Exon/SNP-6 Arrays analyses in monoclonal gammopathy evolution

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High-throughput genomic analysis spanning all regulatory checkpoints

WGA, aCGH/SNP array

Genome

Mutations, copy number

Transcriptional control

RNA transcript

RNA level

GEP array

Methylation array

Exon arrays

miRNA arrays

Proteomics

Acetylome Phosphome*

RNA splicing

RNA level

miRNA

Protein

Functional proteins*

RNA processing

RNA modification

Translation

Post-translational modifications

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CCR Focus

Global View of Myeloma Genome

DNA
• Amplification and Deletion – array CGH
• Single Nucleotide Polymorphism – 500K SNP array

RNA
• Expression changes – expression profile with GeneChip® Human Exon 1.0 ST
• Alternate splicing – genome-wide Exon analysis with GeneChip® Human Exon 1.0 ST
Exon Arrays

• The GeneChip Human Exon 1.0 ST Arrays gives possibility to analyze alternate splicing in myeloma using high throughput exon array analysis.

• Alternate splicing is an important post translational change that alters specificity of gene function.

• They provides information on expression levels for genes, but as the probe sets are spread evenly over each exon, the array data also provides information on presence of each exon and identify recurrent alternately spliced genes.
Modifiers of Transcriptome
Alternative Splicing

- Allows for multiple proteins from one gene with different function, half life or additive activity

Alternative splicing produces multiple protein isoforms
- 92–94% of human genes undergo alternative splicing
- 85% have minor isoform frequency of 15% or more
- Isoform frequency varies between tissues
- Protein isoforms may have related, distinct or even opposing functions
Alternate Splicing is a Frequent Event and Impacts Clinical Outcome In Myeloma

Unsupervised Analysis Identifies Clinically Relevant Subgroups

Spliced Genes Predict Differential Outcome

Gene level xxx, 
\[ p = 0.46 \]

Exon adjusted level xxx, 
\[ p = 0.016 \]

Exon array is vulnerable to SNPs

• SNPs can affect the hybridization of the probes produce misleading exon-level expression values.

• Database for genome-wide search for SNPs within regions that hybridize to probes.

• These affected probes and/or probesets can be filtered in the data processing procedure thus controlling for potential false expression phenotypes when using this exon array.
DNA: SNP-arrays
1. Copy number abnormalities (CNA)
2. Copy number neutral LOH (CNN-LOH)
3. Correlation with fragile sites (FRA)
Genome-Wide Human SNP-Array 6.0 assay protocol (Affymetrix)
SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies: from MGUS to myeloma status

- The whole genome analysis using SNP-arrays revealed an increasing genomic complexity from MGUS to SMM and to MM.
- The transition from MGUS to MM was not associated with a particular chromosomal imbalance, but rather with an expansion of altered clones that were already present in MGUS.
- More than a half of the genetic lesions were located at fragile sites.
Thank you for your attention