Computer Demo
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POLYMORPHISM AND QTL DETECTION USING OLIGO-BASED MICROARRAYS.

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In previous years we have analyzed variation in cell biological phenotypes and gene expression patterns in hematopoietic stem cells of B6, DBA and their BXD recombinant inbred offspring with Affymetrix U74Av2 DNA chips. The data were publicly deposited at www.webqtl.org, allowing QTL identification for any represented transcript and compare these expressions in multiple tissues.

A small fraction (~3%) of all 12422 transcripts was identified as cis-acting (ie. the QTL regulating its expression mapped within 20Mb of the gene itself). We identified 8 strongly cis-acting candidate genes mapping to a small interval on chromosome 11, a region we have previously shown to be involved in stem cell turnover. These transcripts were associated with putative downstream trans-acting targets. It is generally believed than cis-acting transcripts occur due to essential polymorphisms in their promoter regions, which can cause downstream effects in trans. However, regulation in trans can also be caused by equally expressing genes which carry mutations in their CDS (in case of coding mRNA) or by functionally essential polymorphisms in non-coding RNA. In general terms, cis-acting mutations (manifested either by altered function or expression) are considered as a primary cause of genetically inherited variations, in our case hematopoietic stem cells derived from B6, DBA and BXD recombinant inbred mice.

There is a potential risk when oligo-based arrays are used to search for cis-acting candidate genes in genetically distinct samples: hybridization differences may result from a SNP underneath an oligo. To address this issue we performed single probe level analysis, in which each of the 16 perfect match (PM) probes was analyzed independently. We BLASTed all PM oligos against the NCBI full length mRNA database. About 3% of supposedly PM oligos actually carry from 1 to 3 mismatches to the corresponding transcripts, 9.8% of oligos show multiple matches and for 27% of oligos no matches were found. Also, SNP data from Ensembl and Celera were incorporated into the analysis. The data show that only 0.4% of oligos carry SNP, only 21% of SNP-oligos were found in cis-acting probesets. Contrary to early claimsall our data suggest that oligo-based microarrays are insensitive to SNP's. More importantly, it was revealed that most of the differentially expressed cis-acting transcripts carry polymorphisms across the entire transcript. Thus, a search for cis-acting QTLs identify genes carrying allelic polymorphisms.