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Trusted Answers

SureSelect NGS Panels: Customized for Any Application

Agilent Custom Design Application Compendium

Using your vision and your design to tackle human disease

Unraveling the secrets of the human genome has revealed that many diseases have a genetic component. Some diseases are caused by mutations passed from parent to child or germline mutations, while others are caused by acquired or somatic mutations in one or more gene(s) that occur during a person's life. Somatic mutations occur either randomly during cell division, or due to exposure to certain environmental elements and often result in complex diseases like cancer or cardiovascular disease.

Since 2009, Agilent has supported researchers and clinicians in their quest to investigate and combat human diseases with our SureSelect next-generation sequencing (NGS) portfolio and our integrated NGS workflow solutions. The Agilent NGS workflow includes nucleic acid quality control (QC) instrumentation (such as our Fragment Analyzer, TapeStation, and other automated electrophoresis systems), SureSelect library preparation kits, SureSelect target enrichment catalog and custom panels, Bravo NGS and Magnis NGS systems for automation, and Alissa Clinical Informatics for data analysis and interpretation. With these integrated components, our SureSelect panels have played an instrumental role in work that has led to over 4,800 publications.

With SureDesign, Agilent's best-in-class web design portal, customers can leverage our sophisticated probe design algorithms to develop their own panel in a matter of hours. In addition, with the new Agilent design verification process, you can free up valuable lab resources by verifying your custom human panel design before the target enrichment probes are even shipped to you. With recent improvements to probe manufacturing (such as machine-learning-powered probe design, dual strand oligo printing and new probe recovery process), there's never been a better time to use Agilent SureSelect custom target enrichment panels.

The following sections showcase how we have helped enable labs around the globe to accelerate their disease research and clinical assay development in multiple applications areas using our custom SureSelect panels.

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Inherited Disease

Inherited diseases, or genetic disorders, occur when a genetic variation that is passed from a parent to a child results in disease. These variants can range from simple single-gene variants to more complex multigene variants (see next section "Complex Diseases") or abnormalities in chromosome number and/or structure. Inherited diseases can either be obvious at birth, such as Fragile X, or they can develop later in life, like Huntington's disease. Using NGS, clinicians and disease researchers are identifying the genetic drivers of many human diseases and helping to improve quality of life for those who suffer from them.

How our customers are illuminating inherited disease

Study 1

A recent paper[1] from a Harvard retinal degeneration research group used a 260 gene SureSelect custom panel to enrich exons and selected deep intronic regions. With this targeted approach, researchers were able to show that, while the specimens displayed a range of phenotypic severity, the disease could be attributed to biallelic recessive mutations in the retinal dehydrogenase 12 gene (RDH12). They identified that RDH12, which plays a pivotal role in maintaining normal vision, had four novel variants in RDH12 that were attributable to the phenotype.

Study 2

The second study highlighted is from the Manchester Centre for Genomic Medicine[2]. In this work, the authors developed a framework to implement the Exome Depth software package to identify copy number variants (CNVs) from targeted NGS data sets. By leveraging these datasets, researchers were able to increase the diagnostic yield of Mendelian disorders and enhance clinical care. Targeted sequencing was performed using a custom SureSelect panel designed to capture known pathogenic intronic variants and the protein-coding regions of selected NCBI RefSeq transcripts. CNV detection was applied to individuals who lacked molecular diagnosis after routine clinical NGS testing. The authors were able to identify CNVs contributing to the cause of a Mendelian disorder. The findings suggest the integration of CNV detection with routine targeted NGS diagnostic services for Mendelian disorders can provide better identification, and clinical care, of patients who suffer from these disorders.

Complex Disease

While inherited diseases are often the result of a single-gene mutation, complex patterns of inheritance or somatic events can result in multiple genes influencing a disease. This complexity is increased due to the fact that environment can also play a role, which can be seen in cases of diabetes, asthma, cancer, and mental illness. In these diseases, there is no causative single-gene mutation; multiple gene mutations will support an increased risk of disease rather than a definitive prediction of development.

How our customers are tackling complex disease

Study 1

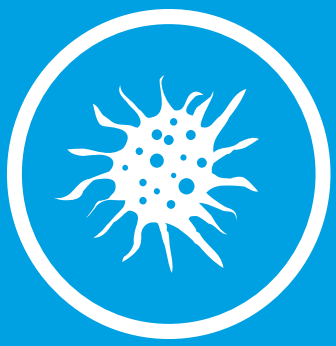
This Mayo Clinic and Johns Hopkins study[3] investigated the diagnostic utility of somatic mutations in the context of cytopenias, which are characterized by a reduction in the number of mature blood cells. The authors applied targeted sequencing to a well-characterized cytopenic cohort. The diagnostic utility of a custom SureSelect panel that targeted 640 genes was compared to a virtual panel of 41 genes. The authors demonstrated that targeted sequencing is able to improve the diagnostic accuracy for unexplained cytopenia.

Study 2

In a rheumatoid arthritis (RA) study from University of Manchester, researchers[4] simultaneously measured ATAC-seq, HiC, Capture HiC, and nuclear RNA-Seq data in stimulated primary T cells to define the complex relationship between DNA activity, interactions, and gene expression. They designed a custom SureSelect panel targeting 5,124 genes associated with RA, the KEGG pathways, and other previously reported relevant genes. The authors reported that small-magnitude changes in DNA interactions and activity dynamics are correlated with much larger changes in gene expression and that the strongest correlations are observed within 200 kb of promoters.

Study 3

Finally, the University of Chile[5] and its worldwide collaborators studied blood samples from 2,100 Latin Americans with proximal muscle weakness. The authors designed a custom SureSelect panel that targeted the exonic regions of 10 genes and deep intronic variants related to muscular dystrophy and Pompe disease. Using ACMG criteria, genetic variants were classified, leading to definitive molecular detection and identification of Pompe disease in some specimens.



Cancer Genomics

Cancer translational research is becoming increasingly reliant on genomics-based assays. These assays are providing predictive information on disease progress and are helping to identify therapeutic targets. The difficulty of studying cancer genomics is not limited to just complex molecular patterns and is compounded by the need to examine multiple analytes. Researchers must look at multiple challenging sample types, including genomic DNA, RNA, cell-free DNA (cfDNA), and DNA from formalin-fixed paraffin-embedded (FFPE) tissue, to get a full picture of the disease. The sensitivity of the tools used is also critical, as early detection of changes to tumor cell mutations is important to understanding (and treating) disease progression.

How our customers are fighting cancer

Study 1

Scientists at Mt. Sinai[6] integrated RNA-Seq, DNA-seq, TCR-seq, and SNP array data across multiple regions of liver cancer specimens to map spatio-temporal interactions between cancer and immune cells. Targeted DNA-seq was applied to determine if regional heterogeneity in expressed mutations was also affecting known hepatocellular carcinoma (HCC) drivers. A custom SureSelect panel was designed to target the exons of 58 of the most frequently mutated genes in HCC. Whole-exome sequencing analysis of one specimen was carried out using the SureSelect Low Input Target Enrichment System with SureSelect XT HS Human All Exon V7. By leveraging this combined data set, the authors demonstrated regional variations of transcription factors at single-cell resolution in HCC.

Study 2

Researchers at Johns Hopkins University[7] used ultra sensitive targeted sequencing analyses of matched cfDNA and white blood cells from the same specimen to identify circulating tumor-derived DNA (ctDNA) alterations. They applied this approach to analyze gastric cancer specimens in a randomized phase III clinical trial. Targeted sequencing was performed using a custom SureSelect panel targeting 58 genes. The authors reported that the presence of ctDNA predicts recurrence when analyzed within nine weeks after pre-operative treatment and after surgery when eligible for multimodal treatment.

Study 3

At the University of Geneva Medical School[8], scientists performed mutational screening of basal cell carcinoma (BCC) samples from sporadic cases to identify new drivers and progression pathways. The study applied whole-exome sequencing, targeted DNA-seq, and RNA-Seq to analyze samples. Exome target enrichment was performed using SureSelect Human All Exon V5. Target enrichment of cancer genes was performed using a custom SureSelect panel designed to target 387 cancer-related genes selected based on their mutation profiles in the COSMIC database and recent reviews. The study identified more than 234,000 somatic coding mutations and found the mutation rate for sporadic BCCs to be the highest observed among cancers.

Clinical Assay Development*

NGS is a powerful tool that is increasingly used to identify genetic causes of disease and to inform the course of targeted therapies. Developing an NGS clinical assay for these approaches requires rigor in every component, including the design and use of the enrichment panel that will target your genomic regions of interest.

How our customers are using SureSelect to power their NGS assays

Study 1

Scientists at the NE Thames Regional Genetics Laboratories[9] developed a definitive noninvasive prenatal screen for cystic fibrosis using targeted sequencing. They designed a custom SureSelect panel targeting the coding regions of the CFTR gene, including 225 heterogeneous SNPs. The method can detect recombinations and has led to significant increase in referrals.

Study 2

Quest Diagnostics[10] developed and validated a 34-gene inherited cancer predisposition panel using targeted sequencing. The authors designed a custom SureSelect panel to capture all coding exons and exon/intron boundaries of 34 hereditary cancer-related genes. In addition, they also included noncoding regions of these genes containing known pathogenic variants, as well as the promoter regions of APC, MLH1, MSH2, and PTEN. The authors performed validation on specimens with known variant status and employed a custom Agilent CGH array to confirm copy-number variant-positive specimens. The results indicate that the 34-gene panel can provide clinically significant information for cancer risk assessment.

Study 3

Researchers at the Poznan University of Medical Sciences[11] applied targeted sequencing to an unrelated cohort affected by craniosynostosis (CS), which is characterized by premature fusion of the cranial sutures. These CS specimens had negative results from preliminary molecular screening via conventional Sanger sequencing. The authors designed a custom SureSelect panel targeting 61 genes and 11 SNVs associated with craniosynostosis and abnormalities of craniofacial development. They also adapted the SureSelect target enrichment protocol for sequencing on the Ion Torrent S5 platform. The approach generated high-quality NGS data and yielded findings consistent with other published reports.

** Agilent SureSelect products are not approved for diagnostic testing, diagnosis, treatment, or mitigation. Customers are responsible for acquiring the necessary certification and/or approvals for use in a clinical setting.*

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