

BIAS AND INFLATED VARIANCE IN THE GENEHUNTER NONPARAMETRIC LINKAGE TEST STATISTIC

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The nonparametric linkage (NPL) analysis technique for sib pairs is a popular method, but surprisingly low power of NPL compared with to the powerful Haseman-Elston (1972) regression is evident, even though both methods theoretically resemble each other. We report that the NPL test statistic of Kruglyak and Lander (1995) is biased and its variance is inflated, which no one has mentioned it so far, and this explains why some applications of NPL analysis with sib pairs data to complex traits and diseases have led to not compelling results. We systematically describe the problems of bias and inflated variance for a single marker situation, which is enough for an explanation of the test statistics, apart from the various analysis strategies of multipoint data. We then extend the NPL test statistic to propose a more powerful one, in which biasedness is corrected along with a more refined variance estimate. Two more nonparametric statistics of legitimate contenders are also described. When these test statistics are compared by a simulation study with its precursor NPL statistic and the Haseman-Elston regression, power of a newly proposed NPL test statistic was greatly enhanced compared to its precursor, and two other NPL statistics also demonstrate equally high powers. Past results obtained using the NPL methods for sib pairs might therefore be worth revisiting to see if significant results can be obtained by use of these newly proposed test statistics.