Genome-wide detection of genomic variation in single cells

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Genome-wide detection of copy number variation in single cells is of interest when mosaicism (genetic variability at the cellular level) is present, such as in embryonic development and in certain types of cancer. However, experimental and conceptual difficulties can make detection problematic. We present an analysis strategy and a software implementation for genome-wide detection of copy number variation in single cells of human embryos and illustrate it using a case study on human blastomeres (the individual cells of an embryo during the first divisions after fertilization).

Conceptually, the absence of a gold standard is problematic: only one blastomere is available and as such only technical replication of the analysis of amplified DNA is possible. High variability in arrays due to amplification of the DNA (because of the tiny amount of DNA in a single cell) decreases the resolution of statistical models used to estimate genomic variations. The combination of the different model results allowed us to distinguish between amplification (several copies of a region), deletion (one of the two copies of a region missing), loss of heterozygosity, and uniparental disomy (both copies of a region inherited from the same parent). Extensions to yet other platforms and models will increase resolution and interpretation of the biological situation. We used this strategy to show that human cleavage state embryos show a surprisingly high level of chromosomal instability.

We calibrated our models using Eppstein-Bar Virus-transformed cells with known aberrations. We analyzed a 1Mb BAC array and an Affymetrix 250K GeneChip SNP array, modeling both copy number state and loss of heterozygosity. Displacement Amplification allowed us to obtain sufficient DNA for genotyping on microarrays. Samples were analyzed using CNAT and CNAG software on the SNP array. The BAC array was analyzed using a mixture model with clone-specific correction to deal with the bias related to GC-content and noise in measurements. The observation of a high level of genomic instability in early embryos has significant implications for our understanding of embryonic development and for clinical applications of genetic screening.