Identifying risk variants for embryo aneuploidy using ultra-low coverage whole-genome sequencing from preimplantation genetic testing

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Aneuploidy frequently arises during human meiosis and is the primary cause of early miscarriage and *in vitro* fertilization (IVF) failure. Individuals undergoing IVF exhibit significant variability in aneuploidy rates, although the exact genetic causes of the variability in aneuploid egg production remain unclear. Preimplantation genetic testing for aneuploidy (PGT-A) using next-generation sequencing is a standard test for identifying and selecting IVF-derived euploid embryos. The wealth of embryo aneuploidy data and ultra-low coverage whole-genome sequencing (ulc-WGS) data from PGT-A has potential for discovering variants in parental genomes that are associated with aneuploidy risk in their embryos. Using ulc-WGS data from ~10,000 PGT-A biopsies, we imputed genotype likelihoods of genetic variants in embryo

genomes. We then used the imputed variants and embryo aneuploidy calls to perform a genome-wide association study of aneuploidy incidence. Finally, we carried out functional evaluation of the identified candidate gene in a mouse oocyte system. We identified one locus on chromosome 3 that is significantly associated with meiotic aneuploidy risk. One candidate gene, *CCDC66,* encompassed by this locus, is involved in chromosome segregation during meiosis. Using mouse oocytes, we showed that CCDC66 regulates meiotic progression and chromosome segregation fidelity, especially in older mice. Our work extended the research utility of PGT-A ulc-WGS data by allowing robust association testing and improved the understanding of the genetic contribution to maternal meiotic aneuploidy risk. Importantly, we introduce a generalizable method that has potential to be leveraged for similar association studies that use ulc-WGS data.