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Cover While much has been revealed about genomic diversity across individuals, very little is understood about genetic alterations within an individual. Single-cell sequencing is emerging as a powerful tool to characterize genomic heterogeneity in populations of cells. In this issue, an approach is developed that allows for reliable detection of megabase-scale copy number alteration in single-cell sequencing data. This approach is applied to sequencing data from normal human brain and skin, providing an estimate of megabase-scale copy number variation in somatic tissues. (Cover illustration by Kristin Knouse. [For details, see Knouse et al., pp. 376–384.])