USING LATENT CLASS MODELS TO REDEFINE THE PHENOTYPE IN COMPLEX DISEASES

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In genetic studies, phenotype misclassification may be an important factor explaining the failure of genetic linkage studies to identify certain genes as responsible for a complex disease. Our hypothesis is that sub-classes of subjects broadly defined as affected may be detectable from differences in their patterns of phenotypic measurements. This leads us to develop statistical models describing the multivariate symptoms of subjects in families as a function of latent homogeneous disease classes. Specifically, we are extending latent class analysis methods to allow dependence between the latent disease class status of relatives within families. Such dependence is taken into account at the class level, and we suppose that the class of an individual may depend on the class of its parents or other relatives through a Markov structure, using appropriate parameterizations of transition probabilities. Furthermore, dependence between the symptoms of an individual can be modeled adequately by using a multivariate distribution with an appropriate correlation structure specific for each class. The special case of ordinal symptom data is considered. The parameters of the Markov structure can be estimated successfully using the EM algorithm. Finally, the method developed is applied to a dataset of 48 extended pedigrees comprising over 400 subjects affected by schizophrenia or bipolar disorder, with 82 symptoms measured on each affected subject.