Frequency and properties of mosaic somatic mutations in a normal developing brain

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As mounting evidence indicates, each cell in the human body has its own genome, a phenomenon called somatic mosaicism. Few studies have been conducted to understand post-zygotic accumulation of mutations in cells of the healthy human body. Starting from single cells, directly obtained from three fetal brains, we established 31 separate colonies of neuronal progenitor cells, and carried out whole-genome sequencing on DNA from each colony. The clonal nature of these colonies allows a high-resolution analysis of the genomes of the founder progenitor cells without being confounded by the artifacts of in vitro single cell whole genome amplification. Across the three brains we detected between 100 and 300 non-germline SNVs per clone. Validation experiments (with PCR, digital droplet PCR, and capture deep sequencing) revealed high specificity (>95%) and sensitivity (>80%) of the SNVs as well as confirmed the presence of over 50% of SNVs in the original brain tissues, thereby proving that the detected SNVs represent genuine mosaic variants present in neuronal progenitors.

The per-cell number of mosaic SNVs increased linearly with brain age allowing us to estimate the mutation rate at 0.5-4.5 per cell division (95% CI). Dozens of SNVs were genotyped in multiple different regions of a brain and even in blood, suggesting that they have likely occurred prior to gastrulation. On a coarse-grained scale mosaic SNVs were distributed uniformly across the genome and were enriched in mutational signatures observed in medulloblastoma, neuroblastoma, as well as in a signature observed in all cancers and in de novo variants and which, as we previously hypothesized, is a hallmark of normal cell proliferation. Correlations with histone marks further strengthened the similarity of mosaic mutations in normal fetal brain with somatic mutations reported for brain cancers. On a smaller scale SNVs were mostly benign, showed no association with any GO category and tended to avoid DNAse hypersensitive sites. These findings reveal a large degree of somatic mosaicism in the developing human brain, link de novo and cancer mutations to normal mosaicism and set a baseline for mosaic genome variation related to human brain development and function.