A New Powerful Study Design for Linkage Analysis of Quantitative Traits: The Single Parental Proband Sib-Pair Study Design

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To unravel the basis of complex genetic diseases, a sample of nuclear families consisting in sib-pairs is often ascertained. Three different ascertainment schemes have been contradictorily discussed regarding their power, cost efficiency, and interpretability [for a detailed discussion see, e.g., 1]. The first approach is to draw sib pairs randomly from the general population (random sib pair – RSP). Secondly, sib pairs may be ascertained via one sibling that has an extreme value regarding the trait of interest (single proband sib pair – SPSP). The SPSP approach has greater statistical power for a broad variety of single locus models than the RSP approach. Thirdly, the double proband sib-pair design, also termed extreme sib-pair (ESP) design may be employed. Here, both siblings have extreme trait values from the top or the bottom tail of the distribution. In the latter two study designs, phenotypic values of siblings are used for selecting nuclear families.
An alternative approach is the following. A clinically relevant expression of a phenotype is often observed in individuals at higher age only, while an intermediate quantitative trait can also be observed early. The older subjects can easily be recruited from a clinic, be the starting point for an ascertainment of a nuclear family, and serve as parents within the nuclear family. This results in the single parental proband sib-pair (SPPSP) design. To our knowledge, this study design has not been theoretically investigated. It has, however, been applied at least twice; in both cases we are aware of for the investigation of the intima media thickness [2,3].
In this presentation, we firstly derive the properties of the SPPSP design with the Haseman-Elston method [4] as method for statistical analysis for a major locus model. Interpretation of the estimated regression parameter is intuitive and analogous to the Haseman-Elston method for both the RSP design and the SPSP design. Second, we perform analytical power and sample size calculations for the SPPSP design and show that this study design is more powerful than the RSP approach in all investigated situations. Third, we validate the analytically calculated sample sizes in a Monte-Carlo simulation study.
The SPPSP study design is a feasible approach with several advantages. It yields up to 10-fold reduced sample size compared with the RSP design. The Haseman-Elston regression approach or variance component models can be used for analytical power and sample size calculations. Practical advantages and disadvantages are analogous to that of the SPSP study design. However, especially for late-onset diseases it might be superior to other study designs.

References

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