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5

静岡県立こども病院　清水健司

症例 5

１ヶ月男児　重度筋緊張低下、小脳低形成、両側異形成腎

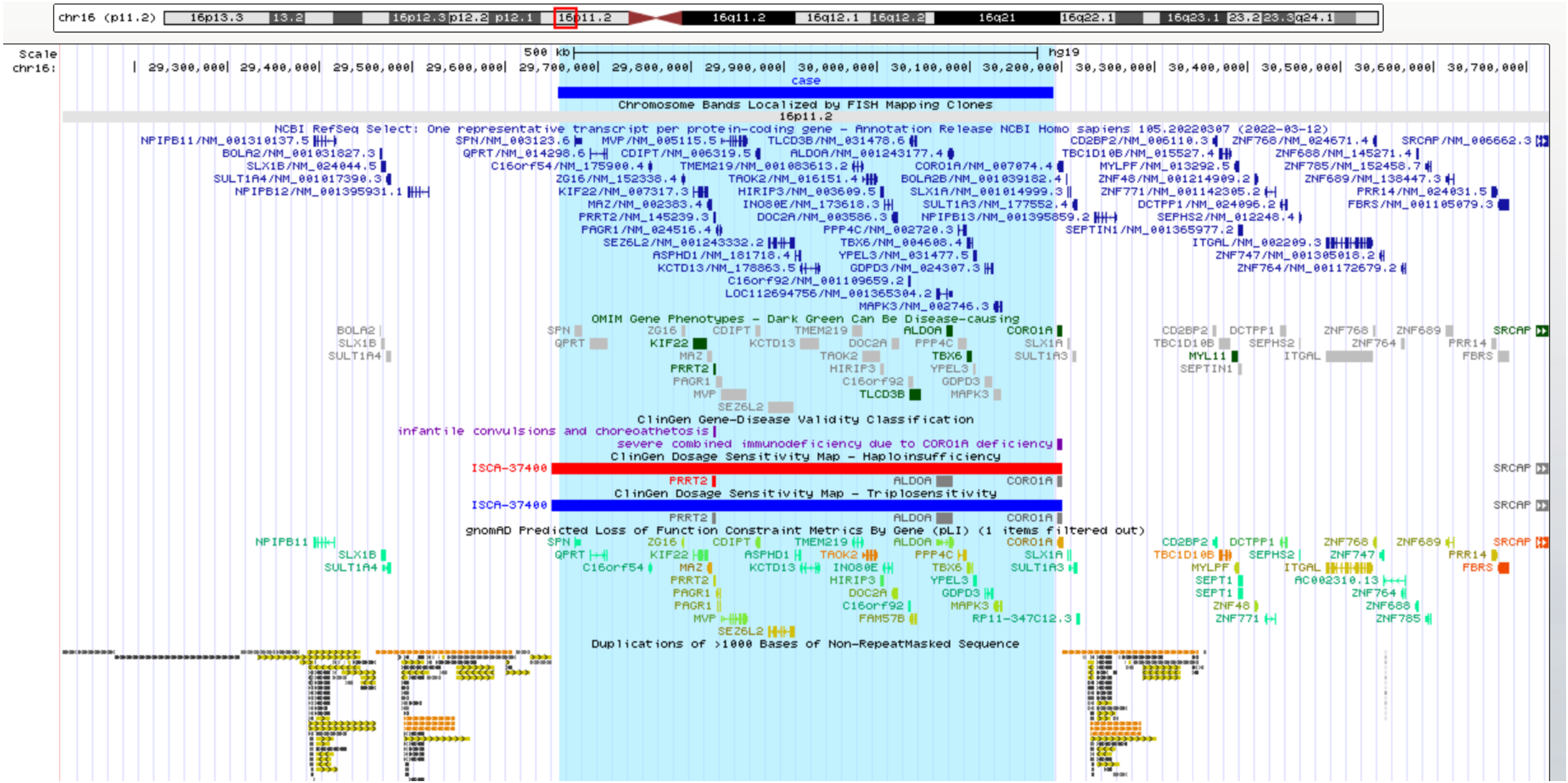
【CNV】chr16:29,656,684-30,190,568　16p11.2　log2ratio=0.53 [Gain]

＊追加設問：当該 CNV と患者の臨床所見との関連について述べよ

症例5　参加者解答より

<u>不完全浸透CNV＋見合わない表現型</u>における病原性分類判断

VUS： 3人　LP：1人　P：3人


chr16 (p11.2)
16p13.3 13.2 16p12.3 p12.2 p12.1 16p11.2 16q11.2 16q12.1 16q12.2 16q21 16q22.1 16q23.1 23.2 23.3 q24.1
Scale
chr16:
500 kb
hg19
29,300,000 29,400,000 29,500,000 29,600,000 29,700,000 29,800,000 29,900,000 30,000,000 30,100,000 30,200,000 30,300,000 30,400,000 30,500,000 30,600,000 30,700,000
case
Chromosome Bands Localized by FISH Mapping Clones
16p11.2
NCBI RefSeq Select: One representative transcript per protein-coding gene - Annotation Release NCBI Homo sapiens 105.20220307 (2022-03-12)
NPIPB11/NM_001310137.5
BOLA2/NM_001031827.3
SLX1B/NM_024044.5
SULT1A4/NM_001017390.3
NPIPB12/NM_001395931.1
SPN/NM_003123.6
QPRT/NM_014298.6
C16orf54/NM_175900.4
ZG16/NM_152338.4
KIF22/NM_007317.3
MAZ/NM_002383.4
PRRT2/NM_145239.3
PAGR1/NM_024516.4
SEZ6L2/NM_001243332.2
ASPHD1/NM_181718.4
KCTD13/NM_178863.5
C16orf92/NM_001109659.2
LOC112694756/NM_001365304.2
MVP/NM_005115.5
CDIPT/NM_006319.5
TMEM219/NM_001083613.2
TAOK2/NM_016151.4
HIRIP3/NM_003609.5
INO80E/NM_173618.3
DOC2A/NM_003586.3
PPP4C/NM_002720.3
TBX6/NM_004608.4
YPEL3/NM_031477.5
GDPD3/NM_024307.3
MAPK3/NM_002746.3
TLCD3B/NM_031478.6
ALDOA/NM_001243177.4
CORO1A/NM_007074.4
BOLA2B/NM_001039182.4
SLX1A/NM_001014999.3
SULT1A3/NM_177552.4
NPIPB13/NM_001395859.2
CD2BP2/NM_006110.3
TBC1D10B/NM_015527.4
MYLPF/NM_013292.5
ZNF48/NM_001214909.2
ZNF771/NM_001142305.2
DCTPP1/NM_024096.2
SEPHS2/NM_012248.4
SEPTIN1/NM_001365977.2
ZNF768/NM_024671.4
ZNF688/NM_145271.4
ZNF785/NM_152458.7
ZNF689/NM_138447.3
PRR14/NM_024031.5
FBRS/NM_001105079.3
ITGAL/NM_002209.3
ZNF747/NM_001305018.2
ZNF764/NM_001172679.2
SRCAP/NM_006662.3
OMIM Gene Phenotypes - Dark Green Can Be Disease-causing
ClinGen Gene-Disease Validity Classification
infantile convulsions and choreoathetosis
severe combined immunodeficiency due to CORO1A deficiency
ClinGen Dosage Sensitivity Map - Haploinsufficiency
ISCA-37400
ClinGen Dosage Sensitivity Map - Triplosensitivity
ISCA-37400
gnomAD Predicted Loss of Function Constraint Metrics By Gene (pLI) (1 items filtered out)
FAM57B
RP11-347C12.3
AC002310.13
SEPT1
Duplications of >1000 Bases of Non-RepeatMasked Sequence

Triplosensitivity (TS) Score Details

TS Score: 3

TS Evidence Strength: **Sufficient Evidence for Triplosensitivity** (Disclaimer)

TS Disease: chromosome 16p11.2 duplication syndrome Monarch

TS Published Evidence:

PUBMED: 18184952

Weiss et al. (2008) reported duplications of this region at 16p11.2 in three families with autism from one clinical cohort and reduced penetrance was noted. It was not found in any controls. In another clinical cohort, the duplication was found in four patients with autism or intellectual disability/developmental delay, but not in any patients who had testing for other diagnoses. In a third cohort, the duplication was not found in any patients with autism, but was observed in two patients with bipolar disorder and five unscreened controls.

PUBMED: 21731881

Rosenfeld et al. (2010) reported duplications of this region at 16p11.2 in 32 patients who had clinical microarray testing for various reasons. Five were de novo, 14 were inherited, and inheritance was unknown for 13. Three patients had an autism spectrum disorder. Four patients had another clinically relevant CNV observed. Detailed clinical information was available for 10 patients and frequent characteristics included delayed development, speech delay, behavioral problems, and variable dysmorphic features. However, some of these patients also had other unrelated diagnoses (Beckwith-Wiedemann syndrome, PKU, and methylmalonic aciduria) or a history of abuse.

PUBMED: 21841781

Coe et al. (2014): In a large-scale case-control comparison study of the relative prevalence of copy number variants in children with ID/DD, MCA, and other developmental phenotypes compared to controls, 16p11.2 (TBX6) proximal region duplications were observed in 62/29,085 cases versus 9/19,584 controls (p=3.50E-07), demonstrating enrichment of this duplication in the clinical population. See also Cooper et al. (2011) PMID 25424174 and Rosenfeld et al. (2013) PMID 23258348.

TS Evidence Comments: Clinical features associated with 16p11.2 (TBX6) proximal region duplication may include: developmental delays (including speech, language and motor delays), intellectual disability, autism spectrum disorder, behavioral problems (including ADHD), psychiatric disorders, seizures, microcephaly, decreased body mass index, congenital anomalies, and

不完全浸透CNV（HI score3）

症例の表現型との合致がなければVUSと評価??

CNV病原性解釈と臨床的影響は切り離す

- **CNVの病原性評価**
  - -当該CNVと疾患との関連が確立していればPathogenic

切り離して考える！

- **臨床的影響**
  - -当該CNVが当該患者の症状（すべて）の原因となっているか？

本症例：16p11.2 microduplicationで起こりうる表現型＜＜当該患者の表現型

★16p11.2 microduplication以外の遺伝学的原因が存在する可能性を検討
double diagnoses /blended phenotype

症例5の注目要素

C. Clinical significance CNVの病原性評価そのものとは切り分けて検討する重要性			
	C1	**primary (diagnostic) findings**	genetic diagnosisが主要な患者の表現型を説明
	C2	**secondary findings (incidental finding)**	genetic diagnosisが（現在の）患者の表現型にはない潜在もしくは将来発症しうる別疾患（特に腫瘍好発や不整脈疾患）を説明
	C3	**recessive carrier**	病原CNVはAR疾患の片アレルのみの検出であり 患者の表現型にはつながらない状況（＊報告対象か否かの議論）
	C4	**unmasked recessive disorder s/o**	病原性CNVはAR疾患の片アレルのみの検出であるが、 患者の表現型が当該AR疾患に特異的である状況
	C5	**plus another genetic cause s/o**	genetic diagnosisが患者の表現型の一部しか説明しておらず さらなる原因診断が求められる