Single-nucleotide polymorphism discovery by targeted DNA photocleavage

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Single-nucleotide polymorphisms are the largest source of genetic variation in humans. We report a method for the discovery of single-nucleotide polymorphisms within genomic DNA. Pooled genomic samples are amplified, denatured, and annealed to generate mismatches at polymorphic DNA sites. Upon photoactivation, these DNA mismatches are then cleaved site-specifically by using a small molecular probe, a bulky metallointercalator, Rhchrysi or Rhphzi. Fluorescent labeling of the cleaved products and separation by capillary electrophoresis permits rapid identification with single-base resolution of the single-nucleotide polymorphism site. This method is remarkably sensitive and minor allele frequencies as low as 5% can be readily detected.

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