Reviewers' Comments  
  
Reviewer: 1  
  
Comments to Author  
The authors addressed an important topic in genetic epidemiology, namely the estimation of heritability in a large family-based ascertained sample. The authors introduced a novel method, namely the use of conditional likelihood, or perhaps more precisely, the “Ascertainment Assumption Free” (AAF) approach of Shute and Ewens (1986) for estimating heritability. Innovative use of the conditional EM algorithm of Jebara and Pentland (1999) was applied.   
  
My comments:   
1. I find the approach used the authors interesting and potentially very important. However, my concern is that the general readership of the paper may find it hard to follow as some of the key results made use of by the authors are probably not well known. Of note, the validity of the approach hinges on the validity of the conditional likelihood given on line 17 of page 11. Through some digging of my own, I linked this approach to the AAF approach of Shute and Ewens (1986), although this was not cited by the authors. (The authors did cite Sawyer (1990), a related paper, but in another context.) I would appreciate more explanation of the rationale behind this method and its relative advantages and disadvantages. Likewise, I think Jebara and Pentland (1999) is a novel approach seldom seen in the genetics literature. The theory of this approach appears to underlie the derivations given on page 11, which was impossible to follow without an understanding of Jebara and Pentland (1999).  
  
2. A commonly used approach for estimating heritability in family data is Hasemen-Elston regression (Haseman and Elston, 1972, Golan et al, 2014). This was not mentioned in the manuscript. I think a comparison of the proposed method with Hasemen-Elston is very much needed.   
  
3. Jebara and Pentland (1999) appears to address a computation rather than statistical issue. It seems to me that other more commonly used approaches such as Newton Raphson would have sufficed for the optimization of the conditional likelihood. Perhaps the authors can make clearer the rationale behind the use of Jebara and Pentland (1999). Is it mainly for speed? If so, perhaps its discussion can be deferred to the appendix/supplementary materials?  
  
4. GCTA is probably not the most relevant method for comparison, given that it was designed for SNP data, whereas the proposed method concerns family/pedigree data.   
  
5. I’m unsure about the benefits of introducing the constraints for 0 < h2 < 1 into the calculations. Apart from making the method more complicated, an estimate of h2 that is outside these normal bounds may indicate something wrong with the data, and the constraints to ensure the estimates fall within the bounds may not be helpful.  
  
6. In principle a major advantage of the method is that it can be readily extended to deal with variance components that are non-additive. However, the method was not applied to estimate these quantities. Why was this not done? Are there any inherent limitations in the method that diminishes its usefulness for estimating these non-linear VC?  
  
7. The grammar of the article needs to be improved. In particular, the result section should be written in the past tense.  
  
8. Line 17 on page 8: The equation misses out the term B\_i^T Sigma\_i^-1 B\_i inside the bracket on the right hand side.

9. It was strange that the test was very inaccurate for q = 0.05 and 0.2 (page 16). Why was this the case?  
  
References:   
  
Ewens and Shute (1986). A resolution of the ascertainment sampling problem I. Theory. Theoretical Population Biology 30(3): 388-412  
  
Hasemand and Elston (1972). The investigation of linkage between a quantitative trait and a marker locus. Behavior Genetics 2(1): 3-19  
  
Golan et al (2014). Measuring missing heritability: Inferring the contribution of common variants. PNAS Vol 111: E5272--E5281

# Reviewer 2

Summary

Kim, Kwak and Won present a novel statistical method to estimate heritability for dichotomous outcomes based on the liability threshold model and compare with the GCTA software, which implements a linear mixed model and estimates variance components using restricted maximum likelihood and was originally proposed for SNP-based heritability estimation, in simulation and show results from their method in a large pedigree data set on Type 2 diabetes from Korea. The statistical model and subsequent care taken to establish the statistical properties of the method are substantial and the score test for testing the significance of the heritability estimate is an interesting result.

The work needs to establish itself in the context of the advancements in heritability estimation and generalised linear mixed model optimisation for dichotomous variables. The large genomic/genetic data sets now available, which are now vast for disease traits, lowers the importance (in my opinion) of pedigree data collection for heritability estimation. Relevant literature needs to be discussed and compared against for the work to be a genuine addition to the genetics literature over and above the manuscript’s statistical achievements. I believe there have been other recent pieces of work that have not been referenced or compared against that address similar problems and models. I believe it necessary for the authors to both discuss these relative to their work and use them (a subset) in their simulation studies.

Major points

As outlined above, the work needs to discuss and compare the proposed method against recent work in this area. In particular, in terms of overcoming case-control ascertainment and implementing at scale with very impressive optimization algorithms for generalized linear mixed models the recent work of Chen et al. 2016 and Zhou et al. 2018 are very important. Both methods estimate variance components and perform LMM variant mapping. Can these be discussed in the context of the proposed method? If they are not adequate for heritability estimation can is be discussed why they are not appropriate?

Furthermore, and perhaps more importantly, fast heritability estimation methods for dichotomous variables have been recently proposed in Golan et al., 2014, Weissbrod et al, 2018 and Bonnet, 2018. Golan et al., 2014 clearly show the downward bias in heritability estimation from GCTA-GREML and the failure of the Lee, 2011 transformation to adequately deal with heterogeneous ascertainment. Golan et al., 2014 provide a very detailed explanation of the reasons why this occurs and summarise the problem in context in a more complete way compared with the current manuscript. Can these methods be discussed in the context of the current method and compared against in the simulation? Furthermore, Loh, 2015 and Bulik-Sullivan, 2015 provide efficient methods to estimate heritability and genetic correlation, which were applied to dichotomous variables, that could be compared and discussed with the proposed method.

The detail regarding the data that are being used for the simulation studies needs further clarification. This has particular importance with the comparison with GCTA, which is designed to work with genotype data. There is mention of genotype data in the simulation description but it is unclear whether this is being used to construct a genetic relatedness matrix or are the pedigree relationships between individuals just being used? The description of “all results were compared again GCTA” on line 34 of page 14 is not adequate for the reader to understand what analysis was performed. It is not clear what β is meant to represent in the simulation study. It is a major genetic effect? Is the method is being proposed as a variant mapping technique as well as a heritability estimation method?

Given the dramatic results of Table 2, all estimates from GCTA being equal to 0, the GCTA analysis needs to be more clearly described and fleshed out. The results of the simulation for ascertained families are extreme for GCTA. Can the authors be sure that this is not a result of the simulation proposed as it is stated that relatives should be removed from the analysis when using GCTA-GREML? You could generate a larger pedigree and just analyse the subset of unrelated individuals, at a dramatic loss in data, using GCTA and provide the estimate. Can a less extreme ascertained family simulation be shown to give the reader an intermediate step to compare these results against? This will reinforce the result as not an edge case of the GCTA-GREML method. Comparison with other methods will also help here. If they are too 0 then this gives further evidence to this result.

Can the simulations include the results from not simulation under the liability threshold model?

Minor points

Line 19: Can the term ‘genetic components’ be more clearly explained.

Line 21: The construction of genetic correlation (?relatedness) matrices from genetic data

date back to earlier than 2015. More references are required here.

Line 30: The missing heritability debate has a large literature, which needs to be cited here.

Line 46: Can the authors clarify how polygenic score methods have been used for heritability estimation.

Page 4, Line 26: Can the phrase ‘negative correlation’ be clarified. Negative correlation between which quantities.

Page 13 Line 57: Is B(2, 0.2) Binomial? Page 14: Can ha be defined.

Page 15: Line 31: One of the scenarios the SE from LTMH is greater than GCTA. Page 16: Line 15: What is meant by ’empirical sizes’. Page 16: Line 58: Should 1736 be 1763? Table 1: Don’t think you need to define SD. Table 2: Needs improved formatting. Table 5. The method appears very conservative in these scenarios for type-1 error. Can this be discussed more in the text.

References

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