Epigenome-wide DNA Methylation Profiling: Methylation Capture Bisulfite Sequencing versus Infinium MethylationEPIC BeadChip

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**Background:** Epigenome-wide association study (EWAS) has been widely applied to identify CpG sites associated with human disease including drug misuse. Up to date, Infinium MethylationEPIC array (EPIC) is commonly used for high-throughput DNA methylation profiling. However, EPIC array covers only 30\% of the human methylome. Whole-genome bisulfite sequencing can overcome this limitation but not feasible for EWAS due to high cost. Methylation Capture bisulfite sequencing (MC-seq) has advantages of extensive coverage in the methylome with affordable price. Here, we compared the features and utilities of MC-seq using SureSelectXT Methyl-Seq for targeted methylation sequencing and EPIC platforms in four peripheral blood mononuclear cells samples.

**Results:** After quality control, a total of 4,146,347 of CpG sites were detected by MC-seq, while only 867,531 CpG sites were detected by EPIC assay. CpGs from MC-Seq were enriched in coding regions and CpGI while CpGs from EPIC array were located in non-coding region and non-CpGI. Among 472,540 common CpG sites between two platforms, methylation at the same CpG was highly correlated in the same sample (r in a range of 0.98~0.99). However, methylation for a small proportion of CpGs (N=60,753) differed significantly between two platforms, with difference of beta values greater than 0.1. The difference of methylation-beta is likely contributed by cross-hybridization in EPIC array.

**Conclusion:** Our results show that MC-seq has significant advantage of CpG coverage in human methylome and provide more accurate methylation detection compared to EPIC array. MC-Seq can be applied for EWAS in a large population with improvement of methylation detection.