Expanded carrier screening by NGS

Bring ECS to your lab with CarrierSeq ECS Kits

Introduction

In today's multiethnic society, some genetic disorders previously confined to specific ethnic groups may now occur at increasing frequency in broader populations. Conventional carrier screening that targets single disorders according to ancestry or family history, based on assumptions about prevalence, may not accurately reflect changing frequencies. New advancements and decreasing costs of genetic analysis technologies such as next-generation sequencing (NGS) are enabling carrier screening research across a broader range of disorders. This type of research enables discovery of carrier status regardless of ancestry or geographic region, with high accuracy, quick turnaround time, and low cost.

Rigorously designed specifically for expanded carrier screening (ECS) research, the Ion Torrent™ CarrierSeq™ ECS Kits for the Ion GeneStudio™ S5 System are an end-to-end solution that includes reagents for library preparation, template preparation, and sequencing, plus software for data analysis and reporting. With CarrierSeq ECS Kits, laboratories can now perform NGS-based expanded carrier screening research in their own labs.

Key benefits

- **Increase carrier status detection rates for a broad range of inherited disorders**—The rigorously designed 420-gene panel enables the analysis of 28,000 non-benign ClinVar variants for single-nucleotide variants (SNVs), insertions and deletions (indels), and copy number variants (CNVs) by NGS.
- **Consolidate stand-alone assays to improve lab efficiency**—Targets that are difficult to detect due to pseudogenes, paralogs (*SMN1* and *SMN2* for spinal muscular atrophy), or occurrence within a locus (*HBA1* and *HBA2* for alpha thalassemia) are consolidated in a single NGS assay.

- **Simplify adoption and implementation in your lab with this end-to-end solution**—Our optimized assay kit streamlines implementation and helps ensure reliable and consistent results by leveraging Ion AmpliSeq™ technology. Intuitive and customizable data analysis software quickly translates data into results and report formats you need.

Rigorously designed content and consolidated assays

CarrierSeq ECS Kits enable the analysis of more than 28,000 non-benign variants from ClinVar and other annotation sources; variants include pathogenic,* likely pathogenic,* and variants of unknown significance (VUS)* in 420 genes implicated in 418 inherited disorders. The panel comprises ~14,000 amplicons that cover the entire coding sequence (CDS) regions of target genes, including intron/exon boundaries for the analysis of SNVs and CNVs across the complete exonic regions of each gene, not only the likely pathogenic variants. Four iterations of the panel design were developed, and testing was conducted with >450 true positive samples** in addition to 68 synthetic variants to ensure optimum performance.

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* From ClinVar and other annotation sources.

** Cell lines described in this study were obtained from the NIGMS Human Genetic Cell Repository, the NHGRI Sample Repository for Human Genetic Research, and the CDC Cell and DNA Repository, all at the Coriell Institute for Medical Research.

Rigorously designed content for accurate detection of CNVs and analysis of difficult-to-call variants (such as *SMN1* and *SMN2* for spinal muscular atrophy or *HBA1* and *HBA2* for alpha thalassemia) in a single assay.

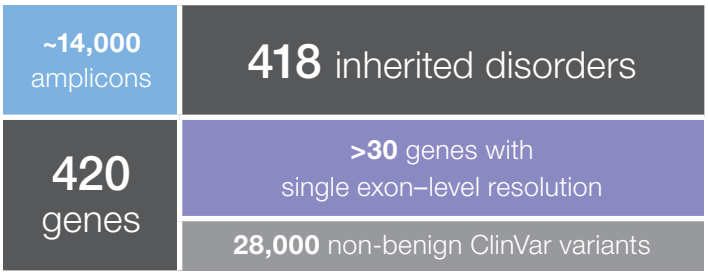


Figure 1. Content for increased detection rates.

CNV detection is an essential part of genetic analysis for inherited disorders. Accurate and reproducible CNV analysis by NGS can be a significant challenge. Through expert design for increased amplicon coverage and software algorithm developments, the CarrierSeq ECS Kits enable robust and accurate CNV analysis (in addition to SNV analysis) to maximize carrier status detection. This includes detection of known carrier variants with single exon–level resolution for >30 focused genes, such as *CFTR* and *DMD* (Table 1).

Genetic variants for a number of the most severe yet prevalent disorders can be challenging to detect by NGS assays, and therefore typically require separate additional stand-alone tests for the causative genes. Our algorithms enable a single assay despite the difficulties in variant calling as a result of pseudogenes, paralogs (such as *SMN1* and *SMN2* for spinal muscular atrophy), or occurrence within a locus (such as *HBA1* and *HBA2* for alpha thalassemia).

Table 1. Partial CarrierSeq ECS gene list.

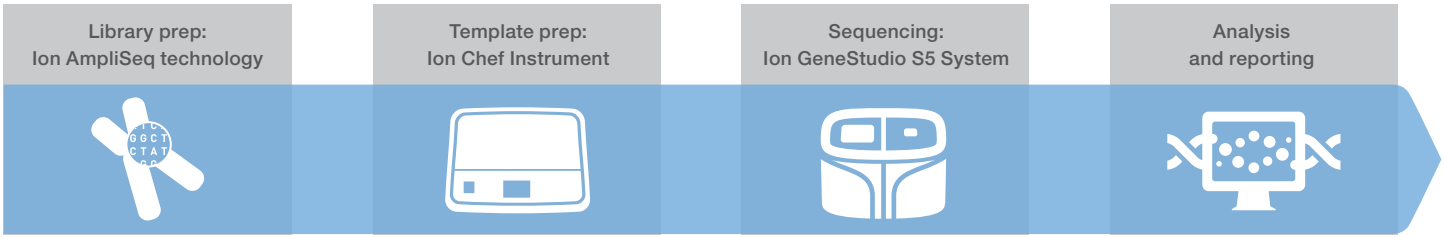
See the complete list at **thermofisher.com/carrierseq**.

Research area	Gene	Targeted ClinVar SNVs/ indels	CNV
Alpha thalassemia	*HBA1/2*	SC*	Yes+
Beta hemoglobinopathies	*HBB*	267	Yes+
Bloom syndrome	*BLM*	126	Yes
Canavan disease	*ASPA*	64	Yes
Congenital amegakaryocytic thrombocytopenia	*MPL*	50	Yes
Cystic fibrosis	*CFTR*	819	Yes+
Dihydrolipoamide dehydrogenase deficiency	*DLD*	24	Yes
Duchenne/Becker muscular dystrophy	*DMD*	634	Yes+
Familial dysautonomia	*IKBKAP*	15	Yes
Familial hyperinsulinism, *ABCC8*-related	*ABCC8*	542	Yes
Fanconi anemia, complementation group A	*FANCA*	87	Yes+
Fanconi anemia, complementation group C	*FANCC*	80	Yes+
Fanconi anemia, complementation group G	*FANCG*	18	Yes
Galactosemia	*GALT*	276	Yes+
Gaucher disease	*GBA*	7*	Yes
Glycogen storage disease, type IA	*G6PC*	85	Yes
Glycogen storage disease, type IB	*SLC37A4*	36	Yes
Joubert syndrome 2	*TMEM216*	15	Yes
Joubert syndrome 7	*RPGRIP1L*	47	Yes
Maple syrup urine disease, type IA	*BCKDHA*	60	Yes
Maple syrup urine disease, type IB	*BCKDHB*	90	Yes
Maple syrup urine disease, type II	*DBT*	44	Yes
Medium-chain acyl-CoA dehydrogenase deficiency	*ACADM*	104	Yes
Mucolipidosis IV	*MCOLN1*	41	Yes+
Nemaline myopathy, *NEB*-related	*NEB*	124	Yes
Niemann-Pick disease, type A/B	*SMPD1*	128	Yes
Phenylketonuria	*PAH*	277	Yes+
Smith-Lemli-Opitz syndrome	*DHCR7*	95	Yes
Spinal muscular atrophy	*SMN1*	SC*	Yes+
Tay-Sachs disease	*HEXA*	166	Yes+
Usher syndrome, type 1F	*PCDH15*	77	Yes+
Usher syndrome, type 3A	*CLRN1*	23	Yes
Walker-Warburg syndrome, *FKTN*-related	*FKTN*	36	Yes

Yes+ = Enhanced amplicon design and coverage.

SC = Special-case gene.

* Specialized algorithms are used for these special-case genes.



Library prep: Rapid preparation of amplicon libraries using the CarrierSeq ECS panel based on the globally recognized Ion AmpliSeq technology
Day 1 of the workflow
Hands-on time: ~1.5 hr

Template prep on Ion Chef Instrument: Robust and automated template preparation with integrated sample tracking using prepackaged and ready-to-use reagent cartridge
Day 1 of the workflow (overnight run)
Hands-on time: 15 min

Sequencing on Ion GeneStudio S5 System: Fast and easy setup of sequencing run using prepackaged reagent cartridge; choice of two different Ion Chip Kits for sample throughput flexibility
Day 2 of the workflow
Hands-on time: 15 min

Data analysis: Complete data analysis workflow to quickly translate data into results, including customizable analysis and reporting options for flexible viewing

Figure 2. Streamlined 2-day workflow for fast turnaround from genomic DNA to variant calls.

Streamlined implementation and workflow

CarrierSeq ECS Kits include reagents for library preparation, template preparation, and sequencing, plus software for data analysis and reporting. The reagents are optimized to work together out of the box (Figure 2).

For library preparation, CarrierSeq ECS Kits use the globally recognized, superior Ion AmpliSeq technology, a fast and simple amplicon-based enrichment method for targeted NGS. The proprietary, proven Ion AmpliSeq technology combines thousands of primer pairs in a single PCR reaction for robust and consistent library preparation. Ion AmpliSeq technology has seen broad global adoption and resulted in over 1,000 peer-reviewed publications across a broad range of applications, including inherited disease and cancer research.

Using the Ion Chef™ and Ion GeneStudio S5 Systems for template preparation and sequencing, and a suite of software programs for data analysis, the CarrierSeq ECS Kits offer a seamless workflow for carrier screening research.

Straightforward and powerful data analysis

Three software tools work together seamlessly to reduce the need for extensive bioinformatics expertise to perform various analyses and provide a concise result report with high confidence (Figure 3).

Torrent Suite™ Software is used for fast and easy sequencing run planning, monitoring, automated sequencing, primary data analysis, and alignment. Data are automatically exported to Ion Reporter™ Software and further processed with preconfigured CarrierSeq workflows to call variants such as SNVs, indels, and CNVs, as well as putative gene conversion events.

Lastly, Carrier Reporter Software, a straightforward yet powerful software, is designed specifically for carrier screening research analysis and reporting. The software automatically classifies the variants based on pathogenicity according to ClinVar, proprietary databases, and the American College of Medical Genetics and Genomics (ACMG)-predicted pathogenicity guidelines. The software also enables the user to customize the variant classifications based on their own guidelines and store them in the system for use in subsequent analyses. The intuitive user interface presents the sequencing QC information and carrier results, including no-call information for individuals or couples. Finally, the software enables customization such that the user may analyze and report only the variants and genes of interest (for example, American College of Obstetricians and Gynecologists (ACOG)-recommended genes for common disorders).

Torrent Suite Software
Plan, monitor, and track your runs all within a browser while reviewing the quality and accuracy of your sequencing run.

Ion Reporter Software
Identify variants such as SNVs, indels, and CNVs with preconfigured and customizable workflows, providing flexibility for users of any experience level.

Carrier Reporter Software
Classify variants according to pathogenicity based on ACMG and ClinVar guidelines. Customize analysis and reporting at variant and gene levels.

Figure 3. Straightforward bioinformatics workflow.

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Flexible throughput

CarrierSeq ECS Kits are available in two different sizes to accommodate laboratories with variable throughput needs. Multiplexing options for 4 or 16 samples per chip (8 or 32 samples per run) for the Ion GeneStudio S5 System provide a cost-effective solution for variable throughput demand and a streamlined path for growth in laboratories that are increasing their carrier screening research or transitioning from outsourcing to an in-house platform.

Summary

Implementing expanded carrier screening research in your own lab is now easier than ever with CarrierSeq ECS Kits and Carrier Reporter Software. This NGS-based end-to-end solution, which includes rigorously designed targeted content, optimized reagents, and intuitive data analysis software tools, is ready to implement without the need for expert-level bioinformatics resources. The assay's ability to enable the analysis of SNVs and CNVs for the evaluation of 420 genes in a single assay, combined with intuitive and customizable analysis and reporting software tools, gives you the confidence you need to provide accurate, quick, and cost-effective results.

Ordering information

Product	Description	Quantity	Cat. No.
CarrierSeq ECS Kit with Ion 530 Chips	4 samples/chip, 8 samples/run	96 samples	A43585
CarrierSeq ECS Kit with Ion 540 Chips	16 samples/chip, 32 samples/run	384 samples	A43586
Instrument			
Ion Chef Instrument	Ion Chef Instrument	1 instrument	4484177
Ion GeneStudio S5 System	Ion GeneStudio S5 Sequencer	1 system	A38194
Ion GeneStudio S5 Plus System	Ion GeneStudio S5 Plus Sequencer	1 system	A38195
Ion GeneStudio S5 Prime System	Ion GeneStudio S5 Prime Sequencer and Torrent Server	1 system	A38196
Data analysis			
Ion Reporter Software	Cloud-based hosted data storage or on-site server options available	Find out more at **thermofisher.com/ionreporter**	
Carrier Reporter Software	Cloud-based or on-site server options available	Find out more at **thermofisher.com/carrierseq**	

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