where pchisq and qchisq are the distribution and quantile function, respectively, of the χ_1^2 distribution. The qchisq(0.05/100000,1,lower.tail = FALSE) part gives the critical value to be evaluated against the noncentral χ_1^2 distribution function for a given NCP. The power of the "screening" test is

$$\begin{aligned}&\Pr(\text{truly associated SNPs are in top 10 out of 100 ,000})\\&\quad * \Pr(\text{second stage SNPs are significant after correction for ten tests}) = \text{pchisq}(\text{qchisq}(10/100000,\text{df} = 1,\\&\quad \text{lower.tail} = \text{FALSE}),\text{df} = 1,\text{ncp} = 15,\text{lower.tail} = \text{FALSE})\\&\quad * \text{pchisq}(\text{qchisq}(0.05/10,1,\text{lower.tail} = \text{FALSE}),\text{df} = 1,\\&\quad \text{ncp} = 15,\text{lower.tail} = \text{FALSE}) = 0.42\end{aligned}$$

If both the proportion of markers and the proportion of information coming from the "between" and "within" stages are varied across the full range of possible values (by, for example, use of two nested loops in R), the power of the "screening" approach is always lower than for the "total" approach.

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Response to Macgregor

To the Editor: We appreciate the opportunity to respond to the letter by Macgregor. Macgregor claims that a total test for family-based designs should be more powerful than a two-stage design of the kind we proposed,[1,2] by drawing an analogy to the population-based scenario illustrated in Skol et al. (2006).[3] It is difficult for us to verify this statement directly because we could not find a precise definition of a "total-family" test neither in Macgregor's letter nor in any of the cited papers.

In Ionita-Laza et al. (2007),[2] we compared our testing strategies directly to pure population-based tests; these define the upper limit in terms of statistical power. However, as shown in our paper, the power differences between our weighted Bonferroni approach and the population-based test are very small; intuitively, we would expect that no test can do better than the total population-based test from an efficiency point of view. Consequently, any "total-family" test can have only marginal improvements over the strategies we proposed.

We believe that the power differences between the total test and the two-stage test shown in Macgregor's letter are overestimated for two reasons. First, as we showed in Ionita-Laza et al. (2007),[2] the weighted Bonferoni offers significant power increases over the Top k approach,[1] which is the only two-stage approach assessed in the simulation studies by Macgregor. Second, in Macgregor's simulation studies, ranking is based on p values in the first stage of the testing strategy. Van Steen et al. (2005)[1] showed that ranking based on conditional power estimates provides greater overall power than ranking based on p values. Intuitively, one expects conditional power to be a better predictor for the FBAT. Besides the genetic effect-size estimate that is based on the between-family component, ranking on conditional power also takes into account important additional information: the number of informative transmissions in the subsequent FBAT statistic. On the other hand, screening based on p values for the between-family component is purely based on the between-family component and does not incorporate any information about the number of informative transmissions, which can

be as important as the genetic effect size for the success of the FBAT.

With respect to the proposed adjustment for population substructure in the total test, we believe that, although it is true in theory that the between-family component can be corrected for population substructure, the adjustment is not trivial in practice. All popular methods for the detection of population substructure have been developed for unrelated subjects. Family data are the strongest form of population substructure, and the effectiveness of these methods has not been tested with family data.

In summary, we believe that Van Steen-type testing strategies are the natural complement for family-based designs. By using a true TDT-type test in the second stage of the testing strategy, they are completely robust against unknown confounding and admixture. Furthermore, by conditioning on the phenotype in the computation of the FBAT, they are also robust against any model misspecification with respect to the phenotype. They vastly increase efficiency over strictly within designs, particularly in the GWA setting. The proposed alternative, which is to analyze family-based data as population-based data, provides only marginal power advantages, whereas the robustness issues remain unsolved.

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