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Identifying genes associated with maternal nondisjunction of chromosome 21

We have conducted the first GWAS to identify genes associated with nondisjunction of chromosome 21 in oocytes. A total of 2,186 study subjects were genotyped on the HumanOmniExpressExome-8v1-2 array. These subjects included over 700 live birth offspring with standard trisomy 21 derived from an error in the oocyte and over 1400 parents. Genotypes for chromosome 21 in children were called using methods we previously developed. Genotypes for parents and child were then used to establish parent of origin, stage (meiosis I or meiosis II) and meiotic recombination patterns for each child.

We used two different designs for conducting the GWAS. In the first, we take advantage of the fact that the etiologies of meiosis I trisomy 21 and meiosis II trisomy 21 appear to be quite different, and perform a GWAS of mothers of meiosis I cases vs. mothers of meiosis II cases. This approach cannot find variants that are common risk factors for both meiosis I and meiosis II errors, but is a well-controlled design for finding variants that are unique to one or the other. The second approach uses the fathers as controls. In that approach, we may also discover genes that affect the likelihood of a fetus with trisomy 21 surviving to term.