Determining the genome-wide kinship coefficient seems unhelpful in distinguishing consanguineous couples with a high versus low risk for adverse reproductive outcome

Abstract

Background: Offspring of consanguineous couples are at increased risk of congenital disorders. The risk increases as parents are more closely related. Individuals that have the same degree of relatedness according to their pedigree, show variable genomic kinship coefficients. To investigate whether we can differentiate between couples with high- and low risk for offspring with congenital disorders, we have compared the genomic kinship coefficient of consanguineous parents with a child affected with an autosomal recessive disorder with that of consanguineous parents with only healthy children, corrected for the degree of pedigree relatedness. Methods: 151 consanguineous couples (73 cases and 78 controls) from 10 different ethnic backgrounds were genotyped on the Affymetrix platform and passed quality control checks. After pruning SNPs in linkage disequilibrium, 57,358 SNPs remained. Kinship coefficients were calculated using three different toolsets: PLINK, King and IBDelphi, yielding five different estimates (IBDelphi, PLINK (all), PLINK (by population), King robust (all) and King homo (by population)). We performed a one-sided Mann Whitney test to investigate whether the median relative difference regarding observed and expected kinship coefficients is bigger for cases than for controls. Furthermore, we fitted a mixed effects linear model to correct for a possible population effect. Results: Although the estimated degrees of genomic relatedness with the different toolsets show substantial variability, correlation measures between the different estimators demonstrated moderate to strong correlations. Controls have higher point estimates for genomic kinship coefficients. The one-sided Mann Whitney test did not show any evidence for a higher median relative difference for cases compared to controls. Neither did the regression analysis exhibit a positive association between case-control status and genomic kinship coefficient. Conclusions: In this case-control setting, in which we compared consanguineous couples corrected for degree of pedigree relatedness, a higher degree of genomic relatedness was not significantly associated with a higher likelihood of having an affected child. Further translational research should focus on which parts of the genome and which pathogenic mutations couples are sharing. Looking at relatedness coefficients by determining genome-wide

SNPs does not seem to be an effective measure for prospective risk assessment in consanguineous parents.