CytoSure

A Sysmex Group Company

Genomic analysis of rare disease

Features

A range of targeted arrays for rare disease areas:

- Up to Medical Exome gene coverage (~5000 genes)
- High-resolution exon coverage of targeted genes
- Backbone gene coverage to provide excellent CNV calling
- Optimsed analytical software - CytoSure Interpret

Introduction

Copy number variation (CNV) contributes as much as 6Mb of the human genome, with an average of 1100 CNVs per individual. As such, the prevalence of CNV suggests that it represents a significant proportion of total genomic variation. CNV occurring within coding or regulatory regions often have an adverse effect on gene expression leading to disease.

A broad spectrum of mutations are found in inherited disease

DMD

Duchenne Muscular Dystrophy

75% CNV 25% SNV

SOCS2

Eye disease

75% CNV 50% SNV

Identifying both CNV and single nucleotide variants (SNV) is important to fully understand the mutation spectrum of these phenotypically and genetically heterogenous diseases.

Expert led array design

Selection of disease associated genes

Research validated lists of genes were developed and tested with our collaborators — ensuring their relevance. False disease associations were eliminated using the latest research literature.

Probe design and array optimisation

OGT has experience in designing microarrays for some of the world's leading researchers to produce pre-validated, optimised aCGH probe designs.

- **Comprehensive, research validated content drawn from multiple databases including ClinVar, OMIM, Orphanet and our collaborators' own database**
- **Highly accurate CNV calling using optimised, pre-validated probe design — for improved coverage and the highest performance**

Advantage of exon-focused design

While many array platforms carry high numbers of probes, the key to a higher resolution is the number of probes in specific regions of interest. Exon-focused designs such as that of the CytoSure® Medical Research Exome array (MREA) enable:

- High-resolution coverage of the targeted genes
- Detection of single-exon micro-CNV
- Identification of more disease-relevant CNVs

The CytoSure Medical Research Exome array (MREA)

The CytoSure MREA offers comprehensive coverage of over 4600 medically relevant genes at exon-level resolution. This makes it an ideal complement to an exome sequencing approach to provide comprehensive mutation spectrum analysis in rare disease. This array has been developed in collaboration with leading molecular genetics experts at Emory University, working with their hand-curated database of genes to ensure the highest disease relevance of all content. As well as probes for targeted genes, genomic backbone probes are included to ensure identification of novel CNV.

Number of genes targeted: 4645

"The OGT array provides us with the exon-level resolution needed to detect CNVs over the medical exome that are missed by NGS and traditional microarray designs, providing additional insights into the mutation spectrum of the sample."

Dr Emily Farrow, Children's Mercy Hospital, Kansas City, KS, USA

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Autism

Autism Spectrum Disorders (ASD) are estimated to affect 21.7 million people globally[1] and are thought to be highly heritable. However, ASD cannot typically be traced to a Mendelian (single-gene) mutation or to a single chromosome abnormality, and none of the genetic syndromes associated with ASD have been shown to selectively cause ASD[2].The large number of autistic individuals with unaffected family members may result from *de novo* CNV[3]. This hypothesis is supported by the discovery of CNV at 11 loci across 8 chromosomes linked to ASD susceptibility[4]. Hence, understanding CNV status in combination with SNV is critical for research into the genetic basis of this disease.

CytoSure Autism Research array:

- Number of genes targeted: 227
- Examples of diseases covered: Autism, hearing loss, X-linked intellectual disability (XLID).

Epilepsy

Epilepsy is a group of neurological diseases characterised by epileptic seizures. The prevalence of Epilepsy is around 1%, meaning that around 65 million people worldwide are living with the disease. Genetics is believed to be involved in the majority of cases, either directly or indirectly. Over 200 single-gene defects have been described[5], but CNV also plays a key role in this disease. One study found 25 of 315 (7.9%) epilepsy patients had CNVs that may contribute to their phenotype[6]. A more recent study identified 437 CNV in 323/805 (40%) individuals with epilepsy (1–4 per patient) ranging from 18kb to 142Mb[7], many of which were associated with the disease.

CytoSure Epilepsy Research array:

- Number of genes targeted: 212
- Examples of diseases covered: Epilepsy, brain malformations, severe combined immune deficiency (SCID).

Neuromuscular Disease (NMD)

Neuromuscular disease covers a wide group of diseases affecting voluntary muscles, either directly (affecting muscle function), or indirectly (affecting nerves or neuromuscular junctions). It is estimated that around 160/100,000 population[8] are affected by some form of neuromuscular disease.

The CytoSure NMD Research array is focused primarily on the muscular dystrophies. Genetic analysis is an important part of research in inherited neuromuscular conditions, and it is important to understand all forms of mutations. In the most common form of muscular dystrophy, Duchenne muscular dystrophy, between 60% and 75% of disease relevant mutations are CNVs[9].

CytoSure NMD Research array:

- Number of genes targeted: 205
- Examples of diseases covered: Duchenne muscular dystrophy (DMD), limb girdle muscular dystrophy (LGMD), congenital muscular dystrophy (CMD), Emery-Dreifuss muscular dystrophy, congenital disorders of glycosylation, maturity onset diabetes of the young.

Cardiomyopathy

Cardiomyopathies are diseases of the heart muscle. While the causes of cardiomyopathies are diverse, a proportion are genetic in origin. CNVs have been associated with a number of cardiomyopathies, including long QT syndrome (LQTS)[10, 11], and dilated cardiomyopathy (DCM)[12] and it is therefore important to include copy number analysis into any research to maximise insights into causal variation.

CytoSure Cardiomyopathy Research array:

- Number of genes targeted: 223
- Examples of diseases covered: Cardiomyopathies [including long-QT-syndrome (LQTS), dilated cardiomyopathy (DCM), left ventricular noncompaction cardiomyopathy (LVNC)], hereditary haemorrhagic telangiectasia, hereditary neuropathies, connective tissue disorders.

Eye Disease

CNV as well as SNV play an important role in many kinds of eye disease. CNVs have been described in both relatively common eye disorders such as late age-related macular degeneration[13] and intraocular pressure[14], as well as rare eye diseases such as Ocular Behcet's disease[15] and Graves ophthalmopathy[16]. Eye abnormalities are also present in one-third of inherited, systemic diseases. For example, a dislocated lens in the eye is associated with Marfan syndrome, a connective tissue disease associated with heart problems. The CytoSure Eye Disease Research array includes genes important for syndromic and non-syndromic inherited retinal and choroidal dystrophies, as well as ocular developmental disorders.

CytoSure Eye Disease Research array:

- Number of genes targeted: 221
- Examples of diseases covered: Retinitis pigmentosa, Stargardt disease, macular dystrophy, flecked-retina disorders, congenital stationary night blindness, Bardet-Biedl syndrome, Usher syndrome.

Hereditary Cancer

Many genes have now been identified which affect an individual's risk of developing cancer during their lifetime, and there are also inherited disorders (such as von Hippel-Lindau syndrome and Lynch syndrome) which have an associated increase in cancer risk (kidney and bowl cancer respectively). CNVs have been strongly associated with a number of cancers including breast cancer, prostate cancer, and nasopharyngeal carcinoma — for example 6p21.3, with single-copy deletion of the *MICA* and *HCP5* genes has been associated with nasopharyngeal carcinoma with an odds ratio of 18.92[17]. The CytoSure Hereditary Cancer Research array includes genes important in syndromic and non-syndromic inherited cancers.

CytoSure Hereditary Cancer Research array:

- Number of genes targeted: 228
- Examples of diseases covered: Hereditary cancers, Kabuki syndrome, proportionate short stature, Lynch syndrome.

Metabolic Disorders

Inherited metabolic diseases comprise a large class of genetic diseases involving disorders of metabolism and while classed as rare disease, as a group are relatively common — as much as one in every 800 live births will have an inherited metabolic disorder[18]. The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products). The metabolic disorders are divided into a number of groups, each still containing many individual disorders, for example there are over 50 lysosomal storage disorders. Due to the large number of metabolic disorders there can be significant heterogeneity between them and understanding the complete genetic picture is made all the more important.

CytoSure Metabolic Disorder Research array:

- Number of genes targeted: 203
- Examples of diseases covered: Metabolic disorders, lysosomal storage disorders, glycogen storage disorders, mitochondrial disorders (nuclear genes only).

Skeletal Dysplasia

Skeletal dysplasia is an umbrella term that includes more than 200 individual inherited conditions that affect bone and cartilage growth. It is typically characterised with short stature and legs, arms, trunk or skull can be of abnormal size and shape. The estimated incidence is 1 in 5000 live births with the most common type being achondroplasia[19]. If untreated, skeletal dysplasia can lead to difficulty breathing, including apnea, spinal problems, fluid build-up around the brain, chronic ear infections, and obesity. Hundreds of genes have now been associated with skeletal dysplasia. Using a hand-curated gene list from our development partners at Emory University, the CytoSure Skeletal Dysplasia Research array contains probes targeting 234 medically-relevant genes.

CytoSure Skeletal Dysplasia Research array:

- Number of genes targeted: 234
- Examples of diseases covered: Skeletal dysplasia, disproportionate short stature, osteogenesis imperfecta, limb malformation.

Ciliopathies

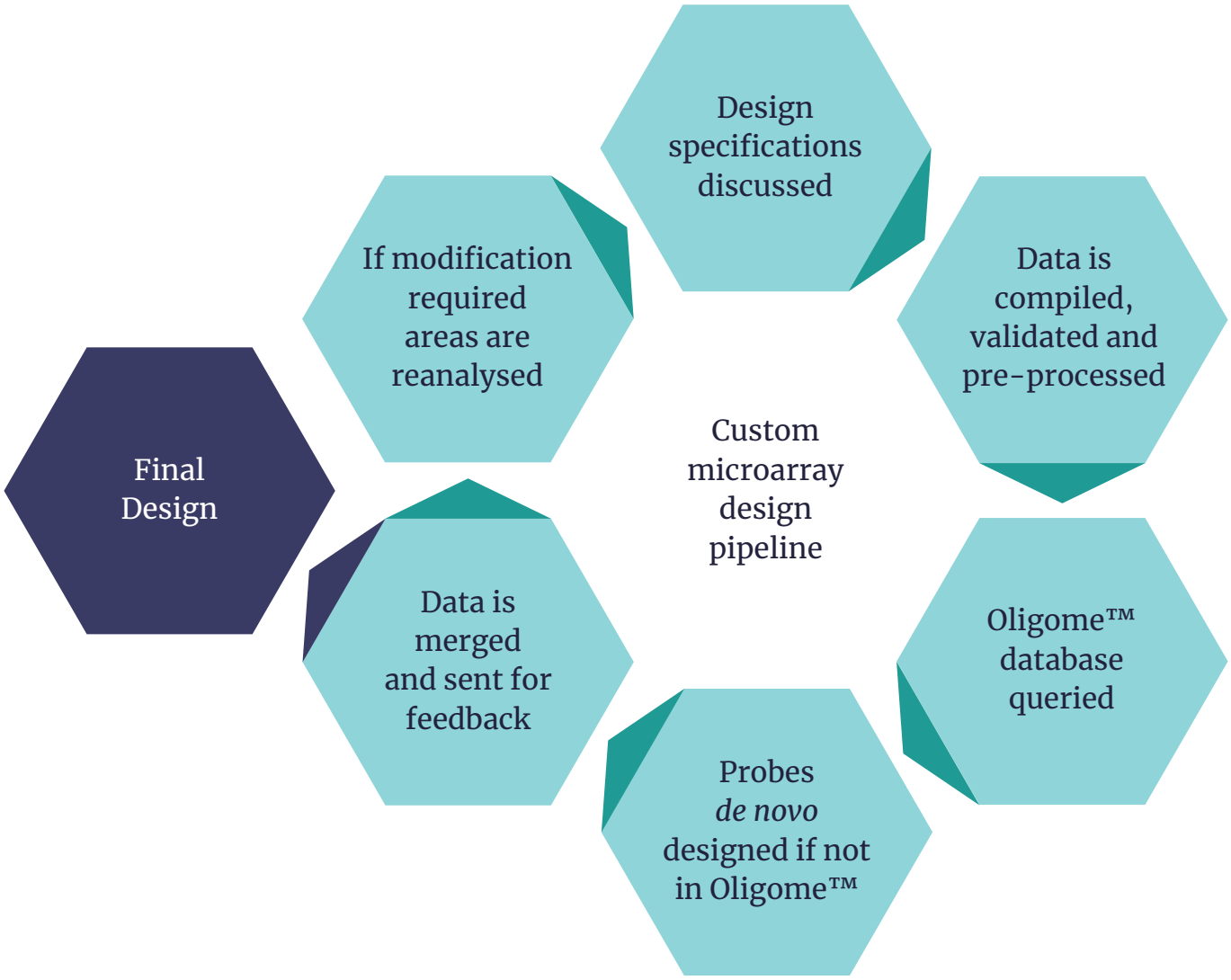
Cilia are hair like protuberances from cells with a complex internal structure and can be either motile or immotile. Dysfunctional cilia are known to underlie a number of often chronically disabling conditions. They affect multiple systems, causing blindness, deafness, chronic respiratory infections, kidney disease, heart disease, infertility, obesity and diabetes, and include diseases such as Bardet-Biedl syndrome (BBS) and polycystic kidney disease (PKD). Understanding of the genetic basis of these disorders is improving all the time, but many genes have now been implicated (e.g. *PKD2* and *PKHD1* in *PKD*[20] and *BBS1*, *BBS7*, *BBS10*, *MKKS* and *ARL6* in BBS[21]). The CytoSure Ciliopathy Research array covers these genes and many more with a known disease relevance.

CytoSure Ciliopathy Research array:

- Number of genes targeted: 207
- Examples of diseases covered: Ciliopathies, Joubert syndrome, Stickler syndrome, hyper IgE syndromes, nephronophthisis.

Custom Array Design

Benefit from our extensive array design expertise to produce an array matching your precise specifications. These arrays are ideal if you want to know the precise coordinates of an aberration by analysing specific areas of the genome at high resolution. Use any of the disease-focused arrays as your starting point and customise to your exacting specifications. Working closely with our experienced design team — one of whom is assigned project leader to ensure continuity of process and communication — the process is made quick, simple and easy.



CytoSure Interpret Software

CytoSure Interpret Software, which is complimentary with all array purchases, offers an impressive combination of features that allow you the choice of standardised data analysis (using the Accelerate Workflow) or customised, user-defined data analysis.

- Fast, accurate and simple analysis of aCGH data for identification of CNV
- Comprehensive data annotation with direct links to external databases and online resources
- Robust relational database allowing sophisticated data querying and filtering
- Fully integrated, automatic analysis of array image files
- Includes the new Exon-Focused Segmentation Algorithm (EFSA) designed and tested specifically for exon-focused arrays

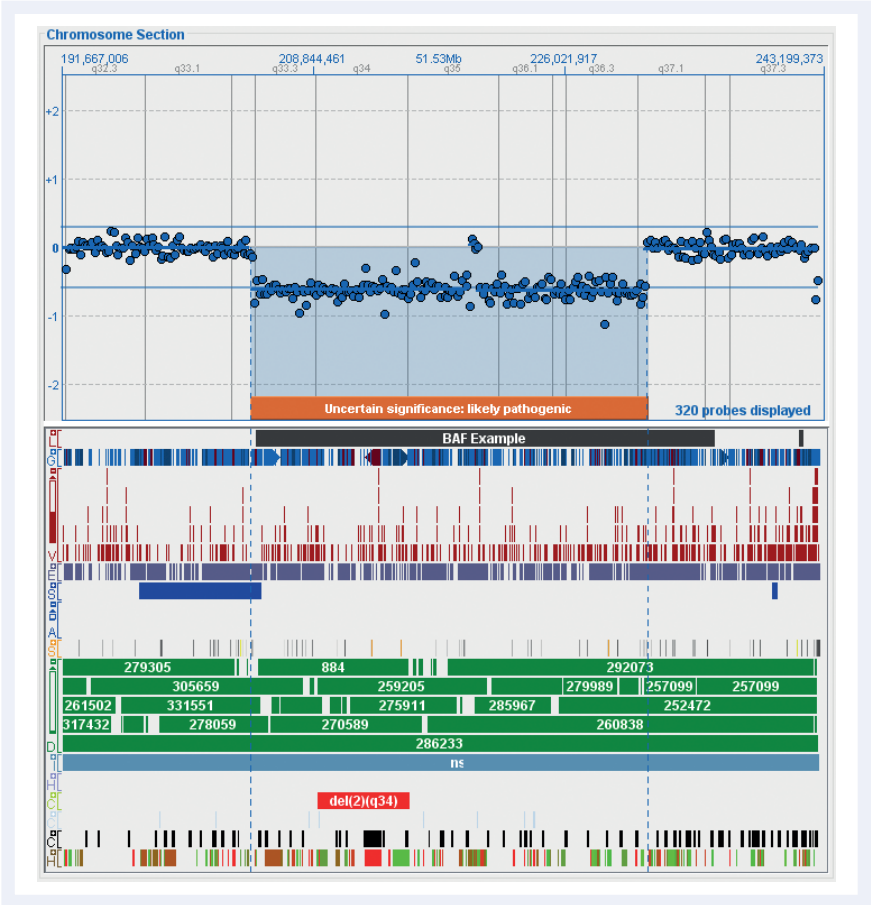


Figure 1: Fast and simple access to results using complimentary CytoSure Interpret Software, with comprehensive annotation tracks to aid interpretation.

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Ordering information

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Product	Genes	Cat. No.
CytoSure Medical Research Exome array (1x1M)	4645	020100
CytoSure Autism Research array (4x180k)	227	700121
CytoSure Epilepsy Research array (4x180k)	212	700112
CytoSure NMD Research array (4x180k)	205	700117
CytoSure Cardiomyopathy Research array (4x180k)	223	700110
CytoSure Eye Disease Research array (4x180k)	221	700113
CytoSure Hereditary Cancer Research array (4x180k)	228	700115
CytoSure Metabolic Disorder Research array (4x180k)	203	700116
CytoSure Skeletal Dysplasia Research array (4x180k)	234	700118
CytoSure Ciliopathy Research array(4x180k)	207	700111
CytoSure DMD Research array (8x60k)	50	020023
CytoSure Custom Molecular array	-	700001
CytoSure Genomic DNA Labelling Kit	-	020022
CytoSure HT Genomic DNA Labelling Kit	-	500040
CytoSure Sample Tracking Spike-ins A – H	-	500050 – 500057
CytoSure Interpret Software	-	020022

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What binds us, makes us.

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