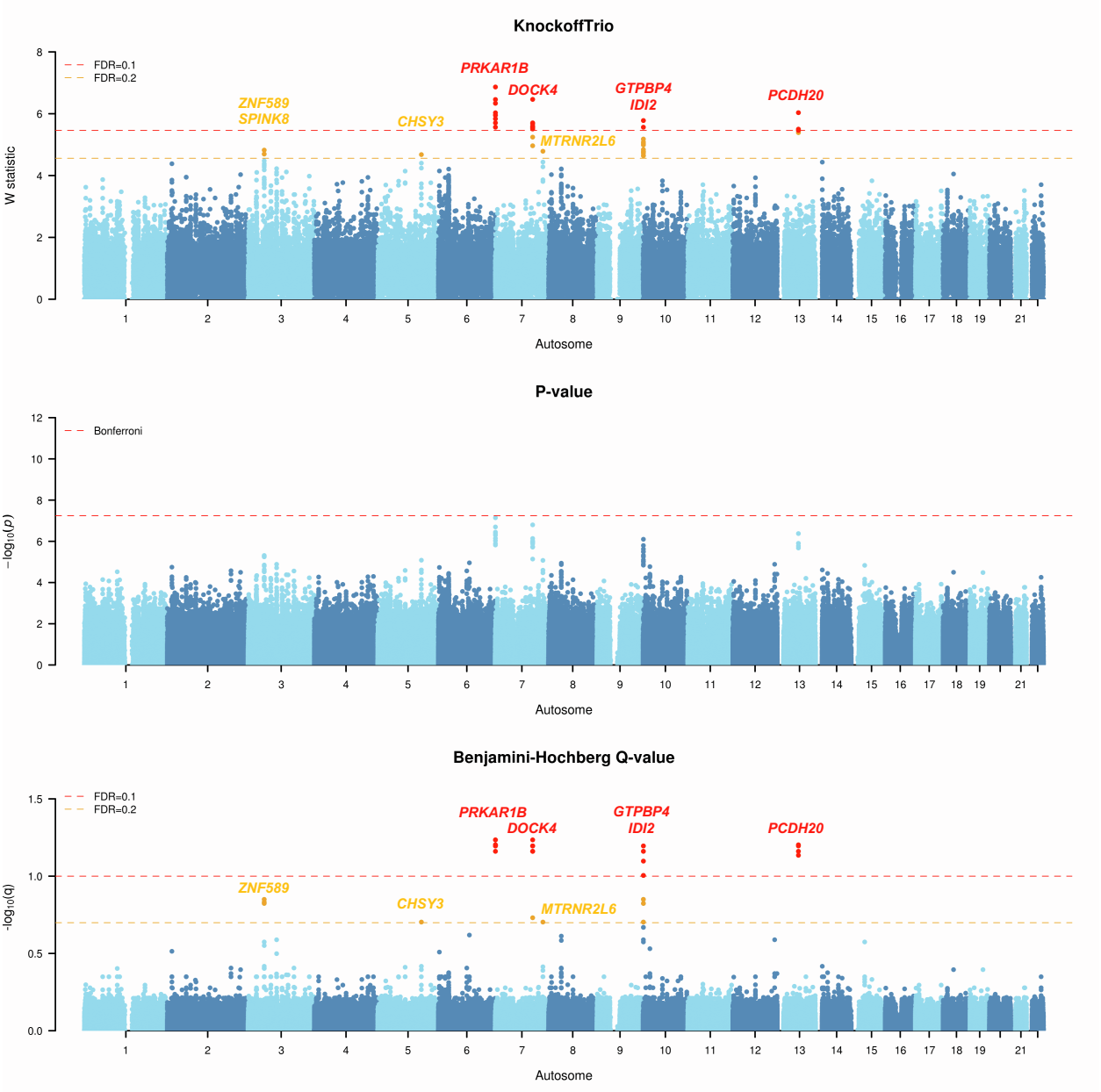

Figure S9: Replication of the Simons Foundation Powering Autism Research (SPARK) KnockoffTrio results. Manhattan plots from KnockoffTrio analysis for the Simons Foundation Powering Autism Research (SPARK) with different random seeds in knockoff generation. The Manhattan plots of the W statistics from KnockoffTrio, the p-values from the conventional association tests with the Bonferroni correction for controlling the FWER, and the Q-values from the BH procedure for controlling the FDR. Different random seeds were used to generate knockoffs than in the main manuscript. The FDR target level for KnockoffTrio and the BH procedure is 0.1 or 0.2. Each locus is annotated with the closest gene name.

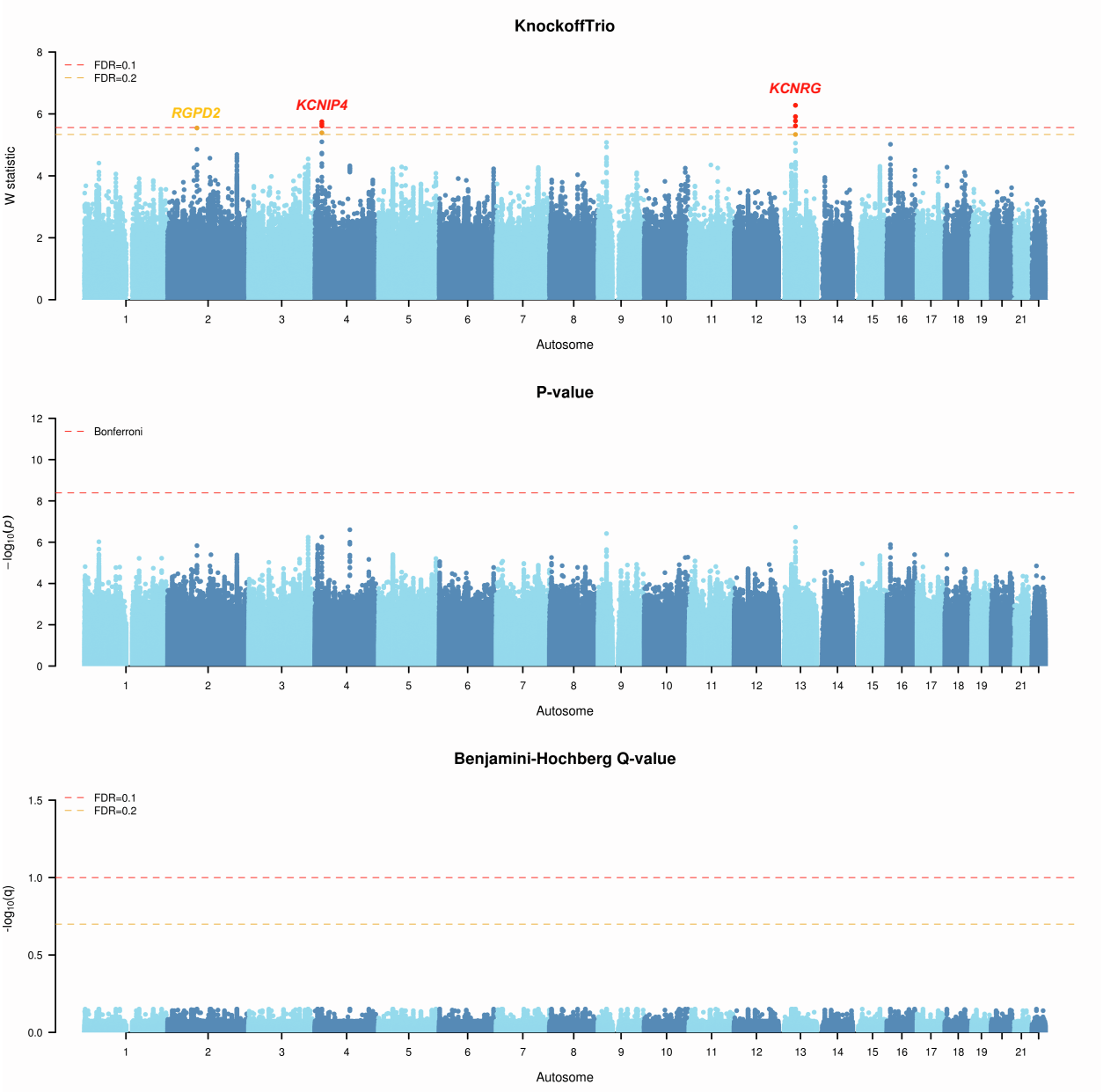

Figure S10: Replication of the Simons Simplex Collection (SSC) KnockoffTrio results. Manhattan plots from KnockoffTrio analysis for the Simons Simplex Collection (SSC) with different random seeds in knockoff generation. The Manhattan plots of the W statistics from KnockoffTrio, the p-values from the conventional association tests with the Bonferroni correction for controlling the FWER, and the Q-values from the BH procedure for controlling the FDR. Different random seeds were used to generate knockoffs than in the main manuscript. The FDR target level for KnockoffTrio and the BH procedure is 0.1 or 0.2. Each locus is annotated with the closest gene name.

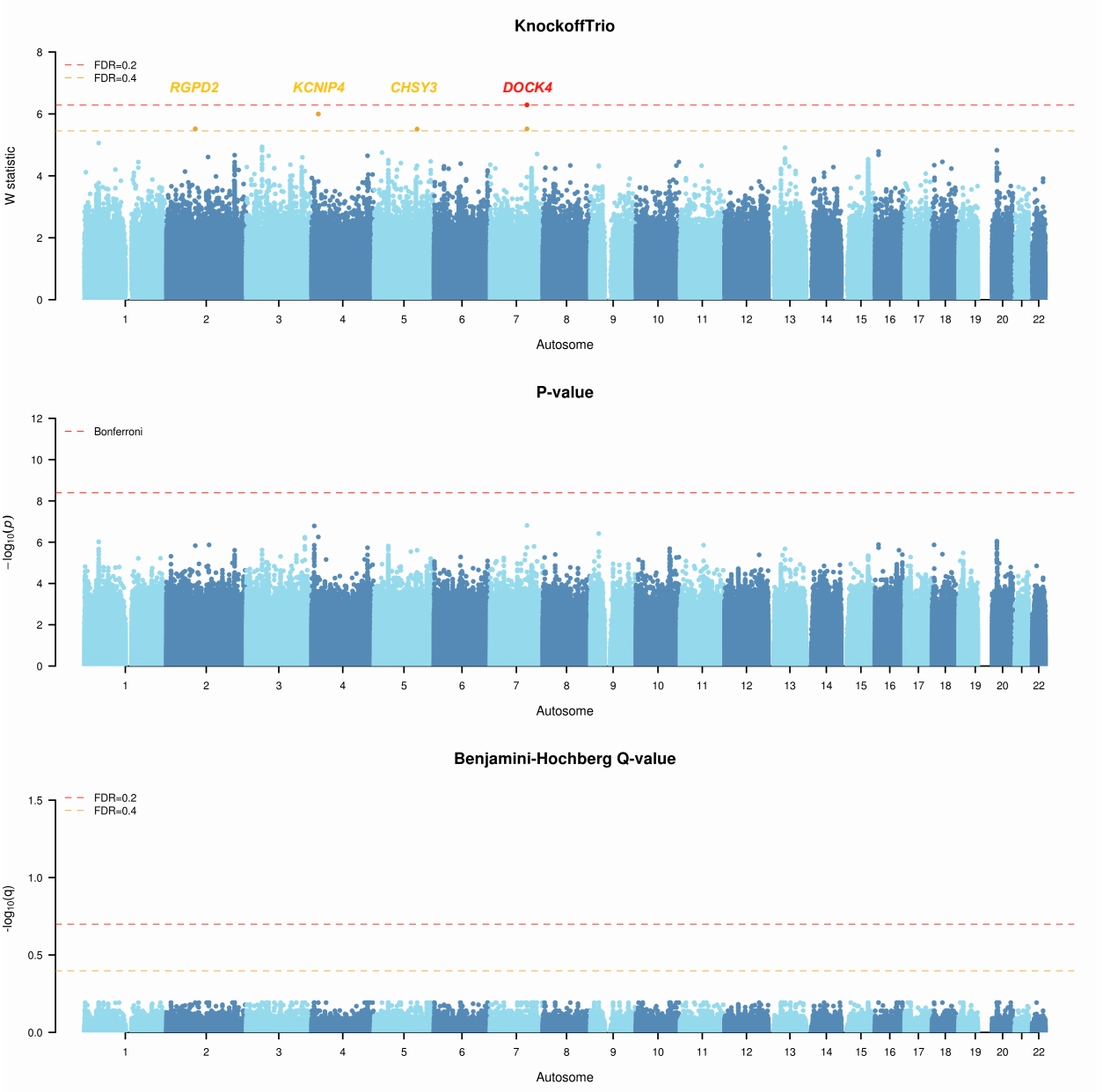

Figure S11: Manhattan plots from KnockoffTrio analysis for the meta-analysis of the AGP, SPARK, and SSC cohorts. The Manhattan plots of the W statistics from KnockoffTrio, the p-values from the conventional association tests with the Bonferroni correction for controlling the FWER, and the Q-values from the BH procedure for controlling the FDR. The FDR for KnockoffTrio and the BH procedure is 0.2 and 0.4. Each locus is annotated with the closest gene name.

Supplemental Tables

Gene	Chr	Position	Variant	Allele	MAF	P	Z	W	Q	BH Q	DTT Size	DTT P
AGP (FDR=0.1)												
NRXN1	2	50805721	rs9284756	A	0.03	7.10E-6	4.49	4.37	0.10	0.28	200K	8.56E-2
ARHGEF10	8	1920247-1920676	rs17756915-rs11136442	-	0.41	1.38E-5	-	4.47	0.10	0.31	2M	4.50E-2
LMNTD1-RASSF8	12	25946268	rs4963941	A	0.10	2.56E-6	4.70	4.84	0.10	0.28	5K	5.30E-2
ALPK3-SLC28A1	15	84881866	rs12917429	T	0.21	6.19E-6	-4.52	4.45	0.10	0.28	100K	2.93E-1
MACROD2	20	14781064	rs6074798	A	0.49	1.02E-6	4.89	4.83	0.10	0.28	20K	2.83E-1
SFARI: SPARK (FDR=0.1)												
ZNF589	3	48262179	rs11709691	G	0.28	4.87E-6	-4.57	5.03	0.06	0.14	2M	9.04E-1
CADM2	3	85395534-85410981	rs75005531-rs1549979	-	0.22	1.30E-5	-	4.76	0.09	0.26	1M	6.77E-1
CHSY3-HINT1	5	130661503	rs17714209	C	0.28	8.25E-6	4.46	4.99	0.06	0.20	1M	2.40E-2
PDGFA-PRKAR1B	7	536383	rs62431385	C	0.10	7.20E-8	-5.39	6.71	0.02	0.06	2M	2.49E-1
DOCK4	7	111986531	rs73210911	A	0.12	1.59E-7	-5.24	6.51	0.02	0.06	2M	4.67E-1
MTRNR2L6-PRSS1	7	142688332	rs13223009	C	0.02	8.42E-6	-4.45	4.71	0.09	0.20	1M	1.01E-1
LARP4B-GTPBP4	10	975370	rs117732138	A	0.02	1.60E-6	4.80	5.48	0.02	0.07	50K	3.18E-1
IDI2	10	1020654	rs77782977	C	0.02	7.95E-7	4.94	5.84	0.02	0.06	20K	1.83E-1
PCDH20-PCDH9	13	63204555	rs12184522	T	0.23	4.21E-7	5.06	6.00	0.02	0.06	2M	2.20E-1
SFARI: SPARK (FDR=0.2)												
SPINK8	3	48316110-48329279	rs74735576-rs13090538	-	0.17	1.58E-5	-	4.39	0.17	0.28	100K	8.28E-1
SLC22A23/PSMG4	6	3285062	rs41301847	G	0.02	1.85E-5	4.28	4.41	0.17	0.31	1K	1.18E-2
BAG4	8	38205717	rs7836805	A	0.24	2.83E-5	-4.19	4.43	0.17	0.40	2M	4.03E-2
CCNB1IP1-PARP2	14	20334133	rs72671266	T	0.02	2.45E-5	-4.22	4.30	0.19	0.38	500K	4.75E-2
SFARI: SSC (FDR=0.1)												
KCNRG-DLEU7	13	50197099	rs2703087	A	0.04	1.88E-7	5.21	6.54	0.10	0.70	1M	9.30E-2
SFARI: SSC (FDR=0.2)												
KCNIP4	4	20917151	rs185413018	T	0.02	5.59E-7	5.00	6.00	0.13	0.70	10K	1.52E-1

Table S1: Analyses of AGP, SPARK, and SSC cohorts with digital twin test (DTT). Gene: loci identified by KnockoffTrio. A single gene name indicates the signal is within or overlaps with the gene. "Gene1/Gene2" indicates the signal overlaps with two genes. "Gene1-Gene2" indicates the signal is between two genes. **MAF**: minor allele frequency of a variant, or average minor allele frequency if a signal contains multiple variants. **P**: KnockoffTrio's ACAT-combined p-values. For single variants, ACAT-combined p-values are equivalent to FBAT p-values. **Z**: FBAT Z-scores for single variants. **W**: KnockoffTrio's feature statistics. **Q**: KnockoffTrio's Q-values. **BH Q**: Benjamini-Hochberg Q-values. **DTT Size**: testing window size for the digital twin test. The unit is base pair. **DTT P**: digital twin test's p-values.

Gene	Chr	Position	Variant	W
SPARK (FDR=0.3, resolution=41 kb)				
ZYG11B	1	52781682	rs74911353	0.002
PLA2G4A-BRINP3	1	190041115	rs17374565	0.004
DYSF-CYP26B1	2	71858486	rs12469485	0.003
FZD5	2	207767140	2-207767140-T-G	0.019
PCDH7-ARAP2	4	33081025	rs78314717	0.002
CCDC192-SLC12A2	5	127948101	rs72792235	0.002
TMEM71-PHF20L1	8	132773968	rs28550258	0.002

Table S2: Analyses of AGP and SPARK cohorts with KnockoffGWAS. Gene: loci identified by KnockoffGWAS. A single gene name indicates the signal is within or overlaps with the gene. "Gene1-Gene2" indicates the signal is between two genes. **Position**: Position of the lead variant of a locus. **Variant**: The lead variant of a locus. **W**: KnockoffGWAS's feature statistics. KnockoffGWAS's feature importance scores were calculated by fitting the Lasso with cross-validation and taking the absolute value of the average estimated regression coefficients, and W, the feature statistics, were feature importance scores for the original minus those for the knockoff cohort.

Supplemental References

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