Cytognomix designs and markets advanced genomic reagents and software products to personalize the diagnosis, evaluation, and management of cancer, prenatal disorders, and other genetic diseases.

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Overview: Advanced Genomic Biotechnology Products and Applications

Cytognomix® Products Facilitate Evaluation and Diagnosis of Cancer, Prenatal Disorders and Genetic Diseases

INTRODUCTION

Cytognomix designs, markets and commercializes advanced reagents and specialized software solutions for genomic and chromosome analysis using patented genome bioinformatics technology. Based in London, Ontario, Canada, Cytognomix has been developing and marketing a wide suite of DNA probe reagents, software based solutions for mutation analysis and companion software to detect chromosome abnormalities since 2009. All the company's products and patented reagents are backed up by highly cited, peer reviewed publications, and are targeted towards Next Generation Sequencing (NGS) and Chromosome-based applications.

Cytognomix's products include genomic microarrays and DNA probes for fluorescence *in situ* hybridization (FISH), microarray genomic hybridization, hybridization enrichment pools for sequence capture. The company has created genome interpretation software and cytogenetic biodosimetry software that can address the diagnostic needs of patients with both inherited and acquired diseases. Our unique Shannon mutation pipeline and Veridical software solutions is a breakthrough in advanced medical technology because these products assist in the accurate prediction of functionally-significant, non-coding variants in complete genome or exome sequences. No other product on the market provides comparable insight into the underlying causes of genetic disorders. Technological solutions introduced in the industry by Cytognomix have enabled probe development for NGS, microarray, and FISH technologies and made chromosome analysis of many important genes possible which was previously not available.

CLINICAL AND DIAGNOSTIC NEED

We design, produce and distribute patented, peer-reviewed genomic products to molecular cytogenetic and diagnostic labs that can be used for both diagnostic, as well as research and development purposes. Cytognomix's precise, comprehensive and sensitive genomic disease tools facilitate accurate detection and interpretation of both point mutations or changes in the chromosome copy number.

THE PROBLEM: INTERPRETATION OF GENE VARIANTS

One of the most crucial issues that most researchers and clinicians face these days is the **lack of information and supportive data available for assessment of gene variants.**

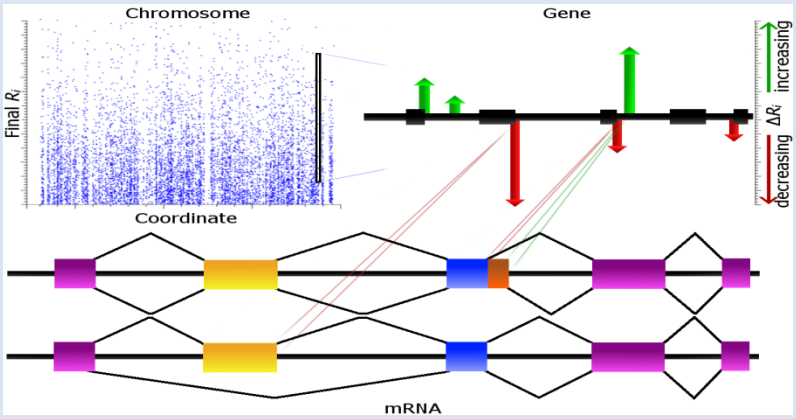
There are a vast number of variants present in normal and disease-carrying individuals. Unfortunately only a fraction of significant variants are catalogued in scientific literature. However, as more and more variants are discovered, the gene variant databases cannot keep up with the flood of data and provide minimal insight into the functional significance of variants. Many of the new variants have not been previously reported, or the complete impact of these existing variants may not have been previously recognized during the research or clinical trials.

Advanced Technological Software Suite for Detection, Interpretation of Genomic Abnormalities and Analysis of Changes in our Genomes.

OUR SOLUTION: SOFTWARE FOR ACCURATE ASSESSMENT OF INDIVIDUAL VARIANT FUNCTIONS

Cytognomix has designed and developed **specialized software for predicting the impact of variants using well-validated and highly cited approaches**. Our software predicts the impact of these new variants by focusing on their properties that have repeatedly matched the findings of previously conducted laboratory studies and in this way the function of these variants is assessed in the most precise manner.

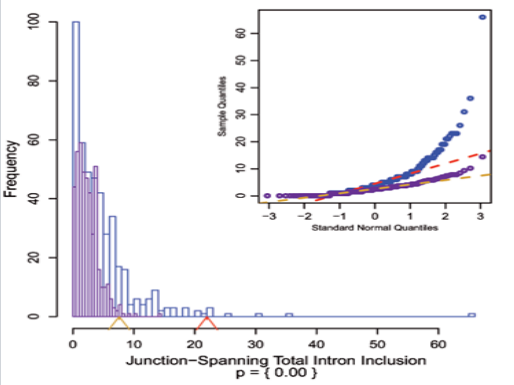
1. THE SHANNON PIPELINE SOFTWARE FOR HIGH THROUGHPUT INTERPRETATION OF GENOMIC VARIATION



Shannon Human Splicing pipeline is an advanced software product used for genome-scale mutation analysis and highly accurate prediction of functional non-coding variants. It can predict variants affecting mRNA splicing. This technology is based on a proven and patented approach that is based on information theory binding site analysis. The software for detection of splicing mutations is unique in the industry. It provides unparalleled insight into the effects of these mutations, both of individual variants and genome-wide studies. Regardless, efficient software ensures the thousands to millions of

gene variants can be analyzed and results delivered rapidly – 10 minutes per genome. The key advantage is that this analysis hones in on a small number of variants that affect the function of genes. The software can distinguish between benign, fully and partially inactivating binding site variants. Our methods have been recommended by the American College of Medical Genetics and Genomics in their published guidelines and standards, and validated in a wide array of hundreds peer-reviewed research studies of splicing mutations. More important, the software is based on a common paradigm that applies to all types of nucleic binding sites (e.g. untranslated regions, transcription factors etc.), and future products will address mutations involving these types of binding sites.

2. The Veridical Software for RNASeq Based Validation of Predicted MRNA Splicing Mutations

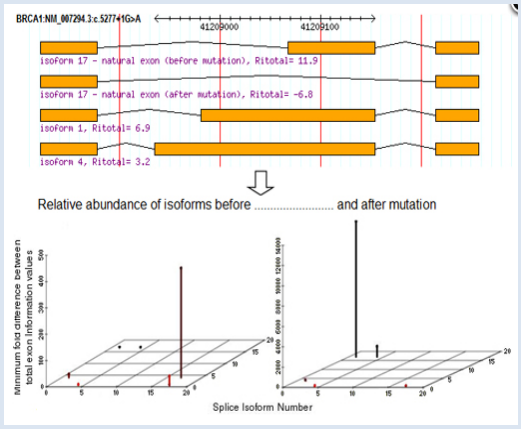


Veridical is the first product to be introduced in the market for detailed assessment of predicted splicing mutation in a genome or exome and validating mutations obtained from NGS using RNASeq-based whole transcriptome data from the same patient. Since publication, the scientific paper describing this product has received considerable attention from the genomics community.

It offers a well-founded statistical approach to validate and confirm the predictions acquired from the Shannon pipeline software and can efficiently and accurately validate thousands of results within a few hours.

3. Automated Splice Site and Exon Definition Server (ASSEDA)

Cytognomix offers subscriptions to ASSEDA - the highly cited and well validated solution recommended by the American College of Medical Genetics and Genomics, which has also been designated as a medical device by the US Food and Drug Administration.



It offers the most detailed and accurate predictions of mRNA splicing mutations based on constitutive and protein binding sites. It not only finds mutations, it also predicts their effects on expression of the gene containing these mutations.

THE PROBLEM: ANALYSIS OF GENE SAMPLES

Another important problem that most of our customers face is how to decide which genes should be analyzed for a particular disease. The same gene panels are used for the analysis of several genetic diseases as well as cancer. However, the composition of these panels needs to be changed frequently for each disease, and customers require the flexibility to adapt to their diagnostic laboratory procedures and stay abreast of the most current research and clinical literature.

OUR SOLUTION: SINGLE COPY PROBE TECHNOLOGIES

At Cytognomix, we have developed dedicated software that can particularly select specific genes for sequencing and copy number analyses. Our solution can be employed for a variety of applications with unmatched flexibility and speed. The following are the main features of our single copy probe technologies:

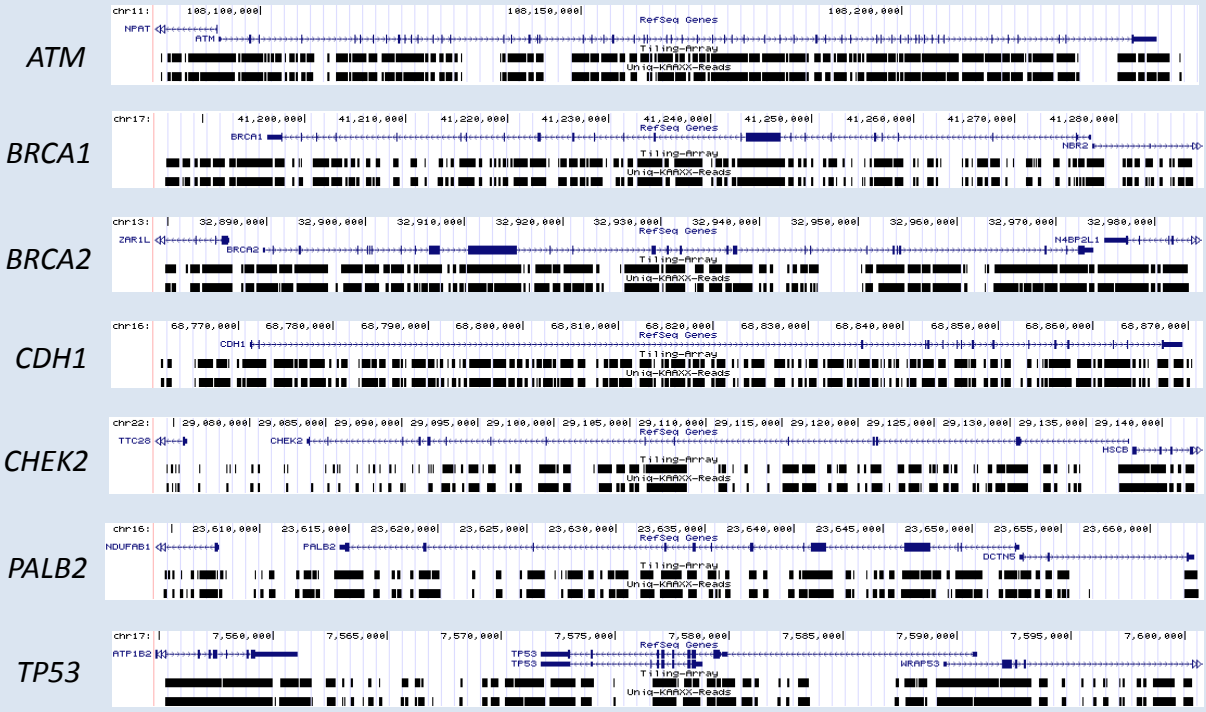
- Our wide suite of patented products allows the customer to select the probes they need, save time and cost and attain accurate results.
- We have predesigned DNA probes across the genome for a variety of molecular diagnostic applications.
- These probes are available on different scales for different analysis requirements (single gene, microarray, or our most popular product: specialized probe sets for targeted capture in next generation sequencing).
- We offer the flexibility to configure these products according to the particular gene sets that the customer chooses.
- We also deliver a cytogenetic decision support tool which allows the customer to query clinical diagnoses, finds the relevant genes at the National Library of Medicine and then use the particular probes with genome browser software.

1. Genomic Microarrays by Cytognomix

Microarray genomic hybridization is employed for the identification of chromosome abnormalities by genome-wide assessment of chromosome copy number. Our low noise, genomic microarray designs compare favorable with the results obtained by other manufactures. The patented single copy technology that enhances reproducibility and accuracy in results and provides higher quality data for regulatory filings. The use of sectored arrays lowers the cost per sample and fewer probes are needed for calling copy number genotypes.

2. Targeted Hybridization Arrays - NGS Hybridization Enrichment Pools for Complete Gene Sequencing

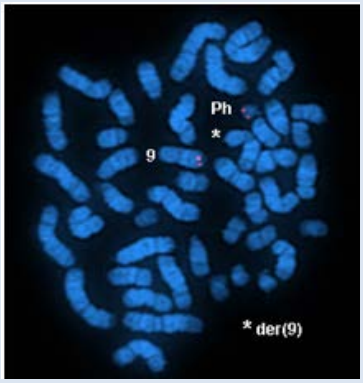
Cytognomix has designed and developed targeted hybridization reagents for NGS enrichment that offer maximal coverage for unique gene sequences. The first of our array capture products is being used successfully for the targeted sequencing of inherited breast cancer genes such as *ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2,* and *TP53*. These hybridization arrays not only capture and detect known coding regions, but also obtain essential sequence information about the sequences surrounding and throughout each gene that control expression levels.



Sequence capture probes (top track) and coverage (bottom) for inherited breast cancer genes (probe design method: Nucleic Ac. Res. 41(7):e81, 2013; covered by US Pats. 7734424, 8209129, 8407013)

3. Customized and Standard SC-FISH DNA Probes

DNA Probes are used for research on congenital diseases, leukemia and other cancers and are employed in tests required to confirm abnormalities in the chromosomes. Both our standard and scFISH probes offer the highest genomic resolution available on the market for detection of minor rearrangements in chromosomes accurately, without compromising sensitivity or specificity. More than 220,000 probes have been designed across the genome. More than 500 have been validated, for more than 50 different genetic disorders and cancer.



Detection of chronic myelogenous leukemia with Cytognomix's single copy DNA probes from the ABL1 gene

THE PROBLEM: DETECTION OF CHROMOSOME CHANGES IN A LARGE-SCALE RADIATION EVENT

Exposure to radiation, whether short term or long term, is dangerous. One of the consequences is significant numbers of chromosome structural changes that can cause cancer. These changes are detected by biodosimetry. The chromosomes have two central constrictions instead of a single one and are termed **dicentric chromosomes (DCs).** Chromosome biodosimetry studies are approved by the World Health Organization as a definitive test for detecting occupational radiation exposures in emergency situations or monitoring the effects of long term exposure to radiation. The analysis typically requires advanced cytogenetic expertise and is labour intensive.

Existing cytogenetic microscope systems locate cells, but cannot accurately detect DCs. This is because the same chromosomes vary in appearance in different cells, and this variability limits specificity and sensitivity of the method. In an emergency response to a large number of individuals exposed to a wide, unknown range of doses, biodosimetry labs need more efficient methods to accurately and rapidly identify DCs.

OUR SOLUTION: IMAGE PROCESSING-BASED BIODOSIMETRY SOFTWARE

Cytognomix has developed novel image processing approaches that can quickly detect DCs regardless of the length, shape and structure of chromosomes. We have automated the detection of centromeres. Our methods select the most optimal cells for analysis and improve detection of DCs by:

- Detecting chromosomes in each image,
- Patented methods to determine the width of chromosomes,
- Accurately locating and counting the number of centromeres.

Cytognomix also developed proprietary software and image analysis methods that can automatically detect chromosome abnormalities and cytogenetic abnormalities using light and fluorescence microscopy. We have created a single computer program that increases the throughput of the process,

without compromising the accuracy of DC detection of the triage assay. The software for automatic detection of DCs has been developed for both Desktop and High Performance Computing systems. It is capable of processing chromosome data from 10,000 individuals in 5 hours, making it the only cytogenetic biodosimetry system that can be used to determine radiation dose when large numbers of people have been exposed.

OUR COMPETITIVE ADVANTAGE: BOTH ADVANCED SOFTWARE AND COMPANION REAGENT SOLUTIONS

Most diagnostic genomic hybridization and sequencing technologies rely on the identification of single copy DNA sequence content. Other approaches in the field require repetitive sequences in the genome to be blocked. The hybridization components used for blocking affect the accuracy of FISH and microarray hybridization, because they introduce noisy results. Cytognomix DNA probes do not require blocking, and produce much cleaner results than those of competitor products.

Cytognomix is known for development and design of sophisticated software solutions and advanced reagents and software that support patented genome bioinformatics technologies. Our *ab-initio* technology derives unique genomic sequence intervals, without blocking repeat sequences - which means diminished noise, faster results and enhanced accuracy. These probes, when used for Next Generation Sequencing, detect many more gene variations than competing products. Our downstream software is uniquely able to handle these DNA sequencing results and generate new insights into the functions of certain gene variants. Our Fluorescence in situ hybridization (FISH) probes, genome-wide microarray and capture enrichment designs are available for any gene or set of genes.

SUMMARY

Cytognomix products make complete gene sequencing of all unique genomic regions possible so that all relevant mutations are detected. Currently, disease gene panels for hybridization enrichment of breast cancer and ovarian cancer are available now. Our next generation sequencing Hybridization Enrichment reagents offer the flexibility to configure gene panels for complete sequencing of any set of genes. The Shannon pipeline, Veridical, and the Automated Splice Site and Exon Definition Server for mRNA Splicing Mutation analysis are the industry-leading options available to researchers and clinicians for identifying disease- causing mutations.

Further reading

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