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Identification of microRNAs and their target genes in Alport syndrome, using deep sequencing of iPSCs samples

Key words: Alport syndrome, miRNA, Solexa sequencing, Gene Ontology, KEGG pathway, iPSCs

Brief introduction:

MiRNAs (microRNAs) are a class of small RNA molecules that are implicated in post-transcriptional regulation of gene expression during development. The discovery and understanding of miRNAs has revolutionized the traditional view of gene expression. Alport syndrome (AS) is an inherited disorder of type IV collagen, which most commonly leads to glomerulonephritis and kidney failure. Patients with AS inevitably reach end-stage renal disease and require renal replacement therapy, starting in young adulthood. In this study, Solexa sequencing was used to identify and quantitatively profile small RNAs from an Alport syndrome family.

(1) We identified 30 known miRNAs that showed a significant change in expression between two individuals. Nineteen miRNAs were up-regulated and eleven were down-regulated. Forty-nine novel miRNAs showed significantly different levels of expression between two individuals.

(2) Gene target predictions for the miRNAs revealed that high ranking target genes were implicated in cell, cell part and cellular process categories.

(3) The purine metabolism pathway and mitogen-activated protein kinase (MAPK) signaling pathway were enriched by the largest number of target genes.

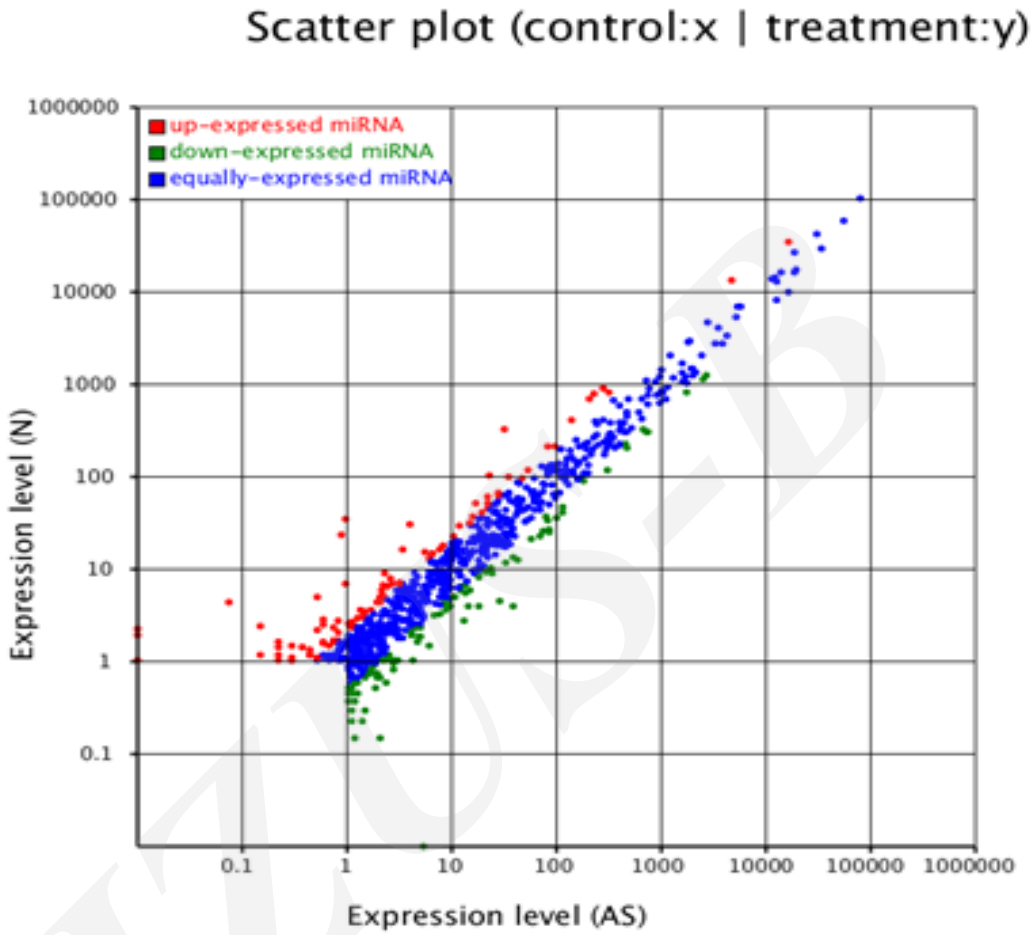

Figure 8 Differential expression scatter plot.

The miRNA differential expression scatter plot (Figure 8) showed that most of the miRNAs were expressed at an equal level, when the AS library was compared with the NC library. There were very few remaining miRNAs that showed significant levels of expression.

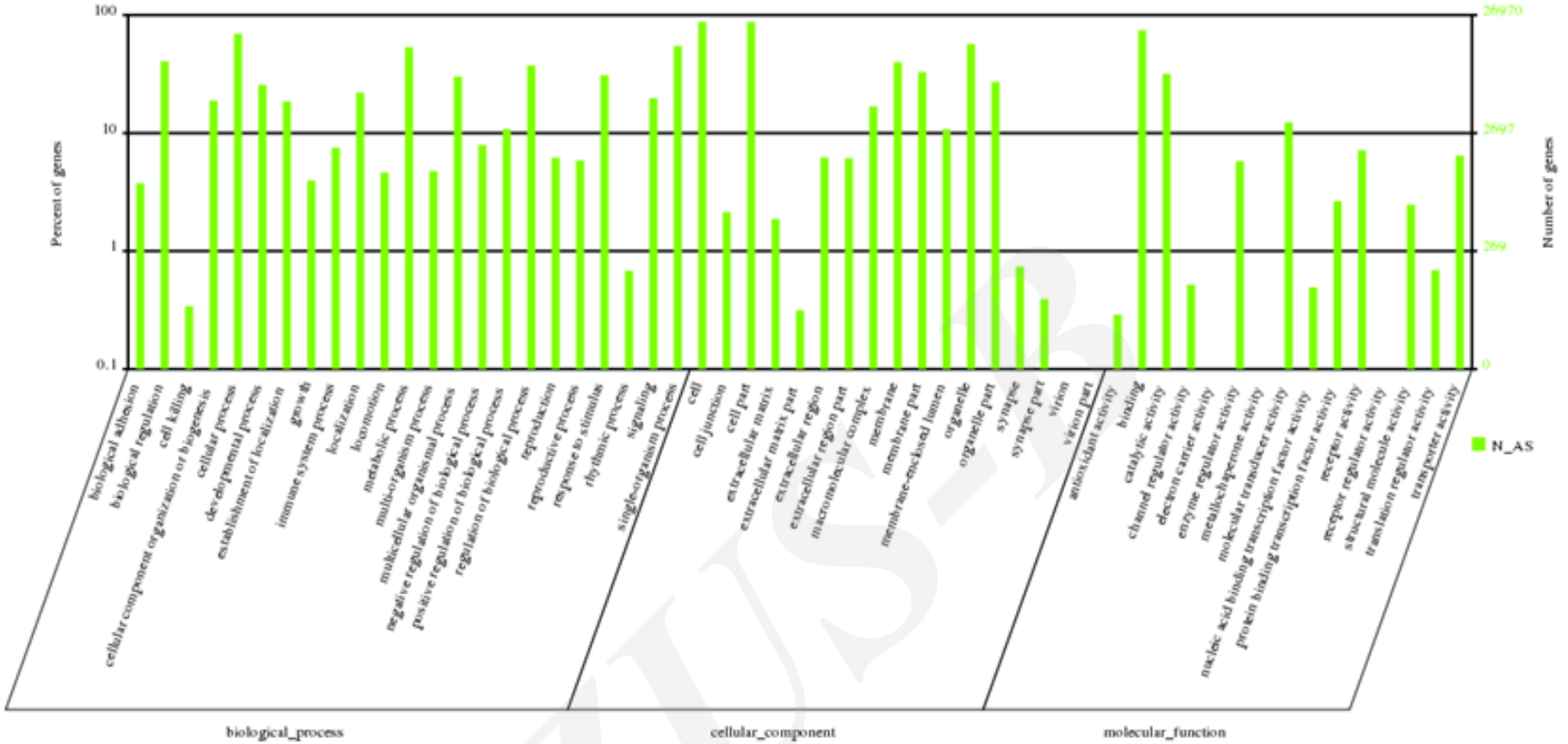

Figure 10 GO annotation and analysis of miRNAs that showed differential expression between the two libraries.

Three ontologies i.e. molecular function, cellular component and biological process, were found to be associated with the pathogenesis of AS (Figure 10). On the basis of the biological process, the genes were classified into 23 categories. The top three over-represented GO terms were cellular process, metabolic process and single-organism process. The genes were also grouped into 17 categories based on cellular components. The largest groups were cell, cell part and organelle. When the genes were grouped by molecular function, there were 15 categories. The most enriched molecular function categories were binding, catalytic activity and molecular transducer activity.

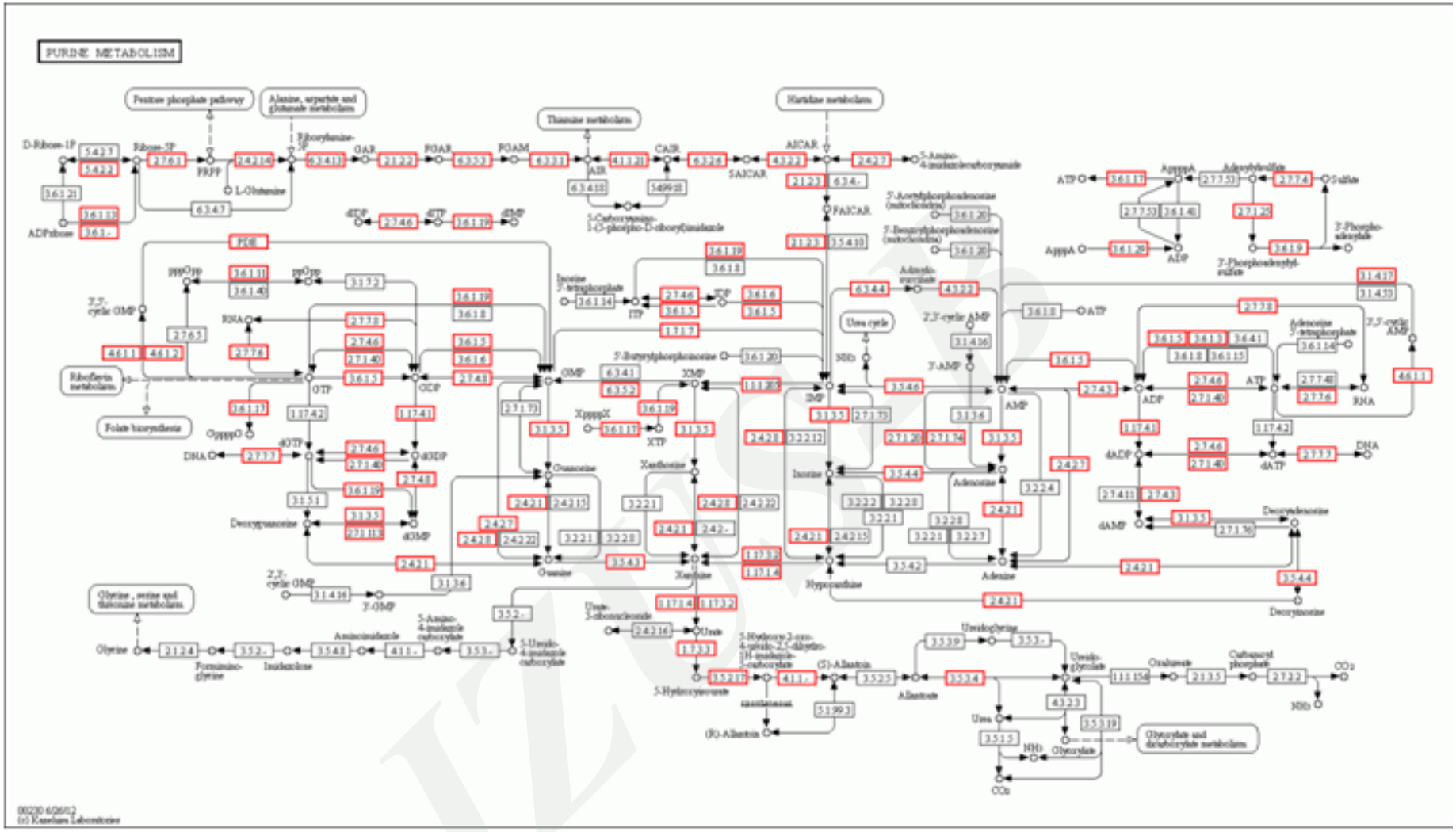

Figure 11 The purine metabolism signaling KEGG pathway, which shows the differentially expressed genes in the AS and NC libraries.

The pathway that was most enriched by the target genes was purine metabolism. We found that 7.35% of target genes could be assigned to this pathway. The red borders indicate the genes that are targets of the differentially expressed miRNAs.

Perspectives and Research Priorities

We obtained the differential expression profiles from an AS family. The differentially expressed miRNAs were subjected to GO enriched and KEGG pathway analysis.

(1) Our study demonstrated that the differential expression miNRA between tha AS and NC.

(2) the target gene from differential expression miRNA enrichment and functional pathway may present an area of research into the pathogenesis of AS.

(3) These data will also serve as a reference to lay a foundation for us to better understand the genetic mutation of AS at the genetic level.