Aneuploidy, i.e., an abnormal number of copies of a genomic region, might be a significant source for neuronal complexity, intercellular diversity, and evolution. Genomic instability associated with aneuploidy, however, can also lead to developmental abnormalities and decreased cellular fitness. While in the normal human brain, the number of hyperploid neurons, i.e. neurons with a more than diploid content of DNA, amounts to about 10%, this number is more than doubled in Alzheimer’s disease (AD). Hyperploid neurons are increased already at preclinical stages of AD and are selectively affected by cell death during progression of the disease. These findings show that neuronal hyperploidy in AD is associated with a decreased viability. Hyperploidy of neurons, thus, represents a direct molecular signature of cells prone to death in AD. This adds hyperploidy to the list of critical molecular events that are shared between neurodegeneration and malignant cell transformation. Irrespectively of whether hyperploidy results from a lack of aneuploidy clearance during brain development or an aberrant attempt of cell cycle re-entry and DNA replication in the adult, it directs our attention to a failure of neuronal differentiation as the critical pathogenetic event and potential therapeutic target in neurodegeneration.