Gamma frailty model for linkage analysis with application to interval censored migraine data

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Studies on several diseases show strong age at onset correlation between family members (e.g., breast cancer and Alzheimer disease). The results of these studies suggest that not only the occurrence, but also the age at onset of the disease is genetically influenced. Therefore information on age at onset is often collected to map the disease gene(s) and the gene(s) that influence the age at onset of the disease. The exact ages are often missing by censoring or truncation. This makes techniques that are often used for mapping genes for complex quantitative traits (Haseman-Elston regression and variance decomposition models) less useful for survival data. Instead, statistical methods for gene-search which combine techniques of survival analysis and methods of quantitative genetics can be used.

Our aim is to test the genetic contribution to the age at which people experience their first migraine attack and to find locations on the chromosomes that show linkage with the genes that influence this age at onset of migraine. The data we use are from a longitudinal study of Dutch twins and their family members. The ages at migraine onset are interval censored. So no exact ages are available; just age intervals in which the age at onset falls. Furthermore, IBD information for 63 to 284 markers on the autosomes is available for 258 dizygotic twins.

The first aim is to test heritability of migraine onset; so to test whether there is a genetic contribution to the variability of age at onset of migraine. The second aim is to test for each of the markers whether they are linked to age at onset of migraine. In order to test for linkage, we model the migraine data of the twins with a correlated gamma frailty model. The frailty term of each twin is decomposed as a linear combination of independent gamma distributed random variables which represent the genetic contribution to the age at onset of migraine due to part of the genome at a marker, genetic contribution due to loci unlinked to the specific marker, contributions due to shared familial effects and to unshared environmental effects. For testing heritability we use the same model, but with a different meaning of the terms of the decomposed frailty variable.

We assume that the frailty variable follows a gamma distribution. Then, an explicit expression of the bivariate survival function in terms of the marginal survival function exists. Estimation of the parameters and testing heritability and linkage are considered in the cases that the marginal survival function is completely unknown (in which case we have a semi-parametric model) and that it belongs to a family of parametric distributions (parametric model). For the parametric and for the semi-parametric model heritability and linkage are tested with the likelihood ratio test.

Heritability was estimated and tested based on data of almost 4,000 twin pairs. Heritability was estimated as 0.42 and 0.37 in the parametric and semi-parametric model, respectively. These values were significant. So, there is a genetic contribution to the variability of age at onset of migraine. Linkage analysis was only based on the genotyped dizygotic twin pairs; 258 pairs in total. The highest lod-score ($=^{10} \log$ (LR-statistic)) was 1.86 at the end of chromosome 19. In practice the value 3 is often taken as a threshold for significant lod-scores. In that case none of the lod-scores is significant. More twins will be genotyped in the near future, so that it gets easier to detect interesting locations on the chromosomes.