

# **Additive Gamma Frailty Models for Genetic Linkage and Association Analysis**

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Many late-onset complex diseases exhibit variable age of onset. Efficiently incorporating age of onset information into genetic linkage and association analysis can potentially increase the power of dissecting complex diseases. In this paper, we treat age of onset as a genetic trait with censored observations. We use multiple markers to infer the inheritance vector at the disease susceptibility (DS) locus in order to extract information about the inheritance pattern of the disease allele in a pedigree. Given the inheritance distribution at the DS locus, we define the genetic frailty for each individual within a nuclear family as the sum of frailties due to a putative major disease gene and a polygenic effect due to any remaining DS loci. Conditioning on these frailties we use the proportional hazards model for the risk of developing disease. We show that a test of linkage can be formulated as a test of zero variance due to a specific locus of the additive gamma frailties. Extensions of the basis additive gamma frailty model to family-based genetic association analysis and multi-locus linkage analysis and the issue of ascertainment correction will also be briefly presented and discussed. Simulations and a breast cancer data example are used for illustration.