

Clariom D microarrays provide a deep view of our transcriptome

The search for complete transcriptome analysis

The Human Genome Project was an enormous success. Not only did it promote our understanding of the content of genomes, but it also brought forth new technologies for collecting sequences and new algorithms for analyzing those sequences. But even as our tools for analyzing the human genome increased in power, the complexity of the genome continued to provide new surprises. For example, when the sequence of the human genome was first announced, the number of expressed protein-coding sequences was hypothesized to be around 22,000. As the analyses became more sophisticated, however, it was clear that the number of expressed sequences was much higher.

Further analyses revealed that these expressed sequences included microRNAs (miRNAs), long noncoding RNAs (lncRNAs), long intergenic noncoding RNAs (lincRNAs), splice isoforms, and circular RNA. An international Sequencing Quality Control (SEQC) consortium showed that in complex transcriptomes, more than 45,000 expressed sequences are detected when deep sequencing of up to a billion reads per sample is performed

In this technical note, we describe how:

- A deep understanding of the transcriptome comes from incorporating multiple gene models
- Comprehensive analysis of the complete transcriptome allows for discovery of new biomarkers associated with disease or physiological states
- Direct measurement of transcript abundance removes read depth considerations in a gene expression experiment
- Applied Biosystems™ Clariom™ D microarrays facilitate complete transcriptome analysis, including coverage of novel noncoding transcripts and splice isoforms

[1]. More recently, the Genotype-Tissue Expression (GTEx) study analyzed the transcriptomes of 31 normal human tissues and found 43,126 genes and many novel isoforms of the genes [2]. Programs like the Human Cell Atlas aim to expand the human catalog of cells beyond the current ~300 defined types [3], adding to the list of what can be expressed in a transcriptome.

Modeling gene structures

To better understand and manage all this information, several attempts have been made to catalog and model these expressed sequences. For example, the National Center for Biotechnology Information (NCBI) and the European Molecular Biology Laboratory (EMBL) are among the 16 public organizations that curate extensive databases of genes like RefSeq (NCBI) and Ensembl (EMBL). Surprisingly, these databases do not overlap as extensively as one might expect, since each is a product of its own distinct curation algorithms (Figure 1). For example, the *SLC18A2* locus can be modeled as having different intron/exon structures, depending on the modeling database used (Figure 2). Thus, a view of a transcriptome can be very limited if we consider only one of these 16 databases. We can obtain a comprehensive map of the transcriptome only by aggregating data from multiple sources. While the validity of every sequence contained in all these databases may be open to interpretation, the totality of possible expressed sequences provides a more complete and reliable view of expressed loci in our chromosomes.

Alternative splicing and a need for higher-resolution transcriptomics

Modern high-resolution transcriptomics aims to resolve transcripts that are up- or downregulated in various tissues or cellular states. This regulation can be measured and is thought of as comprising both gene-level and transcript-level events. When we use the term “gene level”, we typically are attempting to measure the combined transcript-level events along a given gene locus. In higher organisms, almost all coding genes have multiple exons, and depending on the exon usage, the genes have the potential to generate many alternative transcripts (Figure 2).

Simply trying to measure up- or downregulation at the gene level often obscures the changes that happen at the splicing or exon level. Multiple forces can simultaneously regulate gene expression and splicing, such that a ratio of isoforms can be altered with or without changes in the overall combined gene-level expression estimates. How technologies take this complexity into consideration greatly impacts the inherent assumptions behind measurements used for assessing transcriptome change. Modern high-resolution transcriptomics measures exons or sub-exonic events to help ascertain splicing and overall gene-level changes.

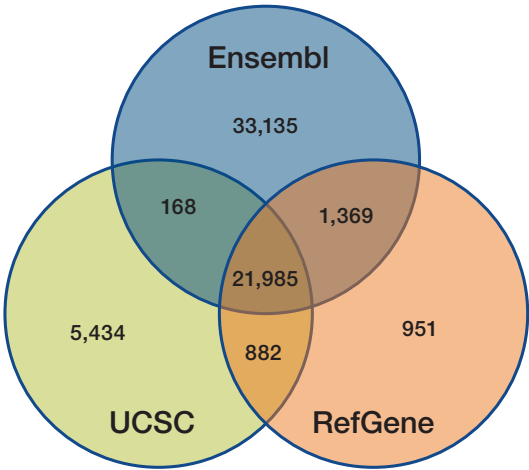


Figure 1. Overlap and uniqueness of RefGene (a subset of the RefSeq database), UCSC, and Ensembl annotation models of genes. In general, the different models have a high degree of overlap—there are 21,958 genes common to all three databases. However, note that more than half of the genes in the Ensembl model are unique.

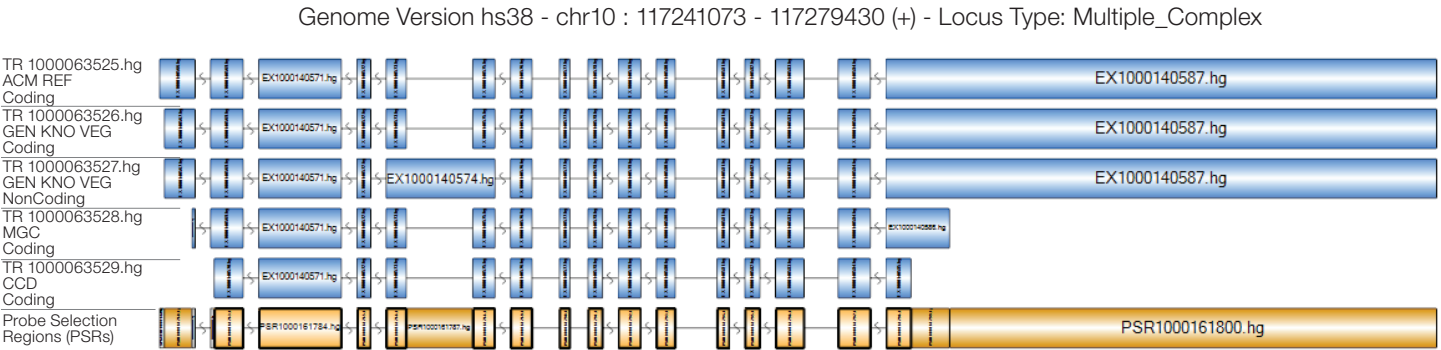


Figure 2. Gene model of *VMAT2*, also known as *SLC18A2*, containing multiple isoforms seen in 6 different public databases. Probe selection regions on the Clariom D array, shown in yellow, can be utilized to detect alternative splicing events and overall gene-level expression.

What has been increasingly clear as technologies mature is that alternative splicing is an important factor in many diseases. For example, cancer cells have been shown to increase proliferation, migration, and ultimately the rate of survival, through alternative splicing [4].

Most technologies used today are still focused on well-annotated genes. However, less well-known sequences, such as noncoding RNAs (ncRNAs), have been shown to regulate the expression of other genes and have been shown to be a rich source of biomarker discovery [5]. If we use technologies that survey uncharacterized gene loci or consider differential exon usage or splicing, the transcriptome comprises much more than the common set of ~20,000 well-annotated genes (Figure 3). A comprehensive biomarker survey should include exon resolution, noncoding RNAs, and undercharacterized genes.

Methods for analyzing the transcriptome

Two techniques are commonly used to analyze changes in gene expression across a transcriptome. One method, using next-generation RNA sequencing (RNA-Seq), uses massively parallel sequencing to sample RNA sequences present in a library. NGS reads are aligned to the genome in RNA-Seq. The read depth is required to find low-abundance transcripts, which can lead to higher cost per sample, depending on the platform [6].

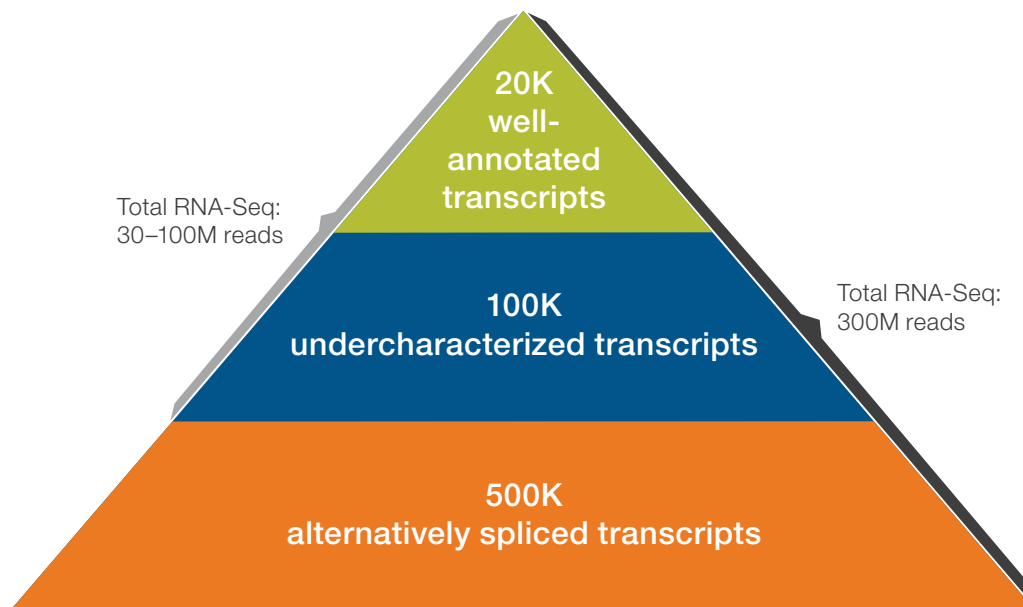


Figure 3. Signature search space can be thought of as the number of transcripts evaluated with different technologies. Note that when sampling technologies such as Illumina™ NGS or Applied Biosystems™ SOLiD™ NGS RNA-Seq are used, very large numbers of events are needed to get deep information about the transcripts present in an experiment. In contrast, the Clariom D array is able to detect these events without sampling, and therefore similar depth can be achieved in one experiment. For details, see reference 1.

Moreover, as with any sampling technology, the more sampling events that are collected, the better the precision of the measurement. For example, a simple experiment can be designed where the values of fold changes in defined samples can be predicted [1]. In an RNA-Seq experiment, the mean absolute deviation from the predicted value drops with increasing sequencing depth (Figure 4). One corollary of this is that more sampling is required in order to measure rare events with statistical confidence. Results from the SEQC consortium showed that deeper sequencing (increased sampling) of the transcriptome is needed to reveal low-abundance transcripts and splice junctions. Thus, read depth should be a key consideration when experimental goals include rarely expressed or low-abundance transcripts, coverage of introns, and nonpolyadenylated (i.e., noncoding) targets [1]. In another example, complex samples such as tumor biopsies may contain multiple cell types. The transcriptome contained in this sample is more complex than that of a homogeneous cell line, and therefore to precisely measure the gene expression changes in the variety of cells present, including the rare ones, more reads are required.

Another strategy for analyzing gene expression changes involves using DNA oligonucleotide microarrays that have been used to analyze gene expression changes across a very large number of targets for close to 30 years. The methods used to generate measurements and analyze the resulting large datasets have been well established and are the gold-standard approaches. Originally, such microarrays only analyzed a few thousand targets. However, technology advances have increased the number of targets that can be analyzed; currently, over 6 million discrete sequences can be analyzed on a single chip. Queries for a very large and complex set of sequences are possible with a single well-established workflow. Moreover, since expression data are captured directly from the signal on the chip, sampling is not required to increase precision or detect rare sequences.

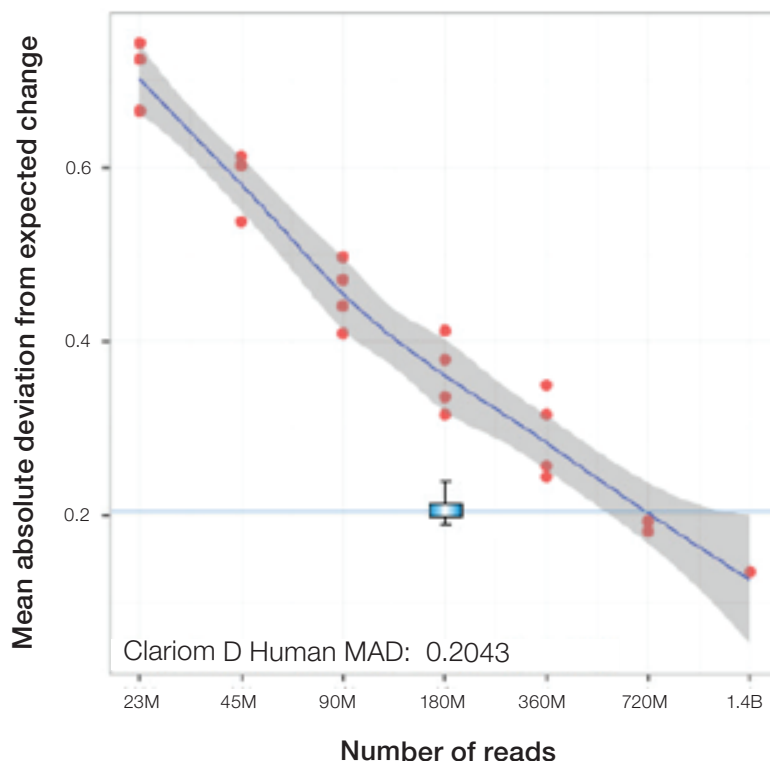


Figure 4. Sequencing depth required for equivalent variation between the Clariom D array and RNA-Seq analysis. By evaluating a tissue mixture model in which RNA from two samples is mixed in known proportions, the mean absolute deviation (MAD) of expression was evaluated across all measured exons. (Modified data from reference 13.)

Clariom D applications: the answer to many research challenges

The Clariom D microarrays represent the latest advances in the family of transcriptome analysis solutions (Table 1). The sequences on the Clariom D arrays are based on coding and noncoding sequences culled from 16 different databases [7], representing over 540,000 transcripts in over 6.7 million probes. Included in these sequences are probes for different splice isoforms, noncoding RNAs (pre-miRNAs, lincRNAs, Piwi-interacting RNAs (piRNAs)), and circular RNAs, as well as annotated and speculative sequences. Querying the multiple transcript models on the Clariom D chip in a single experiment helps ensure that important biomarkers are not missed.

Applied Biosystems™ Transcriptome Analysis Console (TAC) Software was designed to quickly analyze the Clariom D array data. A report of all transcripts and the associated relative expression, using statistical and visualization tools, is provided from the data. Additionally, information regarding the role of these transcripts in biological pathways is provided. Together, the Clariom D solution of microarrays and software provides rapid, easy, and economical tools for obtaining meaningful gene expression data.

Microarrays continue to be an important tool for analyzing gene expression changes. For example, during the fiscal year of 2017–2018, the National Institute of Health (NIH) funded over 200 R01 grants that make use of microarrays to analyze functional changes from gene expression differences. In addition, the number of publications utilizing Clariom D technologies continues to grow. Some recent examples are highlighted below, and a comprehensive list is given in the reference section.

Example 1: Gene expression variation in adipose tissue

Metabolic differences may influence weight gain, but the tissues and mechanisms involved are not known. As part of a study of two different cohorts of women, Arner et al. [8] examined gene expression differences in subcutaneous adipose tissue in baseline and follow-up samples, using the Clariom D microarrays. They found that a subset of previously described lipolysis gene transcripts was lower in the weight-gain samples versus the weight-stable samples. They hypothesized that these results implicate inefficient lipolysis in subcutaneous fat cells as a contributor to long-term weight gain.

Example 2: Systemic dysregulation in subjects with Parkinson’s disease

Miki et al. [9] explored the hypothesis that Parkinson’s disease involves systemic dysregulation of the autophagic pathway. They collected peripheral blood mononuclear cells (PBMCs) from individuals with Parkinson’s disease and unaffected individuals, and used the Clariom D arrays to generate transcriptomic profiles from each group. Using TAC Software to analyze the results, they confirmed that genes involved in autophagy were indeed dysregulated in individuals with Parkinson’s disease. They also confirmed that genes in the lysosomal pathway, another catabolic mechanism, were also dysregulated. Together, these results suggest that systemic alteration of catabolic pathways may be a fundamental aspect of the disease.

Table 1. Clariom D microarrays vs. RNA-Seq solutions.

| | Clariom D | RNA-Seq |
|---------------------------------------|--------------|------------------------|
| Gene models | 16 databases | One database at a time |
| Method of measuring transcript levels | Direct | Sampling |
| Data analysis | TAC Software | Varies |

Example 3: *Ex vivo* breast cancer tumors

Eckhardt et al. [10] were interested in modeling breast cancer tumors grown *ex vivo* in 3 dimensions as a more accurate representation of breast tumors than cultured cells. To show the validity of their model, they needed to show that the *ex vivo*–grown tumor mass had biological characteristics similar to those of the starting tumor. They used the Clariom D arrays to verify that the correlation between the gene expression patterns in the *ex vivo*–grown tumors and the original tumor was highly significant, even when noncoding RNAs were included in the analysis. Thus, they were able to rapidly verify that their *ex vivo* tumor model could be used as a surrogate for the original tumor.

Example 4: lncRNA analysis to examine olfactory function decline

A common feature of aging is the decline in sensory function. To begin to understand olfactory decline, Wang et al. [11] examined expression profiles in young and aged mouse olfactory bulbs using mouse Clariom D microarrays. They obtained distinct sets of coding and noncoding RNAs that were differentially expressed in the two tissue samples from different sources. By performing pathway analysis of the differentially expressed genes, they hypothesized that a decline in olfactory function may be inversely correlated with the expression of some lncRNAs in the neuroactive ligand–receptor interaction pathway.

Summary

Clariom D microarrays are a next-generation, cost-effective solution for comprehensive gene expression analysis. Leveraging RNA discoveries over several years and the information available in several public databases, the Clariom D microarrays enable investigators to find coding, noncoding, or as yet unannotated events with a simple and easy workflow and at exon resolution. Transcriptome complexity or sequencing depth considerations are not a concern with microarrays. Microarrays are built on trusted and well-understood chemistries and algorithms for analyzing gene expression differences. The Clariom D microarrays incorporate information from a large number of different transcript models, giving confidence that important transcript isoforms or noncoding sequences are analyzed. The TAC Software facilitates interpretation of the gene expression data generated by the Clariom D microarrays. Some researchers recently have stated that “modern microarrays can still outperform sequencing for standard analysis of gene expression in terms of reproducibility and costs” [12]. Together, these features make the Clariom D microarrays an ideal and economical choice for gene expression research.

Ordering information

| Product | Cat. No. |
|---------------------------------------------------------------------------------------------------------------------|----------|
| Clariom D Assay, human (includes the whole-transcriptome Clariom D microarray and the GeneChip WT Pico reagent kit) | 902922 |
| Transcriptome Analysis Console (TAC) Software 4.0 | NA |

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