マイクロアレイ染色体検査普及のための産学連携コンソーシアム主催
マイクロアレイ染色体検査解釈ハンズオンウェビナー 2023.9.19

マイクロアレイ染色体検査解釈
ハンズオンウェビナー

中級編　解説資料
症例１

静岡県立こども病院　清水健司

症例 1

0 歳女児：哺乳障害、口蓋裂、副耳、先天性心疾患

【CNV1】chr11:116,751,035-134,934,196　11q23.3q25　log2ratio=0.57 [Gain]

【CNV2】chr22:17,058,946-20,402,677　22q11.1q11.21　log2ratio=0.53 [Gain]

＊追加設問：遺伝カウンセリングにおける留意点を述べよ

症例１　参加者解答（計7名中）とポイント

- Emanuel/der(22)の想起　　5/7
・各CNV毎の病原性解釈施行例　　1/7

- 22番プローブ着眼点　1

- 3:1分離への留意：一般化へ
- 重複CNVにおけるACMGガイドラインSECTION3の積極的使用

chr11:116,751,035-134,934,196　GAIN

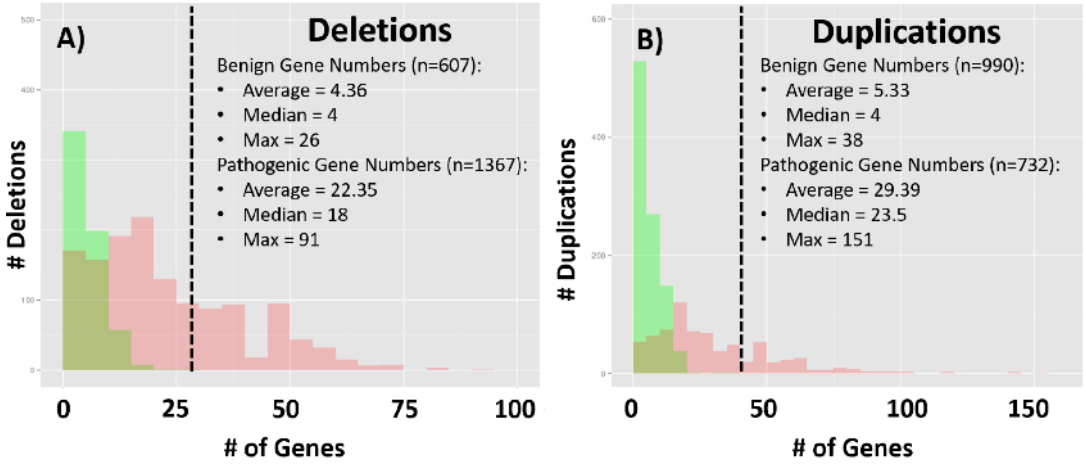
Section 3: Evaluation of gene number

Number of protein-coding RefSeq genes wholly or partially included in the copy-number gain	**3A**. 0–34 genes	0
	3B. 35–49 genes	0.45
	3C. 50 or more genes	0.90

ClinGen Gene ON→Protein Coding フィルターON
→Protein Coding Gene数のチェック
ルーチンで遺伝子数をチェックし
SEC3のエビデンスを確認

Protein Coding Gene Number **169**

0.9　very strong evidence



Supplemental Figure 1.5: Analysis of gene content across clinically-classified copy number variants (CNVs) in dbVar. CNVs involving autosomes with clinical classifications between 200 kb-5Mb within dbVar studies nstd37 and nstd101 were analyzed for gene content. Those CNVs involving known dosage sensitive genes or genomic regions (as documented in dbVar study nstd45) were excluded. Gene arrays and non-protein-coding genes were not included in gene counts. The average, median, and maximum number of genes noted within benign (green) and pathogenic (red) deletions (A) and duplications (B) are depicted.

GRCh37 Search Results

Location: chr11:116,751,035-134,934,196

Genes: On | Regions: Off

327 Total Genes　1 Total Regions

Advanced Filters: Protein Coding

Click on below to view hidden columns

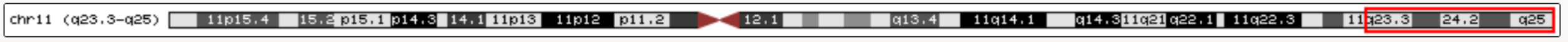
Search in table　GRCh37　Enter cytoband or genomic coordinates　Go!

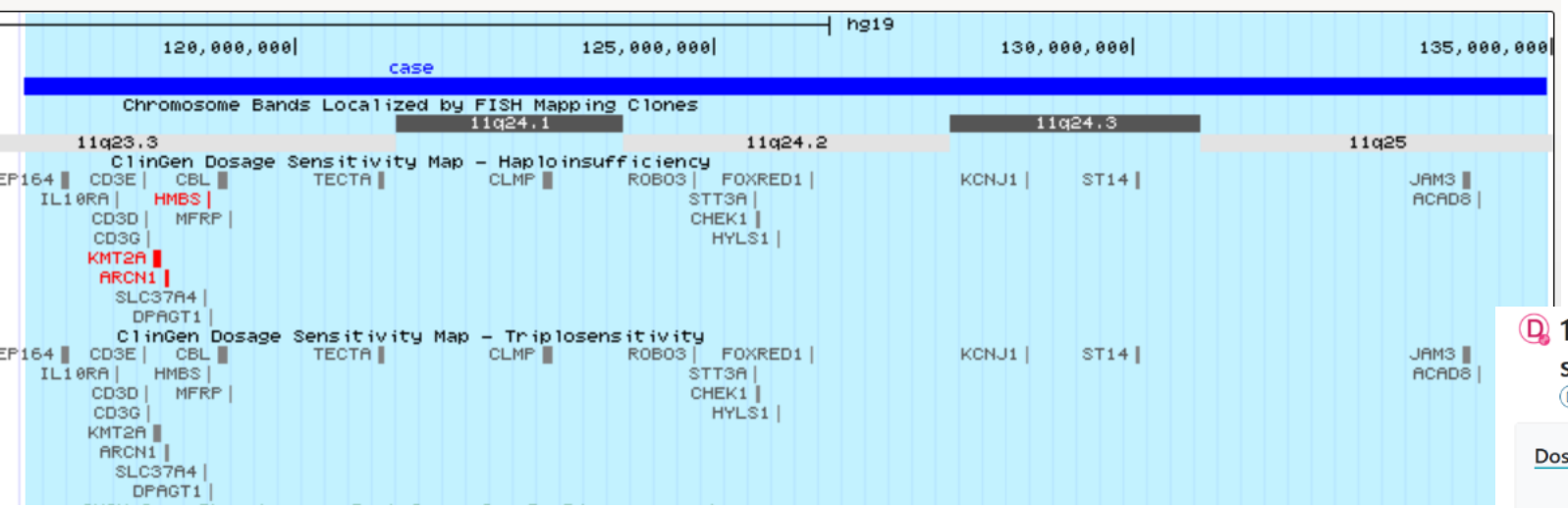
Showing 1 to 25 of 169 rows　25 rows per page

‹ 1 2 3 4 5 6 7 ›

Gene/Region	GRCh37		HI Score	TS Score	OMIM	Morbid	%HI	pLI	LOEUF	Report
OPCML	11	132284559 133402507	Not Yet Evaluated	Not Yet Evaluated	✓	✓	0.92	0.23	0.58	Awaiting Review
CBL	11	119076986 119178859	0 (No Evidence)	0 (No Evidence)	✓	✓	3.6	0	0.5	Complete
DDX6	11	118618472 118661972	Not Yet Evaluated	Not Yet Evaluated	✓	✓	4.6	1	0.17	Awaiting Review
HMBS	11	118955587 118964259	3 (Sufficient Evidence)	0 (No Evidence)	✓	✓	5.34	0.95	0.34	Complete
STT3A	11	125462690 125492654	30 (Autosomal Recessive)	0 (No Evidence)	✓	✓	5.47	0	0.49	Complete
FLI1	11	128556430 128683162	Not Yet Evaluated	Not Yet Evaluated	✓	✓	6.16	0.99	0.28	Awaiting Review

Section 2: Overlap with established triplosensitive (TS), haploinsufficient (HI), or benign genes or genomic regions





Established TS region/genesなし
0 pts

GRCh37 Search Results

Location: chr11:116,751,035-134,934,196

Genes: Off | Regions: On

327 Total Genes

1 Total Regions

Advanced Filters: None

Click on below to view hidden columns

Search in table | GRCh37 | Enter cytoband or genomic coordinates | Go!

Showing 1 to 1 of 1 rows

Gene/Region	GRCh37	HI Score	TS Score	OMIM	Morbid	%HI	pLI	LOEUF	Report
11q23q25 terminal (Jacobsen syndrome) region	11 110,600,000 134,937,416	Not Yet Evaluated	Not Yet Evaluated			-	-	-	Under Group Review

Showing 1 to 1 of 1 rows

Region ONでチェック

11q23q25 terminal (Jacobsen syndrome) region

Region Facts

Dosage Sensitivity Summary (Region)

Dosage ID: ISCA-37499

Curation Status: Under Group Review

Issue Type: Dosage Curation - Region

Description: 11q23q25 Deletion (Jacobsen) Syndrome

Haploinsufficiency: Under Group Review

Triplosensitivity: Under Group Review

Related Links: FLI1, ETS1

Last Evaluated: Under Group Review

Haploinsufficiency (HI) Score Details

Review not yet complete.

Triplosensitivity (TS) Score Details

Review not yet complete.

Name / Description	Location	pLI	LOEUF	sHet	pHaplo	pTriplo	GenCC	OMIM / Morbid	G2P	ClinGen
ARHGEF12 Rho guanine nucleotide exchange factor 12	11 120336413 120489937	1.00	0.18	0.116	1.00	1.00	-	OMIM	-	-
KCNJ5 potassium inwardly rectifying channel subfamily J member 5	11 128891356 128921163	0.00	1.14	0.155	0.94	1.00	Moderate: 1 Limited: 1 Disputed Evidence: 1 Supportive: 2	OMIM Morbid (2)	-	Disputed Evidence: AD
OPCML opioid binding protein/cell adhesion molecule like	11 132414977 133532501	0.32	0.53	0.050	0.98	1.00	-	OMIM Morbid	-	-
DDX6 DEAD-box helicase 6	11 118747763 118791164	1.00	0.17	0.259	0.95	1.00	Strong: 1 Supportive: 1	OMIM Morbid	Strong: Monoallelic	-
IGSF9B immunoglobulin superfamily member 9B	11 133896438 133956968	0.87	0.32	0.207	0.99	1.00	-	OMIM	-	-
NTM neurotrimin	11 131370478 132336822	0.06	0.65	0.172	0.98	0.99	-	OMIM	-	-
KCNJ1 potassium inwardly rectifying channel subfamily J member 1	11 128836315 128867373	0.00	1.43	0.005	0.66	0.99	Strong: 1 Supportive: 1	OMIM Morbid	-	Haploinsufficiency: 30 Triplosensitivity: 0
KMT2A lysine methyltransferase 2A	11 118436456 118526832	1.00	0.07	0.167	1.00	0.98	Definitive: 2 Supportive: 1	OMIM Morbid	Definitive: Monoallelic	Definitive: AD Haploinsufficiency: 3 Triplosensitivity: 0
PAFAH1B2 platelet activating factor acetylhydrolase 1b catalytic subunit 2	11 117144284 117176894	0.93	0.36	0.159	0.90	0.98	-	OMIM	-	-
C2CD2L C2CD2 like	11 119102198 119118544	0.99	0.30	0.115	0.89	0.96	-	OMIM	-	-
PKNOX2 PBX/knotted 1 homeobox 2	11 125164687 125433389	0.99	0.27	0.080	0.99	0.96	-	OMIM	-	-
SIK3 SIK family kinase 3	11 116843402 117098437	1.00	0.12	0.099	0.98	0.96	-	OMIM Morbid	-	-
BACE1	11 117285232 117316259	0.88	0.37	0.006	0.92	0.93	-	OMIM	-	-

DECIPHER提供
pTriploが唯一の
in-Silicoツール
判定基準なし
あくまで補助的

SEC4

Individual case evidence—segregation among similarly affected family members	**4F**. 3–4 observed segregations	0.15
	4G. 5–6 observed segregations	0.30
	4H. 7 or more observed segregations	0.45

0.9+0.3=1.2pts

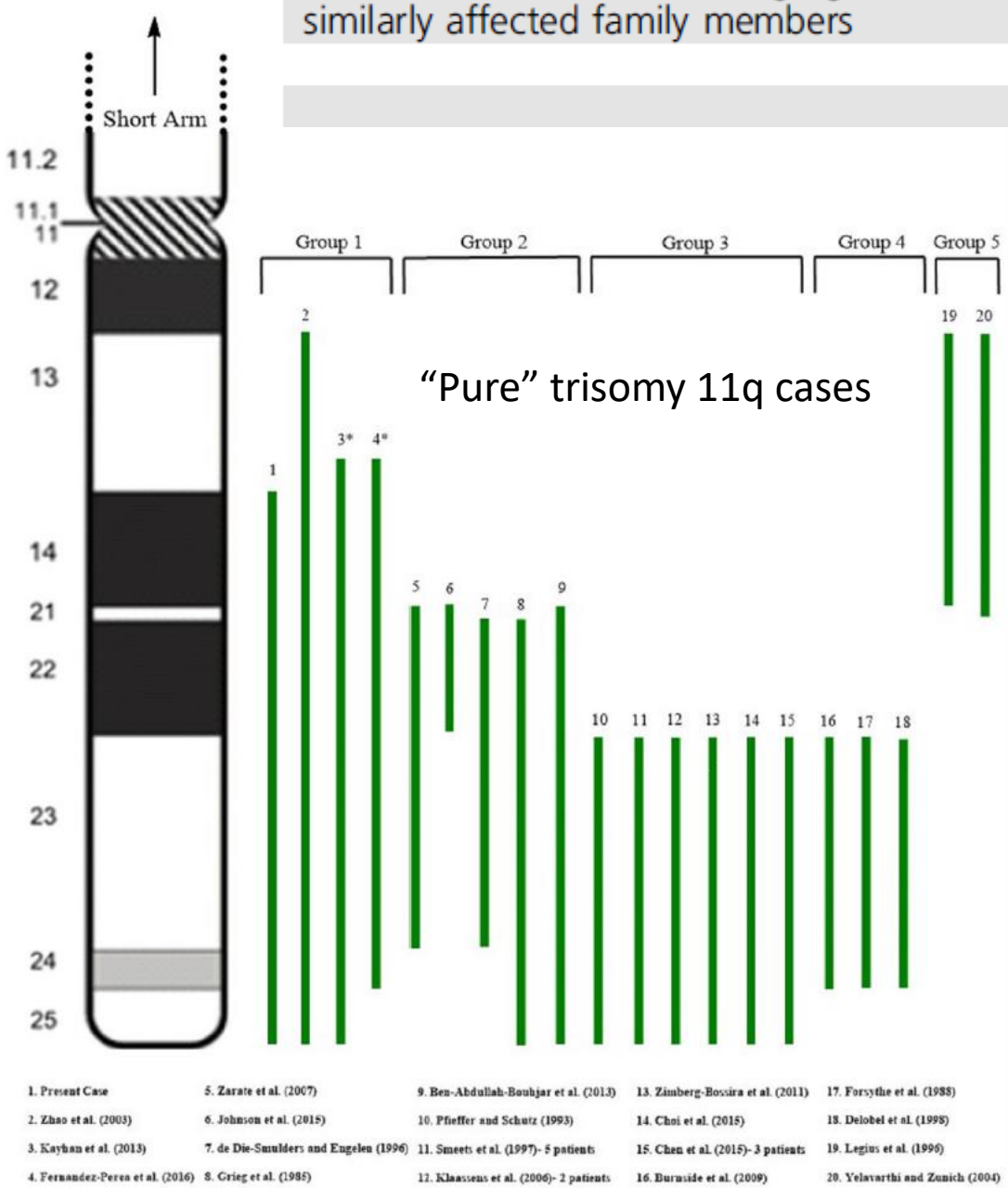


TABLE 3-continued	*Zimberg-Bossira et al. (2011)*	*Choi et al. (2015)*	*Chen et al. (2014)*
Figure 3 reference number	**13**	**14**	**15**
Number of patients	1	1	3 siblings (Patients 1-3)
Cytogenetics and molecular genetics findings	46, XY,der(21)t(11;21)(q23.1;q22.1) pat	46,XY,der(22) t(11;22)(q23.3;q13.3)mat	46,XY(XX),der(10)t(1o;11)(q26;q23) pat, a 15.1Mb duplication of 11q23.3qter and a 470Kb deletion of 10qter
Duplicated segment	q23.1–qter	q23.3-qter	q23.3-qter
Partner chromosome	chromosome 21	chromosome 22	chromosome 10
Most recent age at examination/sex	17 months/M	17 years/M	Patient 1- 19 years/M, Patient 2- 23 years/F, Patient 3- 23 years/M

minimal involvement of another chromosome

CNV1はPathogenic評価

Walker *et al. Molecular Cytogenetics (2022) 15:17*

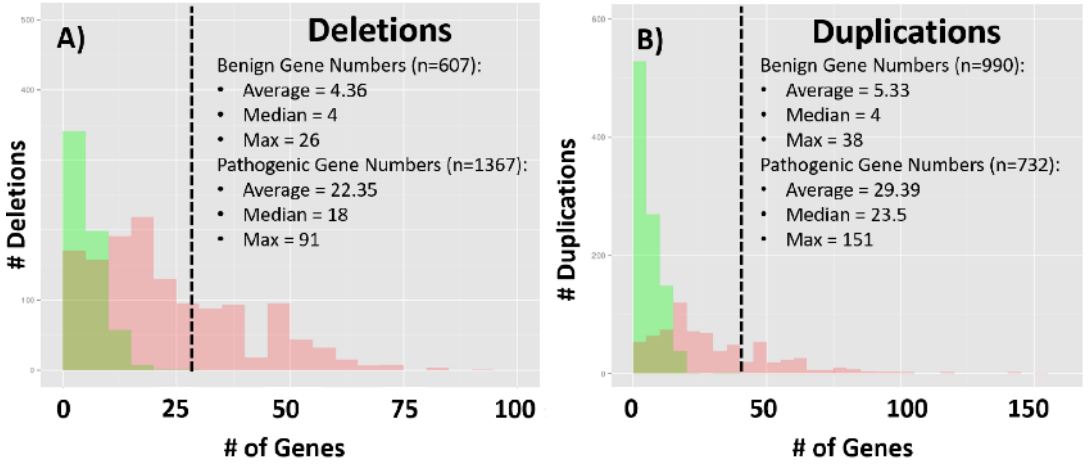
CNV2: chr22:17,058,946-20,402,677 GAIN

Section 3: Evaluation of gene number

Number of protein-coding RefSeq genes wholly or partially included in the copy-number gain	**3A**. 0–34 genes	0
	3B. 35–49 genes	0.45
	3C. 50 or more genes	0.90

Protein Coding Gene Number **48**

0.45 strong evidence



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GRCh37 Search Results

Location: chr22:17,058,946-20,402,677

Genes: On | Regions: On

131 Total Genes | 5 Total Regions

Advanced Filters: Protein Coding

Click on below to view hidden columns

Search in table | GRCh37 | Enter cytoband or genomic coordinates | Go!

Showing 1 to 48 of 48 rows | All rows per page

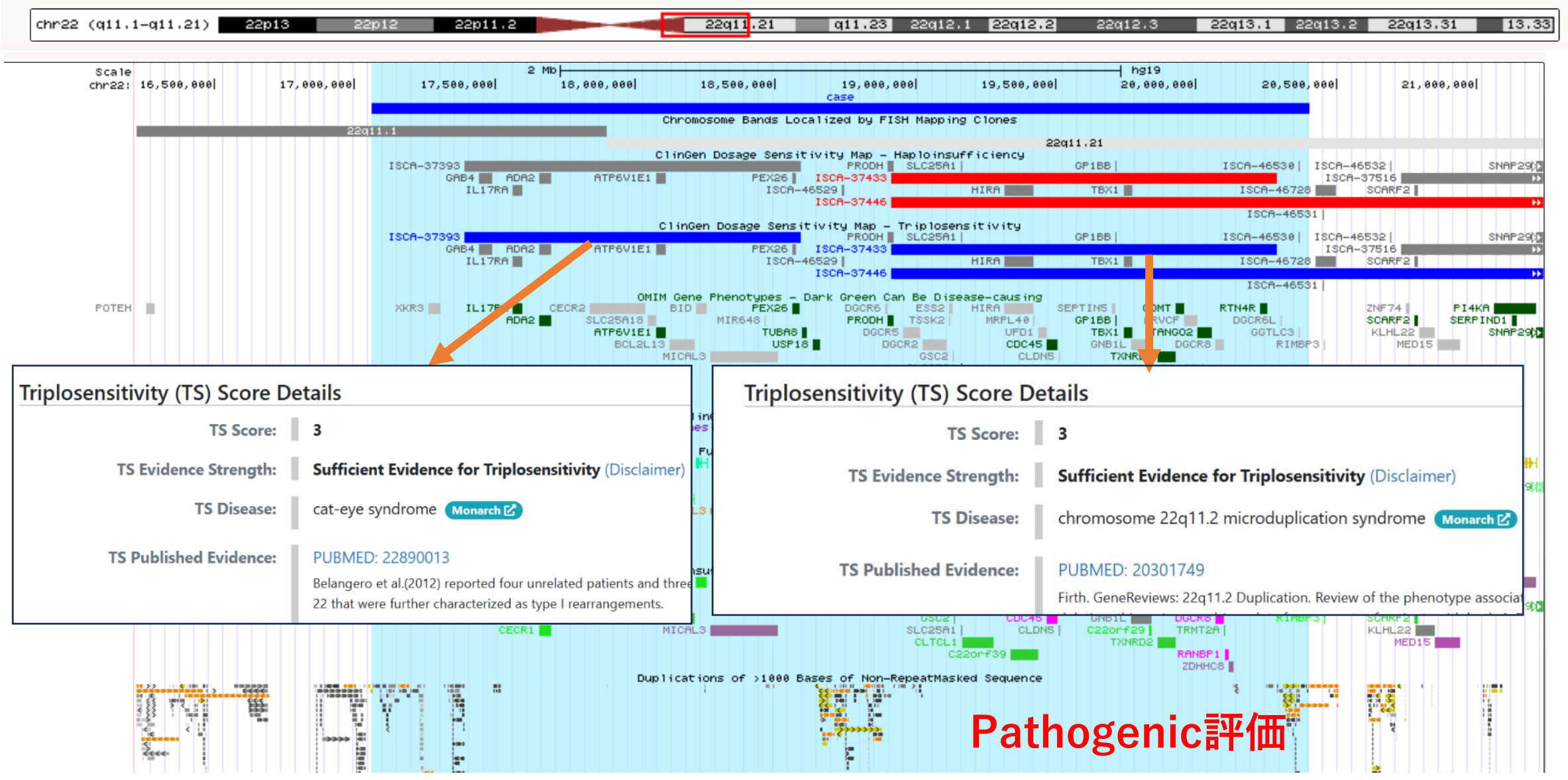
Gene/Region	GRCh37		HI Score	TS Score	OMIM	Morbid	%HI	pLI	LOEUF	Report
IL17RA	22	17565849 17596584	30 (Autosomal Recessive)	Not Yet Evaluated	✓	✓	84.96	0	0.63	Complete
ADA2	22	17659680 17702744	30 (Autosomal Recessive)	Not Yet Evaluated	✓	✓	85.15	0	1.07	Complete
ATP6V1E1	22	18074902 18111588	0 (No Evidence)	0 (No Evidence)	✓	✓	39.36	0.53	0.51	Complete
PEX26	22	18560686 18573797	30 (Autosomal Recessive)	0 (No Evidence)	✓	✓	72.53	0.93	0.37	Complete
TUBA8	22	18593453 18614498	Not Yet Evaluated	Not Yet Evaluated	✓	✓	42.62	0	1.1	Under Secondary Review
USP18	22	18632758 18660164	Not Yet Evaluated	Not Yet Evaluated	✓	✓	74.13	0	0.74	Awaiting Review

Section 2: Overlap with established triplosensitive (TS), haploinsufficient (HI), or benign genes or genomic regions

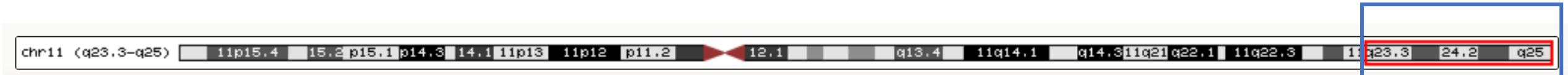
Overlap with ESTABLISHED TS genes or genomic regions

2A. Complete overlap; the TS gene or minimal critical region is fully contained within the observed copy-number gain.

Established Pathogenic regionを包含 **1.0 pt**



Pathogenic評価



複数のCNVによる染色体再構成の可能性を意識する習慣

22番染色体短腕にはアレイプローブ配置なし：実際のCNVから推測　**dup(22)(p13→q11.21)**
11番染色体長腕端部の重複とのコンビネーション

難病情報センター
Japan Intractable Diseases Information Center

お知らせ | 国の難病対策 | 指定難病一覧 | 患者会情報

HOME >> 診断・治療指針（医療従事者向け） >> エマヌエル症候群（指定難病２０４）

エマヌエル症候群（指定難病２０４）

えまぬえるしょうこうぐん

病気の解説（一般利用者向け） | 概要・診断基準等（厚生労働省作成） | よくある質問

「厚生労働省作成の概要・診断基準等及び臨床調査個人票」（PDF版）はこちらにあります。

○ 概要

1．　概要
エマヌエル症候群は特異顔貌、口蓋裂、小頭症、先天性心疾患、精神運動発達遅滞を呈する先天性奇形症候群である。22番過剰派生染色体症候群、11/22混合トリソミーなどとも呼ばれており、染色体転座t(11;22)に由来する22番派生染色体を47本目の染色体として過剰に持つことが本疾患の原因である。近年の分子遺伝学研究の進歩により、本疾患の発生頻度が予想外に高いことがわかってきた。

2．　原因
患者の染色体核型は、47, XX or XY, +der(22)t(11;22)(q23;q11)で、11q23.より遠位側と22q11.より近位側の混合トリソミーである。その染色体領域にあるどの遺伝子が発病に関わっているのか不明である。
ほとんどの場合、両親のどちらかが均衡型染色体転座t(11;22)(q23;q11)の無症状保因者であり、患者の過剰22番派生染色体der(22)は、親の配偶子形成時の第１減数分裂における3：1分離により過剰となる。染色体転座t(11;22)(q23;q11)自体は、11q23と22q11にあるpalindromic AT-rich repeatsが精子形成時に十字架型の２次構造をとることで、染色体DNAが切断され、誤ってつなぎかわることにより発生する。

CNV1:Pathogenic
CNV2:Pathogenic

CNV1とCNV2の組み合わせから
46,XX,+der(22)t(11;22)(q23.3:q11.21) の可能性が高い
→G分染法、特定領域FISH法での上記核型の確証

Emanuel syndromeであり、99%以上が片親の転座保因者（ほとんどが母由来）

表１．t(11;22)転座保因者の妊娠 a

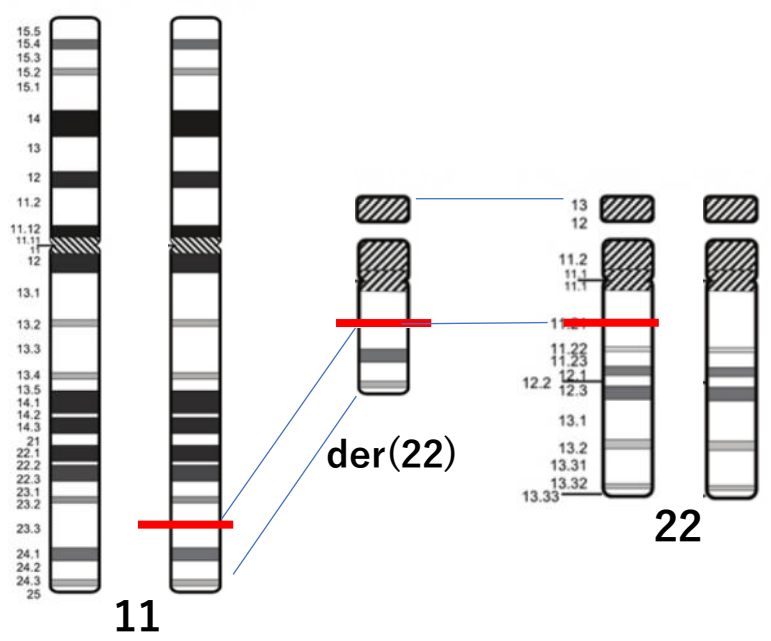
	女性保因者	男性保因者
+der(22)t(11;22)の子	5.7–6.1%	2.2–5%
t(11;22)で生まれた子	55.4%	41.2%
自然流産	23–37%	

染色体異常をみつけたら改訂八版
日本人類遺伝学会　臨床細胞遺伝学認定士制度HP
http://cytogen.jp/index/download.html

症例1ポイント

- **重複CNVの病原性判断要素：**
  蛋白コード遺伝子数 ・重複感受性領域/遺伝子(ClinGen TS score)・文献報告
- **端部着糸型染色体の<u>長腕最近位部</u>まで続くプローブ異常は、短腕を含むコピー数異常である**可能性を示唆
- **<u>端部が絡むCNVを２箇所認める</u>**場合は常に転座を意識

★重複同士/欠失同士の場合も3:1分離に起因する転座としておこりうる



症例1の注目要素

D. Chromosomal rearrangement (s/o) CNVの種類や組み合わせから染色体構成を想起する重要性 発生メカニズムの理解		
D1	**not applicable**	
D2	**full trisomy/full monosomy**	染色体全体にわたる場合のまとまり評価
D3	**umbalanced reciprocal translocation(隣接1型)**	2種類染色体の端部欠失・端部重複
D4	**umbalanced reciprocal translocation(3:1分離)**	CNV上は重複２種類での組み合わせ。少なくとも1箇所はacrocentric染色体
D5	**supernumerary marker chromosome (SMC)**	9p/15q tetrasomy(mosaic)存在への留意
D6	**ring chromsome**	同一染色体両側端部欠失
D7	**unbalanced insertional translocation(duplication)**	non-recurrentな中間部重複への留意
D8	**recombinant chromosome**	同一染色体における一方の端部欠失・もう一方の端部重複
D9	**trisomy mosaic**	連続するlog2値より疑わしい場合・phenotypeとともに