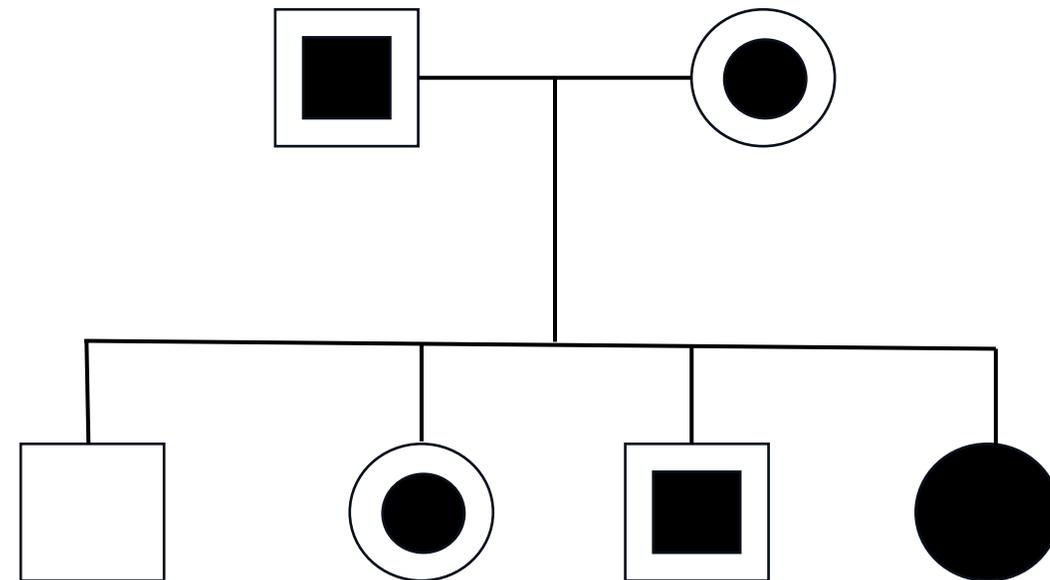


NGSを利用したキャリアスクリーニング

フィルジエン株式会社 バイオインフォマティクス部
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- 妊娠前のカップルに対してキャリアスクリーニングを実施することで、子どもの遺伝性疾患の発症リスクを予測することができます。
- Golden Helix社VarSeq®ソフトウェアでは、次世代シーケンサーより得られたバリエーションデータをもとに、ACMGガイドラインに基づいた遺伝性疾患の病的バリエーションの検出とリスク計算、レポート出力を行うことができます。



Annotation

Variant Filtering

The screenshot displays the VarSeq software interface. At the top, there's a 'GenomeBrowse' window showing a genomic track for chromosome 16, with coordinates 16: 2,495,470 to 16: 2,495,530. Below this, there are tracks for 'Reference Sequence GRCH37 g1k, 1000Genomes', 'RefSeq Genes 105, NCBI' (showing the CCNF gene), and 'OMIM Genes 2010-10-27, UCSC' (showing gene 600227). A 'Variants - NA12878' track shows three variants: NA12878, NA12891, and NA12892. On the left, a 'Trio Analysis' panel shows various filters and statistics. At the bottom, a 'Detail' window shows a table of variant sites.

Variant Sites	Genotypes	Classification	Compound Het Variants				
Chr_Pos	Ref/Alt	Identifier	Proband (NA12878)	Mother (NA12891)	Father (NA12892)	Sequence Ontology	Is CH? Inherited From
11:108183167	A/G	rs659243	G,G	G,G	G,G	missense_variant	False NA
13:49033835	G/A	rs20211...	A,G	A,G	A,G	missense_variant	False NA
14:24567498	A/C	rs30211...	C,C	C,C	C,C	missense_variant	False NA
14:73664751	T/G	rs19972...	G,T	G,T	G,T	missense_variant	False NA
14:106208082	G/T	rs11621...	G,T	T,T	?	missense_variant	False NA
16:2495482	T/G	rs20154...	G,T	T,T	G,T	missense_variant	True Father

Data Analysis

Genome Browser

- 様々なデータベースを用いて、バリエーションデータ（VCFファイル）へアノテーション付けを実行

- RefSeq Genes
- dbSNP
- ClinVar
- OMIM
- CIViC
- ICGC / TCGA
- MSK Impact
- Orphanet
- BRCA Exchange
- PMKB
- dbNSFP
- REVEL
- CADD
- 1000 Genomes
- NHLBI 6500 Exomes
- ExAC Variant
- gnomAD Exomes/Genomes
- GenomeAsia 100K
- 各種遺伝子パネルのターゲットデータ
- ...など

- アノテーション付けされたバリエーションデータより、任意の検索条件でデータのフィルタリングを行うワークフローを作成

- カバレッジ計算やトリオ解析、表現型情報に基づく遺伝子ランキングなどの解析アルゴリズムを搭載

- ゲノムブラウザーにより、サンプルのバリエーションデータやリードアライメントデータ（BAM/CRAMファイル）、また各種アノテーションを可視化

- 有償アドオンによる機能拡張で、CNV検出や臨床的意義の自動評価、パイプライン機能などが利用可能

Gene: ^

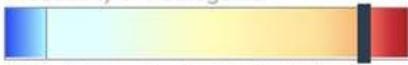
Gene: **NF1** Transcript: **NM_000267.3**

NM_000267.3: c.1466A>G NP_000258.1: p.Y489C

Effect: **Missense** Exon: **13 of 57**
missense_variant

ACMG Scoring: 2 ^

Scored Criteria:
PP2 PP3 PS1
2 criteria currently unscored

Probability of Pathogenic:

87.1% - Predicted Classification: Likely Pathogenic

Classification:
Likely Pathogenic ⊕

Therapeutic Options ^

Drug Sensitivity Interpretations (6) Drug Resistance Interpretations (2) Drug Descriptions

<input checked="" type="checkbox"/> Drugs	Tier	Saved For	Variants	Clinical Trials
<input checked="" type="checkbox"/> Bevacizumab, Ramucirumab, Regorafenib	Tier 1A	Colorectal Adenocarcinoma	<i>Unspecified</i>	0 Selected
<input checked="" type="checkbox"/> Encorafenib + Cetuximab, Encorafenib + Panitumumab	Tier 1A	Colorectal Adenocarcinoma	BRAF V600E (Activating Mutation)	0 Selected
<input checked="" type="checkbox"/> Entrectinib, Larotrectinib	Tier 1A	Solid Tumor Cancers	NTRK1 Fusion (Activating Mutation)	0 Selected
<input checked="" type="checkbox"/> Pembrolizumab	Tier 1A	Solid Tumor Cancers	TMB High	0 Selected
<input checked="" type="checkbox"/> Dostarlimab-gxly, Nivolumab, Nivolumab + Ipilimumab, Pembrolizumab	Tier 1A	Colorectal Adenocarcinoma	MSI High	0 Selected

< 1 of 2 >

■ VSClinical ACMG Guideline

- メンデル遺伝病における生殖細胞系列バリエントを、ACMGガイドラインの評価基準に基づいて分類し、病原性 (Pathogenic) や良性 (Benign) の判定を行う
- 専用の分類用ツールを実行することで、VCFファイルに含まれる全バリエントに対して一括で評価を行い、評価結果に基づきバリエントのフィルタリングが可能

■ VSClinical AMP Guideline

- 各種バイオマーカー (SNV, InDels, CNV, 融合遺伝子, TMB/MSIなど) をAMPガイドラインのエビデンスレベルで分類し、がんの治療薬や臨床試験情報を含めたレポートを作成
- 主要ながんにおけるバイオマーカー情報などを収録した、専用の知識ベースGolden Helix CancerKBが利用可能

VCFファイルのインポート

- ✓ 夫婦またはカップルのVCFファイルをインポート

キャリアバリアントの抽出

- ✓ 常染色体劣性、またはX連鎖性疾患の病的バリアントの抽出
- ✓ ACMGキャリアスクリーニングパネル搭載の遺伝子の絞り込み

バリアントの病原性評価

- ✓ ACMGガイドラインに基づいたバリアントの病原性評価

レポート作成

- ✓ サンプル情報、バリアント情報、さらにバリアントと関連する遺伝性疾患の子どもの発症リスクが記載されたレポートを出力





Import Variants Wizard

Import Variant Sites

① Define Input
② Scan Input
③ **Change Options**
④ Review

Select the samples of interest and appropriately adjust their attributes

Sample Relationships

Individual Samples
 Family Samples
 Tumor/Normal Samples
 Partnered Samples

Add sample fields:

	Original Samples	Samples	Status	Partner	Sex	<input checked="" type="checkbox"/> File Basename
<input checked="" type="checkbox"/> 1	SAMPLE1	SAMPLE1	Primary	SAMPLE2	Female	Sample1
<input checked="" type="checkbox"/> 2	SAMPLE2	SAMPLE2	Partner	SAMPLE1	Male	Sample2



- それぞれパートナーを指定してVCFファイルをインポート

Variants: 255,021 | Variant Genes: 13,092 | Samples: 2

Filter Variants Input: SAMPLE1

Variant Info			SAMPLE1					Partner (SAMPLE2)				
Chr:Pos	Ref/Alt	Identifier	VAF	AD	GQ	GT	Zygosity	VAF	AD	GQ	GT	Zygosity
1:16487	T/C	?	0.280702	41,16	99	0/1	Heterozygous	?	?,?	?	./.	?
1:16495	G/C	?	0.464286	30,26	99	0/1	Heterozygous	0.48	26,24	99	0/1	Heterozygous
1:16534	C/T	?	0.2	44,11	99	0/1	Heterozygous	?	?,?	?	./.	?
1:16949	A/C	?	?	?,?	?	./.	?	0.305085	41,18	99	0/1	Heterozygous
1:16963	G/A	?	0.101695	53,6	92	0/1	Heterozygous	0.114286	62,8	99	0/1	Heterozygous
1:16977	G/A	?	0.136364	57,9	99	0/1	Heterozygous	0.101449	62,7	99	0/1	Heterozygous
1:17020	G/A	?	0.166667	60,12	99	0/1	Heterozygous	0.202899	55,14	99	0/1	Heterozygous
1:17385	G/A	?	0.287879	47,19	99	0/1	Heterozygous	0.125	63,9	61	0/1	Heterozygous
1:109488	G/A	?	?	?,?	?	./.	?	0.140351	49,8	55	0/1	Heterozygous
1:120983	C/T	?	?	?,?	?	./.	?	0.3	42,18	99	0/1	Heterozygous

■ Couples Carrier Screening Template

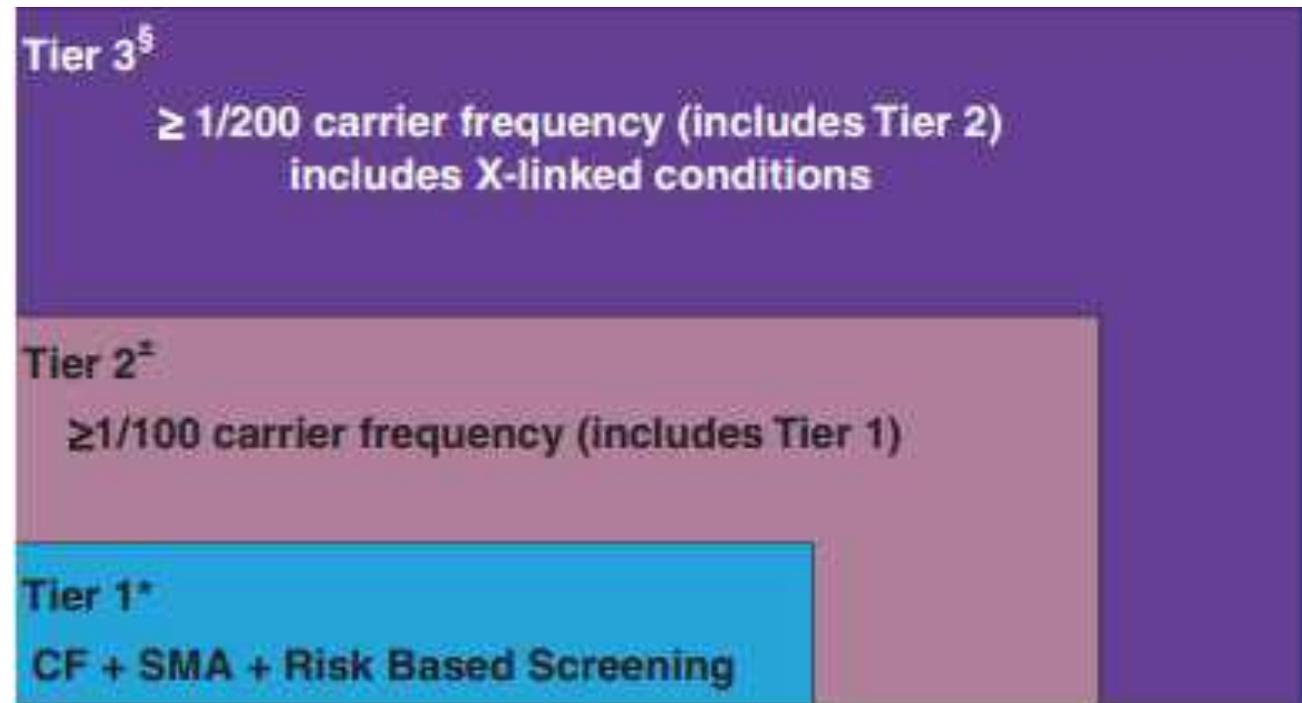
- カップルのサンプルデータを使用して、遺伝性疾患と関連する病的バリエントを絞り込むためのワークフロー
- ACMGキャリアスクリーニングパネル搭載の遺伝子を対象に、ClinVarまたはACMGガイドラインで病的と判定されたバリエントを自動で検出
- 両方のサンプルで病的バリエントが検出された遺伝子の同定も可能

Filter Variants 255,021

- Autosomal Recessive and X-Linked Variants
 - Sample QC Filters 2 139,194
 - Pathogenic Variants 2 2,361
 - ACMG Carrier Panel Genes
 - Gene IDs - RefSeq Genes 110, NCBI
 - ACMG Carrier Screening Panel Gene IDs
 - 2 4
- Workflows
 - Recessive
 - Gene Inheritance is (Default (Recessive), Recessive) 2 4
 - Carrier Variant (Current) is true 2 4
 - 2 4
 - X-Linked
 - X Chr - Not in PAR Regions 1 1
 - 1 1
 - 2 4
 - 2 4
- All Carrier Variants
 - Carrier Variant (Current) is true 2 2
 - 2 2
 - 3 5

■ ACMG Carrier Screening Panel

- 米国人類遺伝学会（ACMG）が発表した、人種を問わず使用可能なキャリアスクリーニング用の遺伝子パネル
- ワークフローでは、保因者頻度が1/200以上の常染色体劣性と、有病率が1/40,000以上のX連鎖性遺伝性疾患の原因遺伝子を解析に用いる
- 必要に応じて遺伝子の追加や削除も可能



Gregg, A.R., Aarabi, M., Klugman, S. *et al.* Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* **23**, 1793–1806 (2021).

バリエントテーブル

Variants: 5 x Variant Genes: 4 x Samples: 2 x ACMG Guidelines x +

Filter Variants: SAMPLE1

Variant Info					SAMPLE1					Partner (SAMPLE2)					Gene	Variant Site ACMG Classifier			
Chr:Pos	Ref/Alt	Identifier	PV	VAF	AD	GQ	GT	Zygosity	VAF	AD	GQ	GT	Zygosity	Gene Names	Classification	Auto Classification	ACMGClassificationCrit...	Gene Inheritance	
7:117548639	G/-	?	●	0.510204	24,25	99	0/1	Heterozygous	?	?,?	?	./.	?	CFTR,CFTR-AS1	Likely Pathogenic,...	Likely Pathogenic,VUS...	PM2,PVS1 Strong,PM2,P...	Recessive,Default (Recessive)	
7:117548640	G/C	?	●	?	?,?	?	./.	?	0.592593	22,32	99	0/1	Heterozygous	CFTR,CFTR-AS1	Likely Pathogenic,...	Likely Pathogenic,VUS...	PM2,PVS1 Strong,PP5,P...	Recessive,Default (Recessive)	
11:89296535	T/C	?	○	0.181818	45,10	99	0/1	Heterozygous	?	?,?	?	./.	?	TYR	VUS/Weak Pathog...	VUS/Weak Pathogenic	PM2	Recessive	
11:89296581	T/C	?	○	0.185185	44,10	99	0/1	Heterozygous	?	?,?	?	./.	?	TYR	VUS/Weak Pathog...	VUS/Weak Pathogenic	PM2	Recessive	
X:153866700	G/A	?	●	0.313726	35,16	99	0/1	Heterozygous	?	?,?	?	./.	?	L1CAM	Pathogenic	Pathogenic	PM2,PVS1,PP5	Recessive	

7:117548639 - G/- (1bp del)

Entrez Gene ID: [1080](#), [111082987](#)

7:117548639 - G/- (1bp del)

Variant Info

Chr.Pos	7:117548639
Ref/Alt	G/-
Identifier	?

Show 4 hidden fields

Flags

Pathogenic Variants

Sample Fields

Sample	SAMPLE1	Partner (SAMPLE2)
Variant Allele Fraction	0.510204	?
Allelic Depths (AD)	24, 25	?, ?
Genotype Qualities (GQ)	99	?
0/1 Genotypes (GT)	0/1	./.
Zygosity	Heterozygous	?

Navigation (7: 117,548,630, 0.4375) 7 20 bp

- ワークフローが完了すると、絞り込まれたバリエントのテーブルが表示される
- バリエントテーブルには、両サンプルのVCFファイルのデータ (VAF, GTなど)、バリエントごとのACMGガイドラインの評価結果、各種データベース (ClinVar, gnomADなど) のアノテーションが表示される
- テーブル上のデータは、バリエントごとに詳細データ表示用画面でも確認可能

詳細表示用画面

絞り込んだバリエント



遺伝子/疾患情報の確認

CFTR Gene Preferences ◀ 1 of 3 ▶

Transcript:

Inheritance Model:

Disorder:

OMIM: MoNDO:

Mutations in CFTR

Mutation	Call State	Classification	Report As
c.1210-2delG	○ ○	Likely Pathogenic	Primary Findings
c.1210-1G>C	○ ●	Likely Pathogenic	Primary Findings

バリエントの病原性評価

GRCh38: chr7: 117,548,640 Mutation: G > C

dbSNP: rs397508178 ClinVar: 53217

Gene: CFTR Transcript: NM_000492.4...

NM_000492.4: c.1210-1G>C NP_000483.3: N/A

Effect: Splice Acceptor Intron: 9 of 26
splice_acceptor_variant

ACMG Scoring

Scored Criteria: PM2 PVS1_Strong PP5

Probability of Pathogenic:

89.2% - Predicted Classification: Pathogenic

Classification: **Likely Pathogenic**

レポート出力

Golden Labs Precision Medicine

Patient Name: Jane Doe Partner Name: John Doe Report Date: [DRAFT]

Patient	Sample Information	Collection Date
Patient Name: Jane Doe DOB: 05/01/1989 Sex: Female MRN: 8041	Referring Facility: Facility Ordering Physician: Physician Type: Blood Additional:	Received Date: 06/01/2023 Order Date: 06/01/2023
Partner Name: John Doe DOB: 03/03/1987 Sex: Male MRN: 491	Referring Facility: Facility Ordering Physician: Physician Type: Blood Additional:	Collection Date: 06/01/2023 Received Date: 06/05/2023 Order Date: 06/01/2023

ACMG CARRIER SCREENING PANEL

ABOUT THE TEST
This carrier status test is a comprehensive Next Generation Sequencing (NGS) panel that detects genetic variants in genes that are associated with an increased risk of having a child with a genetic disorder.

RESULT: POSITIVE

RESULTS SUMMARY
This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below.

Disease	Gene	Variant(s)	Inheritance	Sample	Reproductive Risk
Cystic Fibrosis	CFTR	Detected	Autosomal Recessive	Jane Doe	1 in 4
Fragile X syndrome	FMR1	Not Detected	X-linked Recessive	John Doe	1 in 724
Alpha-Thalassemia	HBA1	Detected	Autosomal Recessive	John Doe	1 in 304,099
Hydrocephalus due to congenital stenosis of aqueduct of Sylvius	L1CAM	Detected	X-linked Recessive	Jane Doe	1 in 23,099
Spinal muscular atrophy	SMN1	Not Detected	Autosomal Recessive		1 in 5,579,044

■ VS Clinical

- バリエントの絞り込みを行った後は、VS Clinicalのダッシュボード画面で続きの解析を行う
- VS Clinicalのダッシュボードでは、データベースや論文の内容を確認しながら、評価結果やレポート内容の編集などを行う

CFTR Gene Preferences < 1 of 113 >

Transcript:

Inheritance Model:

Disorder:

OMIM: [219700](#) MONDO: [0009061](#)

Mutations in CFTR

Mutation	Call State	Classification	Report As
c.1210-2delG	● ○	Likely Pathogenic	Primary Findings
c.1210-1G>C	○ ●	Likely Pathogenic	Primary Findings

Gene Annotations Disorders

NCBI RefSeq

Gene Id:
Name:
Alias:

This gene encodes a transmembrane protein that functions as a chloride channel. It is involved in the regulation of ion transport and is essential for the development and function of the respiratory and digestive tracts. Mutations in this gene can lead to cystic fibrosis, a common genetic disorder.

Source: NCBI RefSeq

Gene Annotations Disorders

NCBI RefSeq CGD **OMIM** GHR

OMIM Genes

Gene Name: OMIM

Description:
The CFTR gene functions as a chloride channel and is involved in the regulation of ion transport and is essential for the development and function of the respiratory and digestive tracts. Mutations in this gene can lead to cystic fibrosis, a common genetic disorder.

References:
[1384328](#)
[21083385](#)
[17331079](#)
[12833419](#)
[1706309](#)
[1545465](#)

[View All 285 References ...](#)

Source: OMIM Genes

Disorders

Conditions:

Congenital bilateral absence of vas deferens	AR
Cystic fibrosis	AR
Bronchiectasis with or without elevated sweat chlori...	AD
Pancreatitis hereditary	AD
Hypertrypsinemia neonatal	?
Sweat chloride elevation without CF	?

- 遺伝子情報の確認画面では、疾患名や遺伝形式、様々なデータベースでの登録情報などを閲覧可能
- データベースへのURLリンクや、論文のアブストラクトなども表示可能

■ ACMGガイドラインによるバリエーションの病原性評価

- バリエーションの一般集団内のアレル頻度、コンピュータによる機能予測、既知の臨床情報などを利用し、バリエーションの病原性スコアを自動計算
- VSClinicalのダッシュボードでは、データベースの情報を閲覧しながら、評価結果やスコアなどをユーザーが調節可能

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder <i>BS1</i> OR observation in controls inconsistent with disease penetrance <i>BS2</i>			Absent in population databases <i>PM2</i>	Prevalence in affecteds statistically increased over controls <i>PS4</i>	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product <i>BP4</i> Missense in gene where only truncating cause disease <i>BP1</i> Silent variant with non predicted splice impact <i>BP7</i>	Multiple lines of computational evidence support a deleterious effect on the gene /gene product <i>PP3</i>	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before <i>PM5</i> Protein length changing variant <i>PM4</i>	Same amino acid change as an established pathogenic variant <i>PS1</i>	Predicted null variant in a gene where LDF is a known mechanism of disease <i>PVS1</i>
Functional Data	Well-established functional studies show no deleterious effect <i>BS3</i>		Missense in gene with low rate of benign missense variants and path. missenses common <i>PP2</i>	Mutational hot spot or well-studied functional domain without benign variation <i>PM1</i>	Well-established functional studies show a deleterious effect <i>PS3</i>	
Segregation Data	Non-segregation with disease <i>BS4</i>		Co-segregation with disease in multiple affected family members <i>PP1</i>	Increased segregation data →		
De novo Data				<i>De novo</i> (without paternity & maternity confirmed) <i>PM6</i>	<i>De novo</i> (paternity & maternity confirmed) <i>PS2</i>	
Allelic Data		Observed in trans with a dominant variant <i>BP2</i> Observed in cis with a pathogenic variant <i>BP2</i>		For recessive disorders, detected in trans with a pathogenic variant <i>PM3</i>		
Other Database		Reputable source w/out shared data = benign <i>BP6</i>	Reputable source = pathogenic <i>PP5</i>			
Other Data		Found in case with an alternate cause <i>BP5</i>	Patient's phenotype or FH highly specific for gene <i>PP4</i>			

Add Variants for SAMPLE1

Sample: < 1 of 2 > SAMPLE1 (Current)

Variants to Select:

Filter Variants (Variants)

Variant	GT
<input type="checkbox"/> CFTR c.1210-2delG	<input type="radio"/>
<input type="checkbox"/> CFTR c.1210-1G>C	<input type="radio"/>
<input type="checkbox"/> TYR c.*1169T>C	<input type="radio"/>
<input type="checkbox"/> TYR c.*1215T>C	<input type="radio"/>
<input checked="" type="checkbox"/> L1CAM p.Q794*	<input type="radio"/>

Allow Reference Genotypes

Select All Clear All Prepare to Add

OR

Add Variants for SAMPLE1

Sample: < 1 of 2 > SAMPLE1 (Current)

Enter Variant:

L1CAM Q794*

e.x. BRAF V600E [show more](#)

Variants Matching Query:

L1CAM c.2380C>T [dbSNP](#) [ClinVar](#)

L1CAM c.2380_2382de...

L1CAM c.2380_2382de...

Sample Zygosity

Ref Heterozygous Homozygous

Read Depths

Alt # alt Total # total VAF Percent %

Father: Mother:

Prepare to Add

バリエントテーブルから選択

バリエント名を手動で入力

Recommended to Score Pathogenic

PM2 → The p.Gln794Ter variant is novel (not in any individuals) in 1kG All. The p.Gln794Ter variant is novel (not in any individuals) in gnomAD v4 All.

PVS1 → This variant is a stop gained variant which occurs in an exon of L1CAM upstream of where nonsense mediated decay is predicted to occur. This variant has been previously classified as pathogenic, indicating that the region is critical to protein function. There are 46 downstream pathogenic loss of function variants, with the furthest variant being 419 residues downstream of this variant. This indicates that the region is critical to protein function. The gene L1CAM has a low rate of benign loss of function variants as indicated by a low upper bound of the observed/expected confidence interval 0.13. The p.Gln794Ter variant is a loss of function variant in the gene L1CAM, which is intolerant of Loss of Function variants, as indicated by the presence of existing pathogenic loss of function variant NP_000416.1:p.V8Gfs*24 and 71 others.

PP5 → The variant p.Gln794Ter has been previously classified as Pathogenic/Likely pathogenic in ClinVar (Variation ID 226120 as of 2024-05-03) with respect to X-linked hydrocephalus syndrome and L1 syndrome with a status of (2 stars) criteria provided, multiple submitters, no conflicts.

バリエントに該当する評価項目と結果を自動検出

- 評価に用いるバリエントは、VCFファイルよりインポートしたバリエントテーブルより選択するか、キーボードでバリエント名を直接入力することも可能
- バリエントを指定すると、該当する評価項目が自動で検出され、評価結果のテキストとともに表示される

Variant	HGVS	AA Change	Clinical Significance
> This Variant	c.2380C>T p.Q794*	Gln → Ter Cag → Tag	Pathogenic ★ ★ ★ ★
> 2811237	c.2381A>G p.Q794R	Gln → Arg cAg → cGg	Uncertain Significance ★ ★ ★ ★
> 2796731	c.2382G>C p.Q794H	Gln → His caG → caC	Likely benign ★ ★ ★ ★

PS3 BS3
Well-established functional studies supportive of a damaging effect on the gene or gene product
In vitro or in vivo functional studies should demonstrate this variant either does or does not alter the primary function of the gene

Damaging effect shown
 Evidence for no damaging effect
 Uncertain

PS4
The prevalence in affected individuals is significantly increased compared with the prevalence in controls
With relative risk or OR > 5.0 (and a CI that does not include 1.0). For rare variants, see strength description.

Yes No Uncertain

自動検出できない項目の評価結果を追加

PP5 BP6
Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation
Examples include pathogenic/benign variants in ClinVar that have clinical assertions done using similar guidelines

Reported pathogenic
 Reported benign
 Uncertain

PP5 scored by Takuya Ozawa 17 days ago
Reasons for Reported Pathogenic:
• The variant p.Gln794Ter has been previously classified as Pathogenic/Likely pathogenic in ClinVar (Variation ID 226120 as of 2024-05-03) with respect to X-linked hydrocephalus syndrome and L1 syndrome with a status of (2 stars) criteria provided, multiple submitters, no conflicts.

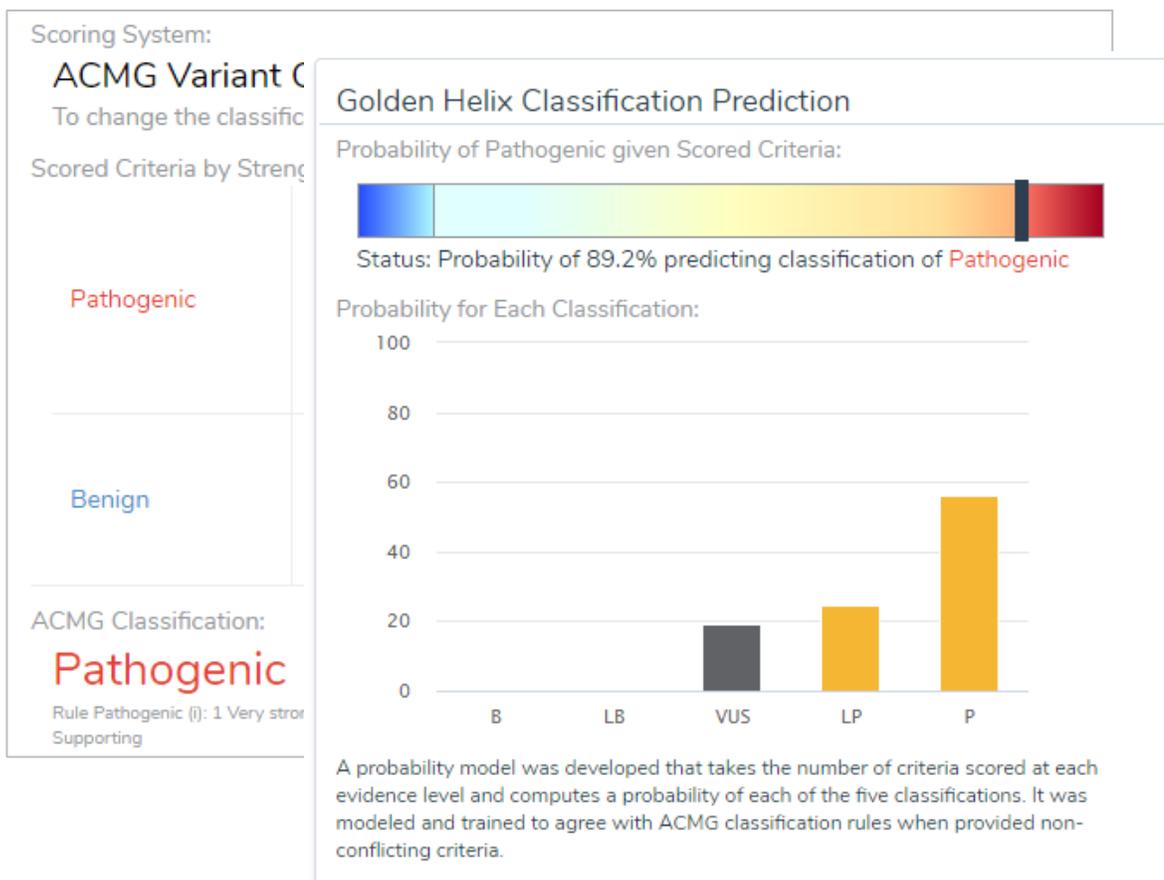
自動評価の結果を編集

- データベースの引用データの表示画面で、評価結果を手動で編集することができ、その結果病原性スコアが変化する
- ACMGガイドラインの評価項目には、VSClinicalで自動検出できない項目もあり、このような項目は手動で評価結果を追加することが可能

Scored Criteria:
PM2 PVS1 PP5
Probability of Pathogenic:
87.9% - Predicted Classification: Pathogenic
Classification:
Pathogenic

評価結果を編集

Scored Criteria:
PM2 PVS1 BP6
Probability of Pathogenic:
66.1% - Predicted Classification: Pathogenic
Classification:
Likely Pathogenic



Scoring Annotations Gene Literature Assessments

Classification: **Pathogenic**

Scored Criteria: **PM2 PVS1 PP5**
Previously Saved: PM2 PVS1 PP5

Evidence for Pathogenic: [Interpretation](#) [Evidence](#) [Comments](#)

The stop gained NM_000425.5(L1CAM):c.2380C>T (p.Gln794Ter) has been reported to ClinVar as Pathogenic/Likely pathogenic with a status of (2 stars) criteria provided, multiple submitters, no conflicts (Variation ID 226120 as of 2024-05-03). The p.Gln794Ter variant is novel (not in any individuals) in 1kg All. The p.Gln794Ter variant is novel (not in any individuals) in gnomAD v4 All. This variant is predicted to cause loss of normal protein function through protein truncation. This variant is a stop gained variant which occurs in an exon of L1CAM upstream of where nonsense mediated decay is predicted to occur. This variant has been previously classified as pathogenic, indicating that the region is critical to protein function. There are 46 downstream pathogenic loss of function variants, with the furthest variant being 419 residues downstream of this variant. This indicates that the region is critical to protein function. The gene L1CAM has a low rate of benign loss of function variants as indicated by a low upper bound of the observed/expected confidence interval 0.13. The p.Gln794Ter variant is a loss of function variant in the gene L1CAM, which is intolerant of Loss of Function variants, as indicated by the presence of existing pathogenic loss of function variant NP_000416.1:p.V8Gfs*24 and 71 others. For these reasons, this variant has been classified as Pathogenic. ⓘ

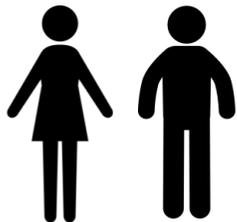
[Add to Interpretation](#)

レポート用テキスト

評価結果サマリー

- 評価結果の編集の完了後、各項目が病原性の可能性を示唆するスコアや良性の可能性を示唆するスコア、最終的な判定結果をまとめたサマリーを表示
- 同時にレポートに記載される臨床的解釈のテキストも出力

サンプル情報の入力



- ✓ カップルそれぞれのサンプル詳細情報（名前、性別など）を入力

AND

バリエーション情報の入力



1. 評価するバリエーションの指定
2. バリエーションの評価の実行
3. バリエーションごとのレポート上の記載を指定
(Primary Findings, Secondary Findings, VUSなど)

レポートテンプレートの選択

- ✓ 遺伝性疾患
- ✓ キャリアスクリーニング
- ✓ がん遺伝子パネル ...など



Clinical Report

- ✓ Word
- ✓ PDF
- ✓ JSON

- VSClinicalにて、サンプル情報の入力とバリエーションの評価を行い、レポートテンプレートを選択すれば、レポートが自動で作成される
- サンプルやバリエーション情報を変更して、レポートを出力し直すことも可能

Carrier Screening Report Template

- **マルチサンプルに対応**：サンプル別にサンプル詳細情報と、検出されたバリエーションをレポートに記載
- **疾患のリスク計算**：バリエーションが検出された遺伝子と対応する疾患の生殖リスクを計算
- **バリエーション情報**：検出されたバリエーションのACMGガイドラインによる評価結果と臨床的解釈をレポート出力
- **疾患の詳細情報**：OMIMに登録されている疾患情報をレポート出力

		Patient Name↓ SAMPLE1	Partner Name↓ SAMPLE2	Report Date↓ (DRAFT)
Patient Patient Name: SAMPLE1 DOB: Sex: Female MRN:		Sample Information Referring Facility: Ordering Physician: Type: Additional:		Collection Date: Received Date: Order Date:
Partner Partner Name: SAMPLE2 DOB: Sex: Male MRN:		Sample Information Referring Facility: Ordering Physician: Type: Additional:		Collection Date: Received Date: Order Date:

ACMG CARRIER SCREENING PANEL

ABOUT THE TEST
This carrier status test is a comprehensive Next Generation Sequencing (NGS) panel that detects genetic variants in genes that are associated with an increased risk of having a child with a genetic disorder.

RESULT: POSITIVE

RESULTS SUMMARY					
This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below.					
Disease	Gene	Variant(s)	Inheritance	Sample	Reproductive Risk
Cystic Fibrosis	CFTR	Detected	Autosomal Recessive	SAMPLE1 SAMPLE2	1 in 4
Fragile X syndrome	FMR1	Not Detected	X-linked Dominant		1 in 7,992,406
Hydrocephalus due to congenital stenosis of aqueduct of Sylvius	L1CAM	Detected	X-linked Recessive	SAMPLE1	1 in 4
Spinal muscular atrophy	SMN1	Not Detected	Autosomal Recessive		1 in 5,579,044

RESULTS SUMMARY

This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below.

Disease	Gene	Variants	Inheritance	Sample	Reproductive Risk
Cystic Fibrosis	CFTR	Detected	Autosomal Recessive	SAMPLE1 SAMPLE2	1 in 4
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Hydrocephalus due to congenital stenosis of aqueduct of Sylvius	L1CAM	Detected	X-linked Recessive	SAMPLE1	1 in 4
Spinal muscular atrophy	SMN1	Not Detected	Autosomal Recessive		1 in 5,579,044

解析結果サマリー

- 解析結果サマリーには、バリエントが検出された遺伝子と疾患名、および疾患の生殖リスクが記載される
- 嚢胞性線維症、脆弱 X 症候群、脊髄性筋萎縮症は、遺伝子にバリエントが検出されなかった場合でもNegative findingsとして記載される
- バリエントが検出されなかった場合の残留リスクは、各疾患の保因者頻度と検出率をもとに、ベイズの定理で計算される

DISEASE	GENE	ETHNICITY	CARRIER FREQUENCY	CARRIER REPRODUCTIVE RISK
Surfactant metabolism dysfunction, pulmonary 3	ABCA3	General	1 in 116	1 in 21,178,404
Stargardt Disease, Type 1	ABCA4	General	1 in 20	1 in 580,644
Diabetes mellitus, permanent neonatal 3	ABCC8	General	1 in 82	1 in 10,510,564
Adrenoleukodystrophy	ABCD1	General	1 in 15,000	1 in 1,199,924
Medium Chain Acyl-CoA Dehydrogenase Deficiency	ACADM	General	1 in 60	1 in 5,579,044
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency	ACADVL	General	1 in 156	1 in 38,464,804
<u>α-Methylacetoacetic aciduria</u>	ACAT1	General	1 in 200	1 in 633,933,769

全疾患のリスク計算の一覧

- バリエントが検出されなかったすべての遺伝子は、疾患名と保因者頻度、残留リスクの一覧表が、補足データとしてレポートに記載される

* PATIENT VARIANT SUMMARY

VARIANTS OF CLINICAL SIGNIFICANCE

GENE & TRANSCRIPT	VARIANT	CRITERIA	CLASSIFICATION
CFTR NM_000492.4	c.1210-2delG	PM2, PVS1_Strong	Likely pathogenic
LOCATION	ALLELE STATE	1KG ALL (NOVEL) ALLELE FREQUENCY	
Intron 9	Heterozygous	Novel	
GENOMIC POSITION	NGS READS SUPPORTING CHANGE		
g.117548639delG	51.02% (25 of 49)		

VARIANT INTERPRETATION: The splice acceptor variant NM_000492.4(CFTR):c.1210-2delG has not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge. The c.1210-2delG variant is novel (not in any individuals) in 1kg All. The c.1210-2delG variant is novel (not in any individuals) in [gnomAD v4 All](#). This variant mutates a splice-acceptor sequence, but is predicted to preserve the reading frame, resulting in in-frame exon skipping. This variant results in the loss of an acceptor splice site for the clinically relevant transcript. There are 9 pathogenic variants in the same region as the variant c.1210-2delG, indicating that the region is critical to protein function. The c.1210-2delG variant is a loss of function variant in the gene CFTR, which is intolerant of Loss of Function variants, as indicated by the presence of existing pathogenic loss of function variant NP_000483.3:p.M1Sfs*39 and 701 others. For these reasons, this variant has been classified as Likely Pathogenic.

バリエーション情報

Golden Labs
Precision Medicine

Patient Name	Partner Name	Report Date
John Doe	John Doe	(EMMIT)
Patient	Sample Information	Collection Date: 06/01/2023
Patient Name: John Doe	Referring Facility: Facility	Received Date: 06/02/2023
DOB: 01/01/1980	Ordering Physician: Physician	Order Date: 06/01/2023
Sex: Female	Test: Blood	
MRN: 1234	Additional:	
Partner	Sample Information	Collection Date: 06/01/2023
Partner Name: John Doe	Referring Facility: Facility	Received Date: 06/02/2023
DOB: 01/01/1987	Ordering Physician: Physician	Order Date: 06/01/2023
Sex: Male	Test: Blood	
MRN: 5678	Additional:	

ACMG CARRIER SCREENING PANEL

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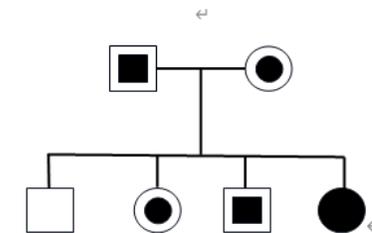
RESULT: POSITIVE

RESULTS SUMMARY
This test shows the presence of clinically significant genetic change(s) in this individual in the gene(s) indicated below.

Disorder	Gene	Variant(s)	Inheritance	Sample	Prevalence (est.)
Cystic Fibrosis	CFTR	Detected	Autosomal Recessive	John Doe	1 in 4
Fragile X syndrome	FMR1	Not Detected	X-linked Recessive	John Doe	1 in 754
Alpha Thalassemia	HBA1	Detected	Autosomal Recessive	John Doe	1 in 304,099
Hydrocephalus due to congenital stenosis of aqueduct of Sylvius	LICAM	Detected	X-linked Recessive	John Doe	1 in 23,099
Spinal muscular atrophy	SMN2	Not Detected	Autosomal Recessive	John Doe	1 in 3,773,044

- レポートにはバリエーションの詳細データや評価結果の情報、疾患の詳細説明などが自動で書き込まれる

AUTOSOMAL RECESSIVE INHERITANCE



WHAT IS SPINAL MUSCULAR ATROPHY?

A rare, genetic, neuromuscular disease characterized by proximal muscle weakness with an early involvement of foot and hand muscles following normal motor development in early childhood, a rapidly progressive disease course leading to generalized areflexic tetraplegia with contractures, severe scoliosis, hyperlordosis, and progressive respiratory insufficiency leading to assisted ventilation. Cranial nerve functions are normal and tongue wasting and fasciculations are absent. Milder phenotype with a moderate generalized weakness and slower disease progress was reported.

疾患情報

お問い合わせ先：フィルジエン株式会社

TEL: 052-624-4388 (9:00～18 : 00)

FAX: 052-624-4389

E-mail: biosupport@filgen.jp