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The power of the transmission disequilibrium test (TDT) with both case–parent and control–parent trios

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Summary

The transmission disequilibrium test (TDT) customarily uses affected children and their parents (often case–parent trios, TDT_D). Control–parent trios are necessary to guard against spurious significant results due to segregation distortion but are not generally utilized in the identification of disease susceptibility loci (DSL). Controls are often easy to recruit and the TDT can easily be extended to include control–parent trios into the analyses with unrelated case–parent trios. We present an extension of the TDT (TDT_{DC}) that incorporates unrelated cases and controls and their parents into a single analysis. We develop a simple and accurate analytical method for computing the statistical power of various TDT (e.g. the TDT_D, TDT_{DC}, TDT_{DC} and TDT_C that employ control–parent trios only) under any genetic model. We investigated the power of these TDT, and particularly compared the relative power of the TDT_D and TDT_{DC}. We found that the TDT_{DC} is almost always more powerful than the TDT_C and TDT_D. The relative power of the TDT_{DC} and TDT_D depends largely upon a number of parameters identified in the study. This study provides a basis for efficient use of control–parent trios in DSL identification.

1. Introduction

Complex diseases refer to diseases determined by multiple genetic and environmental factors (and potentially their interactions). Linkage disequilibrium (LD) is an important mechanism for identifying genes underlying diseases (e.g. Hastbacka *et al*., 1992, 1994; Xiong & Guo,1997; Deng *et al*., 2000*a*). Association studies that depend on LD between markers and disease genes have helped to decipher some genetic bases of differential susceptibility to complex diseases (e.g. Feder *et al*., 1996). Classical association studies such as case–control analyses in unrelated cases and controls may suffer inflated type I errors (Chakraborty & Smouse, 1988; Lander & Schork, 1994; Weir,1996; Spielman & Ewens, 1996) that have not been quantified until rather recently (Deng & Chen, 2000; Deng *et al*., 2000*b*). In addition, population admixture/stratification may mask or reverse true genetic effects in classical association studies (Deng & Li, unpublished data).

Approaches employing nuclear families such as the transmission disequilibrium test (TDT; Spielman *et al*., 1993) are explicitly proposed to identify disease susceptibility loci (DSL). The TDT was developed to control for population admixture/stratification in testing for linkage and/or association between marker loci and DSL. The essence of the TDT is that, in the absence of segregation distortion, in nuclear families with affected offspring and with at least one parent heterozygous for the marker, individual alleles should be transmitted from heterozygous parents to affected progeny randomly with equal probabilities unless the marker locus is linked to *and* is in LD with a DSL or is a DSL itself. The TDT can test for both linkage (in the presence of LD, i.e. association) and association (in the presence of linkage) (Spielman & Ewens, 1996). Unlike customary association studies, LD created by population admixture does not confound the TDT

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testing for linkage and association between marker and DSL (Ewens & Spielman, 1995; Spielman & Ewens, 1996). Recently, the TDT has been extended to nuclear families with multiple children (at least one affected and one unaffected) where parental genotype data are not available (Curtis, 1997; Horvath & Laird, 1998; Spielman & Ewens, 1998; Boehnke & Langefeld, 1997).

When parental genotypes are available, current TDT analyses employ only affected children and their parents to test for linkage and/or association. Commonly employed samples are case–parent trios – nuclear families each of which have one affected child and both parents (at least one parent heterozygous at the marker locus) available. We will use TDT_D to denote the TDT applied to case–parent trios, where the subscript D denotes the affected children in the family trios. For many diseases, it is generally much easier to recruit unaffected control–parent trios than to recruit case–parent trios, partly because control–parent trios are generally more frequent. Most importantly, to rule out potential segregation distortion in meiosis that will render one allele preferentially transmitted to children regardless of their affected status, control–parent trios should be analysed with case–parent trios (Spielman *et al.*, 1993). However, it has not been a practice to combine case–parent and control–parent trios in testing linkage and/or association in the TDT. It has recently been suggested that the TDT applied to control–parent trios alone (denoted as TDT_C, where the subscript C denotes the unaffected children in the family trios) may have higher power than the TDT_D when disease prevalence is greater than 45–55% (Scott *et al.*, 1999). The TDT_C can be viewed as a test for 'healthy' rather than for 'disease' alleles, though, at the same DSL. Hence, even without affected individuals in the sample, one can still infer linkage to a DSL as control individuals may also carry the disease allele for complex diseases. It is also advocated that, in the absence of meiotic segregation distortion, combined analyses of case–parent trios and unrelated control–parent trios in the TDT (the TDT_{DC}, where the subscript DC denotes that both case–parent and control–parent trios are used in analyses) may have greater power than the TDT_D (Boehnke & Langefeld, 1997). This is because if the marker locus under test is a DSL, or is linked to and in LD with a DSL, transmission disequilibrium should occur not only in case–parent trios but also in control–parent trios, although in the opposite direction. However, the specific test of the TDT_{DC} and the conditions in which the TDT_{DC} is more powerful than the TDT_D are not clear, and neither is the significance of the TDT_{DC} in DSL identification. Whittaker & Lewis (1998) investigated the effect of family structure on linkage tests using the TDT. They concluded that incorporation of unaffected sibs (of affected individuals) rarely increases the power of the TDT. However, here we will consider the incorporation of information from unaffected children in control–parent family trios with that from *unrelated* affected case–parent trios. Thus, our consideration here is different from that of Whittaker & Lewis (1998).

In this article we will first present a TDT_{DC} test that efficiently combines information from both case–parent trios and unrelated control–parent trios with each trio having at least one heterozygous parent to test for linkage and association. Second, we will develop a novel and simple method to compute the power of the TDT_D, TDT_C and TDT_{DC} under any genetic model. We will validate the accuracy of this power computation method by comparison with both previous analytical methods and our computer simulations. Finally, and most importantly, under a range of parameter space and genetic models, we will compare the relative powers of the TDT_D, TDT_C and TDT_{DC}.

2. Methods

(i) *Statistical tests*

To illustrate our approach in a simple manner, we consider a two-allele-per-locus model with the marker locus having alleles M and m. For a locus with more than two alleles, the multiple alleles can always be classified into two alleles by designating one or some alleles as M and the rest, collectively, as m. In practice, collapsing of multiple alleles into two alleles is not always straightforward since it is an open question as to which alleles are to be grouped into one allelic class. Inappropriate collapsing may involve some loss of information. The two-allele model can be extended to account for multiple alleles (Sham & Curtis, 1995; Schaid, 1996; Spielman & Ewens, 1996; Lazzeroni & Lange, 1998). The extension can generally be accomplished by testing for global allelic transmission disequilibrium of all alleles instead of two alleles at a time. Therefore, our investigation via the simple two-allele model should be of general significance and forms a basis for future extensions to more complex situations.

In the TDT_D applied to case–parent trios (with at least one parent being heterozygous) where only one affected child from each family is employed, let T and NT denote, respectively, the number of times that the marker allele M is transmitted or not transmitted from a heterozygous parent to affected children. Under the null hypothesis of no linkage or no LD between the marker locus and a DSL, the statistic

$$\chi^2_{TDT_D} = \frac{(T-NT)^2}{T+NT}$$

Table 1. *Denotations of the numbers of alleles transmitted and not transmitted to affected and non-affected children*

	No. of alleles transmitted		
	M	m	Total
Affected	T	NT	$n_{1.}$
Unaffected	T_2	NT_2	$n_{2.}$
Total	$n_{.1}$	$n_{.2}$	n_0

approximately follows a χ^2 distribution with one degree of freedom (d.f.).

In the TDT_C applied to control–parent trios (with at least one parent being heterozygous), let T_2 and NT_2 denote, respectively, the numbers of times that the marker allele M is transmitted or not transmitted from a heterozygous parent to unaffected children. Under the null hypothesis of no linkage or no LD between the marker locus and a DSL, the statistic

$$\chi^2_{TDT_C} = \frac{(T_2 - NT_2)^2}{T_2 + NT_2}$$

approximately follows a χ^2 distribution with 1 d.f.

For the TDT_{DC} applied to both case–parent and unrelated control–parent trios (with at least one parent being heterozygous), let $n_{1.}$ and $n_{2.}$, respectively, denote the total number of alleles (M and m alleles) from heterozygous parents. Let $n_{.1}$ and $n_{.2}$ denote, respectively, the total number of M and m alleles transmitted to affected and non-affected children. The total number of alleles transmitted to all children is n_0. Table 1 illustrates the representations of n's intuitively. The statistic

$$\chi^2_{TDT_{DC}} = \frac{n_0(T \cdot NT_2 - T_2 \cdot NT)^2}{n_{.1}n_{.2}n_{.1}n_{.2}}$$

approximately follows a χ^2 distribution with 1 d.f. under the null hypothesis of no linkage or no LD between the marker locus and a DSL. The TDT_{DC} via $\chi^2_{TDT_{DC}}$ statistic is a contingency table test for association of allele transmissions with disease status in unrelated children. With no linkage or no LD, the allele transmission to children in unrelated case–parent and control–parent trios should be independent and not associated, as will be shown later analytically. This test does not require equal numbers of case–parent and control–parent trios. It will be shown later that, as with other types of TDT the TDT_{DC} is a test for linkage and LD. With two heterozygous parents in a triad, the transmission of alleles from the two parents to their *single* child under study is independent of each other under the null hypothesis.

Under the alternative hypothesis of linkage and LD between the marker locus and a DSL, $\chi^2_{TDT_D}$, $\chi^2_{TDT_C}$ and $\chi^2_{TDT_{DC}}$ each approximately follows a non-central χ^2 distribution with 1 d.f., their respective non-centrality parameters being λ_{TDT_D}, λ_{TDT_C} and $\lambda_{TDT_{DC}}$.

It is noted that the statistics $\chi^2_{TDT_D}$ and $\chi^2_{TDT_C}$ are independent as they employ different samples and the transmission of parental alleles to children in case–parent and unrelated control–parent trios are independent. It is well known that the sum of two independent χ^2 statistics also follows a χ^2 distribution with the d.f. equal to the sum of the d.f.'s of the two summand χ^2 statistics. Therefore, we have a new statistic (TDT_{D+C}):

$$\chi^2_{TDT_{D+C}} = \frac{(T - NT)^2}{T + NT} + \frac{(T_2 - NT_2)^2}{T_2 + NT_2}.$$

Under the null hypothesis of no linkage or no LD between the marker locus and a DSL, $\chi^2_{TDT_{D+C}}$ approximately follows a χ^2 distribution with 2 d.f. Under the alternative hypothesis of linkage and LD between the marker locus and a DSL, $\chi^2_{TDT_{D+C}}$ follows a non-central χ^2 distribution with the non-centrality parameter $\lambda_{TDT_{D+C}} = \lambda_{TDT_D} + \lambda_{TDT_C}$.

(ii) *Power computation*

Although not required for the validity of the TDT, for ease of power computation only, we assume that population is randomly mating and Hardy–Weinberg equilibrium holds. In addition, we assume the absence of segregation distortion (see Section 5) and at most one DSL linked to the marker under study. Let p and q $(= 1 - p)$ denote, respectively the frequencies of the alleles A and a at a DSL. Let f and f' $(= 1 - f)$ denote, respectively, the frequencies of the allele M and m at a marker locus. Let δ denote LD coefficient for the marker locus and the DSL, and θ denote the recombination rate between the marker locus and the DSL. The population haplotype frequencies are, respectively, $P_{AM} = \delta + pf$, $P_{aM} = f - P_{AM}$, $P_{Am} = p - P_{AM}$ and $P_{am} = 1 - f - p + P_{AM}$. Let ϕ_{AA}, ϕ_{Aa} and ϕ_{aa} denote the penetrance (the probability of being affected) of the genotypes AA, Aa and aa, respectively, at the DSL. The population disease prevalence is then

$$\phi = p^2\phi_{AA} + 2pq\phi_{Aa} + q^2\phi_{aa}.$$

For a simple representation of some of our results later, we define:

$$C = p\phi_{AA} + (q - p)\phi_{Aa} - q\phi_{aa}.$$

If we let N be the number of families with one affected child, then the expected number of transmitted M alleles ($E(T)$) from heterozygous parents in families

with one affected child and at least one heterozygous (at the marker locus) parent is then (Appendix):

$$E(T) = 2N[ff' + \delta(f' - \theta)C/\phi],$$

and the expected number of transmitted m alleles ($E(NT)$) is:

$$E(NT) = 2N[ff' + \delta(\theta - f)C/\phi].$$

Therefore, under the alternative hypothesis of linkage ($\theta < 0{\cdot}5$) and LD between the marker locus and the DSL ($\delta \neq 0$), the non-centrality parameter λ_{TDT_D} of the TDT_D test can be computed in a way similar to that in Nielsen *et al.* (1998) and Deng *et al.* (2000*a*) as:

$$\lambda_{TDT_D} = \frac{[E(T) - E(NT)]^2}{E(T) + E(NT)} = N\frac{4(1/2-\theta)^2\delta^2C^2}{[ff'\phi + (1/2-f)\delta C]\phi}. \quad (1)$$

If the marker is the DSL itself ($p = f$ and $P_{AM} = p$), λ_{TDT_D} can be simplified as:

$$\lambda_{TDT_D} = N\frac{2p(1-p)C^2}{(p\phi_{AA} + \phi_{Aa} + q\phi_{aa})\phi}.$$

By the same procedures, we can derive $E(T_2)$ and $E(NT_2)$ to obtain the non-centrality parameters λ_{TDT_C} and $\lambda_{TDT_{DC}}$, respectively, as follows for the TDT_C and the TDT_{DC}:

$$\lambda_{TDT_C} = N\frac{4(1/2-\theta)^2\delta^2C^2}{[ff'(1-\phi) - (1/2-f)\delta C](1-\phi)}, \quad (2)$$

$$\lambda_{TDT_{DC}} = \{8N(\tfrac{1}{2}-\theta)^2[ff'\phi(1-\phi) + (\tfrac{1}{2}-f)(\tfrac{1}{2}-\phi)\delta C]f^2f'^2\delta^2C^2\} \div \{[ff'\phi + (\tfrac{1}{2}-f)\delta C][ff'(1-\phi) - (\tfrac{1}{2}-f)\delta C][ff'\phi(1-\phi) + (f'-\theta)(\tfrac{1}{2}-\phi)\delta C] \times [ff'\phi(1-\phi) + (\theta-f)(\tfrac{1}{2}-\phi)\delta C]\}. \quad (3)$$

In the TDT_{DC} test, unless otherwise specified, there are N case–parent trios and N unrelated control–parent trios. This is because case–parent and control–parent trios are both necessary to test segregation distortion in order to validate the TDT_D result of linkage and association.

From the non-centrality parameters of equations (1)–(3) for the tests of the TDT_D, TDT_C and TDT_{DC}, it is apparent that all are tests of linkage and association (i.e. LD between the marker locus and a DSL), since they all share the same multiplicative factors of $(1/2-\theta)$ and δ. Except under the alternative hypotheses of $\theta < 1/2$ and $\delta \neq 0$, λ_{TDT_D}, λ_{TDT_C} and $\lambda_{TDT_{DC}}$ are all zero and $\chi^2_{TDT_D}$, $\chi^2_{TDT_C}$ and $\chi^2_{TDT_{DC}}$ each follows a central χ^2 distribution with 1 d.f. that is expected under the null hypotheses of no linkage or no LD. The relative magnitude of λ_{TDT_D}, λ_{TDT_C} and $\lambda_{TDT_{DC}}$ under different parameters (such as p, f, θ and δ) reflects the different statistical power of the TDT_D, TDT_C and TDT_{DC}. Based on the non-centrality parameters, the power (η) of the above χ^2 tests (the TDT_D, TDT_C and TDT_{DC}) can be computed by standard procedures that we adopted elsewhere (Deng *et al.*, 2000*b*).

We derived the non-centrality parameters in a very general genetic model, in which the penetrance of each of the three genotypes is defined. This model has been employed before (Deng *et al.*, 2001; Chen & Deng, 2001) and is essential, at least (1) in studies of population admixture when the disease risk that is entirely due to environmental causes is different in different populations (Deng *et al.*, 2000*b*); and (2) in studies where polygenic causes of disease susceptibility need to be considered for complex diseases, which is often the case when multiple children are studied for some families. The genotypic relative risk (GRR) model is commonly employed (e.g. Risch & Merikangas, 1996), which is perfect for analyzing the power of the TDT_D in that only two parameters (relative risks γ and γ_1) regarding penetrance need to be specified in order to characterize the power. In the GRR model, at a DSL, the risk parameters (γ_1, $\gamma \geqslant 1$) of the two genotypes (AA and Aa) relative to the referent genotype (aa) are defined. Thus, the general and three-parameter model can be simply related to the GRR model as: $\gamma_1 = \phi_{AA}/\phi_{Aa}$ and $\gamma = \phi_{Aa}/\phi_{aa}$.

As is common practice (e.g. Risch & Merikangas, 1996; Knapp, 1999) when employing the GRR model, we will define the genetic effects by the relative magnitude of γ and γ_1: for recessive genetic effects, $\gamma = 1$; for additive effects, $\gamma_1 = 2\gamma - 1$; for dominant effects, $\gamma_1 = \gamma$; and for multiplicative effects, $\gamma_1 = \gamma^2$. With multiplicative effects,

$$\lambda_{TDT_D} = N\frac{(1/2-\theta)^2 4\delta^2(\gamma-1)^2}{(p\gamma+q)[(1/2-f)\delta(\gamma-1) + (p\gamma+q)ff']}. \quad (5a)$$

For the DSL itself, the non-centrality parameter can be expressed as:

$$\lambda_{TDT_D} = N\frac{2p(1-p)(\gamma-1)^2}{(p\gamma+q)(\gamma+1)}. \quad (5b)$$

From statistical tables for non-central χ^2 distributions (e.g. Weir, 1996, p. 382) or from most computer packages for statistics (e.g. Wolfram, 1996), we can find that to obtain 80% power with the significance level $\alpha = 5 \times 10^{-8}$, the non-centrality should be 39·605. There are also quick approximations for a non-central χ^2 distribution based on unit normal distribution (e.g. equation A5.17d in Lynch & Walsh, 1998). With the

parameter p, γ assumed in (5b), we can calculate the sample size N needed. The results (not shown here) computed by our approach are close to those obtained using a different method by Risch & Merikangas (1996) under a multiplicative model. For the multiplicative model and when the locus is a DSL and $p = f$, our results for N for 80% power with $\alpha = 10^{-7}$ are essentially the same as those given by another approach (the second approximation of Knapp, 1999). These results are also confirmed by another general power computation method developed by us under various genetic models (Chen & Deng, 2001). These, together with the comparisons with our computer simulations outlined below, validate our analytical power calculation method.

If control–parent trios are considered as in the TDT_C and TDT_{DC}, GRR does not have any advantage compared with our general model. This is because all three penetrance parameters for the three genotypes must be considered as independent parameters in the derivation for the analytical power computation. If we still wish to use the GRR model with the relative risk notation (γ and γ_1) for statistical power computation of the TDT_C and TDT_{DC}, the parameter ϕ_{aa} must be specified for the penetrance of the referent genotype aa. The computation has already been outlined earlier for our general model except that the penetrances for the three genotypes are now simply $\gamma_1\phi_{aa}$, $\gamma\phi_{aa}$, ϕ_{aa} instead of ϕ_{AA}, ϕ_{Aa}, ϕ_{aa} for genotypes AA, Aa and aa, respectively.

To validate our analytical power computation approach, we perform computer simulations for a number of parameters. In the absence of segregation distortion, random mating populations are simulated, in which p, γ_1, γ, ϕ_{aa} are specified together with f, δ and θ (when the marker locus is not a DSL *per se*). For desired statistical power η and significance level α, we first compute the sample size (N) needed by our analytical approaches. Then N case–parent and N unrelated control–parent trios are simulated. The TDT_D is applied to the N case–parent trios, the TDT_C applied to the N control–parent trios and the TDT_{DC} applied to the combined sample of the N case–parent trios and the N control–parent trios. In simulations, we also investigate the effect of the number (where U denotes unaffected) of control–parent trios incorporated with N case–parent trios on the TDT_{DC} power. The simulation procedures are relatively straightforward and thus will not be elaborated here. The statistical power (η') obtained in simulations under the specified α level can be compared with the specified η in the analytical power computation. The closer η' is to η, the more accurate is our analytical power computation. Once our analytical power computation has been validated, the investigation of the relative power of the TDT_D, TDT_C and TDT_{DC} is conducted by our analytical method.

3. Results

(i) *The accuracy of our analytical power computation*

From Table 2 it can be seen that, under various parameters, the sample sizes (N) computed from our analytical method for various tests, if employed in computer simulations, can yield the simulated statistical power (η') that is very close to the statistical power (η) specified to compute N in our analytical method. The results are influenced little by the allele frequency p at the DSL and the accuracy of the analytical results as compared with the simulation results is retained under other genetic models at the DSL as revealed by data not shown here. Therefore, our analytical method is validated by our computer simulation results. This, together with our comparison (outlined earlier) with other analytical methods (Risch & Merikangas, 1996; Knapp, 1999; Cheng & Deng, 2001), validates the accuracy and robustness of our analytical method.

(ii) *General comparison of various TDTs*

It is noted in Table 2 that for specified η and α, first, the sample size N required for the TDT_D is not influenced by ϕ_{aa} and the associated change in ϕ as long as γ and γ_1 remain constant. This is hardly surprising as ϕ_{aa} does not enter into the power computation for the TDT_D as an independent parameter (equation 5b), since it is compounded in the parameters γ and γ_1 in the derivation. This is also why the GRR model in which ϕ_{aa} is set to 1 as a relative term is perfect in the power computation for the TDT_D. Second, the N needed for the TDT_C, TDT_{D+C} and TDT_{DC} decreases with increasing ϕ_{aa} (and increasing ϕ that is due to the increase in ϕ_{aa}) even if γ and γ_1 remain constant. Third, in the investigation for Table 2, the TDT_{DC} is always more powerful than the TDT_D and TDT_{D+C}, and is more powerful than the TDT_D with increasing ϕ_{aa} (and thus increasing ϕ). The difference in N for the TDT_D and TDT_{DC} can be so dramatic that for a specified η and α, N needed for the TDT_{DC} may be much less than that for the TDT_D.

Under the commonly employed multiplicative model in which $\gamma_1 = \gamma^2$, we performed extensive investigations in the parameter space where p varies from 0·08 to 0·800 in increments of 0·08, ϕ_{aa} varies from 0·006 to 0·300 in increments of 0·006, and $\gamma =$ 1·5, 2·0, 4·0. We found that with N control–parent trios in the TDT_C and $N/2$ case–parent trios and $N/2$ control–parent trios in the TDT_{DC}, in less than 5% of the situations investigated is the TDT_C more powerful than the TDT_{DC}. Usually this occurs when the disease allele A is very common ($P > 0{\cdot}45$) and the disease prevalence is greater than 49%. Since from the evolutionary genetics point of view it is rare for a disease allele to reach such a high frequency (unless

Table 2. *N needed to achieve 80% power (η) with $\alpha = 0{\cdot}05$ (computed by our analytical methods) and the power (η') obtained by simulations with the sample size N*

ϕ_{aa}	ϕ	$TDT_D(\eta')$	$TDT_C(\eta')$	$TDT_{D+C}(\eta')$	$TDT_{DC}(\eta')$
0·1	0·175	385 (81·1)	8549 (79·5)	452 (80·8)	522 (80·4)
0·2	0·350	385 (81·1)	1327 (80·8)	366 (81·1)	325 (80·2)
0·3	0·525	385 (81·1)	315 (78·6)	213 (80·1)	174 (80·3)
0·4	0·700	385 (81·1)	71 (80·3)	73 (79·4)	69 (80·4)

In the studies for this table, dominant effects are assumed and $\gamma_1 = \gamma = 2$ and the locus under test is a DSL *per se*. ϕ_{aa} is the genotypic penetrance for the referent genotype aa. The disease allele A frequency p is 0·5. ϕ is the disease population prevalence and can be computed by p, γ_1, γ and ϕ_{aa}. To obtain the power $\eta = 80\%$ with the significance level $\alpha = 5\%$, sample size N is calculated from the theoretical non-centrality parameters as indicated in Section 2. The simulated statistical powers (η', true powers with sample size N) are obtained by counting the times that the null hypothesis is rejected in 5000 repeated simulations performed under the alternative hypothesis.

genetic drift is strong in small populations or genotype by environment interaction exists; Hartl & Clark, 1989), we conclude that in most conditions the TDT_{DC} is more powerful than the TDT_C. In addition, in all the situations investigated, the TDT_{DC} is almost always more powerful than the TDT_{D+C}. Therefore, from hereon, we will focus our investigation on comparing the relative power of the new test TDT_{DC} and the commonly employed TDT_D.

(iii) *Detailed comparison of the TDT_D and TDT_{DC}*

The comparison is made for the case where the marker locus is a DSL (Fig. 1) and for the case when the marker locus is not a DSL but is linked to and is in LD with a DSL (Fig. 2). When the marker locus is a DSL (Fig. 1), for all four genetic models investigated, similar patterns emerge. First, there is a continuous threshold line in the parameter space so that on one side (the upper right side) of the threshold line the TDT_{DC} is more powerful than the TDT_D in that fewer samples are necessary to reach the same power η for a given significance level α. On the other side (the lower left side) of the threshold line, it is the other way around. Second, for a given ϕ_{aa}, with an increasing disease allele frequency p, the power of the TDT_{DC} relative to that of the TDT_D will increase and after a threshold value p the power of the TDT_{DC} will be larger than that of the TDT_D. The threshold frequency p decreases with increasing genetic effects as reflected by the γ_1 or γ. Similarly, for a given value of p, with an increasing ϕ_{aa}, the power of the TDT_{DC} relative to that of the TDT_D will increase and after a threshold value ϕ_{aa} the power of the TDT_{DC} will be larger than that of the TDT_D. Again, the threshold ϕ_{aa} value decreases with increasing genetic effects as reflected by the γ_1 or γ. Therefore, with larger genetic effects γ_1 or γ, or larger ϕ_{aa}, or larger p, the TDT_{DC} is more likely to be more powerful than the TDT_D. It should be noted that the larger γ_1 or γ, and/or the larger ϕ_{aa}, and/or the larger p, the larger the disease population prevalence ϕ.

When the marker locus is not a DSL, the two conclusions summarized above for the case when the marker is a DSL *per se* still hold. (In Fig. 2, in the parameter space to the right of the threshold line, the TDT_{DC} is more powerful than the TDT_D. On the other side (the left side) of the threshold line, it is the other way around.) In addition, it is found that the marker allele frequency f, the recombination rate θ and the degree of LD (δ) between the marker locus and the DSL when $\delta > 0$ have little effect on the relative power of the TDT_{DC} and TDT_D. This is demonstrated in the multiplicative model in the bottom two plots of Fig. 2. It can also be noted that the genetic models (dominant, recessive, etc.) at the DSL is important in determining the parameter space in which the TDT_{DC} is more powerful than the TDT_D. For example, when $\phi_{aa} = 0{\cdot}2$ and $\gamma = 2$, the parameter region in which the TDT_{DC} is more powerful than the TDT_D is larger in the multiplicative model than in the dominant model (Fig. 2).

The above analyses concentrate on parameter regions in which the TDT_{DC} is more powerful than the TDT_D when the same number of case–parent and control–parent trios are included in the TDT_{DC}. In addition to the limited data in Table 2, to give more quantitative indication of the relative power of the TDT_{DC} and TDT_D we present in Fig. 3 the ratio of the sample size needed for the TDT_{DC} to that required for the TDT_D under various parameter values and genetic models. It can be seen (Fig. 3) that the required sample size for 80% power can sometimes be much smaller for the TDT_{DC} than TDT_D when, as in regular case–control analyses, the same number of case–parent and control–parent trios are employed. Importantly,

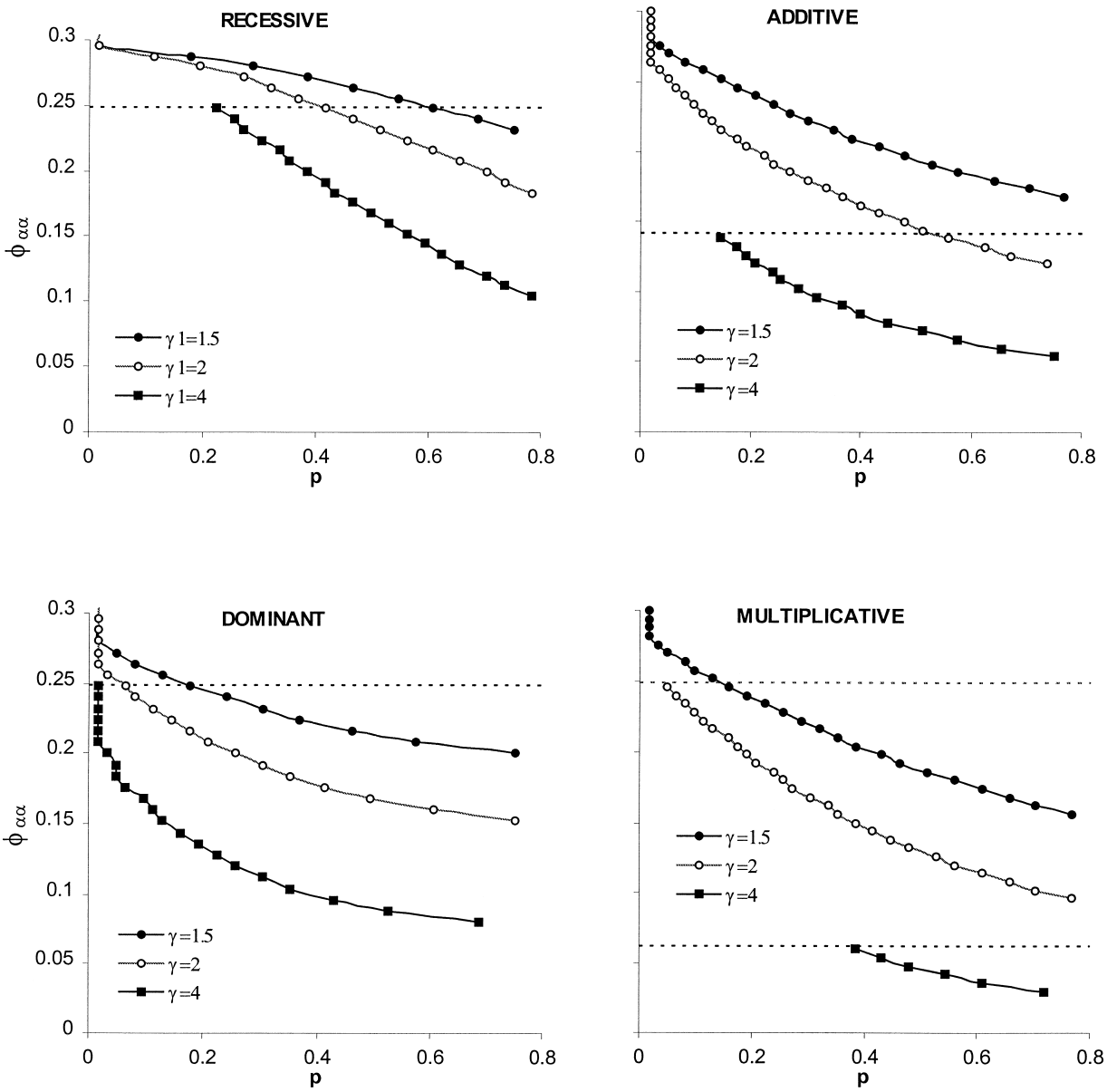

Fig. 1. The regions in the two-dimensional parameter (p and ϕ_{aa}) space in which the TDT_{DC} is more powerful than the TDT_{D} when the marker locus is a DSL *per se* and $p = f$. In the comparison, $\eta = 80\%$ and $\alpha = 0{\cdot}05$. The threshold lines drawn divide the parameter space into two parts. In the parameter space to the upper right of the threshold lines, sample size (N) needed is smaller in the TDT_{DC} than in the TDT_{D}; thus, the TDT_{DC} is more powerful than the TDT_{D}. In the parameter space to the lower left of the threshold lines, it is the other way around. The dashed lines set the upper bound that ϕ_{aa} can take in the constraint that the disease population prevalence ϕ has to be less than 1·0. In the recessive model, γ_1 is specified, and the penetrance for genotypes AA, Aa and aa are, respectively, $\gamma_1\phi_{aa}$, $\gamma\phi_{aa}$ and ϕ_{aa}. For the other three models, γ is specified and γ_1 can easily be inferred from γ and the genetic models under study.

if we increase the number of control–parent trios, which can generally be relatively easily recruited, in the TDT_{DC} analyses, the relative power of the TDT_{DC} increases and can almost always be higher than the TDT_{D} in that the required sample sizes can be much smaller (Fig. 4).

(iv) *Analyses of ϕ in relation to the relative power of the TDT_{DC} and the TDT_{D}*

When the same number of case–parent and control–parent trios are employed (as in regular case–control analyses), there is no direct and constant relationship between ϕ and the relative power of the TDT_{DC} and TDT_{D}. ϕ is determined by ϕ_{aa}, p, γ and γ_1 in a non-linear fashion and one ϕ may correspond to multiple sets of values of ϕ_{aa}, p, γ and γ_1. However, from the following semi-quantitative arguments, we conclude that generally for a range of genetic effects at the DSL ($\gamma \in [1{\cdot}5, 4]$), if $\phi > 0{\cdot}30$, the TDT_{DC} is more powerful than the TDT_{D}. If $\phi < 0{\cdot}2$, the TDT_{D} is more powerful. We consider only the DSL for illustration as θ, δ and f do not have much effect on the relative powers of the

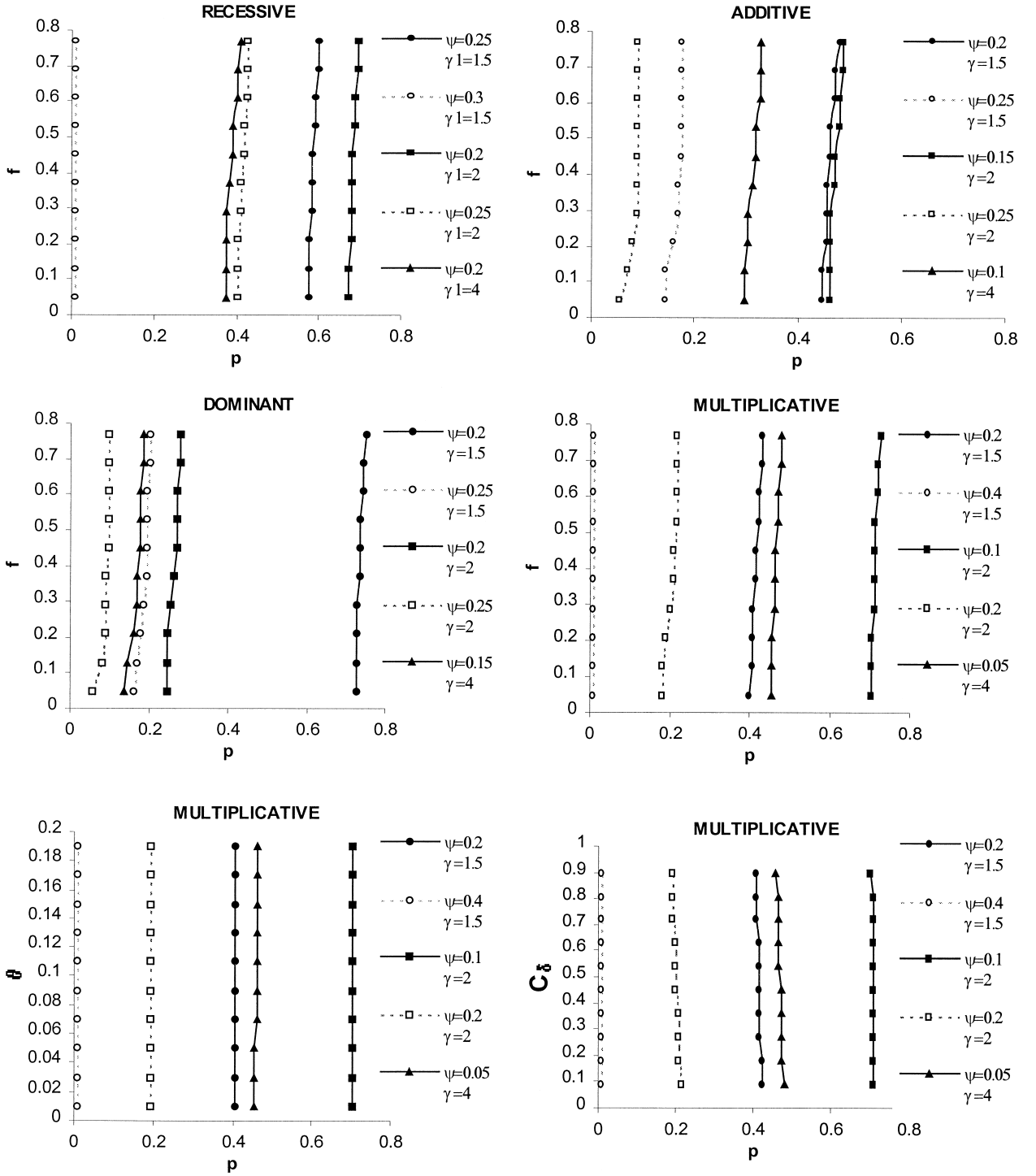

Fig. 2. The parameter space in which the TDT_{DC} is more powerful than the TDT_{D} when the marker locus is not a DSL. In the parameter space to the right of the threshold line, the TDT_{DC} is more powerful than the TDT_{D}. To the left of the threshold line, it is the other way around. In the investigation for the upper four figures, $\theta = 0{\cdot}01$, the LD in population $\delta = 0{\cdot}9\delta_{max}$, where δ_{max} is the maximum LD between the marker and the DSL in a population and can easily be shown to be the minimum of pf and qf. In the bottom left figure $f = 0{\cdot}21$ and $\delta = 0{\cdot}9\delta_{max}$. In the bottom right figure, $f = 0{\cdot}21$ and $\theta = 0{\cdot}01$. C_{δ} is the ratio of the degree of existing LD δ to δ_{max}. ψ is employed to represent ϕ_{aa} due to the difficulty of representing ϕ_{aa} in the figure in our graphical program.

TDT_{DC} when the marker is not a DSL. We consider, as an example, a dominant model with $\gamma = 4$, which is a situation in Fig. 1. Above the threshold line, the TDT_{DC} is more powerful; below the threshold line, the TDT_{D} is more powerful. From our numerical investigation, ϕ corresponding to the values of ϕ_{aa} and p on the threshold is within (0·217, 0·297). In the dominant model, $\phi = [p(2-p)(\gamma-1)+1]\phi_{aa}$. If p and/or ϕ_{aa}

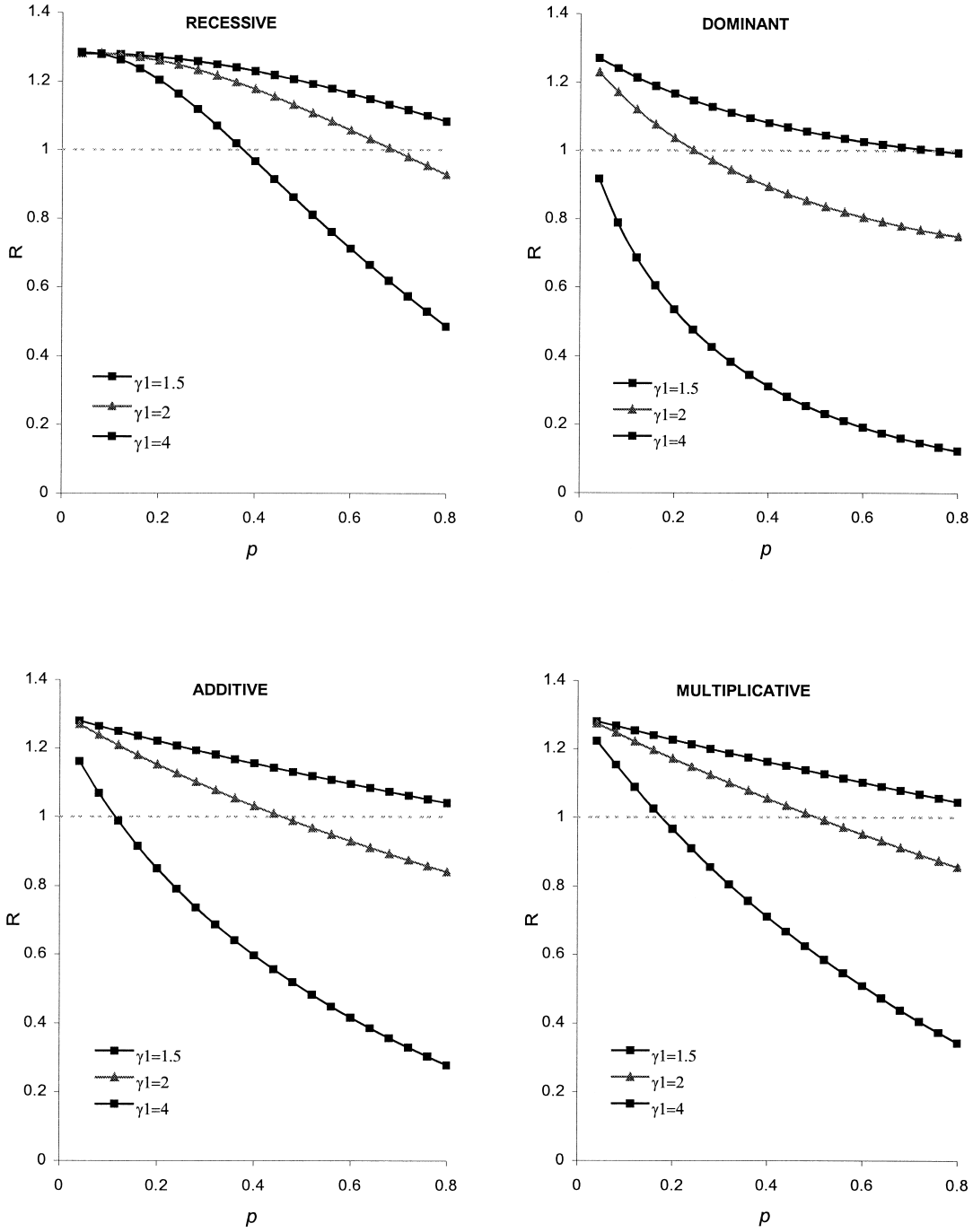

Fig. 3. Numerical comparison of the relative sample sizes needed for the TDT_{DC} and TDT_{D} in order to reach 80% power. The *x*-axis is the allele frequency *p*. The *y*-axis is the ratio (*R*) of the number *N* of nuclear family pairs (*N* case–parent and *N* control–parent trios) needed by the TDT_{DC} to that of nuclear families (case–parent trios) needed by the TDT_{D}. The marker locus is a DSL *per se* and $p = f$. $\alpha = 0{\cdot}05$, $\phi_{aa} = 0{\cdot}2$.

increases, ϕ will increase. In the region above the threshold line, compared with data point of the same p (or ϕ_{aa}) on the threshold line, ϕ_{aa} (or p) is larger, hence ϕ is larger. Therefore, ϕ must be at least greater than the minimum value 0·217 on the threshold line in order for the TDT_{D} to be more powerful; otherwise, the TDT_{D} is more powerful. Similarly, in the region below the threshold line, ϕ must be at least smaller than the maximum ϕ value of 0·297 on the threshold line in order for the TDT_{D} to be more powerful; otherwise, the TDT_{DC} will be more powerful. Similarly, when $\gamma = 1{\cdot}5$ and 2, ϕ must be at least larger than 0·28 and 0·268, respectively, in order for the TDT_{DC} to be more powerful. We can then conclude that for $\gamma \in [1{\cdot}5, 4]$, ϕ has to be at least greater than 0·28 in order for the TDT_{DC} to be more powerful. Therefore, if $\phi < 0{\cdot}28$, the TDT_{D} is more powerful than the TDT_{DC}. Using the same logic, we can conclude that

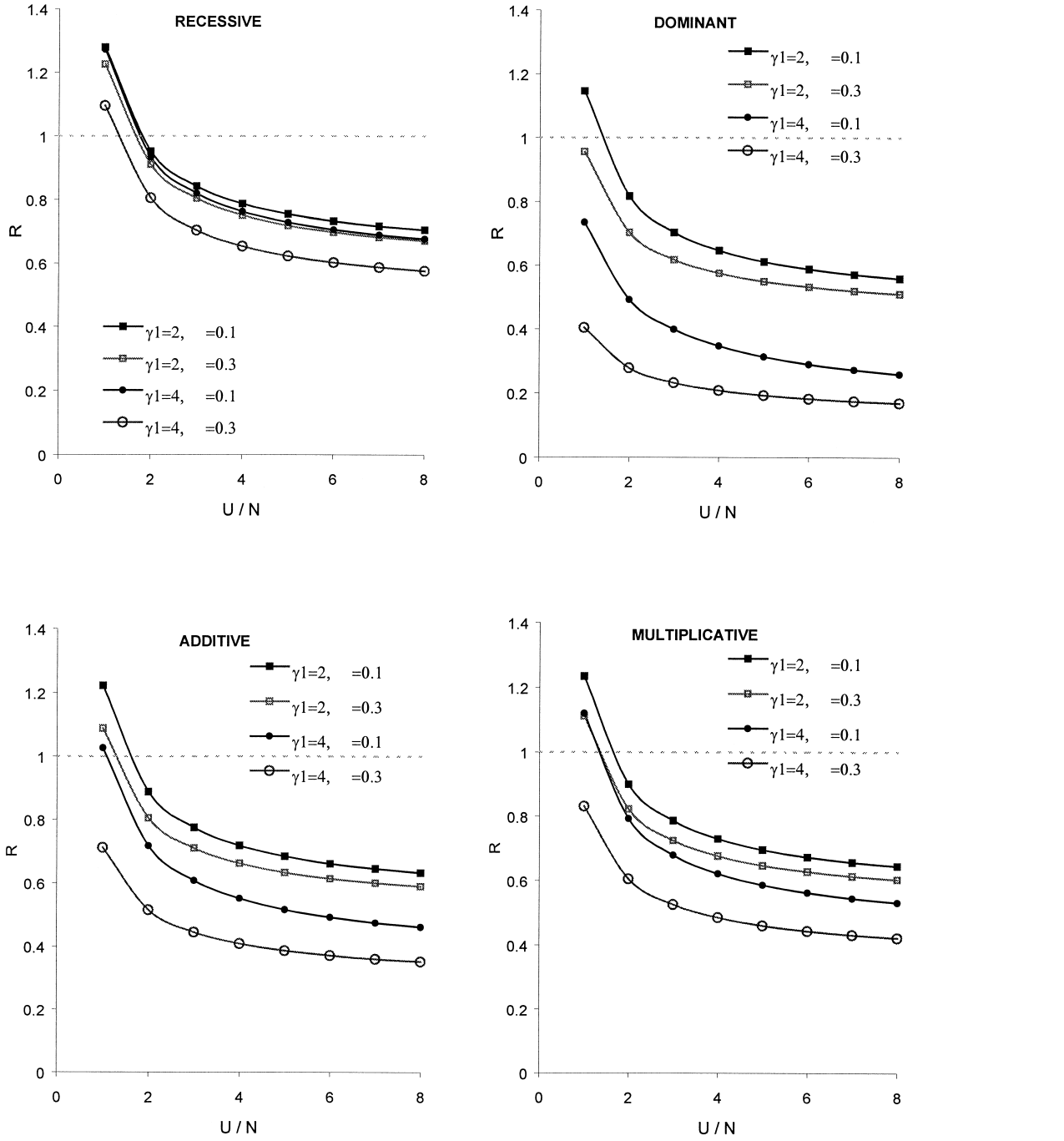

Fig. 4. Numerical comparison of the relative sample sizes needed for the TDT_{DC} and TDT_{D} in order to reach 80% power when the number of control–parent trios is not equal to that of case–parent trios in the TDT_{DC} analyses. The x-axis is the ratio of the number (U, denotes for unaffected) of control–parent trios to that (N) of case–parent trios in the combined sample for the TDT_{DC}. The y-axis is the ratio (R) of the number (N) of nuclear families (N case–parent and U control–parent trios) needed by the TDT_{DC} to that of nuclear families (N' case–parent trios) needed by the TDT_{D}. The marker locus is a DSL *per se* and $p = f$. $\alpha = 0{\cdot}05$, $\phi_{aa} = 0{\cdot}2$. ' = ' indicates frequency p.

when $\gamma \in [1{\cdot}5, 4]$ if $\phi > 0{\cdot}297$, the TDT_{DC} is more powerful than the TDT_{D}.

Extending the above arguments to the other three genetic models, we can conclude that for $\gamma \in [1{\cdot}5, 4]$ that cover a large range of genetic effects at a DSL, if $\phi > 0{\cdot}30$, the TDT_{DC} is more powerful and if $\phi < 0{\cdot}22$, the TDT_{D} is more powerful. If $0{\cdot}22 < \phi < 0{\cdot}30$, the relative power of the TDT_{DC} and the TDT_{D} depends on the genetic effect and model of the DSL under test. Since the above conclusion is obtained through analyses of all the extreme and/or typical genetic models, the conclusion should be robust with respect to the usually unknown genetic models underlying the DSL under study.

4. An example

The usefulness of control–parent trios in increasing the power of DSL identification can be illustrated by an example in the original paper that developed the TDT (Spielman *et al*., 1993). In table 5 of Spielman *et al*. (1993), the TDT_D was applied to case–parent trios in which 62 parent were heterozygous to test for linkage of the insulin gene with insulin-dependent diabetes mellitus (IDDM); the *P* value of the test was 0·004. In table 6 of Spielman *et al*. (1993), some control–parent trios with 52 heterozygous parents were analysed in combination with the case–parent trios to rule out potential segregation distortion. The *P* value of the test (the same as our TDT_{DC}) was less than 0·001 (the approximate *P* value was 0·0007), much more significant than the TDT_D test. The test result of the TDT_{DC} was only employed as evidence for the absence of segregation distortion and for confirmation (rather than for testing) of the linkage finding by the TDT_D in table 5 of Spielman *et al*. (1993). However, if the TDT_{DC} test result (*P* value 0·0007) had been directly employed for the linkage test, the evidence would have been much stronger than that from the TDT_D (*P* value 0·004). This concrete example demonstrates the power and usefulness of the TDT_{DC} in practice.

5. Discussion

We have presented an extension of the TDT (the TDT_{DC}) by effectively incorporating case–parent and unrelated control–parent trios into a single analysis for linkage and association. We derived a simple and novel analytical method for computing the statistical power of the TDT (TDT_D, TDT_C and TDT_{DC}). This analytical approach was validated by computer simulations and by comparison with earlier different analytical methods. Compared with earlier different analytical approximations to the power computation of the TDT_D (Risch & Merikangas, 1996; Knapp, 1999), our method is simpler. Our method is also more general when compared with the method of Risch & Merikangas (1996). In our method, any genetic model can easily be accounted for in the power computation not only for the TDT_D but also for the TDT_C, TDT_{DC} and TDT_{D+C} that employ control–parent trios.

We found that the TDT_{DC} is almost always more powerful than the TDT_C. When the same number of case–parent and control–parent trios are employed, the TDT_{DC} is also frequently more powerful than the TDT_D, particularly for common diseases with population prevalence $\phi > 0{\cdot}30$. The power of the TDT_{DC} can almost always be higher than the TDT_D when appropriate and unequal numbers of case–parent and control–parent trios are used. In some situations, the sample size needed for the TDT_{DC} may be many times less than that for the TDT_D. This, together with the large parameter regions revealed favouring the TDT_{DC}, makes the TDT_{DC} of potential significance in practice. Complex diseases that cause great costs for human health are generally those that are prevalent in human populations, such as hypertension, diabetes, coronary heart diseases and osteoporosis. The prevalences of these common diseases vary widely in different populations (Motulsky, 1996), with some showing a prevalence greater than 30% in some age groups in some populations (e.g. osteopenia, osteoporosis and osteoporotic fractures: Melton, 1993; Deng *et al*., 1998). Therefore, the TDT_{DC} should be of practical value for common complex diseases that result in great health costs.

Segregation distortion is a legitimate concern for significant results obtained in the TDT_D (Spielman *et al*., 1993). With segregation distortion, one allele will be preferentially transmitted to children regardless of the affected status of children. Therefore, control–parent trios are necessary in order to rule out the possibility of segregation distortion producing significant results in the TDT_D. This is necessary in order to validate the significance of a locus tested by the TDT_D in relation to an important DSL. The TDT_C and/or the TDT_{DC} may both be employed to test for segregation distortion. In the TDT_C and/or the TDT_{DC}, if significant results are found and if the same allele is preferentially transmitted to unaffected children (in the TDT_C) compared with that in the TDT_D, or to both affected and unaffected children (in the TDT_{DC}), then segregation distortion, rather than a significant DSL, is suggested. Otherwise, segregation distortion can be ruled out and a significant DSL is suggested. Control–parent trios are not only necessary for validating the significance of the locus in relation to a DSL, as shown here, but combined samples of control–parent and case–parent trios may also substantially increase the power. Therefore, the TDT_{DC} is valuable in that, first, it can test for segregation distortion in order to validate a DSL; and second, it may increase the power in detecting a DSL.

The TDT based on $\chi^2_{TDT_{D+C}}$ (denoted as TDT_{D+C}), like the TDT_{DC}, employs both case–parent and unrelated control–parent trios and can be employed both to test segregation distortion and to map a DSL. The TDT_{D+C} is indicated in Lynch & Walsh (1998) as the χ^2 test for segregation distortion in Spielman *et al*. (1993). However, Spielman *et al*. (1993) employed the TDT_{DC} (which is a contingency table test) instead of the TDT_{D+C} in computing the χ^2 statistic for the segregation distortion test. $\chi^2_{TDT_{D+C}}$ and $\chi^2_{TDT_{DC}}$ computed for the data in table 6 of Spielman *et al*. (1993) are, respectively, 12·1 and 11·5. Thus the

TDT_{DC} yields the same χ^2 statistic given for testing for segregation distortion in Spielman *et al.* (1993). Although based on the same data, $\chi^2_{TDT_{D+C}}$ computed is larger than $\chi^2_{TDT_{DC}}$, the power of the TDT_{D+C} is generally lower than TDT_{DC}. This is because $\chi^2_{TDT_{DC}}$ has only 1 d.f. and $\chi^2_{TDT_{D+C}}$ has 2 d.f.

Under the alternative hypotheses, the non-centrality parameters are derived in relation to the LD coefficient δ and the recombination rate θ between the marker locus under study and a DSL for all the TDT tests investigated here. It is shown that all the non-centrality parameters share a common multiplicative factor $(\frac{1}{2}-\theta)\delta$. Therefore, under the null hypothesis of no linkage ($\theta = 0{\cdot}5$) or no LD ($\delta = 0$), all these non-centrality parameters will be zero. These non-centrality parameters will be non-zero if and only if there is linkage ($\theta < 0{\cdot}5$) and LD ($\delta \neq 0$). Thus our analytical method for computing the power also bears proof that, in the absence of segregation distortion, all these TDT (TDT_D, TDT_C, TDT_{DC} and TDT_{D+C}) are tests for both linkage and LD.

The usefulness of control–parent trios in mapping DSL is rather controversial (Schaid, 1998; Scott *et al.*, 1999). Our results here unambiguously demonstrate that the TDT_{DC} may be more powerful than the TDT_D. The original TDT (TDT_D) (Spielman *et al.*, 1993) has been extended to several types of nuclear families in recent years. One type is nuclear families with multiple children (at least one affected and one unaffected) where parental genotype data are not available (Curtis, 1997; Horvath & Laird, 1998; Spielman & Ewens, 1998; Boehnke & Langefeld, 1998). While this extension is very valuable for late-onset diseases where parents are difficult to obtain for affected cases, Whittaker & Lewis (1999) showed that is usually not as powerful as the TDT_D. The TDT can also be extended to nuclear families with discordant sibs (one affected and one unaffected) and with both parents available. This extension of the TDT has been pursued elsewhere (Deng *et al.*, unpublished data). In addition, nuclear families of different structures (such as those with one or multiple affected children, or one affected and one unaffected child) may be combined for analyses of higher power. An extension of the TDT that can effectively employ all types of eligible nuclear families should be of significant practical value and further work needs to be pursued.

Appendix

Let the subscripts O and P denote, respectively, the child and parental generations. In the study population, the joint probability of the haplotype AM_O in a child and the genotype Mm_P in his/her parent is:

$$\begin{aligned}\Pr(Mm_P, AM_O) &= \Pr[(AM, Am)_P, AM_O] \\ &\quad + \Pr[(AM, am)_P, AM_O] \\ &\quad + Pr[(aM, Am)_P, AM_O] \\ &= 2P_{AM}(p - P_{AM})\tfrac{1}{2} \\ &\quad + 2P_{AM}(1 - p - f + P_{AM})\frac{1-\theta}{2} \\ &\quad + 2(p - P_{AM})(f - P_{AM})\frac{\theta}{2} \\ &= \delta(f' - \theta) + ff'p.\end{aligned}$$

The joint probability that a child has the haplotype AM and his/her parent has the genotype Mm and the child is affected (denoted by D) is:

$$\begin{aligned}\Pr(Mm_P, AM_O, D) &= \Pr(Mm_P, AM_O, A_O)\Pr(D|AA) \\ &\quad + \Pr(Mm_P, AM_O, a_O)\Pr(D|Aa) \\ &= (p\phi_{AA} + q\phi_{Aa})\Pr(Mm_P, AM_O) \\ &= (p\phi_{AA} + q\phi_{Aa})[\delta(f' - \theta) + ff'p]'\end{aligned}$$

where $\Pr(Mm_P, AM_O, A_O)$ is the joint probability that a child has the haplotype AM and his/her parent has the genotype Mm and the other allele at the DSL in the child is A. $\Pr(Mm_P, AM_O, a_O)$ is similarly defined. Similarly, it can be shown that:

$$\Pr(Mm_P, aM_O, D) = (p\phi_{Aa} + q\phi_{aa})[\delta(\theta - f') + ff'q].$$

Therefore, the joint probability that a child has an M allele and is affected and his/her parent has the genotype Mm is:

$$\begin{aligned}\Pr(Mm_P, M, D) &= Pr(Mm_P, AM_O, D) \\ &\quad + \Pr(Mm_P, aM_O, D) \\ &= \delta(f' - \theta)C + ff'\phi.\end{aligned}$$

The expected number of parents heterozygous at the marker locus in such families is $2N\Pr(Mm_P|D)$. Let $\Pr(M|Mm_P, D)$ be the probability that an Mm heterozygous parent transmits the M allele to his/her affected child. The expected number of transmitted M alleles ($E(T)$) from heterozygous parents in families with one affected child and at least one heterozygous (at the marker locus) parent is then:

$$\begin{aligned}E(T) &= 2N\Pr(Mm_P, M|D) \\ &= 2N\Pr(Mm_P, M, D)/\phi \\ &= 2N[ff' + \delta(f' - \theta)C/\phi].\end{aligned}$$

Similarly, the expected number of transmitted m alleles ($E(NT)$) from heterozygous parents in families with one affected child and at least one heterozygous (at the marker locus) parent can be derived as:

$$E(NT) = 2N[ff' + \delta(\theta - f)C/\phi].$$

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References

Boehnke, M. & Langefeld, C. D. (1997). A transmission/disequilibrium test that uses both affected and unaffected offspring. *American Journal Human Genetics* (Supplement) **61**, A269.

Chakraborty, R. & Smouse, P. (1988). Recombination in haplotypes leads to biased estimates of admixture proportions in human populations. *Proceedings of the National Academy of Sciences of the USA* **85**, 3071–3074.

Chen, W.-M. & Deng, H.-W. (2001). An accurate and general approach for computing the power of the transmission disequilibrium test. *Genetic Epidemiology* **21**, 53–67.

Curtis, D. (1997). Use of siblings as controls in case–control association studies. *Annals of Human Genetics* **61**, 319–333.

Deng, H.-W. & Chen, W. M. (2000). Re: 'Biased tests of association: comparison of allele frequencies when departing from Hardy–Weinberg proportions'. *American Journal of Epidemiology* **151**, 335–357.

Deng, H.-W., Li, J. L., Li, J., Davies, M. K. & Recker, R. R. (1988). Heterogeneity of bone mass density across skeletal sites and its clinical implications. *Journal of Clinical Densitometry* **1**, 339–353.

Deng, H.-W., Chen, W. M. & Recker, R. R. (2000*a*). QTL fine mapping by measuring and testing for Hardy–Weinberg and linkage disequilibrium at a series of linked marker loci in extreme samples of populations. *American Journal Human Genetics* **66**, 1027–1045.

Deng, H.-W., Chen, W. M. & Recker, R. R. (2000*b*). Population admixture: detection by Hardy–Weinberg test and its quantitative effects on linkage-disequilibrium methods for localizing genes underlying complex traits. *Genetics* **157**, 885–897.

Deng, H.-W., Chen, W. M. & Recker, R. R. (2001). Powerful and robust tests of linkage and association based on parental genotypes to map loci underlying complex diseases. *Life Science Research* (in press).

Ewens, W. J. & Spielman, R. S. (1995). The transmission/disequilibrium test: history, subdivision, and admixture. *American Journal of Human Genetics* **57**, 455–464.

Feder, J. N., Gnirke, A., Thomas, W. & Tsuchihasi, Z. (1996). A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genetics* **13**, 399–408.

Hartl, D. L. & Clark, A. G. (1989). *Principles of Population Genetics*. Sunderland, MA: Sinauer.

Hastbacka, J., de la Chapelle, A., Kaitila, I., Sistonen, P., Weaver, A. & Lander, E. S. (1992). Linkage disequilibrium mapping in isolated founder populations: diastrophic dysplasia in Finland. *Nature Genetics* **2**, 204–211.

Hastbacka, J., de la Chapelle, A., Mahtani, M. M., Clines, G., ReeveDaly, M. P., Daly, M., Hamilton, B. A. *et al*. (1994). The diastrophic dysplasia gene encodes a novel sulfate transporter: position cloning by fine-structure linkage disequilibrium mapping. *Cell* **78**, 1073–1087.

Horvath, S. & Laird, N. M. (1998). A discordant-sibship test for disequilibrium and linkage: no need for parental data. *American Journal of Human Genetics* **63**, 1886–1897.

Knapp, M. (1999). A note on power approximations for the transmission/disequilibrium test. *American Journal of Human Genetics* **64**, 1177–1185.

Lander, E. S. & Schork, N. J. (1994). Genetic dissection of complex traits. *Science* **265**, 2037–2048.

Lazzeroni, L. C. & Lange, K. (1998). A conditional inference framework for extending the transmission/disequilibrium test. *Human Heredity* **48**, 67–81.

Lynch, M. & Walsh, B. (1998). *Genetics and Data Analysis of Quantitative Traits*. Sunderland, MA: Sinauer.

Melton, L. J. III. (1993). Epidemiology of Age-related Fractures. In *The Osteoporotic Syndrome*. 3rd edn (ed. L. V. Avioli), pp. 17–38. New York: Wiley-Liss.

Motulsky, V. (1996). *Human Genetics*. Berlin: Springer.

Nielsen, D. M., Ehm, M. G. & Weir, B. S. (1998). Detecting marker-disease association by testing for Hardy–Weinberg disequilibrium at a marker locus. *American Journal of Human Genetics* **63**, 1531–1540.

Risch, N. & Merikangas, K. (1996). The future of genetic studies of complex human diseases. *Science* **273**, 1516–1517.

Schaid, D. J. (1996). General score tests for associations of genetic markers with diseases using cases and their parents. *Genetic Epidemiology* **13**, 423–449.

Schaid, D. J. (1998). Transmission disequilibrium, family controls, and great expectations. *American Journal of Human Genetics* **63**, 935–941.

Schaid, D. J. & Jacobsen, S. J. (1999). Biased tests of association: comparisons of allele frequencies when departing from Hardy–Weinberg proportions. *American Journal of Epidemiology* **149**, 706–711.

Scott, L. J., Krolewski, A. & Rogus, J. J. (1999). Comparison of the power of the transmission distortion test (TDT) for affected and unaffected trios when disease is highly prevalent. *American Journal of Human Genetics* (Supplement) **65**, A397.

Sham, P. C. & Curtis, D. (1995). An extended transmission/equilibrium test (TDT) for multi-allelic marker loci. *Annals of Human Genetics* **59**, 323–336.

Spielman, R. S. & Ewens, W. J. (1996). The TDT and other family-based tests for linkage disequilibrium and association. *American Journal of Human Genetics* **59**, 983–989.

Spielman, R. S. & Ewens, W. J. (1998). A sibship test for linkage in the presence of association: the sib transmission/disequilibrium test. *American Journal of Human Genetics* **62**, 450–458.

Spielman, R. S., McGinnis, R. E. & Ewens, W. J. (1993). Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *American Journal of Human Genetics* **52**, 506–516.

Weir, B. S. (1996). *Genetic Data Analysis II*. Sunderland, MA: Sinauer.

Whittaker, J. C. & Lewis, C. M. (1998). The effect of family structure on linkage tests using allelic association. *American Journal of Human Genetics* **63**, 889–897.

Whittaker, J. C. & Lewis, C. M. (1999). Power comparison

of the transmission disequilibrium test and sib-transmission disequilibrium-test statistics. *American Journal of Human Genetics* **65**, 578–580.

Wilson, E. B. & Hilferty, M. M. (1931). The distribution of chi-square. *Proceedings of the National Academy of Sciences of the USA* **17**, 684–688.

Wolfram, S. (1996). *The Mathematica*. Champaign II: Wolfram Research.

Xiong, M. M. & Guo, S. W. (1997). Fine-scale genetic mapping based on linkage disequilibrium: theory and applications. *American Journal of Human Genetics* **60**, 1513–1531.