Research Highlights

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Interrogation of allele-specific gene expression by a digital RNA allelotyping method using padlock-captured SNPs from the transcriptome of human cell lines

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Evaluation of: Zhang K, Li JB, Gao Y *et al.*: Digital RNA allelotyping reveals tissue-specific and allele-specific gene expression in human. *Nat. Methods* 6, 613–618 (2009).

Cis-regulatory polymorphisms can modulate gene expression by both genetic and epigenetic means, where heterozygosity results in the differential expression of two alleles (termed allele-specific gene expression [ASE]). It has been demonstrated that allelic variation in human gene expression exists and *cis*-acting inherited variations in gene expression are relatively common [1]. The methods currently available for detecting ASE mostly rely on microarray hybridization or RNA sequence (transcriptome), but both methods suffer from some drawbacks that could ultimately result in missing the informative SNPs.

The use of molecular inversion probe technology has enabled the analysis of large-scale SNPs where multiplexed analysis of more than 1000 probes can be achieved in a single tube [2]. Taking advantage of this technology and modifying it, Zhang *et al.* developed a digital RNA allelotyping method combining the targeted padlock capture of SNPs, using capture probes generated on programmable microarrays, with subsequent ultra-deep sequencing on an Illumina (CA, USA) GAII analyzer [3]. Using this assay on genomic DNAs and cDNAs from

two Personal Genome Project [101] donors, as well as on two pairs of sibling human embryonic stem-cell lines, the authors successfully demonstrate that the digital RNA allelotyping via padlock-capturing exonic SNPs results in consistent calls that are comparable to the results obtained with the Affymetrix (CA, USA) 500K SNP chip. They report that 11–22% of heterozygous mRNA-associated SNPs showed ASE, where 4.5–8.5% demonstrated tissue-specific *cis*-regulation. In addition, they demonstrate that the allelic ratios were primarily determined by *cis*-regulatory mechanisms in the sense strand, and that ASE was primarily explained by the genetic variations. It is also noteworthy that the padlock capture of expressed SNPs can be improved, which could enable the detection of ASE in less abundant transcripts [3].

Despite recent advances in high-throughput genotyping technologies, determining the causal genetic variants is difficult owing to the strong linkage disequilibrium structure found in the human population, in addition to the fact that only a fraction of SNPs fall within the coding region. In this regard, the targeted capture of SNPs using the padlock probes described in the work by Zhang *et al.* [3] represents an efficient way to selectively focus one's sequencing efforts on the genomic region of interest, which is likely to open a new door towards facilitating the understanding of genetic variations in the human genome.

References

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- 101 Personal Genome Project
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