A HIGH-SPEED METHOD FOR POPULATION PHARMACOKINETIC DATA ANALYSIS IN GENOME-WIDE PHARMACOGENOMIC STUDIES

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Recently, many pharmacogenomic studies have been launched worldwide, such as a pharmacokinetic study including analyses of single-nucleotide polymorphisms (SNPs) in a candidate gene or a genome-wide approach for screening pharmacokinetics-related genes (those that influence drug absorption, distribution, metabolism, and excretion). Furthermore, powerful array-based SNP typing platforms have heralded an era in which a genome-wide association study is a popular or standard strategy, and genotype data on 100 000–1 000 000 SNPs are increasingly available to researchers.

We considered the problem of screening pharmacokinetics-related genes in genome-wide pharmacogenomic studies. In this study, we considered the effect of a biallelic SNP, i.e., the existence of 2 variants for a base at a given locus, on pharmacokinetic parameters. Genome-wide pharmacogenomic studies are typically analyzed using non-compartmental methods followed by analysis of variance or maximum contrast methods on the estimated individual parameters (Nagashima, et al. 2011). Other appropriate approaches include nonlinear mixed-effects models (Bertrand, et al. 2011). However, the computational speed of nonlinear mixed-effects models is frequently slow, because these models must compute the marginal likelihood by integrating out the random effect. Thus, it is difficult to analyze these large data by using nonlinear mixed-effects models.

We proposed a fast population pharmacokinetic data analysis method without using nonlinear mixed-effects models for screening pharmacokinetics-related genes in genome-wide studies. The method applies potentially misspecified models (White, 1982) for considering variability in pharmacokinetic parameters among individuals, and is based on the quasi-maximum likelihood estimator and the sandwich variance estimator (White, 1982) to test the hypothesis that the weighted averages of individual pharmacokinetic parameters is equal in each genotype. The proposed method improves computational speed because it is based on fixed-effect models.

Through a simulation study, we evaluated the computational speed, type-I error rate, and power of the proposed method. The simulation results showed that the proposed method can control the type-I error rate at the nominal level for some situations.

References

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