THE X FACTOR: A ROBUST AND POWERFUL APPROACH TO X-CHROMOSOME-INCLUSIVE WHOLE-GENOME ASSOCIATION STUDIES*

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The X-chromosome is often excluded from genome-wide association studies because of analytical challenges. Some have been investigated such as the random, skewed or no X-inactivation model uncertainty. Others have received little to no attention such as the value in considering non-additive and gene-sex interaction effects, and the inferential consequence of choosing different baseline alleles. Here we propose a unified and flexible regression-based association test for the X-chromosome. We provide theoretical justifications for its robustness in the presence of various model uncertainties, as well as for its improved power under certain alternatives when compared with the existing approaches. For completeness, we also revisit the autosomes and show that the proposed framework leads to a robust and sometimes much more powerful test than the standard method. Finally, we provide supporting evidence by revisiting several published association studies. Supplementary materials for this article are available online.

1. Introduction. Genome-wide association studies have become ubiquitous, delivering significant insights into the genetic determinants of complex traits in the past decade (Visscher *et al.*, 2017). For this reason, it is surprising that it is not a common practice to include the X-chromosome in genome-wide association studies (Wise *et al.*, 2013; Konig *et al.*, 2014).

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The X-chromosome differs from the autosomes in that males have only one copy of the X-chromosome while females have two; and at any given genomic location in females one of the two copies may be silenced (Gendrel & Heard, 2011), referred to as X-chromosome inactivation (XCI). The choice of the silenced copy could be random or skewed towards a specific copy (Wang et al., 2014). These unique aspects lead to more complex analytic considerations for genetic association studies of X-chromosome variants, such as for single nucleotide polymorphisms (SNPs).

A SNP has two alleles, r and R, of which one is the the reference allele and the other is the alternative allele with allele frequency f. An autosome SNP has three genotypes regardless of sex, namely G = (rr, rR, RR). In an association analysis of an autosome SNP, the common practice is to simply model a binary or continuous phenotype Y as an additive function of the number of copies of the alternative allele present in G, that is G = (0, 1, 2). Although both dominant G = (0,1,1) and recessive G = (0,0,1) genetic models of inheritance are possible, among these one degrees of freedom (1 d.f.) models, the additive model retains reasonable power even if the true genetic model is dominant or recessive (Hill et al., 2008; Bush & Moore, 2012). Alternative parameterizations include the 2 d.f. genotypic model that incorporates both the additive $G_A = (0, 1, 2)$ term and the over-dominance term $G_D = (0, 1, 0)$. (For the remainder of the paper, we use dominant and over-dominance interchangeably referring to $G_D = (0, 1, 0)$, unless specified otherwise.) However, the genotypic test is known to be less powerful than the additive test due to the increased d.f., which is unnecessary if the additivity assumption holds.

A simple additive coding for an X-chromosome SNP is, however, not immediate, and several additional points require attention. Table 1 describes eight analytical considerations and challenges (C1-C8) present in X-chromosome-inclusive association studies.

Several association methods have been developed for the X-chromosome, but each solves only some of C1-C8. For example, Zheng et al. (2007) considered only binary outcomes for which both genotype- and allele-based association tests are applicable. Allele-based association test is locally most powerful, but it is sensitive to the Hardy-Weinberg equilibrium (HWE) assumption (Sasieni, 1997; Zheng, 2008). Clayton (2008, 2009) discussed analytical strategies assuming the X-chromosome is always inactivated. Hickey & Bahlo (2011) and Loley et al. (2011) performed simulation studies, each providing a thorough method comparison, e.g. between tests of Zheng et al. (2007) and Clayton (2008). Konig et al. (2014) provided a detailed guideline for including the X-chromosome in genome-wide association studies, rec-

Table 1
Eight analytical considerations and challenges, C1-C8, present in X-chromosome-inclusive association studies. C1-C3 are relevant for both the autosomes and X-chromosome, and C4-C8 are more specific to the X-chromosome.

Problem	Solution	Relevant Sections	
C1: quantitative traits vs. binary outcomes C2: genotype-based vs. allele-based association meth	ods		
Allele-based association tests, comparing allele frequency differences between cases and controls, are locally most powerful. However, they analyze binary outcomes only and are sensitive to the Hardy-Weinberg equilibrium (HWE) assumption (Sasieni, 1997).	Genotype-based regression models, Y -on- G, support various types of outcome data, account for covariate effects with ease, and are robust the HWE assumption.	Sections 1 and 2	
C3: 1 d.f. additive vs. 2 d.f. genotypic models (both Implementing a Y -on- G regression requires assumptions of the underlying true genetic model, e.g. 1 d.f. additive or 2 d.f. genotypic model. For the autosomes, the most common practice is to use the additive test which has better power than the genotypic test under (approximate) additivity, but it cannot capture over-dominant effects. The exact trade-off, however, is not clear.	the additive and over-dominance effects) We provide analytical and empirical evidences supporting the use of geno- typic model when analyzing either the autosomes or X-chromosome. For the X-chromosome, considering the over- dominance effect has the added benefit of resolving of the skewed X-inactivation uncertainty issue.	Sections 2, 3.3, and 4, and C7 below	
C4: sex as a covariate vs. no S main effect Unlike the autosomes, sex is a confounder when analyzing the X-chromosome for traits exhibiting sexual dimorphism (e.g. height and weight). Even for the autosomes, sex can be a confounder if allele frequencies differ significantly between males and females.	To maintain the correct type I error rate control, sex main effect must be considered particular when analyzing the X-chromosome. The resulting association test is also invariant to the choice of the baseline allele.	Sections 3.1 and 5, and C8 below.	
C5: gene-sex interaction vs. no $G \times S$ interaction effe			
Gene-sex interaction might exist, but there is a concern over loss of power due to increased degrees of freedom. In addition, what is the interpretation of gene-sex interaction effect in the presence of X-inactivation?	Under no interaction, power loss of modelling interaction is, surprisingly capped at 11.4% . Models including the $G \times S$ covariate lead to tests invariant to the assumption of X-chromosome inactivation status.	Sections 2.1, 3.2, and 3.4, and C6 be- low	
C6: X-chromosome inactivation (XCI) vs. no XCI XCI occurs if one of the two alleles in a genotype of a female is silenced. Individual-level XCI status requires additional biological information that are not typically available to genetic association studies. Assuming XCI or no XCI at the sample level leads to different genotype coding strategies (Table 2), and it was thought that this will always lead to different association results.	XCI uncertainty implies sex-stratified genetic effect which can be analytically represented by the $G \times S$ interaction effect. Teasing apart these different biological phenomenons require other 'omic' data and additional analyses.	Sections 3.2 and 5, and C5 above	
C7: If XCI, random vs. skewed X-inactivation If the choice of the silenced allele in females is skewed towards a specific allele, the average effect of the rR genotype is no longer the average of those of r and R .	XCI skewness is statistically equivalent to a dominant genetic effect.	Section 3.3 and C3 above	
C8: the choice of the baseline allele for association at For the autosomes, switching the two alleles does not affect the association inference. Is this true for the X- chromosome?	nalysis, r vs. R It is not always true for the X-chromosome, unless S is included in the model.	Sections 3.1 and 5, and C4 above	

ommending different tests for different model assumptions (e.g. presence or absence of an interaction effect, and the XCI status), but it is difficult to check these assumptions in practice. Gao et al. (2015) developed a toolset for conducting X-chromosome association studies, implementing some of the existing methods. More recently, Chen et al. (2017) improved the sex-stratified tests by eliminating genetic model assumptions, but their method is limited to analyzing binary traits and genetic main effects. Focusing on XCI, Wang et al. (2014) proposed a frequentist maximum likelihood solution to deal with no, random or skewed X-inactivation, and in their follow-up work Wang et al. (2017) provided a model selection method. In contrast, Chen et al. (2018) applied the Bayesian model averaging principle (Draper, 1995) to the XCI uncertainty problem. However, both approaches assumed additivity, and it is not clear how to include non-additive genetic effects, along with unknown XCI status, in their respective analytical formulation. The value in considering over-dominance and gene-sex interaction effects, and the inferential consequence of parameterizing the model in terms of defining different baseline (reference or alternative) allele when analyzing the X-chromosome, have received little to no attention.

Table 2 summarizes the various covariate coding schemes for analyzing an X-chromosome SNP when considering all the analytical challenges outlined in Table 1. Note that when the choice of the baseline allele is varied (i.e. either r or R) and the XCI status is unknown, there are four ways to code the additive covariate G_A , and two ways to code the gene-sex interaction covariate G_S .

Using the notations in Table 2, it is immediately clear why the choice of the baseline allele can matter for association analyses of the X-chromosome. Under no XCI, if r was assumed to be the baseline allele there would be one copy of allele R in genotype rR or R, so rR and R would be grouped together for association analyses. However, if R was chosen to be the baseline allele, genotypes rR and r would be grouped together, resulting in different inference; this is in stark contrast to what is known for the autosomes for which the choice of the baseline allele does not affect association evidence.

The goal of this paper is to propose a theoretically justified and robust X-chromosome association method that can simultaneously deal with all eight analytical challenges outlined in Table 1. The proposed method is regression-and genotype-based, allowing for either a continuous or binary phenotype as the outcome variable, adjusting for covariate effects and robust to departure from HWE. The recommended test has three degrees of freedom, including both additive and dominant genetic effects, as well as a gene-sex interaction effect. We show analytically that this ensures that the various model

Table 2

Covariate coding schemes for examining the additive, dominant, gene-sex interaction, and sex effects under different X-chromosome inactivation and baseline allele assumptions. The subscripts A and D represent additive and dominant effects, R or r represents the designated allele of which we count the number of copies present in a genotype (also known as the 'risk' allele, and the corresponding baseline allele would be r or R, respectively), and I or N denotes X-chromosome inactivated or not inactivated.

			X-chromosome	Coding Schemes				
Effect	Covariate	Allele	Inactivation	(Females)		(Males)		
Interpretation	Notation	Choice	(XCI) Status	rr	rR	RR	r	R
	$G_{A,R,I}$	R	Yes	0	0.5	1	0	1
Additive	$G_{A,r,I}$	r	Yes	1	0.5	0	1	0
G_A	$G_{A,R,N}$	R	No	0	1	2	0	1
	$G_{A,r,N}$	r	No	2	1	0	1	0
Dominant G_D	G_D	Either	Either	0	1	0	0	0
Gene-Sex Interaction	GS_R	R	Either	0	0	0	0	1
$GS = G_A \times S$	GS_r	r	Either	0	0	0	1	0
$\operatorname{Sex} S$	S	Either	Either	0	0	0	1	1

uncertainties — no, random, or skewed X-chromosome inactivation, and the choice of the baseline allele — are accounted for. Desirably, the power of the proposed test is well maintained across different genetic models, despite its increased degrees of freedom as compared to a simple additive test.

We organize the remainder of the paper as follows. To inform the choice for X-chromosome association studies, in Section 2 we first shed new light on the merits of genotypic models in the familiar context of analyzing autosome SNPs, and provide analytical power results across all possible genetic models. In Section 3, we present our main theory to address the challenges specific to the X-chromosome, as well as empirical results from simulation studies. In Section 4, we provide corroborating evidence from several applications in favour of the proposed method. Finally in Section 5, we discuss the limitations of our approach and possible future work.

2. Additive vs. Genotypic Models (C3): Robustness of the Genotypic Test. For completeness and a more clear demonstration of this particular model selection challenge in the X-chromosome, we first revisit phenotype-genotype association studies of the autosomes where, traditionally, only the additive coding is implemented. We define the additive model and genotypic model using the generalized linear regression framework (Mc-

Cullagh & Nelder, 1989). Let g be the link function, the additive model is

$$(2.1) g(E(Y)) = \beta_0 + \beta_A G_A,$$

and the genotypic model is

$$(2.2) g(E(Y)) = \beta_0 + \beta_A G_A + \beta_D G_D,$$

where without loss of generality for an autosome SNP, r is the reference allele and chosen to be the baseline, R is the alternative allele and designated as the 'risk' allele with population allele frequency f, and $G_A = (0, 1, 2)$ and $G_D = (0, 1, 0)$ for the three genotypes, rr, rR and RR, irrespective of sex. Additional covariates such as environmental factors Es can be readily added to both models, and the sex S covariate in this case can be statistically viewed as part of the Es since we are analyzing autosome SNPs. The three genotype groups have population frequencies $(1-f)^2$, 2f(1-f), and f^2 assuming Hardy-Weinberg equilibrium. However, we note that the HWE assumption is not required for validity of the proposed regression- and genotype-based association test.

2.1. Power comparison using the general theory of chi-squared distributions. Let W_1 be the standard association test statistic for testing H_0 : $\beta_A = 0$ based on the additive model (2.1), and assume that W_1 follows an asymptotic chi-squared distribution, $\chi^2_{(1,ncp_1)}$. The non-centrality parameter, ncp_1 , captures the true genetic effect size, allele frequency, variance of the error term, and sample size which we study in the next section. Here we simply specify $ncp_1 = 0$ under the null of no association and > 0 under an alternative model. Similarly, let W_2 and $\chi^2_{(2,ncp_2)}$ be the corresponding test statistic and its asymptotic distribution for testing $H_0: \beta_A = 0$ and $\beta_D = 0$ jointly using the genotypic model (2.2).

The power difference between W_1 and W_2 depends on both the non-centrality parameters and the nominal type I error rate, α . When $ncp_1 = ncp_2 = 0$ or $\alpha = 0$, both W_1 and W_2 have no power. At the other extreme when both ncp_1 and ncp_2 are sufficiently large or α close to 1, both W_1 and W_2 have power close to 1. Thus, we expect meaningful power comparison when both the non-centrality parameter and α have moderate values.

First, let us assume that the true genotype effect is indeed additive to study the maximum power loss induced by unnecessarily including the dominant term G_D . In that case, $ncp_2 = ncp_1 = ncp$ and W_2 is less powerful than W_1 . Varying ncp and α values and under additivity, we numerically compute the power of W_1 and W_2 as functions of ncp and α for $ncp \in [0, 100]$

and $-\log_{10} \alpha \in [0, 15]$. The maximum power loss of a 2 d.f. genotypic test is, surprisingly, capped at 11.4%, regardless of the true genetic effect size, sample size, and significance level; the maximum occurs at $\alpha = 0.0025$ and ncp = 10.6. (At the genome-wide significance level of $\alpha = 5 \times 10^{-8}$ (Dudgridge & Gusnanto, 2008), the maximum power loss is 10.3% occurring when ncp = 31.4.) Figure S1 in the Supplementary Materials provides heat plots for power as functions of ncp and α for the two tests, as well as for power loss comparing W_2 with W_1 under additivity.

It needs to be noted that the maximum 11.4% holds for comparing any 2 d.f. χ^2 test with a 1 d.f. χ^2 test, because the derivation is based on ncp and α alone. For instance, for the phenotype-genotype association analyses of interest here, if an assumed 1 d.f. recessive genetic model was the correct one, then power loss of using the 2 d.f. genotypic model is also capped at 11.4%, regardless of the true genetic effect size, sample size, and significance level.

With a bounded power loss, we next investigate the potential power gain (or loss) by using W_2 when the true genotype effect is not additive. In the presence of a dominant effect, $ncp_2 = ncp_1 + \Delta_{12}$, where $\Delta_{12} > 0$ and the value depends on sample size and the degree of departure from additivity. Compared to the maximum power loss of using the genotypic test under additivity, the maximum power gain under non-additivity can be technically as large as $1 - \alpha$ (i.e. close to 100%), when $ncp_1 \to 0$ and $\Delta_{12} \to \infty$. However, to provide more specific numerical results, we consider $ncp_1 = 5$, 10 or 15, Δ_{12} ranging from 0 to 10, and $\alpha = 0.0025$, the worse-case scenario derived above. Results show that once Δ_{12} is as large as half of ncp_1 (i.e. $ncp_2 \approx 1.5 \cdot ncp_1$), the power gain is bigger than power loss when $\Delta_{12} = 0$ (Figure S2). Together these two observations suggest that genotypic models should be considered for use in association studies of autosome SNPs.

2.2. Power comparison using specific genetic models for the autosomes. We rewrite the GLMs (2.1) and (2.2) in matrix forms, $g(E(Y)) = X\beta$, where $\beta = (\beta_0, \beta_A)'$ for the additive model and $\beta = (\beta_0, \beta_A, \beta_D)'$ for the genotypic model, and X is the corresponding design matrix. In each case, $\beta = (\beta_1, \beta_2)'$ and we want to test $H_0: \beta_2 = 0$, where β_2 contains the parameter(s) of interest, e.g. $\beta_2 = (\beta_A, \beta_D)$ for the genotypic model (2.2). To distinguish between the combined regression coefficients in vector form and its partition, we use bold symbols (β) to denote the combination of two partitions, and non-bold symbols (β) to denote each partition throughout our work, although each partition may have dimension ≥ 1 . To compute the non-centrality parameter, we first partition the expected Fisher information

matrix accordingly,

$$H(\beta_1, \beta_2) = \begin{bmatrix} H_{11}(\beta_1, \beta_2) & H_{12}(\beta_1, \beta_2) \\ H_{21}(\beta_1, \beta_2) & H_{22}(\beta_1, \beta_2) \end{bmatrix}.$$

We can then obtain the non-centrality parameter, where

$$ncp = \beta_2' [H_{22}(\beta_1, 0) - H_{21}(\beta_1, 0) H_{11}^{-1}(\beta_1, 0) H_{12}(\beta_1, 0)] \beta_2.$$

The technical details for computing this ncp for different genetic models are given in Appendix B.

Note that when the true model is genotypic but the additive model was used, the computation of the non-centrality parameter is less straightforward because of the model misspecification. Although the derivation is difficult under the standard genotype coding as defined above, a re-parametrization can considerably simplify the computation (Begg & Lagakos, 1992); see Appendix C for technical details.

Figure 1 shows power of the two tests (the 1 d.f. additive test and 2 d.f. genotypic test) for association analyses of an autosome SNP across a range of dominant effects including no dominant effect, and when n = 1,000and $\alpha = 0.0025$; power were computed based on analytically derived ncps and further confirmed by simulation studies, and see Figure S3 for the noncentrality parameter values corresponding to Figure 1. We fix the additive effect at $\beta_A = 0.3$ while varying the dominant effect β_D from -0.6 to 0.6, and we consider three allele frequencies, f = 0.2, 0.5 and 0.8. The results show that the power gain of using the genotypic test (the red solid curve) as compared with the additive test (the black dashed curve) can be more than 40%; the increase can be bigger for other settings (results not shown). In contrast, we have shown in Section 2.1 that the maximum power loss of using the genotypic test under additivity is never more than 11.4% analytically. Indeed, when f = 0.5 and $\beta_D = 0$, $ncp_1 = ncp_2 = ncp \approx 10.6$; recall that ncp = 10.6 and $\alpha = 0.0025$ result in maximum power loss of the genotypic test under additivity (Figure S1). That is, the maximum power loss shown in Figure 1 is close to the global maximum possible, while the power gain seen here can be made bigger by considering other scenarios. Thus, without sacrificing much power under the worse case scenario (11.4%) when $\alpha = 0.0025$ and ncp = 10.6), the potential power gain of the robust genotypic test can be significant across different genetic models.

Remark 1: For robust and powerful association analysis of autosome SNPs, we recommend the following model,

$$g(E(Y)) = \beta_0 + \beta_A G_A + \beta_D G_D$$

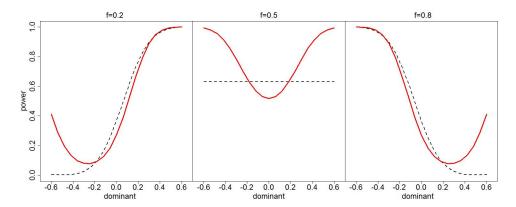


FIG 1. Power comparison between the additive and genotypic tests for association analyses of autosome SNPs across a range of dominant effects, including no dominant effect. The additive effect is fixed at $\beta_A = 0.3$, while the dominant effect β_D ranges from -0.6 to 0.6. The allele frequency f = 0.2, 0.5 and 0.8 for the three plots, respectively, from left to right, the sample size n = 1,000, and the size of the test $\alpha = 0.0025$. The black dashed curves are power of testing $\beta_A = 0$ using the additive model (2.1), and the red solid curves are power of testing $\beta_A = \beta_D = 0$ using the genotypic model (2.2). Result explanations are provided in Sections 2.2 and 5.

and the corresponding 2 d.f. genotypic test, testing

$$H_0: \beta_A = \beta_D = 0.$$

Note that, in practice, the regression model should include relevant covariate Es which are omitted here for notation simplicity. These results also suggest that investigation of the dominant effect for the X-chromosome may be warranted, which we investigate below.

3. X-chromosome Specific Considerations (C4-C8).

3.1. Sex as a confounder (type I error control) and the choice of the base-line allele (C4 and C8): always modelling the S main effect. Sex is a confounder for phenotype-genotype association analysis of an X-chromosome SNP for traits displaying sexual dimorphism. When sex, but not the SNP, is associated with a trait of interest, omitting sex in the analysis leads to false positives. This is because sex is inherently associated with the genotypes of an X-chromosome SNP (Table 2); see Ozbek et al. (2018) for empirical evidence from simulation studies. Thus, correct control of type I error rate provides the first argument for always including S as a covariate in X-chromosome association analyses.

The second advantage of including the S main effect is more subtle but consequential nevertheless. As shown in Table 2, the coding of G_A depends on the choice of the baseline allele (i.e. R or r) and the X-inactivation status (I for XCI and N for no XCI), resulting in a total of four different ways of coding the five genotype groups for association analyses, namely $G_{A,R,I} = (0,0.5,1,0,1)'$, $G_{A,r,I} = (1,0.5,0,1,0)'$, $G_{A,R,N} = (0,1,2,0,1)'$, and $G_{A,r,N} = (2,1,0,1,0)'$. Further, $G_{A,R,N}$ and $G_{A,r,N}$ yield different test statistics, because the two coding schemes lead to different groupings of the genotypes. Note that under no XCI there is no linear transformation that makes $G_{A,R,N}$ and $G_{A,r,N}$ equivalent; under XCI $G_{A,R,I} = 1 - G_{A,r,I}$. An inference that is invariant to the coding choices may seem difficult, but we show that this is achievable for models that include sex as a covariate.

THEOREM 1. Let \mathcal{M}_1 and \mathcal{M}_2 be two generalized linear models with the same link function g, $g(E(Y)) = X_1\beta_1$ and $g(E(Y)) = X_2\beta_2$, where Y is the response vector of length n, X_1 and X_2 are two $n \times p$ design matrices, and β_1 and β_2 are the corresponding parameter vectors of length p. Let $X_1 = (X_{11}, X_{12})$, where X_{11} and X_{12} are $n \times (p-q)$ and $n \times q$ matrices corresponding to, respectively, the (p-q) secondary covariates not being tested and the q primary covariates of interest, and similarly for $X_2 = (X_{21}, X_{22})$, and partitioning the regression coefficients accordingly as $\beta_1 = (\beta'_{11}, \beta'_{12})'$ and $\beta_2 = (\beta'_{21}, \beta'_{22})'$. If there exists an invertible $p \times p$ matrix

$$T=\left(egin{array}{cc} T_1 & T_{12} \ 0 & T_2 \end{array}
ight), \ such \ that \ \ X_2=X_1 \ T \ and \ X_{21}=X_{11} \ T_1$$

where T_1 and T_2 are, respectively, invertible $(p-q) \times (p-q)$ and $q \times q$ matrices, then any of the Wald, Score or LRT tests for testing

$$H_0: \beta_{12} = 0 \text{ and } H_0: \beta_{22} = 0$$

are identical under the two models \mathcal{M}_1 and \mathcal{M}_2 , resulting in the same association inference for evaluating the q primary covariates of interest.

We provide the proof of Theorem 1 in Appendix A. Here, we emphasize that the primary q covariates being tested are *not* required to be linear transformation of each other, e.g., between $G_{A,R,N} = (0,1,2,0,1)'$ and $G_{A,r,N} = (2,1,0,1,0)'$. Instead, the two sub-design matrices, X_{11} and X_{21} corresponding to the secondary p-q covariates (including the unit vector if modelling the intercept) that are *not* being tested must be invertible linear transformations of each other, $X_{21} = X_{11} T_1$ in addition to $X_2 = X_1 T$.

This result may seem somewhat surprising, but the two conditions imply that (a) the two design matrices are equivalent, and (b) under the respective null hypothesis, the two design matrices are also equivalent resulting in identical F-test statistics; see Appendix A for technical details.

In our setting when sex is included in the model, consider only the additive effect for the moment, $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A$. Then the two design matrices corresponding to r or R being the baseline allele, under no XCI, have the structures of

$$X_1 = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 1 \\ 1 & 0 & 2 \\ 1 & 1 & 0 \\ 1 & 1 & 1 \end{pmatrix}, \quad X_2 = \begin{pmatrix} 1 & 0 & 2 \\ 1 & 0 & 1 \\ 1 & 0 & 0 \\ 1 & 1 & 1 \\ 1 & 1 & 0 \end{pmatrix}.$$

It is then easy to identify that $T_1 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$, $T_{12} = (2, -1)'$ and $T_2 = -1$

satisfy the two conditions. Thus, even though $G_{A,R,N} = (0,1,2,0,1)'$ and $G_{A,r,N} = (2,1,0,1,0)'$ are not linear transformation of each other, Theorem 1 allows us to conclude that a (Wald, Score or LRT) test of $H_0: \beta_A = 0$ based on $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A$ is invariant to the two G_A coding schemes, $G_{A,R,N}$ and $G_{A,r,N}$.

Note that the standard case of q primary covariates, X_{12} and X_{22} from two different models, being linear transformation of each other is a special case of Theorem 1, where all elements in T_{12} are zero; the first row can be a constant to allow for a location shift. For example, under the XCI assumption, $X_{12} = G_{A,R,I} = (0,0.5,1,0,1)'$ and $X_{22} = G_{A,r,I} = (1,0.5,0,1,0)'$, and $X_{22} = 1 - X_{12}$. Thus, $T_1 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$, $T_{12} = (1,0)'$, and $T_2 = -1$.

At this point in the methodology development, we now have the model $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A$ that controls type I error rate and is invariant to the choice of the baseline allele when there is no XCI. However, in general the XCI status is unknown. Consider $G_{A,R,I} = (0, 0.5, 1, 0, 1)'$ and $G_{A,r,N} = (2, 1, 0, 1, 0)'$, and

$$X_1 = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 0.5 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 1 & 1 & 1 \end{pmatrix} \text{ and } X_2 = \begin{pmatrix} 1 & 0 & 2 \\ 1 & 0 & 1 \\ 1 & 0 & 0 \\ 1 & 1 & 1 \\ 1 & 1 & 0 \end{pmatrix}.$$

In this case, it is not difficult to show T satisfying the conditions in Theorem 1 does not exit, and the XCI uncertainty remains a challenge.

3.2. Gene-sex interaction and X-chromosome inactivation (XCI) (C5 and C6): value in including the GS interaction effect. Throughout the paper, we define the GS interaction term as $G_A \times S$. Depending on the choice of the baseline allele, GS has two different codings, namely GS_R and GS_r as defined in Table 2. In the previous section, we have shown that when S is included in the model, $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A$, the choice of the baseline allele is no longer a concern if we test $H_0: \beta_A = 0$ within a particular XCI assumption. Interestingly, when both S and GS are included in the model, $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_{GS} GS$, by applying Theorem 1 again, testing $H_0: \beta_A = \beta_{GS} = 0$ is statistically equivalent between the different choices of the baseline allele and the assumptions of the XCI status. For example, consider

$$X_1 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 0.5 & 0 \\ 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 1 \end{pmatrix} \text{ and } X_2 = \begin{pmatrix} 1 & 0 & 2 & 0 \\ 1 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 0 & 0 \end{pmatrix},$$

respectively, for a model assuming XCI and choosing r as the baseline allele (i.e. tracking the number of the 'risk" allele R), and for a model assuming no XCI and choosing R as the baseline allele, we can show that

$$T_1 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, T_{12} = \begin{pmatrix} 2 & 0 \\ -1 & 1 \end{pmatrix}, \text{ and } T_2 = \begin{pmatrix} -2 & 0 \\ 1 & -1 \end{pmatrix},$$

satisfy the linear transformation requirements of Theorem 1.

Figure S4 in the Supplementary Materials summarizes the equivalency between design matrices that correspond to the different coding schemes studied so far; all theoretically results have been confirmed empirically via simulations. Figure S4 implies that for association analyses of the X-chromosome, testing $H_0: \beta_A = \beta_{GS} = 0$, based on the $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_{GS} GS$ model, is invariant to the choice of the baseline allele and the assumption of the X-inactivation status.

In terms of potential loss of power due to increased degrees of freedom as compared to testing only the main additive effect, we appeal to the results from Section 2. Specifically, in the absence of any interaction effect, the maximum power loss of jointly testing the additive and interaction effects is capped at 11.4%, while in the presence of an interaction effect, the maximum power gain can be as high as $1 - \alpha$.

3.3. Random vs. skewed X-inactivation (C7): additional value in modelling the dominant G_D effect. Similar to analyzing the autosomes, the first reason for including the dominant effect is to capture potential departure from additivity, without scarifying significant power in the absence of any dominant effect. For the X-chromosome, another important reason is that the dominant effect can also capture skewness of X-inactivation, if present. Intuitively, if we assume the effects of rr and RR to be, respectively, 0 and 1, the effect of rR will be either 0 or 1 at the individual level, depending on the inactivated allele. If the two alleles are equally likely to be inactivated (i.e. random XCI), the average effect of rR is 1/2 at the population level. If r is more likely to be inactivated (i.e. skewed XCI), the average effect of rRis greater than 1/2. However, it is not difficult to see that this XCI skewness is analytically equivalent to a dominant effect which means that the effect of rR deviates from 1/2. Thus, including the G_D covariate not only captures any dominant effect but also represents any skewness of XCI. The downside of this analytical equivalency however is that, without additional biological information, one can not distinguish between the two scenarios.

Note that coding of the dominant covariate G_D (Table 2) is invariant to the choice of the baseline allele or XCI status. Thus, including G_D in the model does not change the model relationships as specified in Figure S4. Table 3 summarizes the behaviours of various regression models. Jointly testing $H_0: \beta_A = \beta_D = \beta_{GS} = 0$, based on the $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_D G_D + \beta_{GS} GS$ model M_4 , ensures that the inference is invariant to the assumptions of the XCI status and baseline allele, and accounts for over-dominance and XCI-skewness if present, providing strong support for its use.

3.4. Power study of the X-chromosome.

3.4.1. Using the general theory of chi-squared distributions. One concern with the use of the proposed 3 d.f. test is the potential loss of power due to the increased degrees of freedom. However, we can obtain results similar to those shown in Section 2.1. Specifically, let W_1 be a 1 d.f. test statistic that is $\chi^2_{(1,ncp_1)}$ distributed, and W_3 be the proposed 3 d.f. test statistic that is $\chi^2_{(3,ncp_3)}$ distributed. When there are no dominant or interaction effects and the XCI status is precisely known, W_1 , derived from $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A$, with the correct genotype coding, is the optimal test and $ncp_1 = ncp_3 = ncp$. In that case, the maximum power loss of W_3 , remarkably, is capped at 18.8%, regardless of the true additive effect size, sample size and test size; the maximum occurs at $\alpha = 0.0008$ and ncp = 13.4 (Figure S1 in Appendix D). (At $\alpha = 5 \times 10^{-8}$ (Dudgridge & Gusnanto, 2008),

Table 3

Properties of different regression models in the presence of X-chromosome-specific analytical challenges, C4-C8, as detailed in Table 1.

C4: Sex as a confounder and type I error control; C5: Gene-sex interaction; C6: X chromosome inactivation (XCI) vs. no XCI; C7: Random vs. skewed XCI; C8: Choice of the baseline allele. \times indicates a problem if using the corresponding model and test, and \sqrt means no problem. Note that whole-genome considerations such as C1 (continuous vs. binary traits) and C2 (Hardy-Weinberg equilibrium vs. disequilibrium) are naturally dealt with by the genotype-based regression approach, and C3 (the dominant effect) is addressed here. Relevant covariate Es should be included in the model but omitted here for notation simplicity. Joint testing of $H_0: \beta_A = \beta_D = \beta_{GS} = 0$ based on M_4 is the recommended, most robust approach; see Figures 2 and S1 for power comparisons among $M_1 - M_4$.

Model, $g(E(Y)) =$	Testing H_0 :	C4/C8	C6/C7	C5
$M_0: \beta_0 + \beta_A G_A$	$\beta_A = 0$	×	×	×
$M_1: \beta_0 + \beta_S S + \beta_A G_A$	$\beta_A = 0$		×	×
$M_2: \beta_0 + \beta_S S + \beta_A G_A + \beta_D G_D$	$\beta_A = \beta_D = 0$		×	
$M_3: \beta_0 + \beta_S S + \beta_A G_A + \beta_{GS} GS$	$\beta_A = \beta_{GS} = 0$			×
$M_4: \beta_0 + \beta_S S + \beta_A G_A + \beta_D G_D + \beta_{GS} GS$	$\beta_A = \beta_D = \beta_{GS} = 0$			

the maximum power loss is 17.7% occurring at ncp = 32.6.) In the presence of either a dominant or interaction effect or both, however, the power gain of the proposed 3 d.f. test can be in theory as high as $1 - \alpha$.

Compared with a 2 d.f. test when model $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_D G_D$ or $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_{GS} G_{GS}$ being correctly specified, the global maximum power loss of the proposed 3 d.f. test is capped at 7.7%, occurring at $\alpha = 9.12 \times 10^{-5}$ and ncp = 19; at $\alpha = 5 \times 10^{-8}$ (Dudgridge & Gusnanto, 2008), the maximum power loss is 7.5% occurring at ncp = 34.2. See Figure S1 for heat plots of power comparisons.

3.4.2. Using different genetic models for the X-chromosome. We next provide some empirical results based on specific genetic models. Note that tests derived from models that do not include sex as a covariate are susceptible to type I error rate inflation. Thus, power comparisons here focus on $M_1 - M_4$ as specified in Table 3.

Similar to studies of the autosomes in Section 2.2, we need to compute the asymptotic non-centrality parameters of each test statistic for different genetic models with varying degrees of additive, dominant and interaction effects, and under different assumptions of the baseline allele and X-inactivation status. We provide the technical details in Appendices B and C.

We consider n = 1,000, $\alpha = 0.0008$ as derived above in Section 3.4.1, and allele frequency $f_{male} = f_{female} = 0.2$ or 0.5. Results for other parameter values, including differential f values between males and females, are provided in the Supplementary Materials; the case when the baseline alleles differ between males and females is discussed in Section 5. Because of the various analytical equivalencies (between GS interaction and XCI status, and between dominant effect and skewed XCI), we specify the averaged effect size for each of the five genotype groups, i.e., $\mu_{rr}, \mu_{rR}, \mu_{RR}, \mu_{r}$, and μ_R . We fix $\mu_{rr} = -0.3$, $\mu_{RR} = 0.3$ and $\mu_r = 0$, and vary μ_{rR} and μ_R from -0.6 to 0.6. Note that fixing μ_{rr} and μ_{RR} is equivalent to fixing the additive effect $\beta_A = 0.6$ under XCI or $\beta_A = 0.3$ under no XCI, and varying μ_{rR} is equivalent to varying the dominant effect β_D from -0.6 to 0.6. The link with the interaction effect β_{GS} is less clear. Under the XCI assumption, $\beta_{GS} = (\mu_R - \mu_r) - (\mu_{RR} - \mu_{rr})/2 = \mu_R - 0.3$, while under the no XCI assumption, $\beta_{GS} = (\mu_R - \mu_r) - (\mu_{RR} - \mu_{rr})/4 = \mu_R - 0.15$. So, for the μ_R values considered here, β_{GS} ranges from -0.9 to 0.3 under XCI, and from -0.75 to 0.45 under no XCI. For ease of interpretation, Figure 2 uses the 'interaction' and 'dominant' terms to denote the varying degrees of μ_{rR} and μ_R .

Results in Figure 2 demonstrate the merits of the proposed method (testing $\beta_A = \beta_D = \beta_{GS} = 0$ jointly, the red solid curves). While there could be some power loss in the worse case scenario (no G_D dominant or GS interaction effects), it is theoretically capped at 18.8% regardless of the parameter values. On the other hand, compared with the standard 1 d.f. additive test (testing $\beta_A = 0$, the black dashed curves), power gain can be 70% for the cases considered here. When the allele frequency is 0.2 (Figure 2A), the performance of the 2 d.f. additive and interaction test (testing $\beta_A = \beta_{GS} = 0$, the orange dotted curves) is close to the proposed 3 d.f. test. However, that is no longer the case when f = 0.5 (Figure 2B), where the 2 d.f. additive and dominant test (testing $\beta_A = \beta_D = 0$, the green dot-dashed curves) is better and close to the proposed 3 d.f. test. Figures S5 provides additional results for other parameter values, all showing the robustness of the proposed method.

Remark 2: For robust and powerful association studies of the X-chromosome, we recommend the following model,

$$q(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_D G_D + \beta_{GS} GS$$

and the corresponding 3 d.f. test, jointly testing

$$H_0: \beta_A = \beta_D = \beta_{GS} = 0,$$

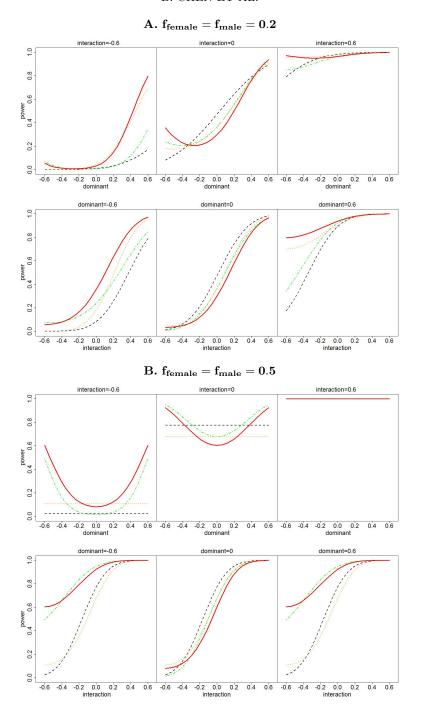


FIG 2. Power comparison for analyzing X-chromosome SNPs. Black dash lines for testing $\beta_A=0$ based on model M_1 as specified in Table 3, green dot-dash curves for testing $\beta_A=\beta_D=0$ based on model M_2 , orange dotted curves for testing $\beta_A=\beta_{GS}=0$ based on model M_3 , and red solid curves for testing $\beta_A=\beta_D=\beta_{GS}=0$ based on the proposed model M_4 . Upper panels in A and B examine power as a function of the dominant effect (or skewness of XCI). Lower panels in A and B examine power as a function of the gene-sex interaction effect (or XCI status). Results for other parameter values including differential f between males and females are shown in Figures S5. The analyses here assume that the true baseline allele is known and f being the allele frequency of the true 'risk' allele, and the true XCI status is known at the population level. Unlike the other methods (M_1-M_3) , the proposed method (M_4) is invariant to the assumptions of the baseline allele and XCI status. Result explanations are provided in Sections 3.4.2.

which not only resolves the C1-C8 analytical challenges simultaneously, but also has the best overall performance across different underlying genetic models. Note that the complete regression model includes relevant covariate Es that are omitted here for notation simplicity.

4. Applications to Published Association Studies.

4.1. Re-analyses of the 60 autosome SNPs potentially associated with various complex traits, selected by Wittke-Thompson et al. (2005). We first reanalyze the 60 autosome SNPs selected by Wittke-Thompson et al. (2005) from 41 case-control association studies of various complex traits, including Alzheimer disease and breast cancer; the genotype count data are available from Table 1 of Wittke-Thompson et al. (2005). Although these SNPs were originally selected by Wittke-Thompson et al. (2005) for a study of departure from Hardy-Weinberg equilibrium, genotype-based methods are robust to the HWE assumption (Sasieni, 1997).

Here we focus on comparing the standard 1 d.f. additive test with the proposed 2 d.f. genotypic test that jointly tests both the additive and dominant effects for the autosomes. We observe that, for about two thirds of the SNPs, p-values of the genotypic test are smaller than those of the additive test, and sometimes substantially so (Figure S6 in the Supplementary Materials). For the remaining SNPs, the genotypic p-values are only slightly bigger than the additive p-values. Although these 60 autosome SNPs can only be presumed to be associated with the various complex traits, the empirical evidence here is consistent with the analytical results in Section 2.

4.2. Evidence from the first (autosome only) genome-wide association study of WTCCC (2007). Further, similar patterns are observed in the first (autosome only) genome-wide association study performed by the Wellcome Trust Case Control Consortium (2007). Their Table 3 lists regions of the genome showing the strongest association signals and provides results from both the 1 d.f. trend test (statistically similar to the additive test considered here) and the 2 d.f. genotypic tests. Their results show that if the additive test provides a smaller p-value, the p-value of the genotypic test is at most one order of magnitude larger, e.g. 1.16×10^{-13} vs. 1.79×10^{-14} for rs1333049 associated with coronary artery disease, the second SNP in Table 3 of WTCCC (2007). On the other hand, the p-value of the 2 d.f. genotypic test can be several orders of magnitude smaller for other SNPs, e.g. 6.29×10^{-8} vs. 2.19×10^{-4} for rs420259 associated with bipolar disorder, the first SNP in Table 3 of WTCCC (2007). Similar statement can be made

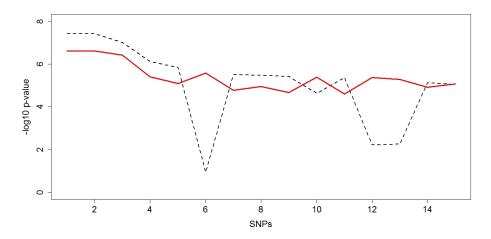
for the Bayes factors obtained under the 1 d.f. additive and 2 d.f. genotypic models by the WTCCC (2007).

4.3. Re-analyses of the (X-chromosome-inclusive) genome-wide association study of Sun et al. (2012). The data consists of 3,199 unrelated individuals with cystic fibrosis (CF) and 570,724 genome-wide SNPs, after standard quality control (Sun et al., 2012). In total, there are 574 cases with meconium ileus (intestinal obstruction at birth seen in $\approx 15\%$ of CF patients (Dupuis et al., 2016)) and 2,625 CF controls, 1,722 males and 1,477 females, and 556,445 SNPs from the autosomes and 14,279 SNPs for the X-chromosome. In Sun et al. (2012) a genome-wide association study of meconium ileus using the standard 1 d.f. additive test for the autosome SNPs was conducted, and X-chromosome inactivation for the X-chromosome SNPs was assumed (i.e. model M_1 in Table 3 with genotype coding under the assumption of XCI). Here we re-analyze the autosomes and X-chromosome SNPs to demonstrate the utility of the proposed methods.

For the autosomes, we contrast the standard 1 d.f. additive test with the proposed 2 d.f. genotypic test as discussed in Section 2. Figure 3A shows the results for the top 15 ranked autosome SNPs, ordered by the minimal pvalue of additive and genotypic tests; the lines connecting the SNPs are used only for visualization purposes. The results here are consistent with those in Section 4.1 and 4.2: If the p-values of the standard 1 d.f. additive test (the black dashed curve) are smaller, then those from the recommended 2 d.f. genotypic test (the red solid curve) are close in magnitude, while the reverse is not true. For example, p-value of the recommended 2 d.f. genotypic test for the 6_{th} SNP (rs2657147) in the plot is more than four orders of magnitude smaller than that of the 1 d.f. additive test. In this case, the genotype counts for rr, rR, and RR are (210, 312, 52) for cases and (1012, 1192, 421)for controls, which yields case/control ratios of (0.208, 0.262, 0.124) clearly suggesting an over-dominance pattern. The HWE test in the control sample has p-value p = 0.026, though smaller than 0.05 clearly passing the standard quality control for genotyping errors requiring HWE test p-value less than 10^{-8} . However, whether this is a true new finding requires further investigation. Figures S7 and S8 in the Supplementary Materials provides genome-wide results.

For the X-chromosome, we compare the $M_1 - M_4$ models and their corresponding tests as detailed in Table 3 and Section 3. For each SNP, we perform six different association tests, depending on which of the $M_1 - M_4$ models was used and if the XCI status needed to be specified, because (a) sex must be included to ensure correct type I error rate control and models

A. Autosome Results



B. X-chromosome Results

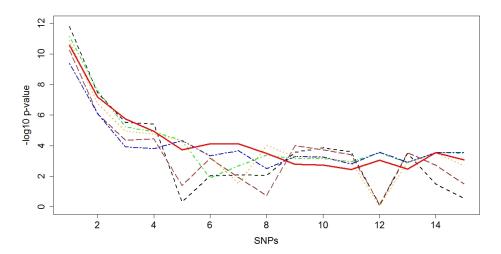


Fig 3. Results of a genome-wide association study of meconium ileus in cystic fibrosis subjects. In total, 3,199 independent cystic fibrosis subjects, 556,445 SNPs auto some SNPs and 14,279 X-chromosome SNPs are analyzed. The SNPs are ordered by the minimal p-value of the different tests considered, and the lines connecting the SNPs are used only for visualization purposes. A: These top 15 ranked autosome SNPs are selected based on either the 1 d.f. additive test or the 2 d.f. genotypic test. The black dashed curve for testing $\beta_A = 0$ using the standard additive model, and the red solid curve for testing $\beta_A = \beta_D = 0$ using the recommend genotypic model that is most robust for analyzing the autosomes. B: These top 15 ranked X-chromosome SNPs are selected based on any of the six tests based on $M_1 - M_4$ models in Table 3: the Black dashed curve for testing $\beta_A = 0$ based on M_1 assuming X-chromosome inactivation (XCI), the brown long-dashed curve for testing $\beta_A = 0$ based on M_1 assuming no XCI, the green dot-dashed curve for testing $\beta_A = \beta_D = 0$ based on M_2 assuming XCI, the blue two-dashed curve for testing $\beta_A = \beta_D = 0$ based on M_2 assuming no XCI, the orange dotted curve for testing $\beta_A = \beta_{GS} = 0$ based on M_3 (invariant to the XCI assumptions if GS is included in the model and tested), and the red solid curve for testing $\beta_A = \beta_D = \beta_{GS} = 0$ based on the recommended model M_4 that is most robust for analyzing the X-chromosome.

including S are invariant to the choice of the baseline allele (Section 3.1), and (b) models including the gene-sex interaction effect are invariant to the assumption of X-inactivation status (Section 3.2). Figure 3B shows the results for the top 15 ranked X-chromosome SNPs, ordered by the minimal p-value of all six tests. The empirical results here are clearly consistent with our earlier analytical results in Section 3.4, showing that joint modelling and testing the additive, dominant and gene-sex interaction effects is the most robust association approach for analyzing the X-chromosome.

5. Discussion. We have shown that in association studies of the X-chromosome, sex main effect must be included to achieve correct type I error rate control. The inclusion of sex also addresses the complication of baseline allele specification that otherwise affects association inference for the X-chromosome. Although the method developed here is motivated by genetic association studies of the X-chromosome, Theorem 1 is applicable to other settings where model uncertainty plays a role. For association studies of the autosomes, sex is not routinely included. However, sex can be a confounder for the autosomes as well, e.g. when there are differential female and male allele frequencies. Thus, we recommend to always include sex as a covariate in association analyses of either autosome or X-chromosome SNPs.

The specific coding for sex does not have an impact on our proposed approach. In Table 2, a female is coded as 0 and a males as 1, and the interaction $G_D \times S$ is reduced to be 0. If a female was coded as 1 and a male as 0, then $G_D \times S$ is the same as G_D . Thus, in either case it is redundant to include $G_D \times S$ in our purposed model.

For genotyping coding, we have used the statistical term baseline allele, which can be either the reference allele or the alternative allele; the other allele can be called the 'risk' allele. In practice, some investigators might choose to define the major allele (the allele with population allele frequency > 0.5) as the baseline allele and the minor allele as the 'risk' allele. Although these different preferences do not affect inference based on models that include sex main effect (Section 3.1), the allele frequency difference between females and males in theory can be so substantial that the minor alleles differ between the two sex groups. The inferential consequence of this technical complication, to the best our knowledge, has not been studied before. However, we note that as we model the gene-sex interaction effect in association analyses of either the autosome or X-chromosome SNPs, we essentially allow for different baseline alleles between females and males. We can prove this theoretically by applying Theorem 1. For example, consider an autosome SNP for which we either define the same or different baseline

alleles for males and females. If we introduce the GS interaction covariate and consider $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_{GS} GS$, we have the following two design matrices,

$$X_1 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 1 & 0 & 2 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 2 & 2 \end{pmatrix} \text{ and } X_2 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 1 & 0 & 2 & 0 \\ 1 & 1 & 2 & 2 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 0 & 0 \end{pmatrix}.$$

It is easy to show that

$$T_1 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, T_{12} = \begin{pmatrix} 0 & 0 \\ 2 & 2 \end{pmatrix}, \text{ and } T_2 = \begin{pmatrix} 1 & 0 \\ -2 & -1 \end{pmatrix}$$

satisfy the conditions of Theorem 1. As a result, testing $H_0: \beta_A = \beta_{GS} = 0$ are equivalent between the two models. Similar results can be obtained for the X-chromosome and can be easily confirmed by simulations. Thus, our theoretical result here also resolves the long-standing analytical difficulty of how to allow different baseline alleles between males and females in genetic association studies. For the X-chromosome, modelling the GS interaction effect has the added benefits of bypassing the X-inactivation uncertainty challenge as discussed in Section 3.2.

We have shown that modelling the genetic dominant effect β_D is beneficial for both the autosomes and X-chromosome. The proposed model can significantly increase test power when β_D is large. When β_D is close to 0, the model is still robust and maintains comparable power with that of the additive model. For the autosomes, we show analytically that even under true additivity, compared with the classical 1 d.f. additive test, the maximum power loss of the 2 d.f. genotypic test is capped at 11.4%, regardless of the sample, genetic effect and test sizes. Similarly, for the X-chromosome analysis, with a 3 d.f. test that includes β_A , β_D and β_{GS} interaction effects, power loss is capped at 18.8% while the gain can be as high as $1 - \alpha$. Our application results provide corroborating evidence. For the X-chromosome, β_D also captures potential skewness of X-inactivation as demonstrated in Section 3.3.

In our autosome studies in Section 2.2, Figure 1 also demonstrates some interesting patterns between power and allele frequencies. When f = 0.5 (middle plot), it is straightforward to see why, for the genotypic test (the red solid curve), the minimum power occurs at $\beta_D = 0$. Interestingly, power of the additive test (the black dashed curve) in this case is constant across the

range of β_D . Let -a, d and a be the true effect sizes of the three genotypes, rr, rR and RR, respectively. The additive effect captured by the additive component is

$$a^* = w_{rr}(d - (-a)) + w_{RR}(a - d) = a + (w_{rr} - w_{RR}) \cdot d,$$

where the weighting factors, w_{rr} and w_{RR} , are proportional to the corresponding genotype frequencies, $(1-f)^2$ and f^2 , respectively. When f=0.5, $w_{rr}=w_{RR}$ and $a^*\equiv a$ which explains why power of the additive test in this plot is constant across the rage of dominant effects. Similarly, when f=0.2 (left plot), $w_{rr}>w_{RR}$ and a^* increases as β_D increases from -0.6 to 0.6, resulting in increased power of the additive test. Power of the genotypic test also depends on the absolute size of β_D , which leads to the non-monotone pattern shown in the plot. Results of f=0.8 mirror those of f=0.2, as expected.

When the true genetic model is unknown, one alternative direction is to consider all possible models and use the 'best' or weighted average. But, such an approach is difficult to implement in practice; see Bagos (2013) for a review. For example, selection bias inherent in choosing the most fitted model must be corrected for, often through computationally intensive simulation studies, and power of this bias-corrected inferential procedure is not clear. On the other hand, ways to obtain a weighted average of the test statistics or p-values across all models can be quite ad hoc, and the optimal weighting factors are difficult to derive.

The proposed full model for analyzing an X-chromosome SNP, $g(E(Y)) = \beta_0 + \beta_S S + \beta_A G_A + \beta_D G_D + \beta_{GS} G_S$, is robust to various model uncertainties, analytically. However, it is not capable of differentiating between the scenarios. Using the available genetic association data, Ma et al. (2015) proposed a variance-based test for detecting X-inactivation by comparing phenotypic variance of the rR group with that of the rr and RR groups in females, but this method is limited to a continuous trait (Soave & Sun, 2017; Deng et al., 2018). Wang et al. (2014) explicitly introduced a parameter to represent the amount of skewness of X-inactivation. Our work here, however, shows that the interpretation of their parameter is confounded with potential dominant genetic effect. How to incorporate additional 'omic' data (Carrel & Willard, 2005) to tease apart different biological phenomenons is an interesting problem that deserves further investigation.

SUPPLEMENTARY MATERIAL

(http://www.e-publications.org/ims/support/dowload/imsart-ims.zip). The

online supplementary materials contain proof of Theorem 1 (Appendix A), non-centrality parameter computation for correctly specified genetic models (Appendix B) and for misspecified genetic models (Appendix C), and additional figures (Appendix D).

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Supplementary Materials for The X factor: A Robust and Powerful Approach to X-chromosome-Inclusive Whole-genome Association Studies

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Appendix A: Proof of Theorem 1

In Appendix A, we prove Theorem 1 stated in Section 3.1.

Case A: Linear Regression

We start from the special case of linear model. For notation simplicity we first rewrite the null hypotheses in matrix form: $H_0: L\beta_1 = 0$ under \mathcal{M}_1 and $H_0: L\beta_2 = 0$ under \mathcal{M}_2 , where $L = (0_{(q,p-q)}, I_q)$ is a combination of $q \times (p-q)$ zero matrix and identity matrix with dimension q.

In the case of the linear model, it is well known (Vandaele, 1981) that the Wald, Score and LRT test statistics for H_0 are all functions of the F-statistic. So it is sufficient to show that the F-statistic is the same for \mathcal{M}_1 and \mathcal{M}_2 . Specifically, the F-statistic under \mathcal{M}_j for j = 1, 2 is

$$F_j = \frac{Q_j/q}{(Y - X_j(X_j'X_j)^{-1}X_j'Y)'(Y - X_j(X_j'X_j)^{-1}X_j'Y)/(n-p)} \sim F(q, n-p),$$

where

$$Q_j = Y'X_j(X_j'X_j)^{-1}L'(L(X_j'X_j)^{-1}L')^{-1}L(X_j'X_j)^{-1}X_j'Y.$$

If X_j denotes the covariate matrix used in model \mathcal{M}_j , then consider a partition of its columns into $X_j = (X_{j1}X_{j2})$ such that the effect of X_{jk} on the response is β_{jk} for j, k = 1, 2.

We partition
$$(X'_j X_j)^{-1}$$
 into 4 blocks: $(X'_j X_j)^{-1} = \begin{pmatrix} X_j^{11} & X_j^{12} \\ X_j^{21} & X_j^{22} \end{pmatrix}$. Then $L'(L(X'_1 X_1)^{-1} L')^{-1} L$

is simplified to $\begin{pmatrix} 0 & 0 \\ 0 & (X_1^{22})^{-1} \end{pmatrix}$, which implies

$$Q_1 = Y'X_1(X_1'X_1)^{-1} \begin{pmatrix} 0 & 0 \\ 0 & (X_1^{22})^{-1} \end{pmatrix} (X_1'X_1)^{-1}X_1'Y$$

Next,
$$X_2 = X_1 T$$
 implies $L'(L(X_2'X_2)^{-1}L')^{-1}L = \begin{pmatrix} 0 & 0 \\ 0 & T_2'(X_1^{22})^{-1}T_2 \end{pmatrix}$, and
$$(T')^{-1}L'(L(X_2'X_2)^{-1}L')^{-1}LT^{-1}$$

$$= \begin{pmatrix} (T_1')^{-1} & 0 \\ (T_2')^{-1}T_{12}'(T_1')^{-1} & (T_2')^{-1} \end{pmatrix} \begin{pmatrix} 0 & 0 \\ 0 & T_2'(X_1^{22})^{-1}T_2 \end{pmatrix} \begin{pmatrix} T_1^{-1} & T_1^{-1}T_{12}T_2^{-1} \\ 0 & T_2^{-1} \end{pmatrix}$$

$$= \begin{pmatrix} 0 & 0 \\ 0 & (X_1^{22})^{-1} \end{pmatrix}.$$

Hence,

$$Q_{2} = Y'X_{1}TT^{-1}(X'_{1}X_{1})^{-1}(T')^{-1}L'(L(X'_{2}X_{2})^{-1}L')^{-1}LT^{-1}(X'_{1}X_{1})^{-1}(T')^{-1}T'X'_{1}Y$$

$$= Y'X_{1}(X'_{1}X_{1})^{-1}\begin{pmatrix} 0 & 0 \\ 0 & (X_{1}^{22})^{-1} \end{pmatrix}(X'_{1}X_{1})^{-1}X'_{1}Y = Q_{1}.$$

On the other hand, $X_2(X_2'X_2)^{-1}X_2 = X_1TT^{-1}(X_1'X_1)^{-1}(T')^{-1}T'X_1' = X_1(X_1'X_1)^{-1}X_1$. Therefore, $F_1 = F_2$. Finally, the Wald, Score and LRT statistics are

$$Wald = \frac{nqF}{n-p}; Score = \frac{nqF}{qF+n+p}; LRT = n\log(1+\frac{qF}{n-p}).$$

Since F does not change, they are all invariant to the linear transformation T between \mathcal{M}_1 and \mathcal{M}_2 .

Case B: Generalized Linear Regression.

In generalized linear model, the three test statistics usually do not have closed forms, and they are calculated from $\hat{\beta}_{j}$ and $\tilde{\beta}_{j}$, the unconstrained and constrained MLE of β_{j} , which are usually estimated by numerical methods. Throughout the proof, we use $\hat{\cdot}$ and $\tilde{\cdot}$ to denote unconstrained and, respectively, constrained (under H_{0}) estimators. For sample size n, we use the standard notations of GLM, where

$$\boldsymbol{\mu} = (\mu_1, ..., \mu_n) = g^{-1}(X\boldsymbol{\beta}),$$

$$V(\mu_i) = Var(Y_i)/\phi, V(\boldsymbol{\mu}) = diag[V(\mu_1), ..., V(\mu_n)],$$

$$w(\mu_i) = 1/(V(\mu_i)[g'(\mu_i)]^2), W(\boldsymbol{\mu}) = diag[w(\mu_1), ..., w(\mu_n)],$$

$$z(\mu_i) = g^{-1}(\mu_i) + g'(\mu_i)(Y_i - \mu_i), z(\boldsymbol{\mu}) = [z(\mu_1), ..., z(\mu_n)].$$

The proof under generalized linear model relies on the following two assumptions:

- 1. $\hat{\beta}_{j}$ and $\tilde{\beta}_{j}$ are estimated by iterative reweighted least squares method, and they have an initial value of 0, i.e., $\hat{\beta}_{j}^{(0)} = \tilde{\beta}_{j}^{(0)} = 0$.
- 2. If the dispersion parameter ϕ is unknown, it is estimated using $\hat{\phi} = h(\hat{\boldsymbol{\mu}})$ and $\tilde{\phi} = h(\tilde{\boldsymbol{\mu}})$ for some function h.

These two assumptions are commonly satisfied in GLM framework. For assumption 1, there is no prior information that the effect size is positive or negative, so it is reasonable to choose an initial value of zero. For assumption 2, there exist several possible estimators of ϕ in practice, but the most commonly used estimators are all functions of μ , e.g., $\hat{\phi} = \frac{1}{n} \sum_{i=1}^{n} \frac{(Y_i - \hat{\mu}_i)^2}{V(\hat{\mu}_i)}$.

We first show that $X_1\hat{\boldsymbol{\beta}_1} = X_2\hat{\boldsymbol{\beta}_2}$, and $X_1\tilde{\boldsymbol{\beta}_1} = X_2\tilde{\boldsymbol{\beta}_2}$. Under assumption 1, $X_1\hat{\boldsymbol{\beta}_1}^{(0)} = X_2\hat{\boldsymbol{\beta}_2}^{(0)}$. If we further assume $X_1\hat{\boldsymbol{\beta}_1}^{(k)} = X_2\hat{\boldsymbol{\beta}_2}^{(k)}$, then it yields $\hat{\boldsymbol{\mu}_1}^{(k)} = \hat{\boldsymbol{\mu}_2}^{(k)}$, $V(\hat{\boldsymbol{\mu}_1}^{(k)}) = V(\hat{\boldsymbol{\mu}_2}^{(k)})$, $W(\hat{\boldsymbol{\mu}_1}^{(k)}) = W(\hat{\boldsymbol{\mu}_2}^{(k)})$ and $Z(\hat{\boldsymbol{\mu}_1}^{(k)}) = Z(\hat{\boldsymbol{\mu}_2}^{(k)})$. At (k+1)th iteration,

$$X_{2}\hat{\boldsymbol{\beta}_{2}}^{(k+1)} = X_{2}[X'_{2}W(\hat{\boldsymbol{\mu}_{2}}^{(k)})X_{2}]^{-1}X'_{2}W(\hat{\boldsymbol{\mu}_{2}}^{(k)})z(\hat{\boldsymbol{\mu}_{2}}^{(k)})$$

$$= X_{1}TT^{-1}[X'_{1}W(\hat{\boldsymbol{\mu}_{1}}^{(k)})X_{1}]^{-1}(T')^{-1}T'X'_{1}W(\hat{\boldsymbol{\mu}_{1}}^{(k)})z(\hat{\boldsymbol{\mu}_{1}}^{(k)})$$

$$= X_{1}\hat{\boldsymbol{\beta}_{1}}^{(k+1)}.$$

Therefore, mathematical induction and a simple limiting argument lead to $X_1\hat{\beta}_1 = X_2\hat{\beta}_2$. Under the null hypothesis, we use the same argument on the submatrix X_{11} , X_{21} and transformation matrix T_1 to show $X_{11}\tilde{\beta}_{11} = X_{21}\tilde{\beta}_{21}$, which leads to $X_1\tilde{\beta}_1 = X_2\tilde{\beta}_2$. It immediately follows that $\hat{\beta}_1 = T\hat{\beta}_2$, $\tilde{\beta}_1 = T\tilde{\beta}_2$, $\hat{\mu}_1 = \hat{\mu}_2$ and $\tilde{\mu}_1 = \tilde{\mu}_2$.

Depending on the type of GLM, the dispersion parameter is either known (e.g., $\phi = 1$ in logistic model) or unknown (e.g., $\phi = \sigma^2$ in linear model). However, the estimators of β remain the same regardless of whether the dispersion parameter ϕ is known or unknown. When ϕ is known, it is trivial that ϕ remains equal under \mathcal{M}_1 and \mathcal{M}_2 . When ϕ is unknown, we replace ϕ by its estimator. Because $\hat{\mu_1} = \hat{\mu_2}$ and $\tilde{\mu_1} = \tilde{\mu_2}$, under assumption 2, $\hat{\phi}$ and $\tilde{\phi}$ also remain unchanged under \mathcal{M}_1 and \mathcal{M}_2 . We discuss below each of the three tests, Wald, Score and LR in detail.

(i) The Wald statistic is

$$Wald_{j} = \frac{n}{\hat{\phi}} \{ \hat{\beta}_{j}' L' [L(X'_{j}W(\hat{\mu}_{j})X_{j})^{-1}L']^{-1} L \hat{\beta}_{j} \}.$$

Because $\hat{\beta}_2 = T^{-1}\hat{\beta}_1$ and $W(\hat{\mu}_2) = W(\hat{\mu}_1)$,

$$Wald_2 = \frac{n}{\hat{\phi}} (\hat{\boldsymbol{\beta}_1}'(T^{-1})'L'[LT^{-1}(X_1'W(\hat{\boldsymbol{\mu}_1})X_1)^{-1}(T')^{-1}L']^{-1}LT^{-1}\hat{\boldsymbol{\beta}_1}).$$

We consider a partition $(X_1'W(\hat{\boldsymbol{\mu_1}})X_1)^{-1}$ and follow the approach used for **Case A** to show

$$(T^{-1})'L'[LT^{-1}(X_1'W(\hat{\boldsymbol{\mu_1}})X_1)^{-1}(T')^{-1}L']^{-1}LT^{-1} = L'[L(X_1'W(\hat{\boldsymbol{\mu_1}})X_1)^{-1}L']^{-1}L.$$

Therefore, $Wald_1 = Wald_2$.

(ii) The Score statistic is defined by Cordeiro et al. (1993) as

$$Score_{j} = \frac{1}{\tilde{\phi}} (Y - \tilde{\boldsymbol{\mu}_{j}})' V(\tilde{\boldsymbol{\mu}_{j}})^{-1/2} W(\tilde{\boldsymbol{\mu}_{j}})^{1/2} X_{j2} (\tilde{R}_{j}' W(\tilde{\boldsymbol{\mu}}) \tilde{R}_{j})^{-1} X_{j2}' W(\tilde{\boldsymbol{\mu}_{j}})^{1/2} V(\tilde{\boldsymbol{\mu}_{j}})^{-1/2} (Y - \tilde{\boldsymbol{\mu}_{j}}),$$

where

$$R_{j} = X_{j2} - X_{j1}(X'_{i1}W(\boldsymbol{\mu_{j}})X_{j1})^{-1}X'_{i1}W(\boldsymbol{\mu_{j}})X_{j2}.$$

First, we note that

$$(X_{21}, X_{22}) = (X_{11}, X_{12}) \begin{pmatrix} T_1 & T_{12} \\ 0 & T_2 \end{pmatrix} = (X_{11}T_1, X_{11}T_{12} + X_{12}T_2)$$

and $W(\tilde{\boldsymbol{\mu_2}}) = W(\tilde{\boldsymbol{\mu_1}})$. Thus

$$\tilde{R}_{2} = X_{11}T_{12} + X_{12}T_{2} - X_{11}T_{1}(T'_{1}X'_{11}W(\tilde{\boldsymbol{\mu}_{2}})X_{11}T_{1})^{-1}T'_{1}X'_{11}W(\tilde{\boldsymbol{\mu}_{2}})(X_{11}T_{12} + X_{12}T_{2})
= X_{12}T_{2} - X_{11}(X'_{11}W(\tilde{\boldsymbol{\mu}_{1}})X_{11})^{-1}X'_{11}W(\tilde{\boldsymbol{\mu}_{2}})X_{12}T_{2}) = \tilde{R}_{1}T_{2}$$

From the estimating equations for the constrained MLE of β ,

$$(Y - \tilde{\boldsymbol{\mu}_i})'V(\tilde{\boldsymbol{\mu}_i})^{-1/2}W(\tilde{\boldsymbol{\mu}_i})^{1/2}X_{i1} = 0.$$

Hence,

$$(Y - \tilde{\boldsymbol{\mu}_2})'V(\tilde{\boldsymbol{\mu}_2})^{-1/2}W(\tilde{\boldsymbol{\mu}_2})^{1/2}X_{22} = (Y - \tilde{\boldsymbol{\mu}_1})'V(\tilde{\boldsymbol{\mu}_1})^{-1/2}W(\tilde{\boldsymbol{\mu}_1})^{1/2}(X_{11}T_{12} + X_{12}T_2)$$
$$= (Y - \tilde{\boldsymbol{\mu}_1})'V(\tilde{\boldsymbol{\mu}_1})^{-1/2}W(\tilde{\boldsymbol{\mu}_1})^{1/2}X_{12}T_2.$$

Therefore,

$$Score_{2} = \frac{1}{\tilde{\phi}} (Y - \tilde{\boldsymbol{\mu}}_{1})' V(\tilde{\boldsymbol{\mu}}_{1})^{-1/2} W(\tilde{\boldsymbol{\mu}}_{1})^{1/2} X_{12} T_{2} (T_{2}' \tilde{R}_{1}' W(\tilde{\boldsymbol{\mu}}_{1}) \tilde{R}_{1} T_{2})^{-1} \cdot$$

$$T_{2}' X_{12}' W(\tilde{\boldsymbol{\mu}}_{1})^{1/2} V(\tilde{\boldsymbol{\mu}}_{1})^{-1/2} (Y - \tilde{\boldsymbol{\mu}}_{1}) = Score_{1}.$$

(iii) The LRT statistic is

$$LRT_{j} = 2\sum_{i=1}^{n} [\log f(Y_{i}, \hat{\boldsymbol{\beta}}_{j}) - \log f(Y_{i}, \tilde{\boldsymbol{\beta}}_{j})].$$

The density function of Y_i belongs to the exponential family

$$f(Y_i, \boldsymbol{\beta_j}) = \exp\left[\frac{Y_i X'_{ij} \boldsymbol{\beta_j} - b(X'_{ij} \boldsymbol{\beta_j})}{\phi} + c(Y_i, \phi)\right],$$

so $X_1\hat{\boldsymbol{\beta_1}} = X_2\hat{\boldsymbol{\beta_2}}$ and $X_1\tilde{\boldsymbol{\beta_1}} = X_2\tilde{\boldsymbol{\beta_2}}$ imply $f(Y_i, \hat{\boldsymbol{\beta_1}}) = f(Y_i, \hat{\boldsymbol{\beta_2}})$ and $f(Y_i, \hat{\boldsymbol{\beta_1}}) = f(Y_i, \hat{\boldsymbol{\beta_2}})$. Therefore, $LRT_1 = LRT_2$.

Appendix B: Non-centrality Parameter Computation for Correctly Specified Genetic Models

We provide the details for computing non-centrality parameters for the tests under different genetic models. When the model is correctly specified, *ncp* may be computed using equation

$$ncp = \beta_2'[H_{22}(\beta_1, 0) - H_{21}(\beta_1, 0)H_{11}^{-1}(\beta_1, 0)H_{12}(\beta_1, 0)]\beta_2.$$
 (1)

as described in Section 2.2.

Equation (1) above computes exact ncp as a function of design matrix X. In order to disentangle (1) from the sample-specific observed genotypes, we consider the asymptotic behaviour of ncp as $n \to \infty$. In order to avoid the uninteresting case in which $ncp \to \infty$ when n grows, we assume $\beta = c/\sqrt{n}$ (see also Cox and Hinkley, 1974; Begg and Lagakos, 1992, 1993; Neuhaus, 1998) for a fixed vector c, so that $\beta \to 0$ and ncp converges to a finite number as $n \to \infty$.

In the case of a linear model with covariate matrix X, $H = \frac{X'X}{\sigma^2}$ regardless of β . Let P be the limit of $\frac{X'X}{n}$:

$$\frac{X'X}{n} \stackrel{p}{\to} P.$$

Corresponding to the split $\boldsymbol{\beta} = (\beta_1, \beta_2)$, P is partitioned as $P = \begin{bmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{bmatrix}$. The asymptotic value of ncp is then computed following equation (1):

$$ncp_{(linear)} \xrightarrow{p} \frac{1}{\sigma^2} c_2' [P_{22} - P_{21}(P_{11})^{-1} P_{12}] c_2,$$

where $c_2 = \beta_2 \sqrt{n}$.

In the logistic model, $H(\boldsymbol{\beta}) = X'W(\boldsymbol{\beta})X$, where $W(\boldsymbol{\beta})$ is the $n \times n$ diagonal matrix with the *ith* diagonal element equal to $\mu_i(\boldsymbol{\beta})(1-\mu_i(\boldsymbol{\beta}))$, and $\mu(\boldsymbol{\beta}) = \frac{\exp(X\boldsymbol{\beta})}{1+\exp(X\boldsymbol{\beta})}$. As $n \to \infty$, $\boldsymbol{\beta} \to \mathbf{0}$ so that $\mu_i(\boldsymbol{\beta})(1-\mu_i(\boldsymbol{\beta})) \stackrel{p}{\to} \frac{1}{4}$, which implies

$$\frac{X'W(\boldsymbol{\beta})X}{n} \stackrel{p}{\to} \frac{P}{4}.$$

Hence, the asymptotic non-centrality parameter under logistic model is

$$ncp_{(logistic)} \xrightarrow{p} \frac{1}{4}c_2'[P_{22} - P_{21}(P_{11})^{-1}P_{12}]c_2.$$

Note that if $\sigma^2 = 4$, the linear and logistic model have equal asymptotic ncp as long as X and β are the same. Under this scenario, in both models

$$ncp \xrightarrow{p} \frac{1}{\sigma^2} c_2' [P_{22} - P_{21}(P_{11})^{-1} P_{12}] c_2.$$
 (2)

This observation allows a convenient derivation of ncp in logistic models by plugging $\sigma^2 = 4$ in the ncp formula for linear models.

Remark 1: Assume that the generative model is genotypic (for autosome SNPs) or model M_4 in Table 3 (for X-chromosome SNPs). If the additive model or one of the models M_1, M_2, M_3 are used for estimation, then the above derivation of ncp is not valid since the estimators for β may be biased due to model misspecification.

However, when the true model is additive or one of models M_1, M_2, M_3 , the derivation for ncp remains valid when using either the genotypic model or M_4 for estimation, as the MLE estimators of β remain unbiased. Therefore, ncp under the genotypic or M_4 model may be computed by equation (1) or (2) regardless of the true model.

Remark 2: Under genotypic model, $\beta_2 = (\beta_A, \beta_B)$

$$P = \begin{pmatrix} 1 & E(G_A) & E(G_D) \\ E(G_A) & E(G_A^2) & E(G_A \cdot G_D) \\ E(G_D) & E(G_A \cdot G_D) & E(G_D^2) \end{pmatrix}.$$

Under M_4 , $\beta_2 = (\beta_A, \beta_D, \beta_{GS})$ and

$$M_4, \ \beta_2 = (\beta_A, \beta_D, \beta_{GS}) \text{ and }$$

$$P = \begin{pmatrix} 1 & E(S) & E(G_A) & E(G_D) & E(GS) \\ E(S) & E(S^2) & E(S \cdot G_A) & E(S \cdot G_D) & E(S \cdot GS) \\ E(G_A) & E(S \cdot G_A) & E(G_A^2) & E(G_A \cdot G_D) & E(G_A \cdot GS) \\ E(G_D) & E(S \cdot G_D) & E(G_A \cdot G_D) & E(G_D^2) & E(G_D \cdot GS) \\ E(GS) & E(S \cdot GS) & E(G_A \cdot GS) & E(G_D \cdot GS) & E(GS^2) \end{pmatrix}.$$

Assuming equal population frequency of females and males, E(S) = 0.5. Other expected values are computed from the 'risk' allele frequencies (f_{female} and f_{male}). Although different codings of G_A and G_I may lead to different expected values, the test statistics are common (following Theorem 1) thus implying that the ncp form is asymptotically coding-invariant.

Appendix C: Non-centrality Parameter Computation for Misspecified Genetic models

Under model misspecification, the derivations in Appendix B may not be applicable. In this section, we provide an alternative approach for deriving ncp by reparametrizing the covariates without changing the test statistics. The approach is illustrated with a series of examples.

Example 1: Additive model is misspecified when dominant effect is present. The following four steps are used to compute the correct ncp:

- **S1** We reparametrize G_A and G_D as G_A^* and G_D^* such that the test statistic for the null H_0 : $\beta_A^* = \beta_D^* = 0$ is the same as that for H_0 : $\beta_A = \beta_D = 0$ under the original genotypic model. From Theorem 1 it is sufficient that $(1, G_A^*, G_D^*)$ is a linear transformation of $(1, G_A, G_D)$.
- **S2** We next test $\beta_A^* = 0$ under the reparametrized genotypic model $Y \sim G_A^* + G_D^*$. Because the reparametrized genotypic model is correctly specified, the asymptotic ncp for this test can be computed following equation (2).
- **S3** We show that when $\operatorname{corr}(G_A^*, G_D^*) = 0$, the re-parametrized additive model: $Y \sim G_A^*$ and genotypic model: $Y \sim G_A^* + G_D^*$ have asymptotic equal ncp for testing $\beta_A^* = 0$.
- S4 We require $(1, G_A^*)$ to be a linear transformation of $(1, G_A)$. Then by Theorem 1, testing $\beta_A^* = 0$ under $Y \sim G_A^*$ has the same test statistic as testing $\beta_A = 0$ under $Y \sim G_A$. Therefore, the correct ncp for testing $\beta_A = 0$ under original additive model $Y \sim G_A$ is asymptotically equal to the ncp computed in step 1.

S1: We define $G_A^* = (-1, 0, 1)$ and $G_D^* = (-2f^2, 2f(1-f), -2(1-f)^2)$ for genotype rr, rR and RR. Direct verification shows $corr(G_A^*, G_D^*) = 0$. Also note that $(1, G_A^*, G_D^*)$ and $(1, G_A^*)$ are linear transformations of $(1, G_A, G_D)$ and $(1, G_A)$. Under the new codings, $\boldsymbol{\beta}$ is also re-parametrized so that $\beta_A^* = \beta_A + \beta_D(1-2f)$ and $\beta_D^* = \beta_D$.

Remark 3 Note that the new codings are hard to interpret and we do not recommend using

them for effect estimates. Their sole purpose is to facilitate the asymptotic calculation of ncp.

S2 See previous section.

S3 For logistic models, Begg and Lagakos (1992) showed the equivalence and we apply their conclusion directly. Here we provide the proof for the linear model.

Because the re-parametrized genotypic model $Y \sim G_A^* + G_D^*$ is correctly specified, the asymptotic ncp for testing $\beta_A^* = 0$ can be computed following equation (2). With the new coding of G_A^* and G_D^* , we have

$$P^* = \begin{pmatrix} 1 & -1+2f & 0 \\ -1+2f & 1-2f+2f^2 & 0 \\ 0 & 0 & 4f^2(1-f)^2 \end{pmatrix}.$$

For testing $\beta_A^* = 0$, β^* is partitioned as $\beta_1^* = (\beta_0^*, \beta_G^*)$ and $\beta_2^* = \beta_A^*$. P^* is partitioned accordingly so that

$$P_{11}^* = \begin{pmatrix} 1 & 0 \\ 0 & 4f^2(1-f)^2 \end{pmatrix}, P_{21}^* = P_{12}^{*\prime} = \begin{pmatrix} -1 + 2f & 0 \end{pmatrix}, P_{22}^* = 1 - 2f + 2f^2.$$

Therefore,

$$ncp \xrightarrow{p} \frac{1}{\sigma^2} c_2^{*'} [P_{22}^* - P_{21}^* (P_{11}^*)^{-1} P_{12}^*] c_2^* = 2f(1-f) \frac{n\beta_A^{*2}}{\sigma^2}.$$

To compute the ncp from the re-parametrized additive model $Y \sim G_A^*$, the model is misspecified so that we need to work on the ncp directly. The chi-squared statistic is

$$W = \frac{\hat{\beta_A^*}' L' (L(X_A^* X_A^*)^{-1} L')^{-1} L \hat{\beta_A^*}}{\sigma^2},$$

where $\hat{\beta}_A^* = (\hat{\beta}_0^*, \hat{\beta}_A^*)'$ is the least square estimator of $(\beta_0, \beta_A)'$, $X_A^* = (1, G_A^*)$ and $L = \begin{bmatrix} 0 & 1 \end{bmatrix}$.

Because the genotypic model is the true model, $Y \sim N(X^*\beta^*, \sigma^2 I_n)$, where $X^* = (1, G_A^*, G_D^*)$ and $\beta^* = (\beta_0^*, \beta_A^*, \beta_D^*)'$. It implies that

$$\hat{\boldsymbol{\beta_A^*}} = (X_A^{*'}X_A^*)^{-1}X_A^{*'}Y \sim N((X_A^{*'}X_A^*)^{-1}X_A^{*'}X^*\boldsymbol{\beta^*}, (X_A^{*'}X_A^*)^{-1}\sigma^2),$$

and thus

$$L\hat{\beta}_{A}^{*} \sim N(L(X_{A}^{*}'X_{A}^{*})^{-1}X_{A}^{*}'X^{*}\beta^{*}, L(X_{A}^{*}'X_{A}^{*})^{-1}L'\sigma^{2}).$$

Therefore, $W \sim \chi^2_{(1,ncp_A)}$ where

$$ncp_{A} = \frac{1}{\sigma^{2}} \beta^{*'} X^{*'} X_{A}^{*} (X_{A}^{*'} X_{A}^{*})^{-1} L' (L(X_{A}^{*'} X_{A}^{*})^{-1} L')^{-1} L(X_{A}^{*'} X_{A}^{*})^{-1} X_{A}^{*'} X^{*} \beta^{*}.$$

Next, $X^*\beta^* = X_A^*(\beta_0^*, \beta_A^*)' + \beta_D^*G_D^*$, so we may decompose ncp_A into three parts such that $ncp_A = a_1 + a_2 + a_3$, where

$$a_{1} = \frac{1}{\sigma^{2}} (\beta_{0}^{*}, \beta_{A}^{*}) L' (L(X_{A}^{*}'X_{A}^{*})^{-1}L')^{-1} L(\beta_{0}^{*}, \beta_{A}^{*})',$$

$$a_{2} = \frac{2}{\sigma^{2}} \beta_{D}^{*} G_{D}^{*}' X_{A}^{*} (X_{A}^{*}'X_{A}^{*})^{-1} L' (L(X_{A}^{*}'X_{A}^{*})^{-1}L')^{-1} L(\beta_{0}^{*}, \beta_{A}^{*})',$$

$$a_{3} = \frac{1}{\sigma^{2}} \beta_{D}^{*} G_{D}^{*}' X_{A}^{*} (X_{A}^{*}'X_{A}^{*})^{-1} L' (L(X_{A}^{*}'X_{A}^{*})^{-1}L')^{-1} L(X_{A}^{*}'X_{A}^{*})^{-1} X_{A}^{*}' G_{D}^{*} \beta_{D}^{*}.$$

Because

$$\frac{1}{n}G_D^{*}X_A^* \stackrel{p}{\to} (E[G_D^*], E[G_A^*G_D^*]) = (0, 0)$$

and

$$\boldsymbol{\beta^*} = \frac{\boldsymbol{c^*}}{\sqrt{n}} \stackrel{p}{\to} \mathbf{0},$$

we have $a_2 \stackrel{p}{\to} 0$ and $a_3 \stackrel{p}{\to} 0$. To compute a_1 ,

$$\frac{1}{n}X_A^{*'}X_A^* = \frac{1}{n} \begin{pmatrix} n & \sum G_A^* \\ \sum G_A^* & \sum G_A^{*2} \end{pmatrix} \xrightarrow{p} \begin{pmatrix} 1 & -1+2f \\ -1+2f & 1-2f+2f^2 \end{pmatrix},$$

which implies

$$nL(X'_A X_A)^{-1} L' \xrightarrow{p} \frac{1}{2f(1-f)}.$$

Therefore,

$$ncp_A \stackrel{p}{\to} a_1 \stackrel{p}{\to} 2f(1-f)\frac{n\beta_A^{*2}}{\sigma^2},$$

which completes the proof that the two asymptotic non-centrality parameters are equal.

Example 2: M_1 , M_2 and M_3 are misspecified models when M_4 is the true model.

As in the previous example, the reparametrized coding $(1, S^*, G_A^*, G_D^*, GS^*)$ must be a linear transformation of $(1, S, G_A, G_D, GS)$, and $(1, S^*)$ must also be a linear transformation of (1, S).

The way to code G_A and GS is not an issue because we can show the equivalency of $(1, S, G_A, G_D, GS)$ under each way of coding by applying Theorem 1, as summarized in Figure S4. The requirements in **S3** and **S4** are discussed below for models $M_1 - M_3$.

 $\mathbf{M_1}$ To compute ncp_1 for testing $\beta_A = 0$ under M_1 , we require

$$\operatorname{corr}(G_D^*, G_A^*) = \operatorname{corr}(GS^*, G_A^*) = 0,$$

and $(1, S^*, G_A^*)$ is linear transformation of $(1, S, G_A)$.

 $\mathbf{M_2}$ To compute ncp_2 for testing $\beta_A = \beta_D = 0$ under M_2 , we require

$$\operatorname{corr}(GS^*, G_A^*) = \operatorname{corr}(GS^*, G_D^*) = 0,$$

and $(1, S^*, G_A^*, G_D^*)$ is linear transformation of $(1, S, G_A, G_D)$.

 $\mathbf{M_3}$ To compute ncp_3 for testing $\beta_A = \beta_{GS} = 0$ under M_3 , we require

$$\operatorname{corr}(G_D^*, G_A^*) = \operatorname{corr}(G_D^*, GS^*) = 0,$$

and $(1, S^*, G_A^*, GS^*)$ is linear transformation of $(1, S, G_A, GS)$.

We can show ncp_1 , ncp_2 and ncp_3 are asymptotically equal to the ncps for testing $\beta_A^* = 0$, $\beta_A^* = \beta_D^* = 0$ and $\beta_A^* = \beta_{GS}^* = 0$ under the correctly specified re-parametrized model M_4 : $Y \sim S^* + G_A^* + G_D^* + GS^*$, which can be computed using equation (2). The proof under logistic model is a direct application of Begg and Lagakos (1992)'s result. The proof under linear models is omitted because it is similar to the **Example 1** above but much more lengthy.

The remaining question is to find the re-parametrized codings satisfying the above conditions. We provide such codings in Table S1.

Table S1: Re-parametrized codings of additive, dominant, interaction and sex effect

	Female			Male	
Coding	rr	rR	RR	r	R
G_A^*	-1	0	1	-1	1
G_D^*	$-2f_{female}^2$	$2f_{female}(1 - f_{female})$	$-2(1-f_{female})^2$	0	0
GS^*	$-f_{female}$	$\frac{1}{2} - f_{female}$	$1 - f_{female}$	$\frac{f_{female}(1 - f_{female})}{2(1 - f_{male})}$	$-\frac{f_{female}(1-f_{female})}{2f_{male}}$
<i>S</i> *	-1	-1	-1	1	1

Remark 4: If the missing covariates in the misspecified model are uncorrelated to the covariate being tested, for finite sample it is well-known that the estimator from misspecified model should be unbiased but less efficient. However, we find the ncps are asymptotically equal under the true model and under the misspecified model using re-parametrized codings. This suggests that the misspecified model is asymptotically as efficient as the true model,

in contradiction with the finite sample result. This tension appears because we assume that the nuisance parameter β_1 also converges to 0. For instance, Begg and Lagakos (1992) considered the situation in which only β_2 converges to 0, and their derivations showed that the asymptotic relative efficiency of the misspecified model and true model is less than 1, in agreement with small sample results.

Remark 5: The ncp computation in our paper focuses on linear and logistic regressions, but it is possible to extend to other generalized linear models (GLMs). Although there is no result to be directly used for GLMs in general, Neuhaus (1998) extended Begg and Lagakos (1992)'s relative efficiency calculation to GLMs. It can be used to extend the asymptotic equivalence of ncp to other types of GLM.

Appendix D: Additional Figures

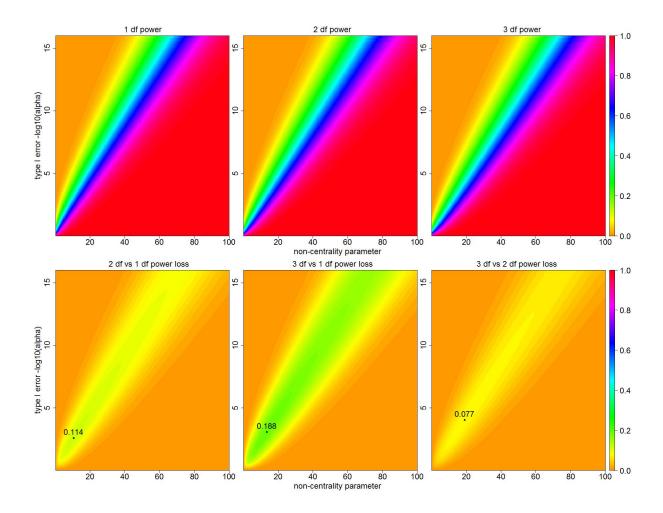


Figure S1: Heat plots of power and power loss for 1, 2 and 3 degree of freedom chi-squared distributions. Upper panels: Power of $W_1 \sim \chi^2_{(1,ncp)}$, $W_2 \sim \chi^2_{(2,ncp)}$ and $W_3 \sim \chi^2_{(3,ncp)}$ as a function of $-\log_{10} \alpha$ (type I error) and non-centrality parameter. Lower panels: Power loss of W_2 vs W_1 , W_3 vs W_1 and W_3 vs W_2 as a function of $-\log_{10} \alpha$ and non-centrality parameter assuming equal non-centrality parameter within each pair. Black dots correspond to maximum power loss: $\alpha = 0.0025$ and ncp = 10.6 for left panel, $\alpha = 0.0008$ and ncp = 13.4 for middle panel and $\alpha = 9.12 \times 10^{-5}$ and ncp = 19 for right panel.

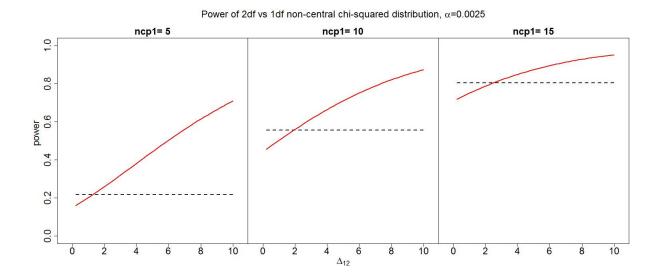


Figure S2: Test power comparison between $W_1 \sim \chi^2_{(1,ncp_1)}$ and $W_2 \sim \chi^2_{(2,ncp_2)}$, when $ncp_1 = 5, 10$ or 15 and $\Delta_{12} = ncp_2 - ncp_1$ varying from 0 to 10. Black dash curves are power of W_1 ; red solid curves are power of W_2 . Type I error $\alpha = 0.0025$.

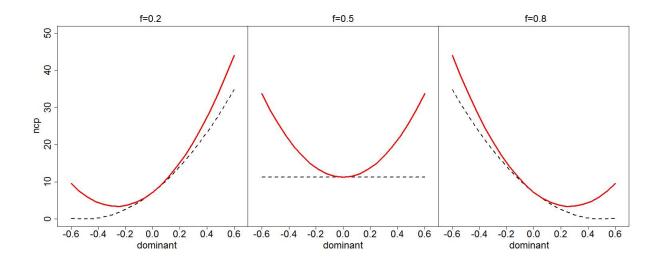


Figure S3: Non-centrality parameter comparison between the additive and genotypic tests for association analyses of autosome SNPs across a range of dominant effects, including no dominant effect. The additive effect is fixed at $\beta_A = 0.3$, while the dominant effect β_D ranges from -0.6 to 0.6. The allele frequency f = 0.2, 0.5, and 0.8 for the three plots, respectively, from left to right, the sample size n = 1,000, and the size of the test $\alpha = 0.0025$. The black dashed curves are power of testing $\beta_A = 0$ using the additive model, and the red solid curves are power of testing $\beta_A = \beta_D = 0$ using the genotypic model.

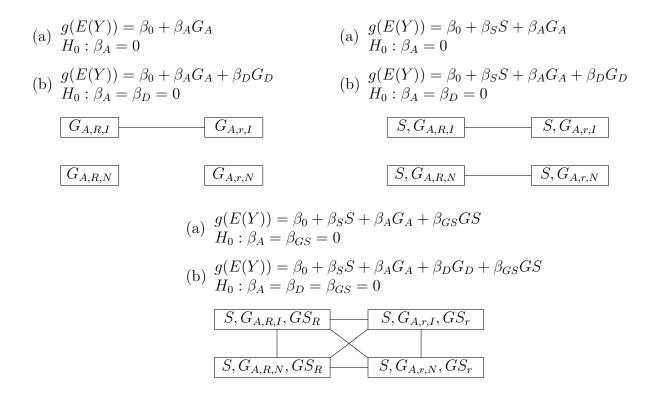
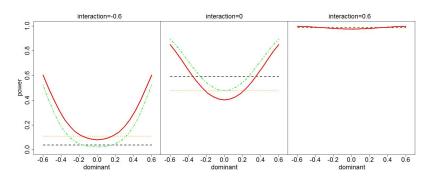
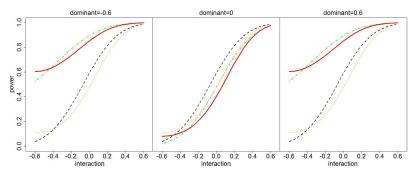


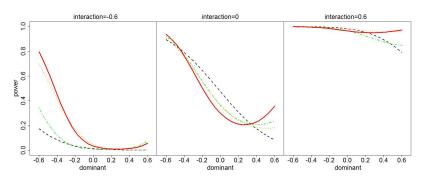
Figure S4: Equivalency between different regression models for association studies of the X-chromosome. The subscript R or r represents the designated allele of which we count the number of copies present in a genotype ('risk' allele), and I or N denotes X-chromosome inactivated or not inactivated. Two group of codings connected by a straight line if there is an invertible linear transformation between the design matrices as specified in Theorem 1, and the resulting test statistics for testing the specified H_0 will be identical to each other. Part (a) corresponds to models and tests without the dominant covariate, G_D , and part (b) corresponds to models and tests with G_D included. Inclusion of G_D has no effect to the linear relationships established in part (a), because there is only one G_D coding as defined in Table 2.

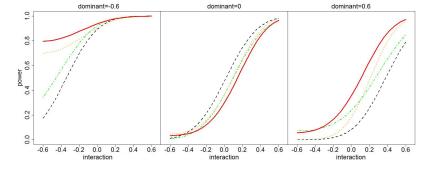
$A.\ f_{female} = 0.2, f_{male} = 0.5$



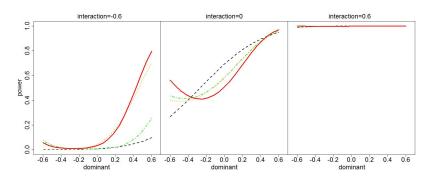


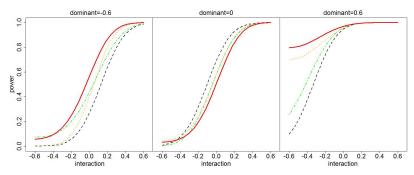
$B.\ f_{female} = 0.2, f_{male} = 0.8$



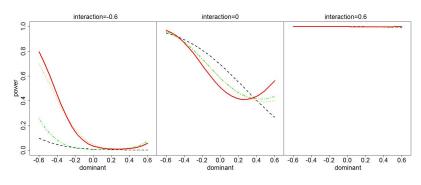


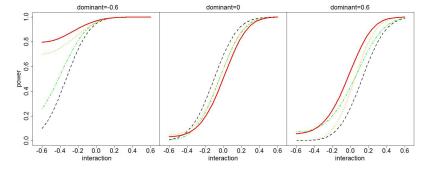
$C.\ f_{female} = 0.5, f_{male} = 0.2$



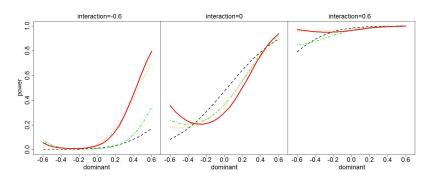


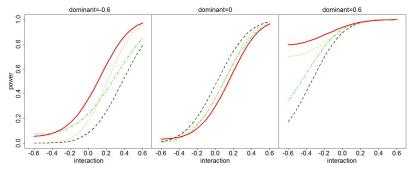
$D.~f_{female} = 0.5, f_{male} = 0.8$



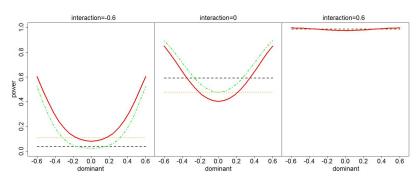


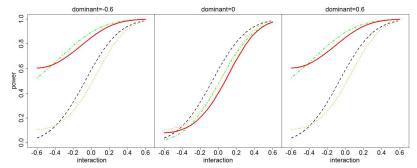
$E.\ f_{female} = 0.8, f_{male} = 0.2$





$F.\ f_{female} = 0.8, f_{male} = 0.5$





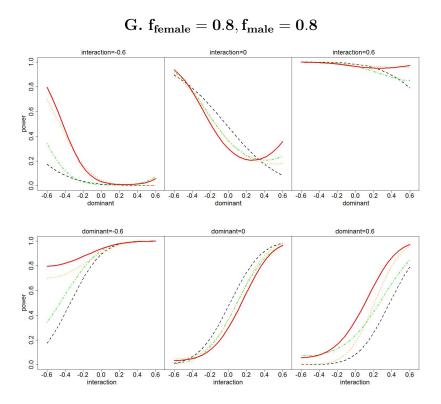


Figure S5: Power comparisons for analyzing X-chromosome SNPs. Additional values of f which are not presented in Figure 2 are specified through part A to G. Black dash curves for testing $\beta_A = 0$ based on model M_1 , green dot-dash curves for testing $\beta_A = \beta_D = 0$ based on model M_2 , orange dotted curves for testing $\beta_A = \beta_{GS} = 0$ based on model M_3 , and red solid curves for testing $\beta_A = \beta_D = \beta_{GS} = 0$ based on the proposed model M_4 . Upper panels examine power as a function of dominant effect (or skewness of XCI). Lower panels examine power as a function of gene-sex interaction effect (or XCI status).

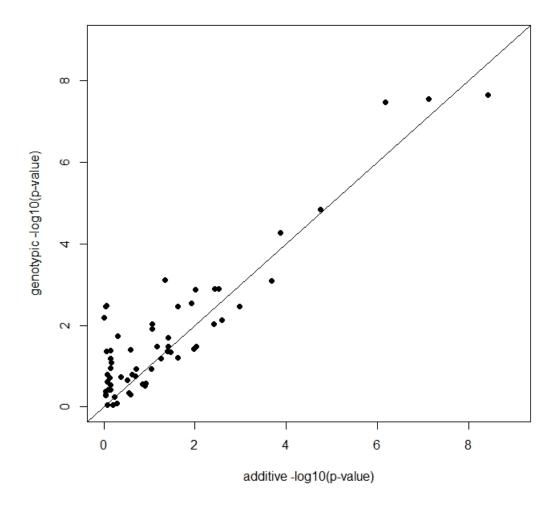


Figure S6: Results of re-analyses of the 60 autosomal, presumably associated, SNPs selected by Wittke-Thompson et al. (2005) from 41 association studies. X-axis is the p-value, on the $-log_{10}$ scale, obtained from the standard 1 d.f. additive test and the Y-axis is the recommended 2 d.f. genotypic test.

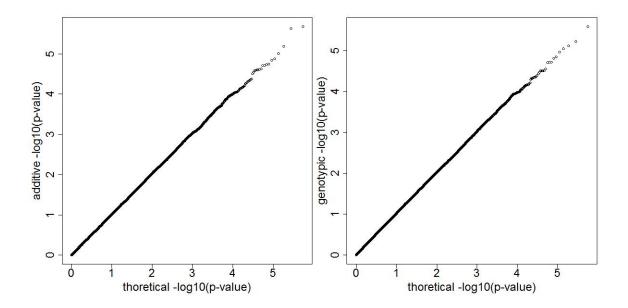


Figure S7: QQ-plots of the 556,445 autosome SNPs from cystic fibrosis study in Section 4.3. Left panel: p-values of the additive test on $-log_{10}$ scale. Right panel: p-values of the genotypic test on $-log_{10}$ scale. The QQ-plots imply that p-values are approximately Uniform(0,1) distributed for either test.

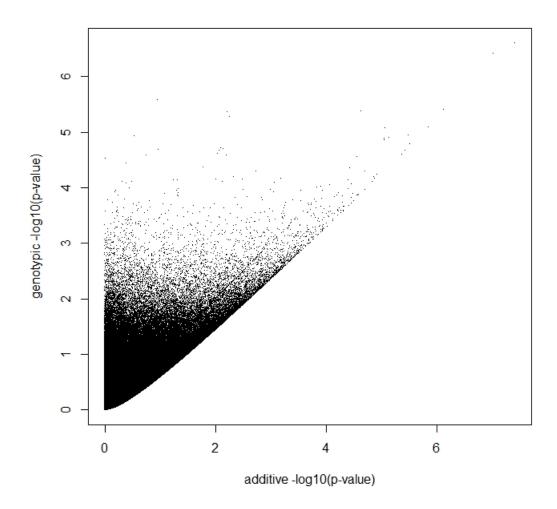


Figure S8: p-values of the additive test vs. genotypic test on $-\log_{10}$ scale of the 556,445 autosome SNPs from cystic fibrosis study in Section 4.3. Due to the capped maximal power loss computed in Section 2.1, p-values under genotypic model is possible to be much smaller than additive model, but not possible to be much greater than additive model, which clearly demonstrates the benefit of genotypic model. It needs to be noted that the capped power loss does not contradict to the fact that the overall p-values under both additive and genotypic model have the same Uniform(0,1) distribution, as shown in Figure S7.

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