

Heterotaxy and Situs Inversus Panel

Test code: CA2301

Is ideal for patients with a diagnosis of laterality disorder.

About Heterotaxy and Situs Inversus

Heterotaxy is a disorder in which the internal organs are abnormally arranged in the chest and abdomen and there are often associated complex cardiovascular malformations. Right isomerism sequence (asplenia syndrome, Ivemark sequence, right atrial isomerism) causes a complex congenital heart disease, two morphologically right atria and often a single ventricle and AVSD, TGA and anomalous pulmonary venous drainage. The spleen can be absent and there may be abnormal folding of the intestines. In left isomerism sequence (polysplenia syndrome) there are two morphologically left atria and absence of the sinoatrial node that may cause complete heart block. The associated heart defects are not usually as severe as in right isomerism. Multiple small spleens may be found and there may be abnormal folding of the intestines. Isomerism sequence occurs with an incidence of 1/24,000 and accounts for about 1 % of congenital heart defects. Situs inversus is a condition with a complete mirror image arrangement of the internal organs. It affects approximately 1/10,000 individuals and is associated with an increased risk of congenital heart disease. Situs inversus can also occur in association with primary ciliary dyskinesia. A proportion of the laterality disorders are explained by mutations in known genes and can be inherited in an autosomal dominant, autosomal recessive or X-linked manner.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Heterotaxy and Situs Inversus Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ACVR2B	Heterotaxy, visceral, 4, autosomal	AD	1	2
ANKS6	Nephronophthisis	AR	9	12
ARMC4*	Ciliary dyskinesia	AR	18	17
C21ORF59	Ciliary dyskinesia	AR	5	4
CCDC103	Ciliary dyskinesia	AR	4	5
CCDC114	Ciliary dyskinesia	AR	9	8
CCDC151	Ciliary dyskinesia, primary, 30	AR	7	2
CCDC39	Ciliary dyskinesia	AR	39	47
CCDC40	Ciliary dyskinesia	AR	33	43
DNAAF1	Ciliary dyskinesia	AR	19	38
DNAAF2	Ciliary dyskinesia	AR	13	6
DNAAF3	Primary ciliary dyskinesia	AD/AR	11	5
DNAAF5	Ciliary dyskinesia	AR	9	5

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DNAH11*	Ciliary dyskinesia	AR	66	130
DNAH5	Ciliary dyskinesia	AR	140	197
DNAI1	Ciliary dyskinesia	AR	17	35
DNAI2	Ciliary dyskinesia	AR	19	6
DNAL1	Ciliary dyskinesia	AR	3	1
DYX1C1	Ciliary dyskinesia	AR	15	12
FOXH1	Congenital heart malformations, Holoprosencephaly	AD		33
GDF1	Transposition of the great arteries, dextro-looped 3, Double-outlet right ventricle	AD	11	15
INVS	Nephronophthisis	AR	16	34
LEFTY2*	Left-right axis malformations	AD	1	3
LRRC6	Ciliary dyskinesia	AR	10	19
MMP21	Heterotaxy, visceral, 7	AR	4	18
NODAL	Heterotaxy, visceral	AD	4	15
PIH1D3#	Ciliary dyskinesia, primary, 36	XL	2	12
PKD1L1	Heterotaxy, visceral, 8, autosomal	AR	2	6
SPAG1	Primary ciliary dyskinesia	AR	18	11
TTC25#	Ciliary dyskinesia, primary, 35	AR	2	2
ZIC3	Heterotaxy, visceral, VACTERL association, Congenital heart defects, nonsyndromic	XL	15	41
ZMYND10	Ciliary dyskinesia	AR	8	16

*Some regions of the gene are duplicated in the genome leading to limited sensitivity within the regions. Thus, low-quality variants are filtered out from the duplicated regions and only high-quality variants confirmed by other methods are reported out. [Read more.](#)

Gene, refers to HGNC approved gene symbol; Inheritance to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL); ClinVar, refers to a number of variants in the gene classified as pathogenic or likely pathogenic in ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>); HGMD, refers to a number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD, <http://www.hgmd.cf.ac.uk/ac/>). The list of associated (gene specific) phenotypes are generated from CDG (<http://research.nhgri.nih.gov/CGD/>) or Orphanet (<http://www.orpha.net/>) databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
CCDC39	Chr3:180367941	c.1167+1248A>G	NM_181426.1	

Test performance

The Blueprint Genetics heterotaxy and situs inversus panel covers classical genes associated with nephronophthisis, congenital heart malformations, heterotaxy, visceral, ciliary dyskinesia and left-right axis malformations. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient's phenotype is suggestive of a specific mutation type.

Bioinformatics

The target region for each gene includes coding exons and ± 20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the "Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited to, [1000 Genomes Project](#), [gnomAD](#), [ClinVar](#) and [HGMD](#) into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent diagnostics where customers have easy access to crucial details of the analysis process.

Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the [Blueprint Genetics Variant Classification Schemes](#) based on the [ACMG guideline 2015](#). Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size < 10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in

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population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation databases to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the Heterotaxy and Situs Inversus Panel

ICD-10	Disease
Q61.5	Nephronophthisis

Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- [Goossens E et al. Implementation of the American College of Cardiology/American Heart Association 2008 Guidelines for the Management of Adults With Congenital Heart Disease. Am J Cardiol. 2015 Aug 1;116\(3\):452-7.](#)
- [Baumgartner H et al. ESC Guidelines for the management of grown-up congenital heart disease \(new version 2010\). Eur Heart J. 2010 Dec;31\(23\):2915-57.](#)
- [GeneReviews - Primary Ciliary Dyskinesia](#)
- [Children's Heart Federation - Laterality Disturbance and Heart Defects](#)
- [NORD-Ivemark Syndrome](#)
- [GARD - Heterotaxy](#)
- [GARD - Ivemark Syndrome](#)
- [NORD - Primary Ciliary Dyskinesia](#)
- [PCD Family Support Group](#)
- [PCD Foundation](#)