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Covariate adjusted inference of parent-of-origin effects using case–control mother–child paired multilocus genotype data

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Abstract

It is of great interest to identify parent-of-origin effects (POEs) since POEs play an important role in many human heritable disorders and human early life growth and development. POE is sometimes referred to as imprinting effect in the literature. Compared with the standard logistic regression analyses, retrospective likelihood-based statistical methods are more powerful in identifying POEs when data are collected from related individuals retrospectively. However, none of existing retrospective-based methods can appropriately incorporate covariates that should be adjusted for if they are confounding factors. In this paper, a novel semiparametric statistical method, M-HAP, is developed to detect POEs by fully exploring available information from multilocus genotypes of case–control mother–child pairs and covariates. Some large sample properties are established for M-HAP. Finite sample properties of M-HAP are illustrated by extensive simulation studies and real data applications to the Jerusalem Perinatal Study and the Danish National Birth Cohort study, which confirm the desired superiority of M-HAP over some existing methods. M-HAP has been implemented in the updated R package CCMO.

KEYWORDS

case–control study, haplotype, mother–child pair, multilocus genotype, parent-of-origin effect

1 | INTRODUCTION

Genome-wide association studies (GWAS) have been successfully adopted for detecting causal genetic variants associated with complex human disorders and shed some light on the genetic architecture of such disorders. Nevertheless, as shown in Eichler et al. (2010), a large proportion of the genetic heritability remains unexplained and is partially accounted by genetic effects related to parental origin of children alleles. Parent-of-origin effects (POEs) exist if the alleles with different parental origins have different contributions to the phenotype of interest. For example, the phenotype of the child could be mainly influenced by the allele inherited

from mother while the allele from the father has little or no effect. POEs are known to contribute to human early life growth and development (Peters, 2014; Petry et al., 2007). Furthermore, increasing evidence suggests that POEs play an important role in some neonatal diseases, such as Silver-Russell syndrome, Angelman syndrome and Beckwith-Wiedemann syndrome (Lim & Maher, 2009).

Family-based design is commonly used to detect POEs. Based on such kind of design, a variety of statistical methods have been proposed to assess POEs. Weinberg et al. (1998) extended the log linear model in Wilcox et al. (1998) to include both imprinting and maternal effects through examining the relative risks associated with offspring and maternal genotypes. As shown in Weinberg et al. (1998), imprinting effects can be fitted using an expectation-maximization (EM) algorithm. A similar model was provided by Ainsworth et al. (2011), which parameterizes genetic effects in a way similar to that of Weinberg et al. (1998). Basing on the multinomial model provided by Ainsworth et al. (2011), Howey and Cordell (2012) developed the software EMIM to detect POEs. EMIM maximizes the multinomial likelihood through a direct search algorithm while Weinberg et al. (1998) uses an EM algorithm to fit the log linear model. Weinberg (1999) proposed a TDT-like method for assessing POEs, which stratifies the transmission or nontransmission allele counts into a 2×2 table according to the parental origin of the alleles and adopts the Fisher's exact test or the chi-squared test to test the POEs. However, as noted by Weinberg (1999), this method does not incorporate maternal effects that serve as confounding factors in assessing POEs. A similar TDT-like method was implemented in the software PLINK (Purcell et al., 2007), which is widely adopted to analyze POEs (Orton et al., 2011; Wang et al., 2012). Yang and Lin (2013) proposed a partial likelihood approach for detecting imprinting and maternal effects (LIME) based on a multiplicative relative risk model. LIME does not rely on the assumption about mating type probabilities and rarity of the disease, which contributes to its robustness to violation of the usual assumptions without a notable loss of power. Han et al. (2013) and F. Zhang et al. (2016) extended the approach of Yang and Lin (2013) to include additional siblings of probands. Their simulation results showed that recruiting additional affected siblings can improve the power of testing POEs. Furthermore, F. Zhang et al. (2019) extended LIME to the discordant sibpair design and developed a method LIME$_{DSP}$). LIME$_{DSP}$ makes use of all available sibship data and does not require control families. Other methods like the logistic regression model and the generalized linear model are also adopted to detect POEs (Burns et al., 2005; Zhabotynsky et al., 2019).

The use of triads is attractive in POE analyses. However, fathers are sometimes much harder to recruit than mothers in some genetic studies (Yang & Lin, 2013). In this paper, we focus on the case–control mother–child pair design, a special family-based design, which is widely used in studies for neonatal diseases (Fu et al., 2013; Mendonça et al., 2019; van de Putte et al., 2020). As shown in Weinberg and Umbach (2005), the case–control mother-child pairs design permits the estimation of maternal, offspring, and parent-of-origin effects. Since maternal genotype data can provide partial parent-of-origin information, this design is helpful in improving the POE inference efficiency (Weinberg & Shi, 2009). POEs can be detected using mother–child pairs' genotypes at a single locus and some methods reviewed above can be directly used (Ainsworth et al., 2011; Howey & Cordell, 2012; Weinberg & Shi, 2009; Yang & Lin, 2013).

Assessing POEs relies on the availability of parent-of-origin information of two children alleles. The parent-of-origin information can be unambiguously inferred from the genotypes of mother and child if at least one of them is homozygous. For example, if the genotypes of mother and child are AA and Aa, respectively, then the parental origins of children alleles A and a should be mother and father, respectively. On the other hand, if the genotypes of both mother and child are heterozygous, the parent-of-origin information is ambiguous. As shown in Yang and Lin (2013), simply ignoring mother–child pairs with unambiguous parent-of-origin information would result in an estimation bias and a loss of inference efficiency. Incorporating the genotype data from tightly linked loci is helpful to determine parental origins of children alleles, and methods using multilocus genotype data can be much more powerful in detecting POEs, compared with single-locus based methods (Gjessing & Lie, 2006; Howey et al., 2015; Lin et al., 2013; F. Zhang & Lin, 2020). Gjessing and Lie (2006) developed a software HAPLIN based on a log linear model similar to the model in Weinberg et al. (1998), which could utilize multilocus genotypes to improve the power for detecting POEs. Lin et al. (2013) used a logistic regression model to model the POEs and estimated unknown parameters by maximizing a retrospective likelihood function that incorporates genotype data from multiple loci. Moreover, Howey et al. (2015) updated their software EMIM to take advantage of haplotypes estimated with SHAPEIT2 (Delaneau et al., 2013), so as to improve the power for detecting POEs. Very recently, F. Zhang and Lin (2020) extended LIME (Yang & Lin, 2013) by exploiting additional information from multilocus genotypes to help infer the parental origins of children alleles. Nevertheless, the existing

statistical methods exploiting multilocus genotypes from mother–child pairs cannot incorporate covariates that should be adjusted for in the analysis of POEs if these covariates are confounders.

In this paper, we aim to develop a multilocus statistical method to detect POEs by adjusting for covariates using mother–child paired data. The key idea is to adopt an imputation-like strategy to handle missing parent-of-origins by borrowing the information from multilocus genotypes. The advantage of our method is at least threefold. First, it is generally more powerful than single-locus methods in assessing POEs. Second, it is computationally very efficient compared with those expectation-maximization algorithm-based methods for handling missing parent-of-origins. Third, it is robust to model misspecification to a large extent.

The rest of this paper is organized as follows. Our proposed method is described in Section 2, which includes a model quantifying parent-of-origin effect, a strategy used to infer parental origins by incorporating multilocus genotypes, and a rigorous statistical inference procedure based on a modified profile likelihood function. In Section 3, extensive simulation studies are used to evaluate the desired advantages of the proposed method over some existing methods. In Section 4, the proposed method is applied to the Jerusalem Perinatal Study and the Danish National Birth Cohort study. Finally, some concluding remarks are provided in Section 5.

2 | METHOD

2.1 | Notations and model

Let Y denote the status of a disease of interest coded by 1 or 0, depending on the presence or absence of the disease. We are interested in association analysis between the disease and a single-nucleotide polymorphism (SNP). Hereafter, "test locus" is used to denote such SNP. Let the major allele and minor allele of the test locus be A and a, respectively. Let G^m, G^f, and G^c denote the genotypes of mother, father, and child, respectively. Let G_m^c and G_f^c be children alleles inherited from the mother and father, respectively, which are coded as 1 (or 0) if the inherited allele is a (or A). The ordered genotype is denoted by (G_m^c, G_f^c). For instance, (0, 1) means that an A allele is inherited from the mother and an a allele is inherited from the father. Numbers 0, 1, and 2 are used to represent the unordered genotypes AA, Aa, and aa, respectively. Let X denote a vector of covariates, which could consist of continuous variables and/or categorical variables.

We propose to use a logistic regression model to quantify genetic parent-of-origin effect on the phenotype, which extends the model adopted in Lin et al. (2013) by taking into account the effect of covariates:

$$\begin{aligned}\text{logit pr}\left(Y = 1|G^m, G^c, G_m^c, G_f^c, X\right) &= \beta_0 + \beta_1 G^m \\ &+ \beta_2 G^c + \beta_3\left(G_m^c - G_f^c\right) + \beta_4^\tau X, \end{aligned} \quad (1)$$

where $\text{logit}(t) = \log\{t/(1-t)\}$ is the logit function, β_0 is baseline log-odds, β_1, β_2, and β_3 are log-odds ratio (OR) parameters quantifying maternal effect, children effect, and POE, respectively, and β_4 is log-OR parameter quantifying the covariate effect. Let $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)^\tau$ denote regression parameters. Note that model (1) can be more complicated by involving gene–gene interaction effects and gene–environment interaction effects, but we do not consider these interaction effects for the sake of simplicity of statement. Note that the maternal effect is assumed to be additive for the sake of statement simplicity, though this additive assumption can be easily relaxed. A small scale of simulation study showed that misspecifying the maternal model had little impact on POE inference results (Figure S2). Therefore, we still adopt the additive model for the maternal effect.

2.2 | Inference of the parental origins using multilocus genotypes

The parent-of-origin information, that is, phased alleles G_m^c and G_f^c, can be unambiguously inferred using G^c and G^m if and only if at least one of these two genotypes is homozygous. In another word, the parent-of-origin information is not available if the genotypes of both mother and child are heterozygous, which leads to a major challenge in the inference of parent-or-origin effects. Simply ignoring those families without parent-of-origin information can result in both efficiency loss and estimation bias (Yang & Lin, 2013).

A simple strategy to handling such incomplete-information families is to use observed data likelihood. As shown in Lin et al. (2013), under the Mendelian inheritance law,

$$\begin{aligned}\text{pr}(Y|G^m = G^c = 1) = p_a \text{pr}(Y|G^m = 1, G_m^c = 0, G_f^c \\ = 1) + (1 - p_a)\text{pr}(Y|G^m = 1, G_m^c = 1, G_f^c \\ = 0),\end{aligned}$$

where $p_a := \text{pr}(G_f^c = 1) = \text{pr}(a)$ is the minor allele frequency (MAF). Since only mother–child pairs are involved, the covariates are usually collected from mothers, so that G^c and X can be reasonably assumed to be

conditionally independent given G^m. Consequently, the above equation can be extended to incorporate covariates:

$$\begin{aligned}\mathrm{pr}(Y|G^m = G^c = 1, X) &= p_a \mathrm{pr}(Y|G^m = 1, G_m^c = 0, G_f^c = 1, X) \\ &\quad + (1 - p_a)\mathrm{pr}(Y|G^m = 1, G_m^c = 1, G_f^c \\ &= 0, X). \end{aligned} \tag{2}$$

Refer to Supporting Information Appendix A for a proof of (2). Lin et al. (2013) proposed another strategy, which borrows the information of SNPs tightly linked with the test locus to infer the parental origins. A computationally intensive expectation-maximization algorithm was developed in Lin et al. (2013) to fully exploit the information from multilocus genotypes, without incorporating covariates.

In this paper, we propose to replace p_a in (2) by the conditional probability of $G_f^c = 1$ given multilocus genotypes. Hereafter, those SNPs tightly linked with the test locus are referred to as "adjacent loci". If the adjacent loci are in strong linkage disequilibrium (LD), then the probability of recombination among these loci in a single meiosis would be very small, and the child would inherit an entire haplotype from the mother with a very large probability. Consequently, we assume that the child inherits an entire haplotype from the mother to simplify statistical inference. Let the number of adjacent loci be $K - 1$ so that the total number of SNPs is K. Let the joint genotypes of mother and child at the K SNPs be denoted by $\mathcal{G}^m = (G^m, G_2^m, ..., G_K^m)$ and $\mathcal{G}^c = (G^c, G_2^c, ..., G_K^c)$, respectively, where G_j^m and G_j^c are the genotypes of mother and child at the jth adjacent locus $(j = 2, ..., K)$. Let $\{h_1, h_2, ..., h_T\}$ denote all T possible haplotypes associated with the K SNPs, with the corresponding haplotype frequencies being $\boldsymbol{\mu} = (\mu_1, \mu_2, ..., \mu_T)$ and $\sum_{i=1}^T \mu_i = 1$. Let the unordered diplotype of mother be denoted by $h_1^m h_2^m$. Let the ordered child diplotype be denoted by (h_m^c, h_f^c), where h_m^c and h_f^c are inherited from mother and father, respectively. Here $h_1^m, h_2^m, h_m^c, h_f^c \in \{h_1, h_2, ..., h_T\}$. Since h_m^c is inherited from mother, it should be either h_1^m or h_2^m. Let $H(\mathcal{G}^m, \mathcal{G}^c)$ denote the set of all pairs of unordered maternal diplotype and ordered child diplotype, $(h_1^m h_2^m, (h_m^c, h_f^c))$, that are compatible with the mother–child genotype pair $(\mathcal{G}^m, \mathcal{G}^c)$. Note that the parental origins of children alleles (G_m^c, G_f^c) at the test locus can be directly inferred from ordered children diplotype (h_m^c, h_f^c). Similarly, let $H^f(\mathcal{G}^m, \mathcal{G}^c)$ denote the set of all pairs of unordered maternal diplotype and ordered child diplotype, $(h_1^m h_2^m, (h_m^c, h_f^c))$, that are compatible with the mother–child genotype pair $(\mathcal{G}^m, \mathcal{G}^c)$ while the child inherits a minor allele a from father. Given observed genotypes, the conditional probability of the child inheriting a minor allele from father can be written as

$$\begin{aligned} p_f &:= \mathrm{pr}\left(G_f^c = 1|\mathcal{G}^m, \mathcal{G}^c\right) \\ &= \frac{\sum_{\left(h_1^m h_2^m, \left(h_m^c, h_f^c\right)\right) \in H^f(\mathcal{G}^m, \mathcal{G}^c)} \mathrm{pr}\left(h_1^m h_2^m, \left(h_m^c, h_f^c\right)\right)}{\sum_{\left(h_1^m h_2^m, \left(h_m^c, h_f^c\right)\right) \in H(\mathcal{G}^m, \mathcal{G}^c)} \mathrm{pr}\left(h_1^m h_2^m, \left(h_m^c, h_f^c\right)\right)}. \end{aligned} \tag{3}$$

Under Hardy–Weinberg equilibrium (HWE), random mating, and Mendelian inheritance law, $\mathrm{pr}(h_1^m h_2^m, (h_m^c, h_f^c))$ can be expressed as a function of $\boldsymbol{\mu}$ (Lin et al., 2013). Specifically, for $h_1^m = i$, $h_2^m = j$, $h_m^c = k$, and $h_f^c = l$, the probability $\mathrm{pr}(h_1^m h_2^m, (h_m^c, h_f^c))$ is equal to $\mu_i \mu_j \mu_l$ if $k = i$ or $k = j$ and 0 otherwise. In the situation where the genotypes of both mother and child are heterozygous, p_a in Equation (2) can be replaced by p_f to result in the following approximation:

$$\begin{aligned}\mathrm{pr}(Y|G^m = G^c = 1, X) \approx p_f \mathrm{pr}(Y|G^m = G^c = 1, G_m^c = 0, G_f^c = 1, X) \\ + (1 - p_f)\mathrm{pr}(Y|G^m = G^c = 1, G_m^c = 1, G_f^c = 0, X).\end{aligned} \tag{4}$$

It follows from (1) and (3) that the right side of (4) is a function of haplotype frequencies $\boldsymbol{\mu}$ and regression parameters $\boldsymbol{\beta}$ for given observed data. In practice, the haplotype frequencies $\boldsymbol{\mu}$ can be estimated using existing programs such as the R package `haplo.stats` (Sinnwell & Schaid, 2020). With estimated $\boldsymbol{\mu}$, the approximated penetrance function given in the right side of (4) is a function of $\boldsymbol{\beta}$. Compared with Equation (2), the approximation (4) properly exploits the haplotype information inferred from multilocus genotypes, and it should be intuitively more helpful in detecting POEs.

2.3 | Statistical inference based on a modified profile likelihood

Let $(Y_u, G_u^m, G_u^c, G_{mu}^c, G_{fu}^c, X_u)$ denote the analogue of $(Y, G^m, G^c, G_m^c, G_f^c, X)$ for the uth family, $u = 1, ..., n$. Assume that data (Y_u, G_u^m, G_u^c, X_u), $u = 1, ..., n$, are collected from a case–control study with n_1 cases $(Y_u = 1)$ and n_0 controls $(Y_u = 0)$, so that $n = n_1 + n_0$. Note that (G_{mu}^c, G_{fu}^c) cannot be directly inferred from the genotype pair (G_u^m, G_u^c) if $G_u^m = G_u^c = 1$. Throughout this paper, we assume random mating, Mendelian inheritance law, and conditional independence between G^c and X given G^m. Furthermore, we assume that the disease prevalence $\mathrm{pr}(Y = 1)$ is known *a prior* to be f:

$$\mathrm{pr}(Y=1)=f. \tag{5}$$

Our statistical inference procedure is based on the retrospective likelihood function $\prod_{u=1}^{n}\mathrm{pr}(G_u^m, G_u^c, X_u|Y_u)$ under the constraint (5), which is proportional to $\prod_{u=1}^{n}\mathrm{pr}(Y_u, G_u^m, G_u^c, X_u)$. We allow the distribution of X to be nonparametric. Specifically, the empirical likelihood approach (Owen, 2004) is adopted by introducing probability masses $\pi_u := \mathrm{pr}(X_u)$, $u = 1, ..., n$, which satisfy the constraint

$$\sum_{u=1}^{n}\pi_y = 1. \tag{6}$$

Denote $\boldsymbol{\pi} = (\pi_1, ..., \pi_n)$. In view of the conditional independence between G_u^c and X_u given G_u^m,

$$\begin{aligned}\mathrm{pr}\left(Y_u, G_u^m, G_u^c, X_u\right) &= \mathrm{pr}\left(Y_u|G_u^m, G_u^c, X_u\right)\mathrm{pr}\left(G_u^c|G_u^m, X_u\right)\\ &\quad \mathrm{pr}\left(G_u^m|X_u\right)\mathrm{pr}(X_u)\\ &= \mathrm{pr}\left(Y_u|G_u^m, G_u^c, X_u\right)\mathrm{pr}\left(G_u^c|G_u^m\right)\\ &\quad \mathrm{pr}\left(G_u^m|X_u\right)\pi_u.\end{aligned}$$

As discussed in Section 2.2,

$$\begin{aligned}\mathrm{pr}\left(Y_u|G_u^m, G_u^c, X_u\right) &= \mathrm{pr}\left(Y_u|G_u^m, G_u^c, G_{mu}^c, G_{fu}^c, X_u\right) \ \text{if}\ G_u^m\\ &\neq 1 \ \text{or}\ G_u^c \neq 1,\end{aligned}$$

and

$$\begin{aligned}\mathrm{pr}\left(Y_u|G_u^m, G_u^c, X_u\right) \approx p_{fu}\mathrm{pr}\left(Y_u|G_u^m = G_u^c = 1, G_{mu}^c = 0, G_{fu}^c = 1, X_u\right)\\ + (1-p_{fu})\mathrm{pr}\left(Y_u|G_u^m = G_u^c = 1, G_{mu}^c = 1, G_{fu}^c\right.\\ \left. = 0, X_u\right) \ \text{if}\ G_u^m = G_u^c = 1,\end{aligned}$$

where p_{fu} is an analogue of p_f (see the definition in Equation 3) for the uth mother–child pair. The probability $\mathrm{pr}(G_u^c|G_u^m)$ can be written as a function of MAF θ under the Mendelian inheritance law and random mating, as shown in Table S1. The relationship between G_u^m and X_u can be quantified by the double additive regression model (H. Zhang et al., 2020):

$$\mathrm{pr}(G^m = k|X) = \frac{\xi_k(\theta, F)\exp\{k\eta^\tau X\}}{\sum_l \xi_l(\theta, F)\exp\{l\eta^\tau X\}}, \tag{7}$$

where $\xi_k(\theta, F) = \mathrm{pr}(G^m = k)$ and η is a vector of regression parameters. Here $k = 0, 1, 2$, $\mathrm{pr}(G^m = 2) = (1-F)\theta^2 + F\theta$, $\mathrm{pr}(G^m = 1) = 2(1-F)\theta(1-\theta)$, $\mathrm{pr}(G^m = 0) = (1-F)(1-\theta)^2 + F(1-\theta)$. Note that F is a measure characterizing departure from HWE, and $F = 0$ if and only if HWE holds.

Denote $\Theta = (\beta^\tau, \eta, \theta, F)^\tau$. The observed data likelihood can be expressed as

$$\begin{aligned}L(\Theta, \boldsymbol{\pi}) &= \prod_{u=1}^{n}\mathrm{pr}\left(Y_u, G_u^m, G_u^c, X_u\right)\\ &= \prod_{u=1}^{n}\mathrm{pr}\left(Y_u|G_u^m, G_u^c, X_u\right)\mathrm{pr}\left(G_u^c|G_u^m\right)\\ &\quad \mathrm{pr}\left(G_u^m|X_u\right)\pi_u,\end{aligned} \tag{8}$$

where Θ and $\boldsymbol{\pi}$ satisfy the constraints (5) and (6). Similar to H. Zhang et al. (2020), the profile likelihood function

$$\ell_p(\Theta) := \max_{\boldsymbol{\pi}}\ell(\Theta, \boldsymbol{\pi})$$

can be obtained using the Lagrange multiplier method, which is equal to (refer to Supporting Information Appendix B for a proof)

$$\begin{aligned}\ell(\Theta, \lambda) &= \sum_{u=1}^{n}\log\mathrm{pr}\left(Y_u|G_u^m, G_u^c, X_u\right)\\ &\quad + \sum_{u=1}^{n}\log\mathrm{pr}\left(G_u^c|G_u^m\right) + \sum_{u=1}^{n}\log\mathrm{pr}\left(G_u^m|X_u\right)\\ &\quad - \sum_{u=1}^{n}\log[n\{1 + \lambda(H_u(\Theta) - f)\}],\end{aligned} \tag{9}$$

where λ_Θ is the solution to the following equation with respect to λ:

$$\sum_{u=1}^{n}\frac{H_u(\Theta) - f}{1 + \lambda(H_u(\Theta) - f)} = 0. \tag{10}$$

Here, $H_u(\Theta)$ is defined as

$$\begin{aligned}H_u(\Theta) = \sum_j\sum_k\sum_l\Big[&\mathrm{pr}\left(Y = 1|G^m = j, G_m^c = k, G_f^c = l, X_u\right)\\ &\times \mathrm{pr}\left(G_m^c = k|G^m = j\right)\mathrm{pr}\left(G_f^c = l\right)\mathrm{pr}(G^m = k|X_u)\Big],\end{aligned} \tag{11}$$

and $\mathrm{pr}(Y = 1|G^m = j, G_m^c = k, G_f^c = l, X_u) = \mathrm{pr}(Y = 1|G^m = j, G^c = k + l, G_m^c = k, G_f^c = l, X_u)$.

The maximum profile likelihood estimator of Θ can be obtained by jointly solving the score equations

$$\frac{\partial \ell(\Theta,\lambda)}{\partial \lambda}=0 \quad \text{and} \quad \frac{\partial \ell(\Theta,\lambda)}{\partial \Theta}=0, \tag{12}$$

Note that $\ell(\Theta,\lambda)$ is not a true log likelihood function since λ is a Lagrange multiplier instead of a parameter in our model. As shown in H. Zhang et al. (2018), the solution is a saddle point of $\ell(\Theta,\lambda)$. Therefore, it is computationally unstable to solve the score equations (12). The profile likelihood function (9) can be slightly modified to resolve this numerical problem. Specifically, λ_Θ is replaced by its limiting value λ_0 as in H. Zhang et al. (2018, 2020). The validity of this modification is based on the following lemma (refer to Supporting Information Appendix C for a proof):

Lemma 1. *Let Θ_0 denote the true value of Θ and the "true" value λ_0 is defined as the solution to the equations*

$$E\left[\frac{\partial \ell(\Theta,\lambda)}{\partial \Theta}\right]\Big|_{\Theta=\Theta_0,\lambda=\lambda_0}=0, \quad E\left[\frac{\partial \ell(\Theta,\lambda)}{\partial \lambda}\right]\Big|_{\Theta=\Theta_0,\lambda=\lambda_0}=0. \tag{13}$$

If the parent-of-origin information is available for all mother–child pairs, then the "true" value λ_0 has a closed form given by

$$\lambda_0=\frac{n_1}{nf}-\frac{n_0}{n(1-f)}.$$

Based on Lemma 1, the modified profile likelihood

$$\ell_{\mathrm{mp}}(\Theta) \coloneqq \ell(\Theta,\lambda_0)$$

can be maximized to yield an estimator $\hat{\Theta}$, which can be obtained by solving the equation

$$\frac{\partial \ell_{\mathrm{mp}}(\Theta)}{\partial \Theta}=0. \tag{14}$$

Define

$$A(\Theta_0)=\frac{1}{n}E\left[\frac{\partial^2 \ell_{\mathrm{mp}}(\Theta)}{\partial\Theta\partial\Theta^\tau}\right]\Big|_{\Theta=\Theta_0} \quad \text{and} \quad \Sigma(\Theta_0) = \frac{1}{n}\mathrm{cov}\left(\frac{\partial \ell_{\mathrm{mp}}(\Theta)}{\partial \Theta}\right)\Big|_{\Theta=\Theta_0}. \tag{15}$$

Some asymptotic properties of $\hat{\Theta}$ are provided in the following theorem (refer to Supporting Information Appendix D for a proof).

Theorem 1. *Under some regularity conditions, the following large sample properties hold:*

(i) *With probability tending to* 1, *there exists a solution to the score Equations (12), denoted as $(\tilde{\Theta},\tilde{\lambda})$, which is consistent for (Θ_0,λ_0).*
(ii) *With probability tending to* 1, *there exists a solution $\hat{\Theta}$ to Equation (14), which is consistent for Θ_0.*
(iii) *Both $\tilde{\Theta}$ and $\hat{\Theta}$ are asymptotically normally distributed, with the same asymptotic expectation Θ_0 and the same variance-ovariance matrix:*

$$\sqrt{n}(\hat{\Theta}-\Theta) \xrightarrow{D} N\{0, A^{-1}(\Theta_0)\Sigma(\Theta_0)A^{-1}(\Theta_0)\}.$$
$$\xleftarrow{D} \sqrt{n}(\tilde{\Theta}-\Theta)$$

Consequently, the modified MLE $\hat{\Theta}$ is as efficient as the original MLE $\tilde{\Theta}$ that maximizes the profile likelihood function (9).

Significance tests and confidence intervals of the unknown parameters Θ (including the POE parameter β_3) can be constructed based on Theorem 1. Specifically, $A(\Theta_0)$ can be consistently estimated by

$$\hat{A}(\hat{\Theta}) \coloneqq \frac{1}{n}\frac{\partial^2 \ell_{\mathrm{mp}}(\Theta)}{\partial\Theta\partial\Theta^\tau}\Big|_{\Theta=\hat{\Theta}},$$

and $\Sigma(\Theta_0)$ can be consistently estimated by the summation of two corresponding sample variance-covariance matrices multiplied by the respective numbers of cases and controls divided by the total sample size n, which is denoted by $\hat{\Sigma}(\hat{\Theta})$. Consequently, the limiting variance-covariance matrix of $\sqrt{n}\hat{\Theta}$ can be consistently estimated by $\hat{A}^{-1}(\hat{\Theta})\hat{\Sigma}(\hat{\Theta})\hat{A}^{-1}(\hat{\Theta})$. Significance tests and confidence intervals of Θ can be constructed according to the asymptotic normality of $\hat{\Theta}$ and its estimated variance-covariance matrix.

2.4 | Implementation of the proposed method

The new method developed in this paper has been implemented in an updated version of R package `CCMO`, which is available from GitHub (http://github.com/zhanghfd/CCMO). The main function `MultiLociPOE` provides estimates of unknown parameters (MAF θ and log-odds ratios $\boldsymbol{\beta}$ and η) and corresponding significance test results. The inputs of `MultiLociPOE` include the disease statuses and diplotypes for mother–child pairs, covariates, an indicator for the test

locus, a disease prevalence, a matrix consisting of possible haplotypes in the cohort, and a vector consisting of the corresponding haplotype frequencies. An additional function `MultiLociPOE.input`, a wrap-up of the function `haplo.em` in the R package `haplo.stats`, is provided to obtain all possible haplotypes and their frequencies as inputs of `MultiLociPOE`.

3 | SIMULATION STUDIES

3.1 | Considered methods and data generation

Extensive simulation studies were conducted to evaluate the performance of the modified profile likelihood method developed in this paper, which is referred to as "M-HAP" hereafter. An ideal version of "M-HAP" was also considered, which uses the true parent-of-origin information and is referred to as "TRUE." Note that TRUE cannot be used in real data analyses. The method developed by Lin et al. (2013), referred to as "P-HAP", was also included, which also explores multilocus genotype data but cannot incorporate covariates. In M-HAP and P-HAP, those haplotypes with estimated frequencies smaller than the threshold 0.0004 were discarded, as did in Lin et al. (2013). Our simulation results demonstrated that it had little impact on POE inference results by estimating haplotype frequencies and discarding rare haplotypes, refer to Figure S5 and Table S7 for details. Two additional methods were considered in our simulation studies. One was designed for evaluating maternal, parent-of-origin, and interaction effects based on multinomial modeling (Howey & Cordell, 2012). This method was implemented in the standalone software "EMIM" (version 3.22). Note that EMIM cannot incorporate covariates and it currently cannot use multilocus genotypes to infer the parent-of-origin information for control mother–child pairs. Consequently, we used the basic version of EMIM that only uses single-SNP genotypes. The other one is the standard prospective logistic regression method, referred to as "LOG." LOG uses the parent-of-origin information inferred from multilocus genotypes and discards those mother–child pairs without parent-of-origin information.

Haplotypes were generated based on published haplotype frequencies on five SNPs in the genomic region *GPX1* (Chen et al., 2004), refer to supplementary tab. S-1 in Lin et al. (2013) for haplotype structure and pairwise r^2 among the five SNPs and supplementary tab. S.2 for pairwise D' among the five SNPs. This genomic region contains seven possible haplotypes, and the five SNPs were shown to be in relatively strong LD. Maternal and paternal diplotypes were independently generated by assuming HWE, and children haplotypes were generated under the assumption of no recombination among these SNPs. Specifically, in each replication of simulations, maternal and paternal diplotypes were generated for 30, 000 nuclear families under HWE and random mating, and children diplotypes and parent-of-origin information were generated following the Mendelian inheritance law. Multilocus genotypes of mothers and children (i.e., G^m and G^c) were extracted from their diplotypes, which were used as inputs of all considered methods. Furthermore, the true parent-of-origin information was used in TRUE. The five SNPs in the genomic region *GPX1* were designated in turn as causal SNPs, and the genotypes g^m and g^c at the causal SNP were then extracted. A covariate X was generated according to the linear model

$$X = \zeta(g^m - E(g^m)) + e, \tag{16}$$

or model

$$X = \zeta((g^m)^2 - E(g^m)^2) + e, \tag{17}$$

where the error term e is a standard normal random variable independent of g^m and ζ is a parameter characterizing the association strength between g^m and X. Here X was normalized to have mean zero so as to reduce potential estimation bias due to multicollinearity. The disease statuses of children were generated according the penetrance model (1), the disease prevalence was fixed at 0.05, and the slope β_0 was accordingly determined once $\beta_1, ..., \beta_4$, and ζ were given.

3.2 | POE test performance

First, the value of ζ in model (16) was fixed at zero, so that X was not a confounder in disease-gene association analysis. In such situation, both EMIM and P-HAP should be valid in detecting POEs. The log-OR parameters β_1, β_2, β_4 were fixed at log(1.2), and The POE parameter β_3 was set to be 0 or log(1.5). For each parameter combination, $n_1 = 200$ case mother–child pairs (children were diseased) and $n_0 = 200$ control mother–child pairs (children were non-diseased) were sampled from the 30, 000 mother–child pairs. Based on 1000 replications of simulations, the type-I error rates ($\beta_3 = 0$) and powers ($\beta_3 = \log(1.5)$) were estimated for all considered methods at nominal level 5%, as shown in Figure 1.

Evidently, all of the five methods had type-I error rates well controlled around the nominal level 5% in all considered simulations. M-HAP was much more

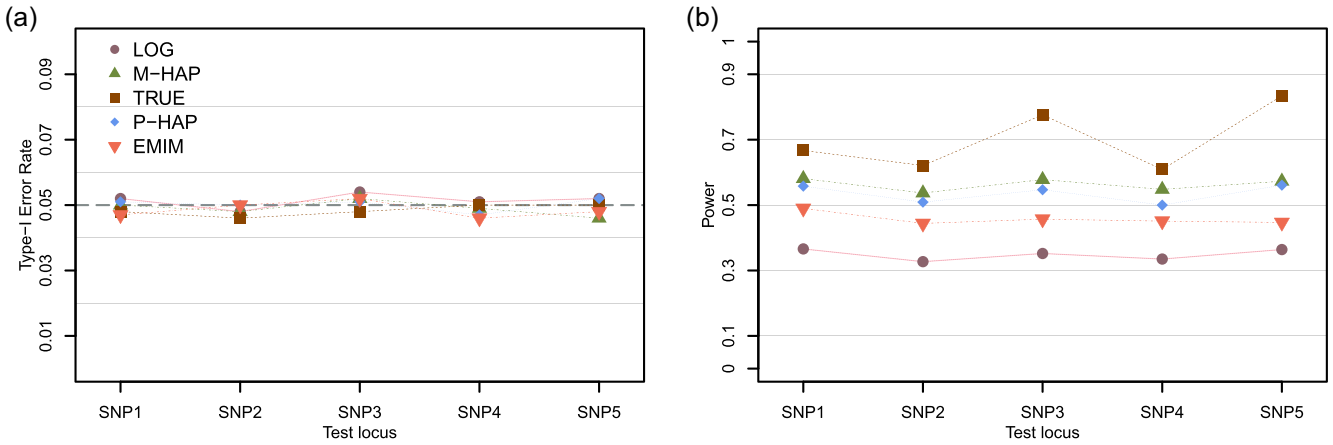

FIGURE 1 Type-I error rates (a, $\beta_3 = 0$) and powers (b, $\beta_3 = \log(1.5)$) for testing parent-of-origin effects (POEs) on five single-nucleotide polymorphisms (SNPs) in gene *GPX1*. The five SNPs were treated as causal loci in turn. EMIM, a method developed in Howey and Cordell (2012); LOG, the standard prospective logistic regression method; M-HAP, our proposed method; P-HAP, a method developed in Lin et al. (2013); TRUE, the ideal version of M-HAP exploiting the true parent-of-origin information

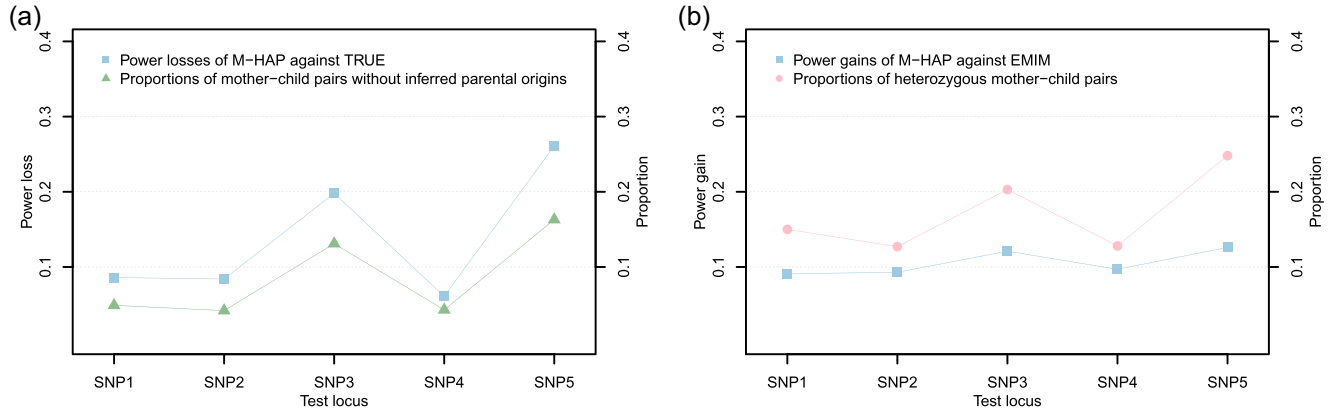

FIGURE 2 Power losses of M-HAP against TRUE (a) and power gains of M-HAP against EMIM (b) for testing parent-of-origin effects (POEs) at five single-nucleotide polymorphisms (SNPs) in gene *GPX1*. EMIM, a method developed in Howey and Cordell (2012); M-HAP, our proposed method; TRUE, the ideal version of M-HAP exploiting the true parent-of-origin information

powerful than LOG, with power gains ranging from 20.9% to 22.6%, demonstrating the advantage of exploiting information including HWE, Mendelian law, and conditional independence between g^c and X given g^m. As expected, TRUE was uniformly more powerful than the other four methods. Compared with TRUE, the power losses of M-HAP varied from SNP to SNP, depending on the proportion of mother–child pairs whose parent-of-origin could not be inferred ("missing proportion" hereafter) (Figure 2a). For example, the missing proportions at SNP2 and SNP3 were 4.2% and 13.1%, corresponding to power losses of 8.4% and 19.8%, respectively. M-HAP uniformly outperformed EMIM at all five test loci, demonstrating the advantage of exploiting multilocus genotype information. The relative performance of M-HAP against EMIM largely depended on the proportion of heterozygous mother–child pairs at each test locus (Figure 2b). For example, the heterozygous mother–child pairs proportion was relatively smaller for SNP4 (12.8%) compared with SNP5 (24.8%), and the power gain of M-HAP against EMIM was smaller for SNP4 (9.7%) compared with SNP5 (12.6%). Note that M-HAP slightly outperformed P-HAP at all five SNPs, with power gains ranging from 1.2% to 4.8%.

Then, power trend of the considered methods against the sample size was evaluated with the causal SNP being fixed at SNP3 (MAF = 0.283). Again, the log-OR parameters β_1, β_2, β_4 were fixed at $\log(1.2)$, and ζ was fixed at 0. The sample size varied from 200 to 1000 and $\beta_3 = 0$ or $\log(1.2)$. Results are summarized in Figure 3. Under the null hypothesis ($\beta_3 = 0$), all methods had type-I error rates well controlled around the nominal level 5% (ranging from 4.4% to 5.6%). Under the alternative hypothesis ($\beta_3 = \log(1.2)$), the power of each considered method

was increasing with the sample size. The power of LOG was the lowest among the considered methods as LOG could not deal with those mother–child pairs without parent-of-origin information. Evidently, M-HAP and P-HAP exploiting multilocus genotypes uniformly outperformed the single SNP-based method EMIM, demonstrating that exploiting multilocus genotypes significantly enhanced the ability to determining the parent-of-origin information and consequently improving the power for testing POEs. M-HAP was also shown to be slightly more powerful than P-HAP and less powerful than TRUE.

Next, various numbers of adjacent loci were used to demonstrate the effect of haplotype length. With an increased number of SNPs, the parent-of-origin information could be identified more unambiguously, which should result in a more powerful M-HAP in testing POEs. Data were again generated with the causal locus being SNP3 in the genomic region *GPX1*. Again, the log-OR parameters β_1, β_2, β_4 were fixed log(1.2), ζ was fixed at 0, and the sample size was fixed at 200. The POE parameter was $\beta_3 = 0$, log(1.2), log(1.5), or log(2.0). Results are summarized in Figure 4. Shown in the *x*-axis is the number of adjacent loci plus one (i.e., the total number of involved SNPs). Evidently, the POE test power steadily increased with K, and the power gain became minor when K was larger than 3 (Figure 4).

After that, we considered jointly testing maternal effects and POEs. The log-OR parameters β_2, β_4 were fixed log(1.2), ζ was fixed at 0, and the sample size was fixed at 200.

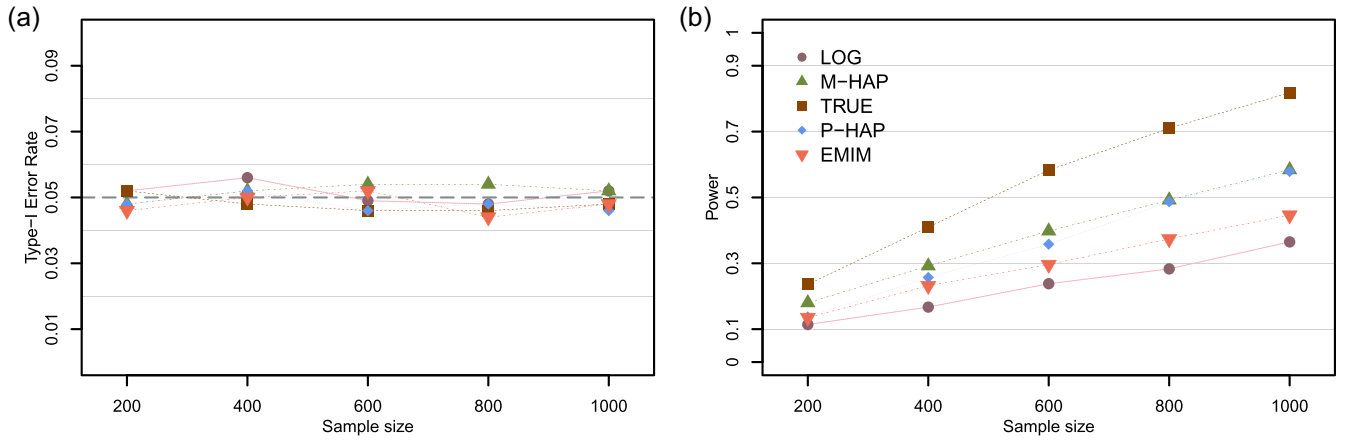

FIGURE 3 Type-I error rates (a: $\beta_3 = 0$) and powers (b: $\beta_3 = \log(1.2)$ for testing parent-of-origin effects (POEs) with different sample sizes. Sample size, common sample size shared by cases and controls. EMIM, a method developed by Howey and Cordell (2012); LOG, the standard prospective logistic regression method; M-HAP, our proposed method; P-HAP, a method developed by Lin et al. (2013); TRUE, an ideal version of M-HAP using true parent-of-origin information

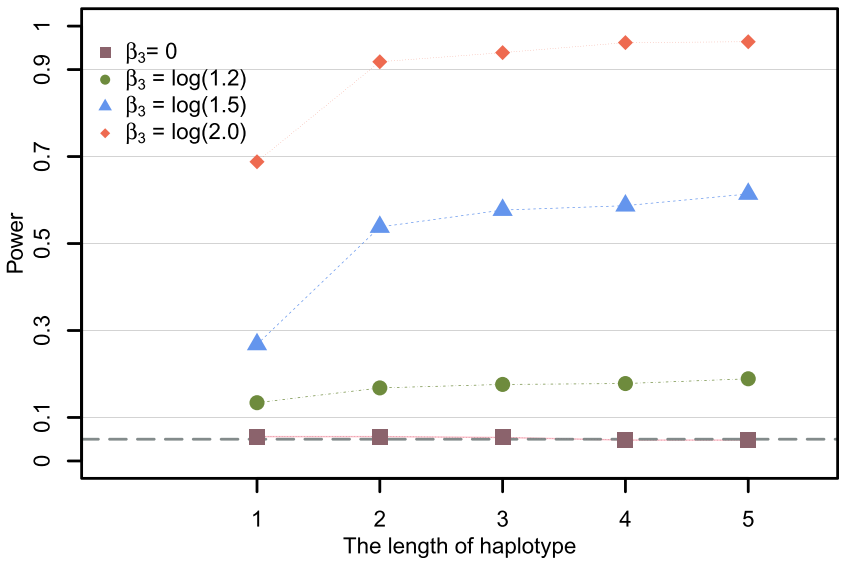

FIGURE 4 Parent-of-origin effect (POE) test power of M-HAP against the length of haplotype (the total number of involved single-nucleotide polymorphisms [SNPs]) for various POE parameter values ($\beta_3 = 0$, log(1.2), log(1.5), log(2.0)). In the *x*-axis, "1" means that only the test locus SNP3 was used; "2" means that one adjacent locus (i.e., SNP4) was used; "3" means that two adjacent loci were used (i.e., SNP2 and SNP4); "4" means that three adjacent loci were used (i.e., SNP1, SNP2, and SNP4); "5" means that four adjacent loci were used (i.e, SNP1, SNP2, SNP4, and SNP5)

The maternal effect parameter β_1 and POE parameter $\beta 3$ were set to be 0 or log(1.2). Results are summarized in Figure 5. As shown in Figure 5a, all five methods had type-I error rates well controlled around the nominal level 5% at all five loci. As shown in Figure 5b, M-HAP was much more powerful than LOG with power gains ranging from 18.1% to 26.8%, and it was only slightly less powerful than TRUE and slightly more powerful than P-HAP and EMIM.

Finally, non-zero ζ values were used to evaluate the performance of the considered methods in the presence of a confounding covariate. SNP1 was selected as the causal locus and the log-OR parameters were fixed at $\beta_1 = \beta_4 = \log(1.8)$, $\beta_2 = \log(1.5)$, and $\beta_3 = 0$ when testing the POEs, while the log-OR parameters were fixed at $\beta_1 = \beta_3 = 0$ and $\beta_2 = \beta_4 = \log(1.2)$ when jointly testing maternal effects and POEs. Again, the sample size was fixed at 200. The POE test results are displayed in panel A of Figure 6. With ζ in model (17) varying from -1 to 1, M-HAP, LOG, and TRUE had type-I error rates well controlled around the nominal level 5%, and EMIM had decreasing type-I error rates (from 8.1% to 2.6%), while P-HAP also had decreasing type-I error rates (from 6.5% to 3.2%) (Figure 6a). The results of jointly testing maternal effects and POEs are displayed in Figure 6b. With ζ in model (17) varying from $-\log(1.5)$ to $\log(1.5)$, M-HAP, LOG, and TRUE had type-I error rates well

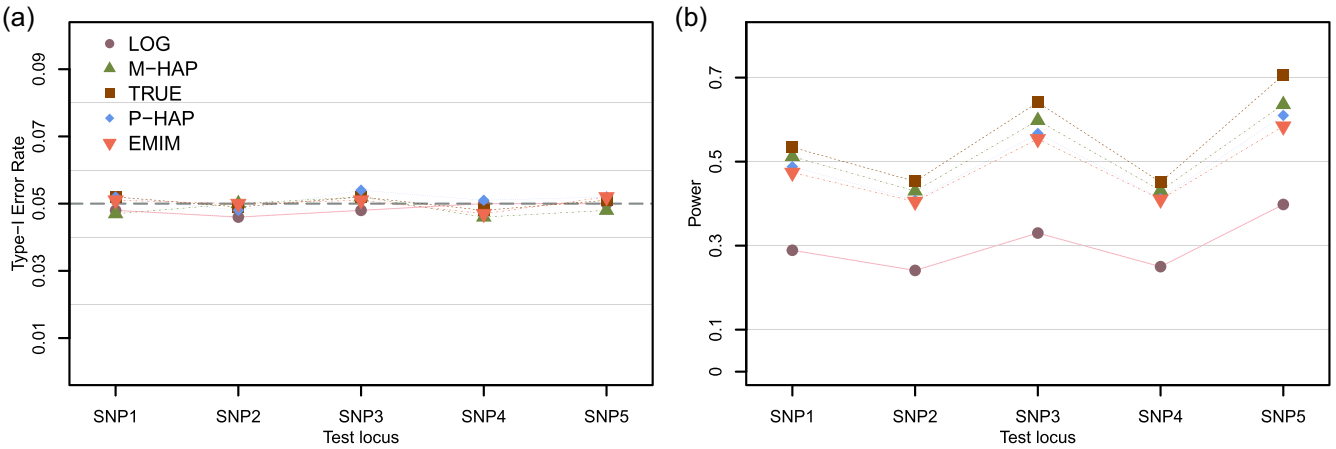

FIGURE 5 Type-I error rates (a, $\beta_1 = \beta_3 = 0$) and powers (b, $\beta_1 = \beta_3 = \log(1.2)$) for jointly testing maternal effects and parent-of-origin effects (POEs) on five single-nucleotide polymorphisms [SNPs] in gene *GPX1*. The five SNPs were treated as causal loci in turn. EMIM, a method developed in Howey and Cordell (2012); LOG, the standard prospective logistic regression method; M-HAP, our proposed method; P-HAP, a method developed by Lin et al. (2013); TRUE, the ideal version of M-HAP exploiting the true parent-of-origin information

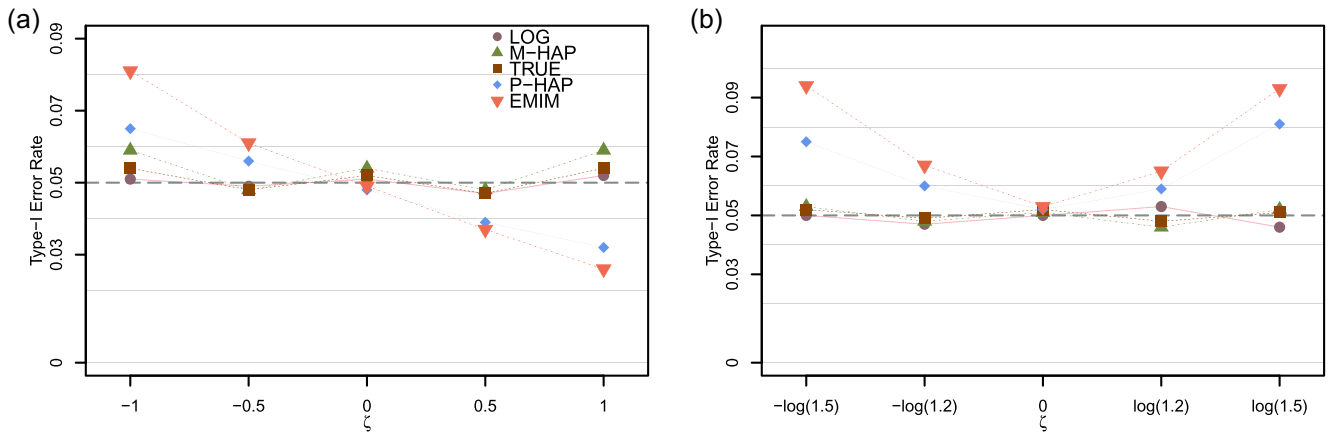

FIGURE 6 Type-I error rates for testing parent-of-origin effects (POEs) (a, $\beta_3 = 0$) or jointly testing maternal effects and POEs (b, $\beta_1 = \beta_3 = 0$) with a confounding covariate. In (a), the log-OR parameters β_1, β_2, and β_4 were fixed at log(1.8), log(1.5), and log(1.8), respectively while the confounding effect ζ ranged from -1 to 1. In (b), the log-OR parameters β_2, and β_4 were fixed at log(1.2) while the confounding effect ζ ranged from $-\log(1.5)$ to $\log(1.5)$. The test locus was fixed to be SNP1 and $X = \zeta((g^m)^2 - E(g^m)^2) + e$. EMIM, a method developed by Howey and Cordell (2012); LOG, the standard prospective logistic regression method; M-HAP, our proposed method; P-HAP, a method developed by Lin et al. (2013); TRUE, the ideal version of M-HAP exploiting the true parent-of-origin information

TABLE 1 Simulation results of M-HAP for various covariate configurations

		M-HAP					LOG				P-HAP			
Scenario[a]	log-OR[b]	True	Bias	SE	SEE	CP	Bias	SE	SEE	CP	Bias	SE	SEE	CP
Ind	β_1	0.182	−0.036	0.228	0.231	0.955	0.025	0.261	0.271	0.958	0.053	0.213	0.217	0.956
	β_2	0.182	−0.015	0.170	0.170	0.952	0.014	0.230	0.232	0.957	−0.016	0.172	0.170	0.944
	β_3	0.405	0.028	0.193	0.198	0.948	0.018	0.252	0.255	0.949	−0.039	0.182	0.183	0.953
	β_4	0.182	0.004	0.104	0.106	0.955	0.005	0.112	0.111	0.955				
Dep1	β_1	0.182	−0.068	0.231	0.235	0.945	0.046	0.267	0.272	0.950	0.148	0.221	0.218	0.882
	β_2	0.182	0.008	0.164	0.168	0.956	0.017	0.229	0.232	0.952	0.012	0.175	0.171	0.940
	β_3	0.405	0.012	0.193	0.197	0.952	0.011	0.254	0.256	0.946	−0.036	0.186	0.182	0.944
	β_4	0.182	0.011	0.103	0.104	0.951	0.003	0.110	0.107	0.942				
Dep2	β_1	0.182	−0.006	0.226	0.228	0.955	0.002	0.280	0.271	0.944	0.052	0.231	0.217	0.929
	β_2	0.182	0.042	0.172	0.169	0.944	0.013	0.244	0.232	0.936	0.048	0.180	0.168	0.939
	β_3	0.405	−0.026	0.186	0.189	0.950	0.013	0.259	0.255	0.945	−0.075	0.178	0.182	0.935
	β_4	0.182	−0.011	0.101	0.101	0.942	0.002	0.106	0.106	0.950				
Dep3	β_1	0.182	−0.030	0.223	0.226	0.956	0.011	0.281	0.273	0.949	0.132	0.225	0.215	0.900
	β_2	0.182	0.052	0.175	0.171	0.940	0.023	0.242	0.232	0.953	0.053	0.182	0.167	0.939
	β_3	0.405	−0.040	0.188	0.193	0.951	0.027	0.264	0.254	0.949	−0.075	0.176	0.181	0.937
	β_4	0.182	−0.009	0.098	0.100	0.954	−0.001	0.104	0.106	0.954				

Abbreviations: Bias, estimation bias for log-OR; CP, empirical coverage probability of 95% confidence intervals; LOG, the standard prospective logistic regression method; M-HAP, our proposed method; P-HAP, a method developed in Lin et al. (2013); SE, empirical standard error; SEE, mean estimated standard error; True, the true value of log-OR.

[a]Ind, covariate being independent of maternal genotype ($X = e$); Dep1, covariate being dependent of maternal genotype ($X = \log(1.5)(g^m - E(g^m)) + e$); Dep2, covariate being dependent of paternal genotype ($X = \log(1.5)(g^f - E(g^f)) + e$); Dep3, covariate being dependent of maternal genotype and paternal genotype ($X = \log(1.5)(g^m - E(g^m)) + \log(1.5)(g^f - E(g^f)) + e$). Here, the error term e followed the standard normal distribution and was independent of g^m.

[b]β_1, log-OR for maternal genetic effect; β_2, log-OR for children genetic effect; β_3, log-OR for POE; β_4, log-OR for the covariate effect.

controlled around the nominal level 5% while P-HAP and EMIM could not maintain the type-I error rates when the absolute value of ζ deviated from zero. In summary, the type-I error rates of EMIM and P-HAP were distorted in the presence of a confounding covariate while our method M-HAP was robust to the presence of a confounding covariate.

3.3 | Estimation performance

Simulation studies were conducted to examine the estimation performance of M-HAP, LOG, and P-HAP in terms of estimation bias and variance. Data were generated in a similar way as in the above subsection. Again, SNP1 was selected as the causal locus and $\beta_1, \beta_2, \beta_3$, and β_4 were fixed at log(1.2), log(1.2), log(1.5), and log(1.2), respectively. The sample size was fixed at 200. Two simulation scenarios were considered to mimic independence and moderate correlation between maternal genotype and covariate, respectively, that is, $\zeta = 0$ and $\zeta = \log(1.5)$ in model (16). Simulation results are summarized in Table 1 based on 1000 replications of simulations.

M-HAP and LOG appeared to be unbiased in both scenarios. On the other hand, P-HAP was unbiased in the independence scenario but was evidently biased in the dependence scenario. This indicated that M-HAP was more robust to the misspecification of distribution $\mathrm{pr}(G^m, X)$ compared with P-HAP. All of the three methods had mean estimated standard errors (SEEs) close to the empirical standard errors (SEs). The empirical coverage probabilities of the 95% confidence interval (CPs) for the three methods were close to the nominal level 95% except that P-HAP was liberal in dependence scenario 1. The SEs of M-HAP were around 14%, 29%, 25%, and 6% lower than LOG for $\beta_1, \beta_2, \beta_3$, and β_4, respectively. On the other hand, the SEs of M-HAP

TABLE 2 Simulation results of M-HAP for a sensitivity analysis with HWE violated

E	Bias	SE	SEE	T1E	*E*	Bias	SE	SEE	T1E
−0.03	−0.019	0.201	0.207	0.051	0.40	−0.037	0.227	0.231	0.054
0.00	−0.016	0.200	0.203	0.048	0.60	−0.041	0.252	0.253	0.052
0.20	−0.026	0.208	0.210	0.052	0.80	−0.055	0.318	0.315	0.058

Abbreviations: Bias, mean of the β_3 estimates minus the true β_3 value; *E*, fixation index used to characterize the departure from HWE (Satten & Epstein, 2010); HWE, Hardy–Weinberg equilibrium; SE, estimated standard error of the β_3 estimates; SEE, mean estimated standard error of the β_3 estimates; T1E, type-I error rate for testing parent-of-origin effect β_3.

were 6% and 4% higher than P-HAP for β_1 and β_3, respectively, while the SE of M-HAP for β_2 was close to that of P-HAP. In summary, M-HAP was more efficient than LOG and was more unbiased than P-HAP.

We also considered two more simulation scenarios, where the covariate was associated with paternal genotype g^f. Simulation results are again summarized in Table 1 based on 1000 replications of simulations. In dependence scenario 2 (Dep2), the covariate was associated with paternal genotype g^f; in dependence scenario 3 (Dep3), the covariate was associated with both maternal genotype g^m and paternal genotype g^f. Evidently, in both scenarios, M-HAP and LOG were more unbiased than P-HAP, and the former two methods maintained coverage probabilities around the nominal level but P-HAP could be considerably liberal. These simulation results indicate that M-HAP was robust to the violation of conditional independence of X and G^c given G^m to some extent.

In the above simulations, only one covariate was involved. We also considered simulation scenarios with two covariates, and the corresponding simulation results are summarized in Tables S4 and S5. The results were similar. That is, P-HAP was evidently biased when the covariate was moderately associated with maternal genotype and paternal genotype while M-HAP and LOG were still quite unbiased.

3.4 | Sensitivity analyses w.r.t. HWE, prevalence, and LD

First, a sensitivity analysis was conducted for the robustness of the proposed method M-HAP by violating the assumption of HWE. In case HWE does not hold, a fixation index E (different from F in model (7)) can be used to characterize the departure from HWE (Satten & Epstein, 2010):

$$\mathrm{pr}(h_1, h_2) = \begin{cases} E\mathrm{pr}(h_1) + (1-E)\mathrm{pr}^2(h_1), & \text{for } h_1 = h_2, \\ (1-E)\mathrm{pr}(h_1)\mathrm{pr}(h_2), & \text{for } h_1 \neq h_2, \end{cases} \tag{18}$$

where (h_1, h_2) is an ordered diplotype and $\mathrm{pr}(h_1, h_2)$ is the corresponding frequency. Since $\mathrm{pr}(h_1, h_2) \geq 0$ for any haplotype pair (h_1, h_2), E should satisfy the constraint $-\min_h[1 - \mathrm{pr}(h)]^{-1} \leq E \leq 1$. SNP1 was chosen as the causal locus and the genotype data from the remaining four SNPs were used to infer parental origins. The log-OR parameters were fixed at $\beta_1 = \beta_2 = \beta_4 = \log(1.2)$, $\beta_3 = 0$ or $\log(1.5)$. Furthermore, ζ in model (16) was fixed at $\log(1.5)$ to mimic a moderate correlation between G^m and X. Various fixation indexes, from the minimal possible value to 0.8, were considered. Presented in Table 2 are estimation and test results of M-HAP based on 5,000 replications of simulations. As expected, the estimation bias of M-HAP (fixation index F incorporated in (7)) appeared to be negligible and the type-I error rates were well controlled around the nominal level 5%. This indicated that M-HAP was robust to the violation of HWE through the incorporation of F in (7) to a large extent.

Additional simulations were conducted to examine possible efficiency loss of incorporating the fixation index F in model (7) when HWE held. The test results are summarized in Figure S1. Evidently, the two versions of M-HAP (fixing $F = 0$ vs. estimating F in (7)) performed very comparably in terms of both type-I error rates and powers, indicating that incorporating fixation index resulted in little power loss while well controlling type-I error rates. On the other hand, additional simulations indicated that fixing $F = 0$ in M-HAP could result in inflated type-I error rates when HWE was seriously violated (results not shown).

Then, another sensitivity analysis was conducted to study whether M-HAP is robust to the misspecification of disease prevalence f. All parameters in the above sensitivity analysis were adopted. The true f was 0.05 but it was specified to be 0.01, 0.1, or 0.5 in M-HAP. Simulation results are summarized in Table S6. The estimates of the POE parameter β_3 appeared to be unbiased and the corresponding type-I error rates were quite close to the nominal level, no matter how serious f was misspecified. This could be due to the conjecture that misspecifying f has impact only on the intercept in the logistic regression model (H. Zhang et al., 2020).

Finally, a sensitivity analysis was conduct to study whether M-HAP is robust to the assumption of no recombination among adjacent loci (i.e., the adjacent loci were in very strong LD). Specifically, the map distance between any two adjacent loci was set to be 0.1 cM, which was larger than the one for the real data described in the next section. The corresponding recombination rate between any two adjacent loci was 0.001 according to the Haldane map function. With specified recombination rates, multiple SNP diplotypes were generated according to the Markov chain property. The other settings were similar to those for Table 1. As shown in Table S3 and Figure S4, the estimation biases were negligible, the coverage probabilities of confidence intervals were close to the nominal level, and the type-I error rates were well controlled around the nominal level.

4 | REAL DATA APPLICATIONS

4.1 | The Jerusalem Perinatal Study (JPS)

We applied the considered four methods (i.e., M-AHP, P-HAP, EMIM, and LOG) to case–control mother–child paired data from the JPS (Harlap et al., 2007). This study included prenatal and perinatal archival survey and medical record data for 17,003 families of Jerusalem between the years 1974 to 1976. Between the years 2007 and 2009, around 1500 SNPs in multiple candidate gene regions were genotyped for 1250 mother–child pairs in the JPS, which were selected based on children's birth weight and mothers' prepregnancy body mass index (pp-BMI) (Hochner et al., 2012). According to Wu et al. (2016), a protein encoded by gene *PPARGC1A* could regulate genes involved in energy metabolism, which might be associated with children birth weight. Our aim was to detect POEs of several candidate SNPs in gene *PPARGC1A* on intrauterine growth reflected by children birth weight. We selected nine SNPs in gene *PPARGC1A* based on LD strength ($D' > 0.6$). Figures S7 and S8 show the LD structures of these nine SNPs. The pairwise D' and r^2 of the nine SNPs appeared to be relatively large, indicating strong LDs within these nine SNPs. The maximal map distance among these nine SNPs was around 0.025 cM, which was smaller than the one for our sensitivity analysis presented in the last paragraph of Section 3.4. Therefore, the no-recombination assumption required for M-HAP and P-HAP is approximately satisfied. We focused on a sub-cohort with mothers' pp-BMI <25 and used 2.5 kg as the cutoff point for low birth weight. The resulting sub-cohort size was 658 pairs, consisting of 96 pairs with low birth weight (<2.5 kg) and 562 control pairs with normal or high birth weight (>2.5 kg). There were 297 children with low birth weight among the 8238 eligible children with maternal pp-BMI <25, so the prevalence of low birth weight was specified to be $297/8,238 \approx 0.036$. As shown in Mallia et al. (2017), pp-BMI is an established risk factor for low birth weight. Therefore, pp-BMI was included as a covariate in M-HAP and LOG. Estimated haplotype frequencies are reported in Table S8. Table S9 shows estimated MAFs, p-values for testing HWE, and p values for testing independence between maternal genotypes and pp-BMI. All of the MAFs of the nine SNPs were >0.05, so that all considered methods should be applicable as these methods are valid for common SNPs in general. For several SNPs, pp-BMI was significantly associated with maternal genotypes, so that P-HAP and EMIM could be biased in POE inference. All p values for testing POEs are displayed in Figure S6, and estimation results for three potentially significant SNPs (p value <5%) are reported in Table 3.

We have the following observations. First, pp-BMI was not significantly associated with maternal genotype of the three SNPs (p values for testing $H_0 : \eta = 0$ were greater than 0.05), suggesting that all of the four considered methods could be applicable. Second, the estimated log-ORs by M-HAP, LOG, and P-HAP were consistent in the sense that they shared the same signs across the three SNPs. Third, the estimated standard errors were uniformly smaller for M-HAP compared with LOG and P-HAP, suggesting that M-HAP might be more efficient in estimating POEs. Finally, only M-HAP produced suggestively significant POEs (p value < 5%) for the three SNPs, though they were not significant after Bonferroni correction (Figure S6). Our analysis results were consistent with those of Lin et al. (2013). Further investigation is warranted to confirm these POEs.

4.2 | The Danish National Birth Cohort (DNBC)

We applied the considered four methods (i.e., M-AHP, P-HAP, EMIM, and LOG) to case–control mother–child paired data from the DNBC (Olsen et al., 2001). DNBC is a well-established, prospective cohort. To reduce potential bias in data collection and sampling, this study enrolled women early in pregnancy, before any adverse pregnancy outcomes (Olsen et al., 2001). Data posted on dbGaP (http://dbgap.ncbi.nlm.nih.gov) contain genotypes and clinical records of 720 case mother–child pairs with spontaneous onset of labor or preterm premature rupture of membranes and 906 control mother–child pairs with the children being born at ~40 weeks'

TABLE 3 POE analysis results for three potentially significant SNPs in the Jerusalem Perinatal Study

SNP[a]	Method[b]	Log-OR[c]	SE[d]	95% CI[e]	*p* Value[f]	$\hat{\eta}$ (*p* value)[g]
rs2932965	M-HAP	−0.579	0.244	[−1.058, −0.099]	0.018	0.014 (0.302)
	LOG	−0.215	0.291	[−0.787, 0.357]	0.462	
	P-HAP	−0.051	0.294	[−0.628, 0.526]	0.810	
	EMIM				0.828	
rs8192678	M-HAP	0.457	0.230	[0.005, 0.909]	0.047	0.005 (0.673)
	LOG	0.358	0.261	[−0.153, 0.869]	0.170	
	P-HAP	0.338	0.238	[−0.129, 0.805]	0.150	
	EMIM				0.168	
rs2970853	M-HAP	−0.515	0.231	[−0.968, −0.061]	0.026	0.001 (0.892)
	LOG	−0.319	0.250	[−0.808, 0.171]	0.202	
	P-HAP	−0.138	0.251	[−0.629, 0.353]	0.425	
	EMIM				0.442	

Abbreviations: POE, parent-of-origin effect; SNP, single-nucleotide polymorphism.

[a]Test locus.

[b]M-HAP, our proposed method; LOG, the standard prospective logistic regression method; P-HAP, a method in Lin et al. (2013); EMIM, a method in Howey and Cordell (2012).

[c]Estimated POE $\hat{\beta}_3$.

[d]Estimated standard error of $\hat{\beta}_3$.

[e]95% confidence interval of β_3.

[f]*p* value for testing $H_0 : \beta_3$.

[g]Estimated η value (*p* value for testing $H_0 : \eta = 0$).

gestation, which were drawn from a genome-wide case–control study (Ryckman et al., 2012). According to G. Zhang et al. (2017), some variants in gene *TEKT3* were shown to be significantly associated with preterm birth. Among these significant SNPs, rs2024157 was also genotyped in the DNBC study. The aim of the current analysis was to assess whether variants tightly linked to rs2024157 had any significant POE on preterm birth. In additional to rs2024157, we selected seven SNPs tightly linked to rs2024157 ($D' > 0.6$). Figures S9 and S10 show the LD structures of these eight SNPs. The pairwise D' and r^2 of the eight SNPs appear to be relatively large, indicating strong LD within these eight SNPs. The maximal map distance among these eight SNPs was around 0.05 cM, which was smaller than the one for the sensitivity analysis presented in the last paragraph of Section 3.4. Therefore, the no-recombination assumption required for M-HAP and P-HAP is approximately satisfied. We focused on a subset with complete genotype data on these eight SNPs, which consisted of 1464 mother–child pairs with 635 case pairs and 829 control pairs. Since the preterm birth rate in Denmark was around 5% (Blencowe et al., 2012), the prevalence of preterm birth was specified to be 5% in M-HAP. Again, pp-BMI was included as a covariate in M-HAP and LOG. Estimated haplotype frequencies are reported in Table S10. Table S11 shows estimated MAFs, *p* values for testing HWE, and p-values for testing independence between maternal genotypes and pp-BMI. The MAFs of all of the eight SNPs were shown to be >5%, so that all considered methods should be applicable as these methods are valid for common SNPs in general. For several SNPs, pp-BMI was significantly associated with maternal genotypes, so that P-HAP and EMIM could be biased in POE inference.

All p-values for testing POEs are displayed in Figure S11, and estimation results for four potentially significant SNPs (*p* value < 5%) are reported in Table 4. M-HAP exclusively identified three SNPs (rs7502492, rs1870428, and rs1380179) with significant POE effects. Among the three existing methods, only EMIM identified one significant SNP (rs1870429) (*p* value < 5%). However, none of them were significant after Bonferroni correction. As shown in Table 4, the estimated log-ORs by M-HAP, LOG, and P-HAP were consistent in the sense that they shared the same signs across the four SNPs and the estimated standard errors were uniformly smaller for M-HAP compared with LOG and P-HAP, suggesting that M-HAP might be more efficient in estimating POEs. Further investigation is warranted to confirm these POEs.

TABLE 4 POE analysis results for four potentially significant SNPs in gene *TEKT3* in the Danish National Birth Cohort study

SNP[a]	Method[b]	Log-OR[c]	SE[d]	95% CI[e]	*p* Value[f]	$\hat{\eta}$ (*p* value)[g]
rs7502492	M-HAP	−0.273	0.135	[−0.539, −0.008]	0.044	0.013 (0.153)
	LOG	−0.100	0.160	[−0.404, 0.224]	0.574	
	P-HAP	−0.193	0.141	[−0.469, 0.083]	0.171	
	EMIM				0.237	
rs1870428	M-HAP	−0.357	0.143	[−0.639, −0.076]	0.013	0.021 (0.035)
	LOG	−0.140	0.155	[−0.444, 0.163]	0.364	
	P-HAP	−0.226	0.152	[−0.523, 0.072]	0.137	
	EMIM				0.385	
rs1380179	M-HAP	−0.337	0.144	[−0.622, −0.054]	0.020	0.022 (0.030)
	LOG	−0.070	0.157	[−0.377, 0.237]	0.655	
	P-HAP	−0.241	0.154	[−0.543, 0.061]	0.117	
	EMIM				0.383	
rs1870429	M-HAP	−0.211	0.138	[−0.482, 0.060]	0.126	0.002 (0.838)
	LOG	−0.213	0.150	[−0.507, 0.080]	0.153	
	P-HAP	−0.103	0.147	[−0.391, 0.185]	0.484	
	EMIM				0.045	

Abbreviations: POE, parent-of-origin effect; SNP, single-nucleotide polymorphism.

[a]Test locus.

[b]M-HAP, our proposed method; LOG, the standard prospective logistic regression method; P-HAP, a method in Lin et al. (2013); EMIM, a method in Howey and Cordell (2012).

[c]Estimated POE $\hat{\beta}_3$.

[d]Estimated standard error of $\hat{\beta}_3$.

[e]95% confidence interval of β_3.

[f]p Value for testing $H_0 : \beta_3$.

[g]Estimated η value (p Value for testing $H_0 : \eta = 0$).

5 | DISCUSSION

Genetic effects related to parent-of-origin have been identified to be possible causal factors related to children early-life development and disorders. The ability to detecting POEs relies on the availability of the parent-of-origin information of children alleles. When the genotypes of both mother and child are heterozygous, the parental origins of two children alleles are ambiguous. In this paper, an efficient and robust multilocus statistical method, M-HAP, is developed for assessing POEs based on case–control mother–child paired data by incorporating covariates. M-HAP uses multilocus genotypes to infer parent-of-origin information. Available information, including Mendelian inheritance law, HWE, random mating, and conditional independence between children genotype and covariates given maternal genotype, are fully explored in M-HAP.

Many softwares have been developed to infer haplotypes using SNP genotypes from unrelated individuals and parent–child triads or mother/father–child pairs, to name a few, `HAPLORE` (K. Zhang et al., 2005), `Beagle` (Browning & Browning, 2007), and `SHAPEIT2` (Delaneau et al., 2013). The inferred haplotypes can be directly used to determine parental origins. As demonstrated by the simulation results of Delaneau et al. (2013), the average false assignment rates of parental origins were very low when mother–child pairs data were used. This motivated our haplotype-based method M-HAP for detecting POEs exploiting multilocus genotype data. Single-SNP genotypes cannot determine the parental origins when the genotypes of both mother and child are heterozygous. Simply ignoring these mother–child pairs with ambiguous parent origins may lead to estimation bias and loss of statistical efficiency for detecting POEs. A naïve strategy is to use the parental origin inferred from the haplotype with maximal likelihood, but this could result in a potential estimation bias and inflated type-I error rate (Howey et al., 2015). Instead, we propose to replace the log-likelihood function adopted in M-HAP by its conditional expectation with

respect to missing parental origin given multilocus genotypes. With this strategy, M-HAP successfully maintained type-I error rates around the nominal level in our simulation studies. We also developed a rigorous expectation-maximization algorithm to explore multilocus genotypes in a separate paper (Tian et al., 2021).

Directly maximizing the profile likelihood function (9) is often infeasible due to computation difficulty. To resolve this problem, we propose to replace the Lagrange multiplier involved in the profile likelihood function by its limiting value without sacrificing statistical efficiency. This greatly enhances the computational feasibility of M-HAP. In the simulation studies described in Section 3.3, it took a laptop with a 2.0 GHz Intel i7 core CPU around 3 s on average for M-HAP analyzing a single simulated data set (200 case pairs and 200 control pairs), compared with 160 s by P-HAP. Moreover, the estimation and test results in our simulation studies indicate that M-HAP was statistically more efficient than the other considered methods. In the presence of a confounding covariate, EMIM and P-HAP could produce distorted type-I error rates while M-HAP still had well-controlled type-I error rates. In summary, M-HAP is attractive owing to its computational feasibility, statistical efficiency, and robustness.

Departure from HWE could result in inflated type-I error rates in M-HAP. This problem could be partly resolved by introducing a fixation index, as demonstrated in Section 3.4. M-HAP was shown to be quite robust to the misspecification of phenotype prevalence, which could be due to the conjecture that misspecifying the phenotype prevalence has impact only on the intercept estimation in model (H. Zhang et al., 2020).

The current version of M-HAP was specifically designed for analyzing case–control mother–child paired data. Nevertheless, M-HAP can be easily extended to further incorporate genotype data from fathers, which offer additional information for identifying parental origins. It is of interest to extend M-HAP to handle nuclear families with more than one child and missing genotypes, which deserves further investigation.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The JPS data are not applicable for data sharing. The DNBC data were made available on the dbGAP website (study accession: phs000103.v1.p1).

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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