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Autozygosity-Linked to a Wide Range of Human Traits

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Commentary

Autozygosity occurs when two chromosomal segments that are identical from a common ancestor are inherited from each parent. This occurs at high rates in the offspring of mates who are closely related (inbreeding), but also occurs at lower levels among the offspring of distantly related mates. Here, we use runs of homozygosity in genome-wide SNP data to estimate the proportion of the autosome that exists in autozygous tracts in 9,388 cases with schizophrenia and 12,456 controls. We estimate that the odds of schizophrenia increase by ~17% for every 1% increase in genome-wide autozygosity. This association is not due to one or a few regions, but results from many autozygous segments spread throughout the genome, and is consistent with a role for multiple recessive or partially recessive alleles in the etiology of schizophrenia. Such a bias towards recessivity suggests that alleles that increase the risk of schizophrenia have been selected against over evolutionary time.

For genomic analyses, genetic data from crossbreds is frequently generated. The goal of this study is to use genotypic information from SNP arrays in 1,173 crossbreds to evaluate autozygosity and genetic differentiation in Landrace by Large-White breeds. To assess the probability of autozygosity, a maximum likelihood technique was developed. FST and the difference in allele frequencies between the two parental breeds at each Single-Nucleotide Polymorphism (SNP) site were used to study regions of breed differentiation. To estimate allele frequencies in parental populations, a maximum likelihood technique was presented. For segments with at least 25, 15, and 5 SNPs, the average length of runs of homozygozity (ROH) across the genome was 3.91, 2.3, and 0.7 Mb, respectively. For segments with at least 25, 15, and 5 SNPs, the average age to merge was 46, 414, and 388 years, respectively. The chance of autozygosity was not uniform throughout the crossbred genome, with most chromosomes having a larger probability of autozygosity in the middle. In most chromosomes, there was a positive and substantial link between autozygosity and distance to the closest telomere, which could be explained by the increased recombination rate near telomeres.

In many species, the offspring of related parents suffer reduced reproductive success, a phenomenon known as inbreeding depression. In humans, the importance of this effect has remained unclear, partly because reproduction between close relatives is both rare and frequently associated with confounding social factors. Here, using genomic inbreeding coefficients (FROH) for 1.4 million individuals, we show that FROH is significantly associated with apparently deleterious changes in 32 out of 100 traits analysed. These changes are associated with runs of homozygosity (ROH), but not with common variant homozygosity, suggesting that genetic variants associated with inbreeding depression are predominantly rare. The effect on fertility is striking: FROH equivalent to the offspring of first cousins is associated with a 55% decrease [95% CI 44-66%] in the odds of having children. Finally, the effects of FROH are confirmed within full-sibling pairs, where the variation in FROH is independent of all environmental confounding.

Inbreeding depression refers to lower fitness among offspring of genetic relatives. This reduced fitness is caused by the inheritance of two identical chromosomal segments (autozygosity) across the genome, which may expose the effects of (partially) recessive deleterious mutations. Even among outbred populations, autozygosity can occur to varying degrees due to cryptic relatedness between parents. Using dense genome-wide single-nucleotide polymorphism (SNP) data, we examined the degree to which autozygosity associated with measured cognitive ability in an unselected sample of 4854 participants of European ancestry. We used runs of homozygosity—multiple homozygous SNPs in a row—to estimate autozygous tracts across the genome.

We found that increased levels of autozygosity predicted lower general cognitive ability, and estimate a drop of 0.6 s.d. among the offspring of first cousins (P=0.003–0.02 depending on the model). This effect came predominantly from long and rare autozygous tracts, which theory predicts as more likely to be deleterious than short and common tracts. Association mapping of autozygous tracts did not reveal any specific regions that were predictive beyond chance after correcting for multiple testing genome wide. The observed effect size is consistent with studies of cognitive decline among offspring of known consanguineous relationships. These findings suggest a role for multiple recessive or partially recessive alleles in general cognitive ability, and that alleles decreasing general cognitive ability have been selected against over evolutionary time.

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