產前全基因檢測的分析諮詢原則

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GA 25+0

Ventriculomegaly, VSD, PLSVC (持續性左側上腔靜脈 persistent left superior vena cava)

Karyotyping, Array CGH : WNL

MRI : Asymmetric ventriculomegaly, the right ventricle measured 13mm

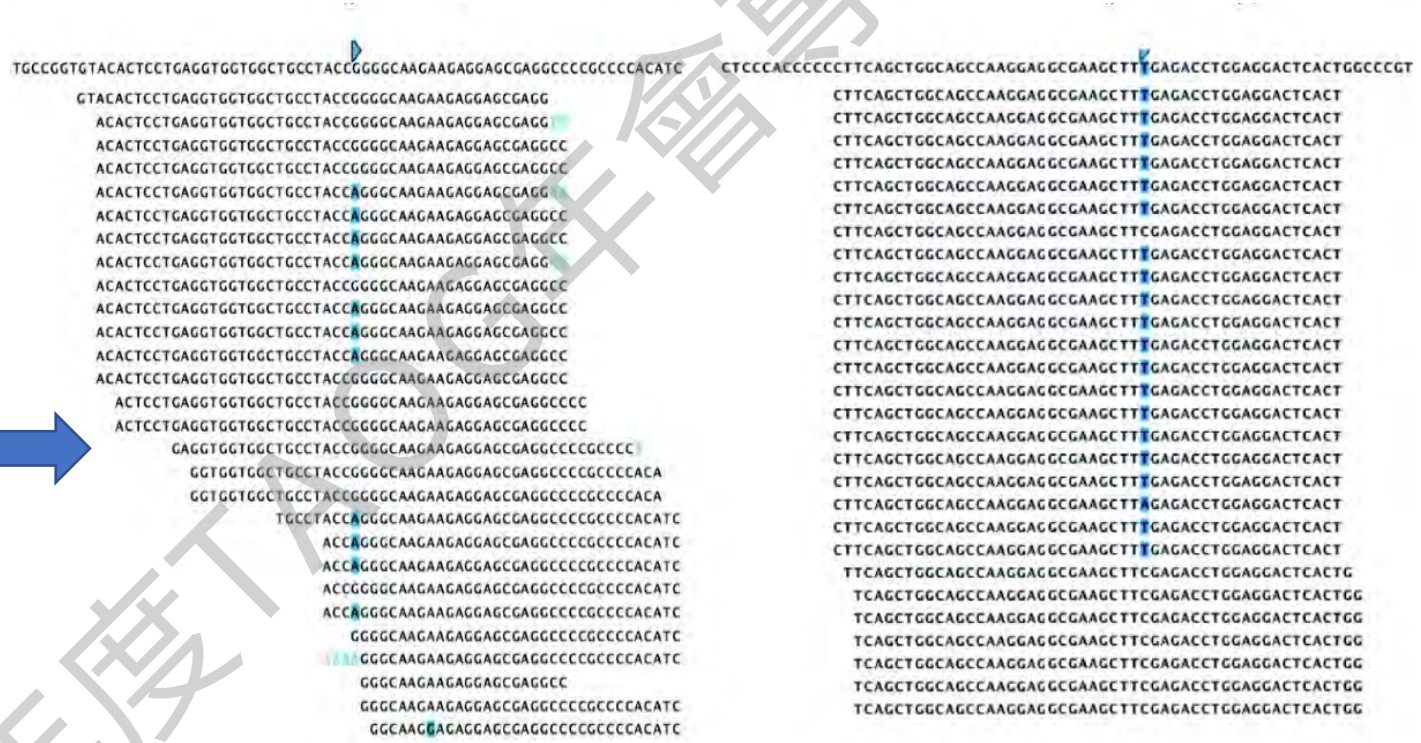
考量重點

1. Array CGH, 僅測染色體片段變化(CNV)，解析度約 50 kb，更細微的染色體變化側不到
2. 基因的變異測不到
3. 也有可能是後天因素所造成的
4. 精確地找到致病原因，才有辦法做出正確的決策

NGS 全基因定序

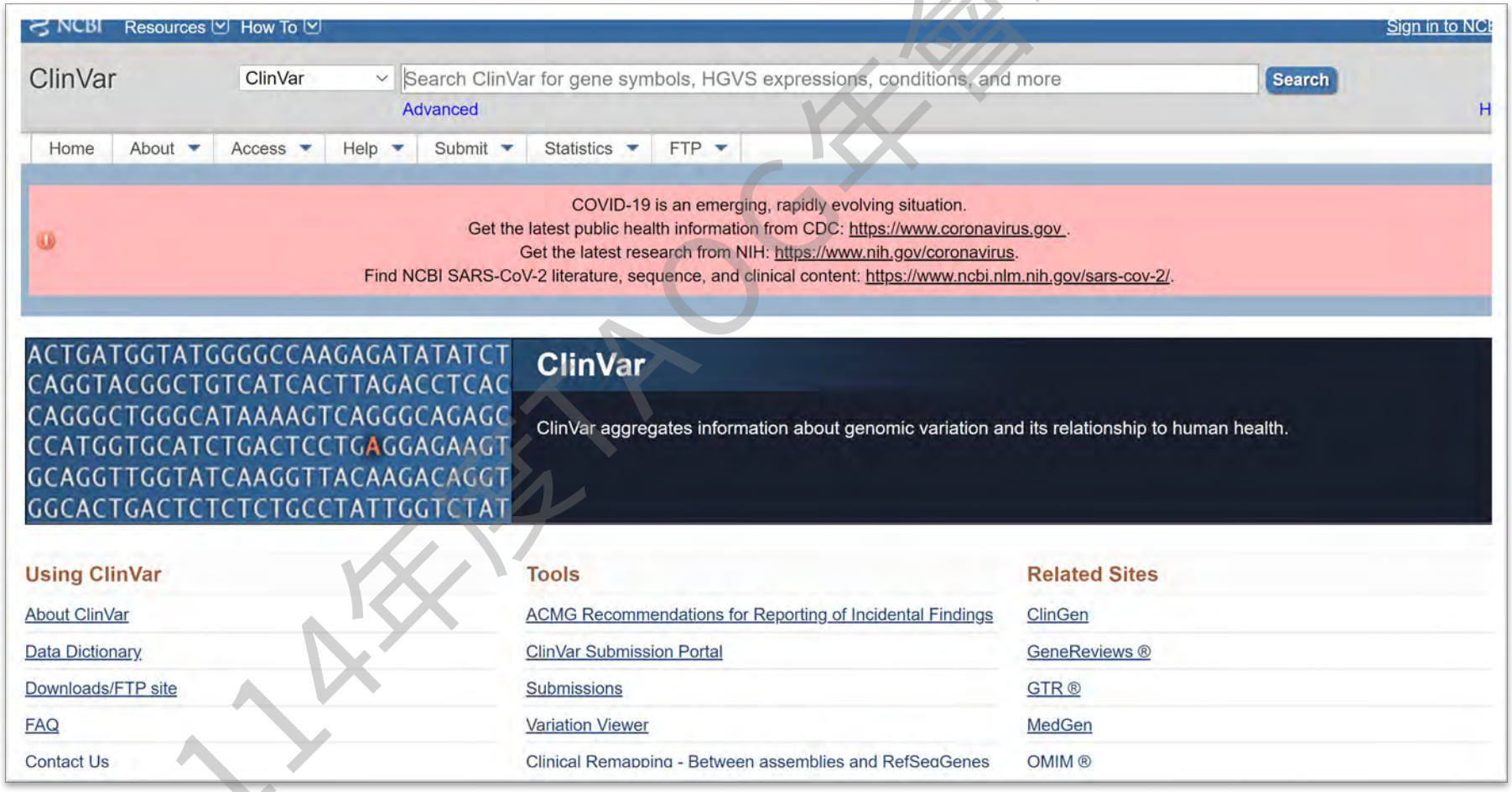
Reference sequence

reads



全部基因體變異序列

ClinVar 全世界最大的臨床基因資料庫
521萬筆資料

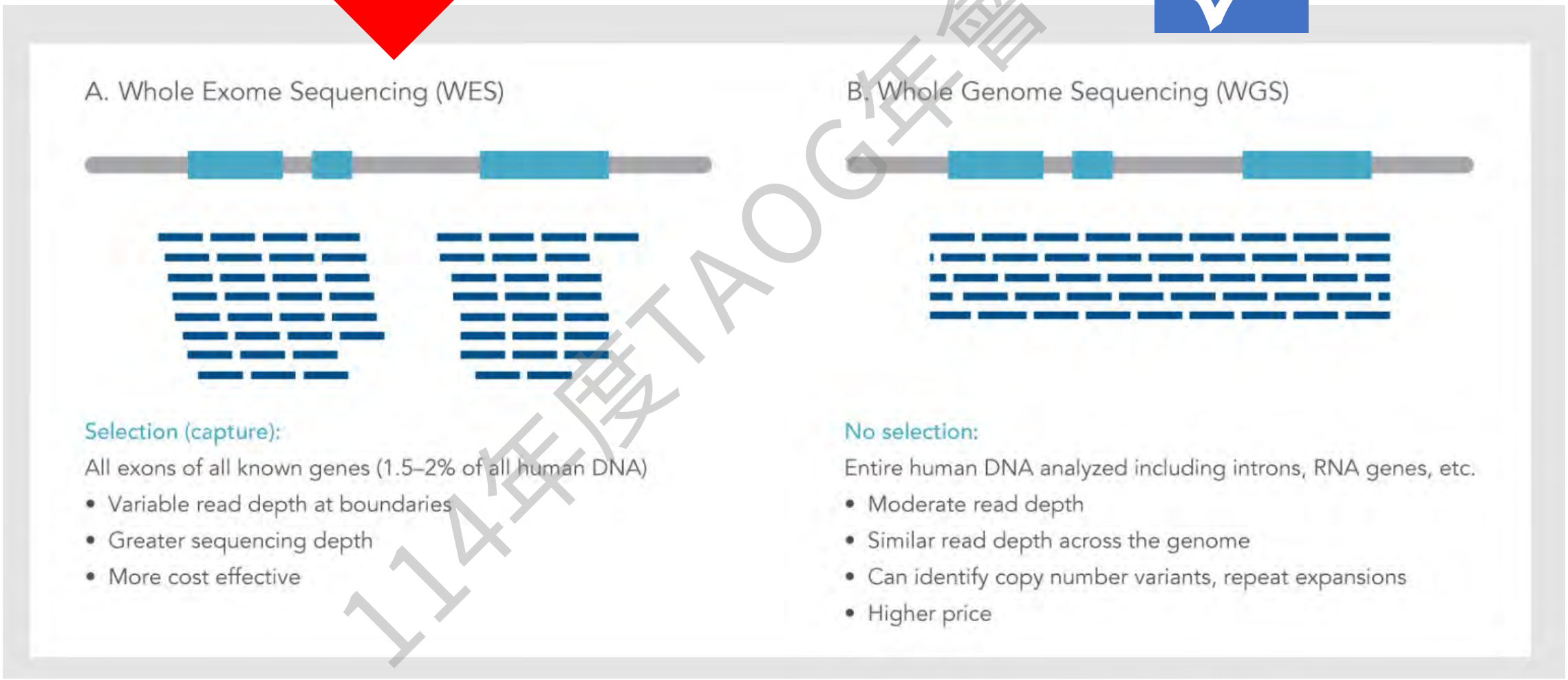


ClinVar變異點臨床作用分類 clinical significance

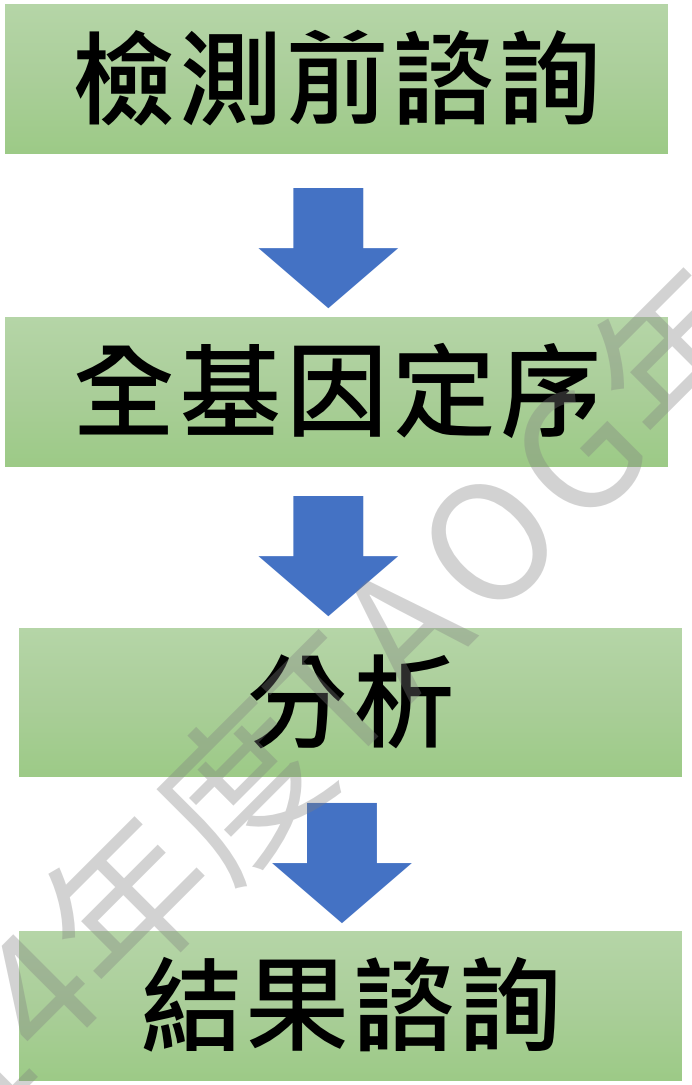
Germline classification	Guidance for use in ClinVar SCV records
Benign	As recommended by ACMG/AMP for variants classified for Mendelian diseases.
Likely benign	As recommended by ACMG/AMP for variants classified for Mendelian diseases.
Uncertain significance	As recommended by ACMG/AMP for variants classified for Mendelian diseases.
Likely pathogenic	As recommended by ACMG/AMP for variants classified for Mendelian diseases.
Pathogenic	As recommended by ACMG/AMP for variants classified for Mendelian diseases.
Likely pathogenic, low penetrance	As recommended by ClinGen for variants with decreased penetrance for Mendelian diseases.
Pathogenic, low penetrance	As recommended by ClinGen for variants with decreased penetrance for Mendelian diseases.
Uncertain risk allele	As recommended by ClinGen for variants with decreased penetrance for Mendelian diseases.
Likely risk allele	As recommended by ClinGen for variants with decreased penetrance for Mendelian diseases.
Established risk allele	As recommended by ClinGen for variants with decreased penetrance for Mendelian diseases.
drug response	A general term for a variant that affects a drug response, not a disease.
association	For variants identified in a GWAS study and further classified for disease.
protective	For variants that decrease the risk of a disorder, including infections.
Affects	For variants that cause a non-disease phenotype, such as lactose intolerance.
conflicting data from submitters	Only for submissions from a consortium, where groups within the consortium have conflicting classifications of a variant but provide a single submission to ClinVar. This value was only used for early submissions from one consortium. Currently, we ask that a consortium come to its own consensus on a variant's classification before submission to ClinVar.
other	If ClinVar does not have the appropriate term for your submission, we ask that you submit "other" as the classification and include the appropriate term as "Explanation if classification is other or drug response".
not provided	For submissions without a of classification of the variant. The primary goal of ClinVar is to archive variant classifications, so submissions with a classification of "not provided" are limited to: • "literature only" submissions that only report a publication about the variant, without providing a classification • "research" submissions that provide functional data (e.g. undetectable protein level) but no classification of the variant for a disease • "phenotyping only" submissions from clinics or physicians that provide additional information about individuals with the variant, such as observed phenotypes, but do not provide a classification of the variant
'-'	This value may not be submitted. It is used in the file variant_summary.txt.gz in the path https://ftp.ncbi.nlm.nih.gov/pub/clinvar/tab_delimited/. This file reports '-' in the ClinicalSignificance column for a variant that was submitted to ClinVar only in combination with another variant (*e.g.* a submission for classification of a haplotype or a genotype) and was not classified explictly. In that case, ClinVar has no classification specific to that variant. To find the record that includes that variant, you can query ClinVar by the AlleleID,*e.g.* https://www.ncbi.nlm.nih.gov/clinvar/?term=38420[alleleid].

WES or WGS

WES 僅測exomes, 存在 read gap, 驗CNV不準

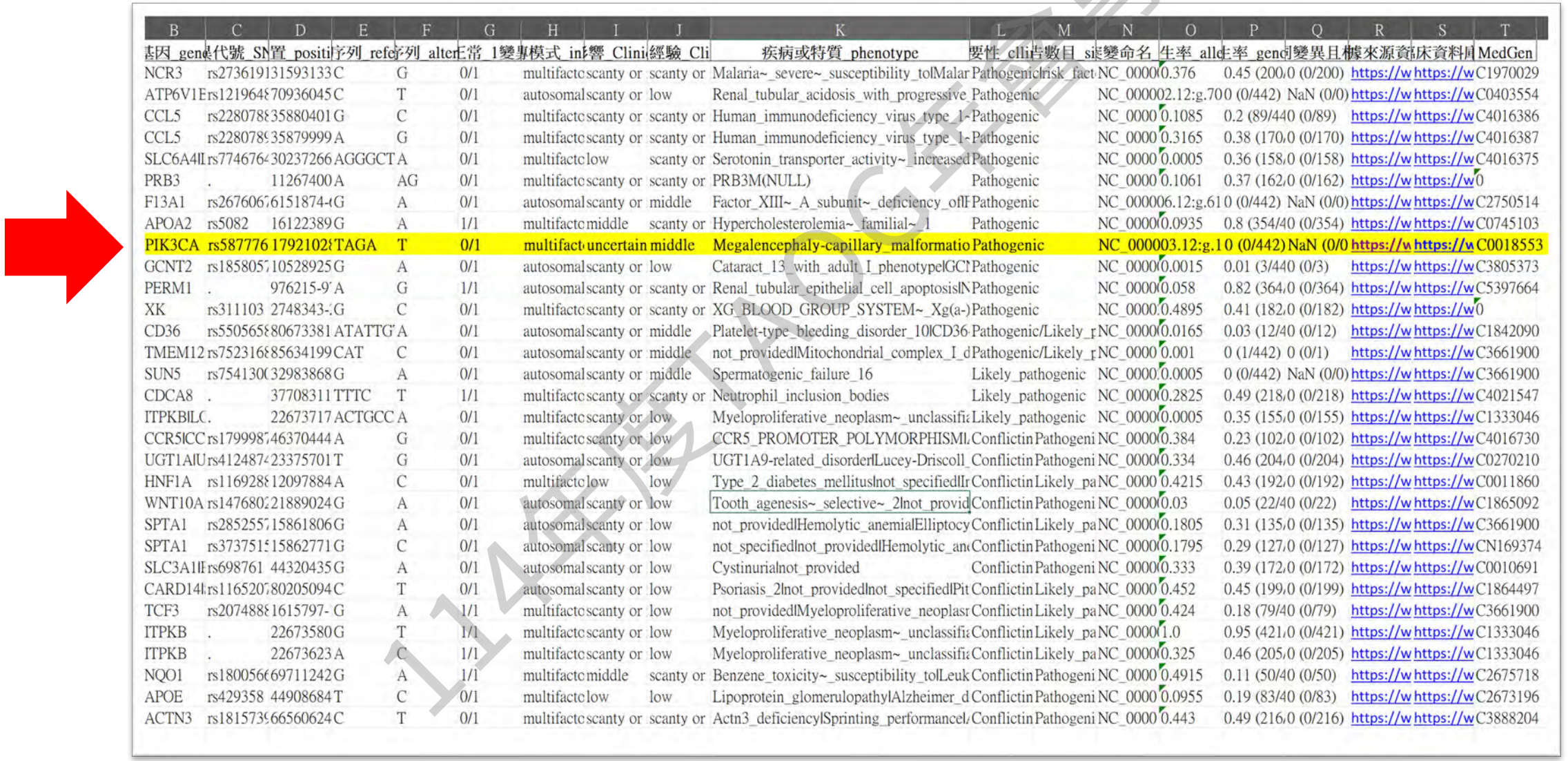


Ventriculomegaly
VSD



抽羊水

將基因體中 全部致病性基因 列出來



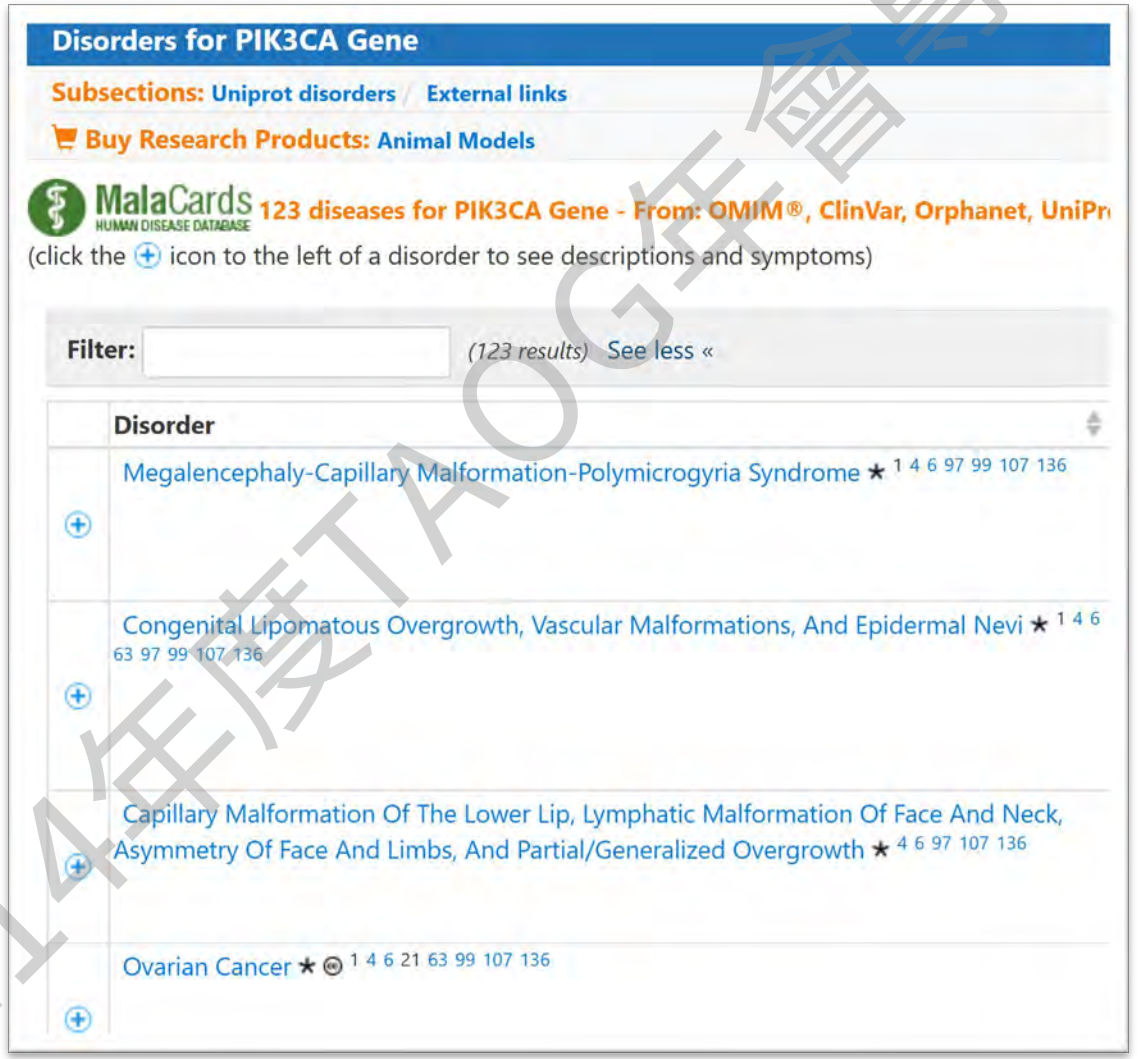
B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
基因_gene	代號_SN	置_positi	序列_refe	序列_alter	正常_1	變異模式_in	影響_Clini	經驗_Cli	疾病或特質_phenotype	要性_clli	告數目_si	變命名	生率_alle	生率_gen	變異且	據來源資	床資料庫	MedGen
NCR3	rs2736191	31593133	C	G	0/1	multifacto	scanty or	scanty or	Malaria~_severe~_susceptibility_tol	Malar	Pathogenic	risk_fact	NC_0000	0.376	0.45 (200/0	(0/200)	https://w	https://w	C1970029
ATP6V1E	rs1219648	70936045	C	T	0/1	autosomal	scanty or	low	Renal_tubular_acidosis_with_progressive	Pathogenic		NC_000002.12:g.70		0 (0/442)	NaN (0/0)		https://w	https://w	C0403554
CCL5	rs2280788	35880401	G	C	0/1	multifacto	scanty or	scanty or	Human_immunodeficiency_virus_type_1~	Pathogenic		NC_0000	0.1085	0.2 (89/440	(0/89)		https://w	https://w	C4016386
CCL5	rs2280789	35879999	A	G	0/1	multifacto	scanty or	scanty or	Human_immunodeficiency_virus_type_1~	Pathogenic		NC_0000	0.3165	0.38 (170/0	(0/170)		https://w	https://w	C4016387
SLC6A4I	rs7746764	30237266	AGGGCT	A	0/1	multifacto	low	scanty or	Serotonin_transporter_activity~_increased	Pathogenic		NC_0000	0.0005	0.36 (158/0	(0/158)		https://w	https://w	C4016375
PRB3	.	11267400	A	AG	0/1	multifacto	scanty or	scanty or	PRB3M(NULL)	Pathogenic		NC_0000	0.1061	0.37 (162/0	(0/162)		https://w	https://w	0
F13A1	rs2676067	6151874-	G	A	0/1	autosomal	scanty or	middle	Factor_XIII~_A_subunit~_deficiency_offl	Pathogenic		NC_000006.12:g.61		0 (0/442)	NaN (0/0)		https://w	https://w	C2750514
APOA2	rs5082	16122389	G	A	1/1	multifacto	middle	scanty or	Hypercholesterolemia~_familial~_1	Pathogenic		NC_0000	0.0935	0.8 (354/40	(0/354)		https://w	https://w	C0745103
PIK3CA	rs587776	1792102	TAGA	T	0/1	multifacto	uncertain	middle	Megalencephaly-capillary_malformatio	Pathogenic		NC_000003.12:g.1		0 (0/442)	NaN (0/0		https://w	https://w	C0018553
GCNT2	rs1858057	10528925	G	A	0/1	autosomal	scanty or	low	Cataract_13_with_adult_I_phenotype	GCI	Pathogenic	NC_0000	0.0015	0.01 (3/440	(0/3)		https://w	https://w	C3805373
PERM1	.	976215-9	A	G	1/1	autosomal	scanty or	scanty or	Renal_tubular_epithelial_cell_apoptosis	N	Pathogenic	NC_0000	0.058	0.82 (364/0	(0/364)		https://w	https://w	C5397664
XK	rs311103	2748343-4	G	C	0/1	multifacto	scanty or	scanty or	XG_BLOOD_GROUP_SYSTEM~_Xg(a-)	Pathogenic		NC_0000	0.4895	0.41 (182/0	(0/182)		https://w	https://w	0
CD36	rs5505658	80673381	ATATTG	A	0/1	autosomal	scanty or	middle	Platelet-type_bleeding_disorder_10	CD36	Pathogenic/Likely_p	NC_0000	0.0165	0.03 (12/40	(0/12)		https://w	https://w	C1842090
TMEM12	rs7523168	85634199	CAT	C	0/1	autosomal	scanty or	middle	not_provided	Mitochondrial_complex_I_d	Pathogenic/Likely_p	NC_0000	0.001	0 (1/442)	0 (0/1)		https://w	https://w	C3661900
SUN5	rs7541300	32983868	G	A	0/1	autosomal	scanty or	middle	Spermatogenic_failure_16	Likely_pathogenic		NC_0000	0.0005	0 (0/442)	NaN (0/0)		https://w	https://w	C3661900
CDCA8	.	37708311	TTTC	T	1/1	multifacto	scanty or	scanty or	Neutrophil_inclusion_bodies	Likely_pathogenic		NC_0000	0.2825	0.49 (218/0	(0/218)		https://w	https://w	C4021547
ITPKB|LC	.	22673717	ACTGCC	A	0/1	multifacto	scanty or	low	Myeloproliferative_neoplasm~_unclassifi	Likely_pathogenic		NC_0000	0.0005	0.35 (155/0	(0/155)		https://w	https://w	C1333046
CCR5|CC	rs1799987	46370444	A	G	0/1	multifacto	scanty or	low	CCR5_PROMOTER_POLYMORPHISM|	Conflictin	Pathogeni	NC_0000	0.384	0.23 (102/0	(0/102)		https://w	https://w	C4016730
UGT1A1|U	rs4124874	23375701	T	G	0/1	autosomal	scanty or	low	UGT1A9-related_disorder|Lucey-Driscoll_	Conflictin	Pathogeni	NC_0000	0.334	0.46 (204/0	(0/204)		https://w	https://w	C0270210
HNF1A	rs1169288	12097884	A	C	0/1	multifacto	low	low	Type_2_diabetes_mellitus|not_specified|r	Conflictin	Likely_pa	NC_0000	0.4215	0.43 (192/0	(0/192)		https://w	https://w	C0011860
WNT10A	rs1476802	21889024	G	A	0/1	autosomal	scanty or	low	Tooth_agenesis~_selective~_2|not_provid	Conflictin	Pathogeni	NC_0000	0.03	0.05 (22/40	(0/22)		https://w	https://w	C1865092
SPTA1	rs2852557	15861806	G	A	0/1	autosomal	scanty or	low	not_provided|Hemolytic_anemia|Elliptocy	Conflictin	Likely_pa	NC_0000	0.1805	0.31 (135/0	(0/135)		https://w	https://w	C3661900
SPTA1	rs3737515	15862771	G	C	0/1	autosomal	scanty or	low	not_specified|not_provided|Hemolytic_an	Conflictin	Pathogeni	NC_0000	0.1795	0.29 (127/0	(0/127)		https://w	https://w	CN169374
SLC3A1|I	rs698761	44320435	G	A	0/1	autosomal	scanty or	low	Cystinuria|not_provided	Conflictin	Pathogeni	NC_0000	0.333	0.39 (172/0	(0/172)		https://w	https://w	C0010691
CARD14|	rs1165207	80205094	C	T	0/1	autosomal	scanty or	low	Psoriasis_2|not_provided|not_specified|Pit	Conflictin	Likely_pa	NC_0000	0.452	0.45 (199/0	(0/199)		https://w	https://w	C1864497
TCF3	rs2074888	1615797-	G	A	1/1	multifacto	scanty or	low	not_provided|Myeloproliferative_neoplasr	Conflictin	Likely_pa	NC_0000	0.424	0.18 (79/40	(0/79)		https://w	https://w	C3661900
ITPKB	.	22673580	G	T	1/1	multifacto	scanty or	low	Myeloproliferative_neoplasm~_unclassifi	Conflictin	Likely_pa	NC_0000	1.0	0.95 (421/0	(0/421)		https://w	https://w	C1333046
ITPKB	.	22673623	A	C	1/1	multifacto	scanty or	low	Myeloproliferative_neoplasm~_unclassifi	Conflictin	Likely_pa	NC_0000	0.325	0.46 (205/0	(0/205)		https://w	https://w	C1333046
NQO1	rs1800566	69711242	G	A	1/1	multifacto	middle	scanty or	Benzene_toxicity~_susceptibility_tol	Leuk	Conflictin	Pathogeni	NC_0000	0.4915	0.11 (50/40	(0/50)		https://w	https://w	C2675718
APOE	rs429358	44908684	T	C	0/1	multifacto	low	low	Lipoprotein_glomerulopathy|Alzheimer_d	Conflictin	Pathogeni	NC_0000	0.0955	0.19 (83/40	(0/83)		https://w	https://w	C2673196
ACTN3	rs1815739	66560624	C	T	0/1	multifacto	scanty or	scanty or	Actn3_deficiency|Sprinting_performance|	Conflictin	Pathogeni	NC_0000	0.443	0.49 (216/0	(0/216)		https://w	https://w	C3888204

推薦資料庫 GeneCards

GeneCards Summary for PIK3CA Gene

PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) is a Protein Coding gene. Diseases associated with PIK3CA include Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome and Congenital Lipomatous Overgrowth, Vascular Malformations, And Epidermal Nevi. Among its related pathways are Downstream signaling of activated FGFR2 and Translation Insulin regulation of translation. Gene Ontology (GO) annotations related to this gene include *transferase activity, transferring phosphorus-containing groups* and *protein serine/threonine kinase activity*. An important paralog of this gene is PIK3CD.

查基因相關疾病



Disorders for PIK3CA Gene

Subsections: Uniprot disorders / External links

Buy Research Products: Animal Models

MalaCards HUMAN DISEASE DATABASE **123 diseases for PIK3CA Gene - From: OMIM®, ClinVar, Orphanet, UniPr**

(click the ⊕ icon to the left of a disorder to see descriptions and symptoms)

Filter: *(123 results)* See less «

Disorder
Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome ★ 1 4 6 97 99 107 136
Congenital Lipomatous Overgrowth, Vascular Malformations, And Epidermal Nevi ★ 1 4 6 63 97 99 107 136
Capillary Malformation Of The Lower Lip, Lymphatic Malformation Of Face And Neck, Asymmetry Of Face And Limbs, And Partial/Generalized Overgrowth ★ 4 6 97 107 136
Ovarian Cancer ★ 1 4 6 21 63 99 107 136

查基因相關疾病

Summaries for Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome

MedlinePlus Genetics[43]

Megalencephaly-capillary malformation syndrome (MCAP) is a disorder characterized by overgrowth of several tissues in the body. Its primary features are a large brain (megalencephaly) and abnormalities of small blood vessels in the skin called capillaries (capillary malformations).

In individuals with MCAP, megalencephaly leads to an unusually large head size (macrocephaly), which is typically evident at birth. After birth, the brain and head continue to grow at a fast rate for the first few years of life; then, the growth slows to a normal rate, although the head remains larger than average. Additional brain abnormalities are common in people with MCAP; these can include excess fluid within the brain (hydrocephalus) and abnormalities in the brain's structure, such as those known as Chiari malformation and polymicrogyria. Abnormal brain development leads to intellectual disability in most affected individuals and can also cause seizures or weak muscle tone (hypotonia). In particular, polymicrogyria is associated with speech delays and difficulty chewing and swallowing.

The capillary malformations characteristic of MCAP are composed of enlarged capillaries that increase blood flow near the surface of the skin. These malformations usually look like pink or red spots on the skin. In most affected individuals, capillary malformations occur on the face, particularly the nose, the upper lip, and the area between the nose and upper lip (the philtrum). In other people with MCAP, the malformations appear as patches spread over the body or as a reddish net-like pattern on the skin (cutis marmorata).

In some people with MCAP, excessive growth affects not only the brain but other individual parts of the body, which is known as segmental overgrowth. This can lead to one arm or leg that is bigger or longer than the other or a few oversized fingers or toes. Some affected individuals have fusion of the skin between two or more fingers or toes (cutaneous syndactyly).

Additional features of MCAP can include flexible joints and skin that stretches easily. Some affected individuals are said to have doughy skin because the tissue under the skin is unusually thick and soft.

The gene involved in MCAP is also associated with several types of cancer. Only a small number of individuals with MCAP have developed tumors (in particular, a childhood form of kidney cancer known as Wilms tumor and noncancerous tumors in the nervous system known as meningiomas).

OMIM®[59]
(Updated 24-11-27)

Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) is characterized by a spectrum of anomalies including primary megalencephaly, prenatal overgrowth, brain and body asymmetry, cutaneous vascular malformations, digital anomalies consisting of syndactyly with or without postaxial polydactyly, connective tissue dysplasia involving the skin, subcutaneous tissue, and joints, and cortical brain malformations, most distinctively polymicrogyria (summary by Mirzaa et al., 2012). This disorder is also known as the macrocephaly-capillary malformation (MCM)

OMIM 資料庫

#602501

Table of Contents

Alternative titles; symbols

MACROCEPHALY-CAPILLARY MALFORMATION; MCM
MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME
MACROCEPHALY-CUTIS MARMORATA TELANGIECTATICA CONGENITA; MCMTC
MEGALENCEPHALY-CUTIS MARMORATA TELANGIECTATICA CONGENITA

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
3q26.32	Megalencephaly-capillary malformation-polymicrogyria syndrome, somatic	602501		3	PIK3CA	171834

Clinical Synopsis ▾ | PheneGene Graphics ▾ ?

比對資料庫及胎兒症狀

CARDIOVASCULAR

Heart

- Ventricular septal defect

SKELETAL

- Joint laxity

Hands

- Syndactyly
- Polydactyly

Feet

- Syndactyly
- Polydactyly

SKIN, NAILS, & HAIR

Skin

- Thick, loose, doughy skin
- Cutaneous vascular malformations
- Patchy, reticular stains
- Cutis marmorata

MUSCLE, SOFT TISSUES

- Thickened subcutaneous tissue

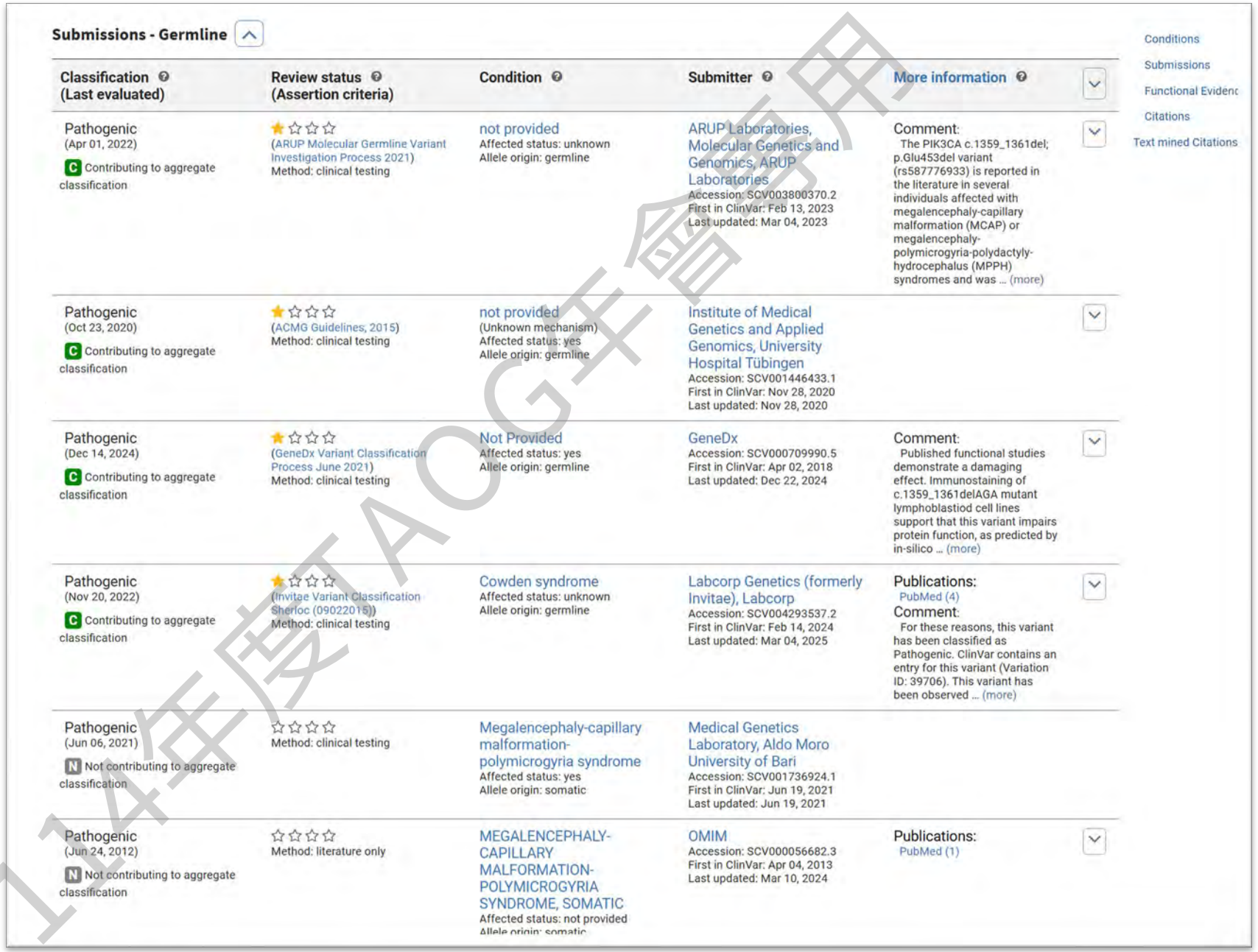
NEUROLOGIC

Central Nervous System

- Developmental delay
- Mental retardation
- Hypotonia
- Seizures
- MRI shows brain asymmetry
- Ventriculomegaly
- Hydrocephalus
- Large cerebellum, progressive
- Cerebellar tonsil herniation
- Crowding of the posterior fossa
- Cavum septum pellucidum
- Cavum vergae
- Polymicrogyria
- Cortical dysgenesis
- Thickened corpus callosum
- Thickened optic nerve sheath

查變異點證據力

查變異點證據力

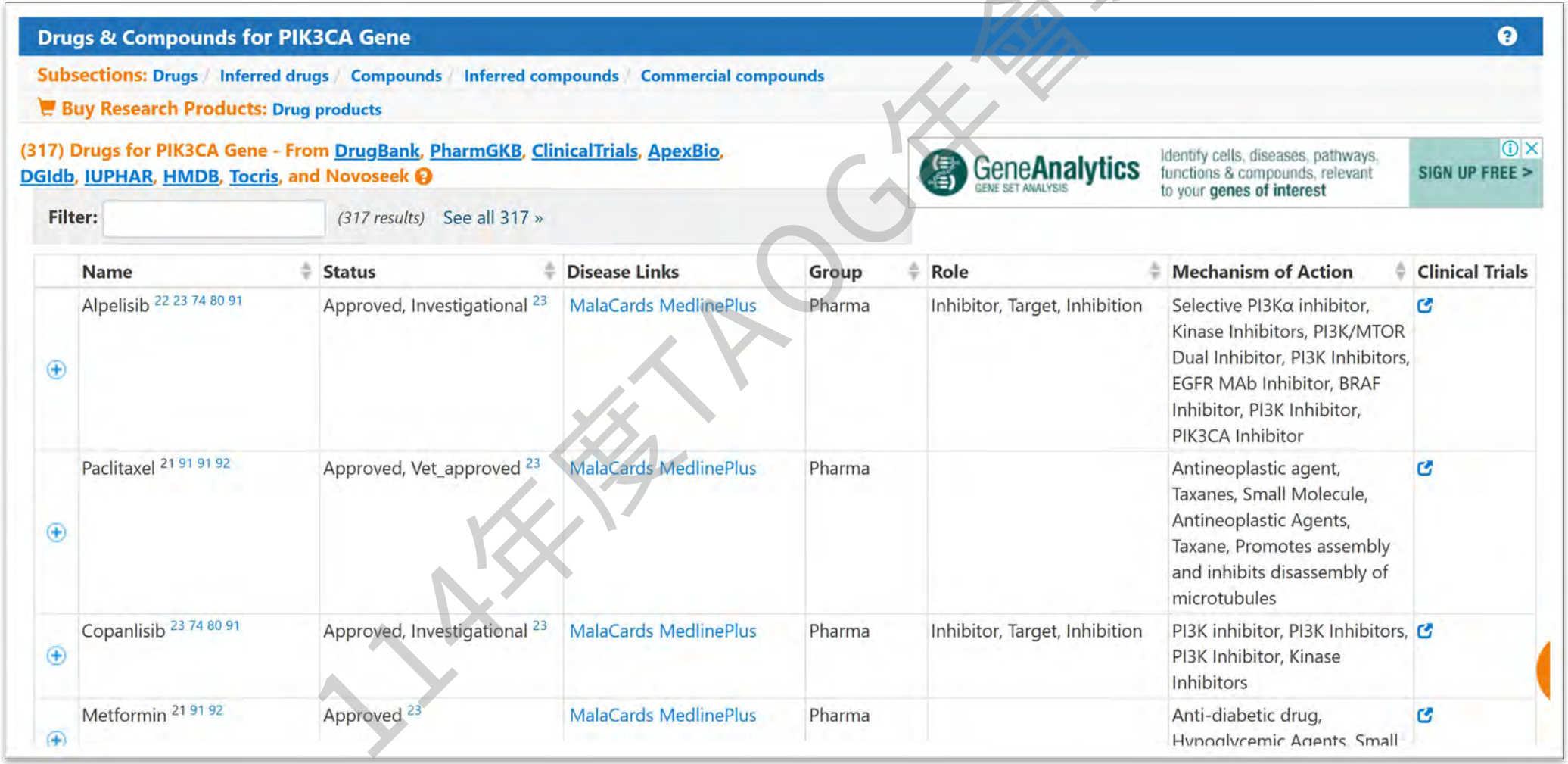


Submissions - Germline

Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter	More information
Pathogenic (Apr 01, 2022) C Contributing to aggregate classification	★☆☆☆ (ARUP Molecular Germline Variant Investigation Process 2021) Method: clinical testing	not provided Affected status: unknown Allele origin: germline	ARUP Laboratories, Molecular Genetics and Genomics, ARUP Laboratories Accession: SCV003800370.2 First in ClinVar: Feb 13, 2023 Last updated: Mar 04, 2023	Comment: The PIK3CA c.1359_1361del; p.Glu453del variant (rs587776933) is reported in the literature in several individuals affected with megalencephaly-capillary malformation (MCAP) or megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndromes and was ... (more)
Pathogenic (Oct 23, 2020) C Contributing to aggregate classification	★☆☆☆ (ACMG Guidelines, 2015) Method: clinical testing	not provided (Unknown mechanism) Affected status: yes Allele origin: germline	Institute of Medical Genetics and Applied Genomics, University Hospital Tübingen Accession: SCV001446433.1 First in ClinVar: Nov 28, 2020 Last updated: Nov 28, 2020	
Pathogenic (Dec 14, 2024) C Contributing to aggregate classification	★☆☆☆ (GeneDx Variant Classification Process June 2021) Method: clinical testing	Not Provided Affected status: yes Allele origin: germline	GeneDx Accession: SCV000709990.5 First in ClinVar: Apr 02, 2018 Last updated: Dec 22, 2024	Comment: Published functional studies demonstrate a damaging effect. Immunostaining of c.1359_1361delAGA mutant lymphoblastiod cell lines support that this variant impairs protein function, as predicted by in-silico ... (more)
Pathogenic (Nov 20, 2022) C Contributing to aggregate classification	★☆☆☆ (Invitae Variant Classification Sherloc (09022015)) Method: clinical testing	Cowden syndrome Affected status: unknown Allele origin: germline	Labcorp Genetics (formerly Invitae), Labcorp Accession: SCV004293537.2 First in ClinVar: Feb 14, 2024 Last updated: Mar 04, 2025	Publications: PubMed (4) Comment: For these reasons, this variant has been classified as Pathogenic. ClinVar contains an entry for this variant (Variation ID: 39706). This variant has been observed ... (more)
Pathogenic (Jun 06, 2021) N Not contributing to aggregate classification	☆☆☆☆ Method: clinical testing	Megalencephaly-capillary malformation-polymicrogyria syndrome Affected status: yes Allele origin: somatic	Medical Genetics Laboratory, Aldo Moro University of Bari Accession: SCV001736924.1 First in ClinVar: Jun 19, 2021 Last updated: Jun 19, 2021	
Pathogenic (Jun 24, 2012) N Not contributing to aggregate classification	☆☆☆☆ Method: literature only	MEGALENCEPHALY-CAPILLARY MALFORMATION-POLYMICROGYRIA SYNDROME, SOMATIC Affected status: not provided Allele origin: somatic	OMIM Accession: SCV000056682.3 First in ClinVar: Apr 04, 2013 Last updated: Mar 10, 2024	Publications: PubMed (1)

Conditions
Submissions
Functional Evidenc
Citations
Text mined Citations

查相關治療藥物文獻



Drugs & Compounds for PIK3CA Gene

Subsections: Drugs / Inferred drugs / Compounds / Inferred compounds / Commercial compounds

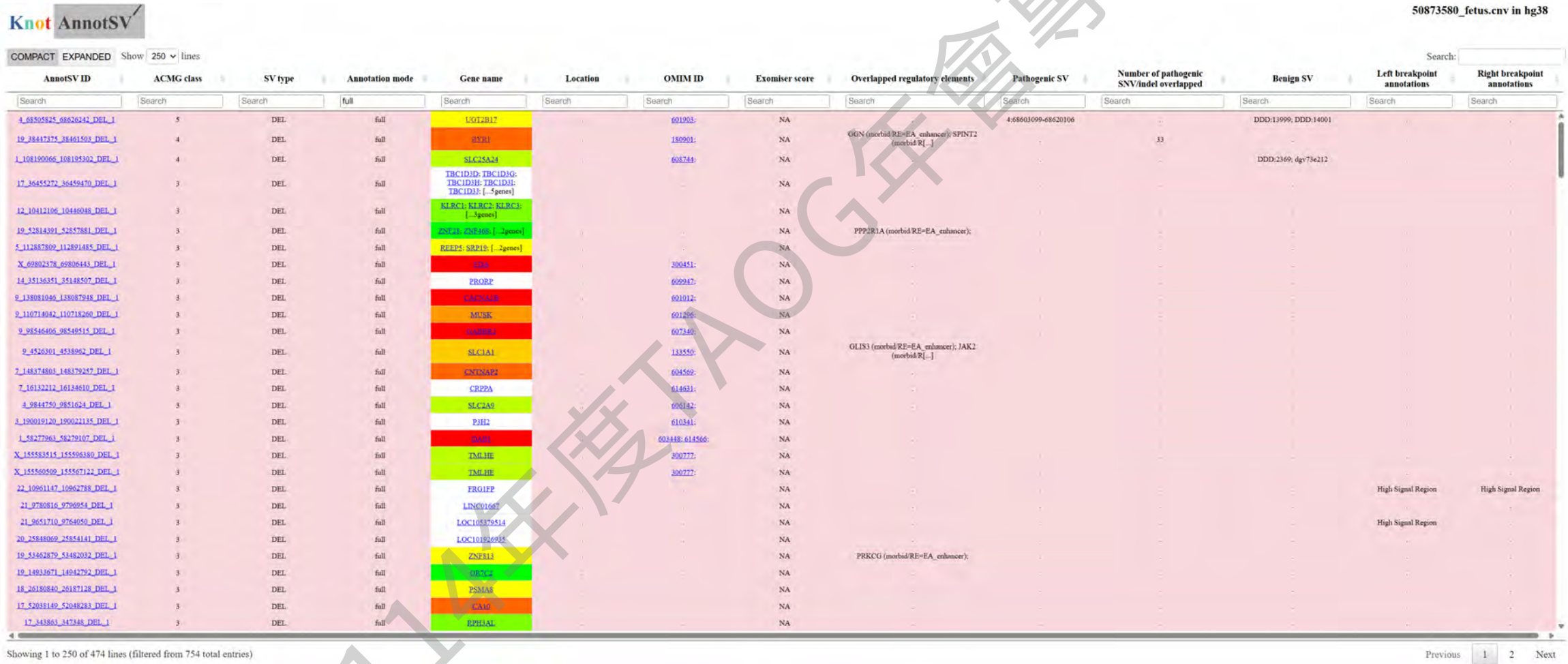
Buy Research Products: Drug products

(317) Drugs for PIK3CA Gene - From DrugBank, PharmGKB, ClinicalTrials, ApexBio, DGIdb, IUPHAR, HMDB, Tocris, and Novoseek

Filter: (317 results) See all 317 »

Name	Status	Disease Links	Group	Role	Mechanism of Action	Clinical Trials
Alpelisib [22 23 74 80 91]	Approved, Investigational [23]	MalaCards MedlinePlus	Pharma	Inhibitor, Target, Inhibition	Selective PI3Kα inhibitor, Kinase Inhibitors, PI3K/MTOR Dual Inhibitor, PI3K Inhibitors, EGFR MAb Inhibitor, BRAF Inhibitor, PI3K Inhibitor, PIK3CA Inhibitor	
Paclitaxel [21 91 91 92]	Approved, Vet_approved [23]	MalaCards MedlinePlus	Pharma		Antineoplastic agent, Taxanes, Small Molecule, Antineoplastic Agents, Taxane, Promotes assembly and inhibits disassembly of microtubules	
Copanlisib [23 74 80 91]	Approved, Investigational [23]	MalaCards MedlinePlus	Pharma	Inhibitor, Target, Inhibition	PI3K inhibitor, PI3K Inhibitors, PI3K Inhibitor, Kinase Inhibitors	
Metformin [21 91 92]	Approved [23]	MalaCards MedlinePlus	Pharma		Anti-diabetic drug, Hypoglycemic Agents, Small	

WGS CNV 分析



Knot AnnotSV

50873580_fetus.cnv in hg38

COMPACT EXPANDED Show 250 lines

Search:

AnnotSV ID	ACMG class	SV type	Annotation mode	Gene name	Location	OMIM ID	Exomiser score	Overlapped regulatory elements	Pathogenic SV	Number of pathogenic SNV/indel overlapped	Benign SV	Left breakpoint annotations	Right breakpoint annotations
Search	Search	Search	full	Search	Search	Search	Search	Search	Search	Search	Search	Search	Search
4_68505825_68626242_DEL_1	5	DEL	full	UGT2B17		601903;	NA		4:68603099-68620106		DDD:13999; DDD:14001		
19_38447375_38461503_DEL_1	4	DEL	full	SYR1		180901;	NA	GGN (morbid/RE=EA_enhancer); SPINT2 (morbid/R[...]		33			
1_108190066_108195302_DEL_1	4	DEL	full	SLC25A24		608744;	NA				DDD:2369; dgv73e212		
17_36455272_36459470_DEL_1	3	DEL	full	TBC1D3D; TBC1D3Q; TBC1D3H; TBC1D3I; TBC1D3J; [...5genes]			NA						
12_10412106_10446048_DEL_1	3	DEL	full	KLRC1; KLRC2; KLRC3; [...3genes]			NA						
19_52814391_52857881_DEL_1	3	DEL	full	ZNF28; ZNF468; [...2genes]			NA	PPP2R1A (morbid/RE=EA_enhancer);					
5_112887809_112891485_DEL_1	3	DEL	full	REEP5; SRP19; [...2genes]			NA						
X_69802378_69806443_DEL_1	3	DEL	full	FGF16		300451;	NA						
14_35136351_35148507_DEL_1	3	DEL	full	PRORP		609947;	NA						
9_138081046_138087948_DEL_1	3	DEL	full	CACNA1B		601012;	NA						
9_110714042_110718260_DEL_1	3	DEL	full	MUSK		601296;	NA						
9_98546406_98549515_DEL_1	3	DEL	full	GABBR2		607340;	NA						
9_4526301_4538962_DEL_1	3	DEL	full	SLC1A1		133550;	NA	GLIS3 (morbid/RE=EA_enhancer); JAK2 (morbid/R[...]					
7_148374803_148379257_DEL_1	3	DEL	full	CNTNAP2		604569;	NA						
7_16132212_16134610_DEL_1	3	DEL	full	CRPPA		614631;	NA						
4_9844750_9851624_DEL_1	3	DEL	full	SLC2A9		606142;	NA						
3_190019120_190022135_DEL_1	3	DEL	full	PSH2		610341;	NA						
1_58277963_58279107_DEL_1	3	DEL	full	ZA63		603448; 614566;	NA						
X_155583515_155596380_DEL_1	3	DEL	full	TMLHE		300777;	NA						
X_155560509_155567122_DEL_1	3	DEL	full	TMLHE		300777;	NA						
22_10961147_10962788_DEL_1	3	DEL	full	FRG1FP			NA					High Signal Region	High Signal Region
21_9780816_9796954_DEL_1	3	DEL	full	LINC01602			NA						
21_9651710_9764050_DEL_1	3	DEL	full	LOC105379514			NA					High Signal Region	
20_25848069_25854141_DEL_1	3	DEL	full	LOC101926935			NA						
19_53462879_53482032_DEL_1	3	DEL	full	ZNF813			NA	PRKCG (morbid/RE=EA_enhancer);					
19_14933671_14942792_DEL_1	3	DEL	full	OR7C2			NA						
18_26180840_26187128_DEL_1	3	DEL	full	PSMA8			NA						
17_52038149_52048283_DEL_1	3	DEL	full	CA10			NA						
17_343863_347348_DEL_1	3	DEL	full	EPHA3L			NA						

Showing 1 to 250 of 474 lines (filtered from 754 total entries)

Previous 1 2 Next

WGS, or WES + SNP array

✓ WGS

- 4個禮拜左右可發報告
- 目前可做到最完整的胎兒產前基因檢測
- 包含染色體數目、 CNV、SV 、幾乎所有的基因密碼變異
- 30x下 解析度達5kb (SNP array 為50 kb)

報告文字說明

適應症 Indication	胎兒腦室擴大及心室中隔缺損
結果 Result	請參考下列敘述

說明 Interpretation:

基因分析顯示胎兒在位於染色體 3 上的 PIK3CA 基因中，發現了一個特定的變異：NM_006218.4(PIK3CA):c.1356AGA[1] (p.Glu453del)，基因變異代號為 rs587776933。該變異導致正常序列 TAGA 變為 T，並且胎兒的基因型為 0/1（異合子）。

變異評估

1. 基因功能影響：
   - PIK3CA 基因編碼的蛋白參與細胞增殖、分化及血管生成的信號傳遞，此變異可能破壞正常蛋白結構與功能。
   - 此變異（p.Glu453del）已被臨床基因資料庫記錄，並具中等臨床相關性證據。
2. 潛在影響：
   - 此變異可能與胎兒中樞神經系統及血管系統發育異常有關。
   - 需進一步結合臨床影像學檢查與其他先天異常特徵（如腦室擴大、心血管結構異常等）進行綜合判斷。

建議

1. 臨床對照：
   - 建議將此基因變異與胎兒的臨床異常（如腦室擴大、心臟缺陷等）進行對照，以評估其因果關係。
2. 專家諮詢：
   - 聯繫遺傳學專家及多學科團隊進行進一步解讀與諮詢。

報告文字說明

PIK3CA 基因, 基因型 0/1, 基因變異臨床重要性是 Pathogenic, 代號是 NC_000003.12:g.179210290AGA[1] 的基因變異說明

根據您的檢測結果，涉及的基因是染色體 3 上的 PIK3CA 基因，這基因在您的 DNA 中發現了一個特定的變異代號為 rs587776933。這個變異是由正常序列 TAGA 變為 T。您有這個基因變異的基因型是 0/1，這意味著您是帶有這個變異的人。

這裡的遺傳模式被歸類為多因素遺傳，這意味著這種基因變異可能會增加某些先天疾病的風險，但是否真的會影響健康，還需要考慮很多後天環境與生活方式因素。簡單來說，即使有這個基因變異，也不代表一定會生病，因此需要避免一些可能誘發疾病的後天因素。

關於這個特定變異，根據我們的資料中心，它對健康的影響目前是不確定的，需要進一步確定。這也提醒我們，儘管這基因變異已被標記為具有一定臨床重要性，但需要更多的研究資料及身體檢查來確認它是否會對您造成影響。這意味著，建議您考慮到專科醫師進一步諮詢，以便更全面地理解這個基因變異可能帶來的健康意涵。

就目前的發現來看，這個 PIK3CA 基因變異與 Megalencephaly-capillary malformation-polymicrogyria syndrome 這種綜合症有關。這是一種影響大腦結構的先天性狀況，但如前所述，不一定會因為這個基因變異導致這種症狀的出現。

目前，變異在我們實驗室資料庫中的發生率是 0%，這意味著我們未見到過這個變異的報告。也就是說，在我們的實驗室環境下，這個變異是非常少見的。

最後，這基因變異的臨床證據顯示為中等水平，建議您與醫學專家進一步商討，以便根據您的臨床症狀和家族遺傳背景做出更具體的健康評估。記得在日常生活中注重健康生活方式，以減少可能的後天風險因素。

臨床變異證據來源資料庫 ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/variation/39706/

基因異常臨床資料庫 GeneCards: https://www.genecards.org/cgi-bin/carddisp.pl?gene=PIK3CA

基因變異點都要考慮到

影響力及證據力

案例：懷孕，前胎 Lissencephaly

NM_006009.4(TUBA1A):c.641G>A (p.Arg214His)

考量點

→是否就是這基因單獨造成？

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	Supporting information (See all)
Pathogenic (Feb 03, 2017)	criteria provided, single submitter (ACMG Guidelines, 2015) Method: clinical testing	not provided Allele origin: de novo	Center for Pediatric Genomic Medicine,Children's Mercy Hospital and Clinics Accession: SCV000511367.1 Submitted: (Feb 17, 2017)	Evidence details
Pathogenic (Aug 01, 2017)	criteria provided, single submitter (ACMG Guidelines, 2015) Method: clinical testing	Lissencephaly 3 (Sporadic) Allele origin: de novo	Institute of Human Genetics,Friedrich-Alexander-Universität Erlangen-Nürnberg Accession: SCV000586724.1 Submitted: (Aug 03, 2017)	Evidence details Comment: De novo missense variant identified in a female patient with severe ID, severe epilepsy, developmental regression, scoliosis, hypotonia, MRI: agenesis of corpus callosum, Dandy-Walker malformation, ... (more)
Pathogenic (Oct 31, 2018)	criteria provided, single submitter (ACMG Guidelines, 2015) Method: clinical testing	Lissencephaly 3 Allele origin: unknown	Fulgent Genetics,Fulgent Genetics Accession: SCV000893302.1 Submitted: (Nov 14, 2018)	Evidence details Publications PubMed (1) DOI: 10.1038/gim.2015.30
Pathogenic (Oct 05, 2018)	criteria provided, single submitter (GeneDx Variant Classification (06012015)) Method: clinical testing	Not Provided Allele origin: germline	GeneDx Accession: SCV000490865.2 Submitted: (Jan 29, 2019)	Evidence details Comment: The R214H variant in the TUBA1A gene has been reported previously as a de novo heterozygous pathogenic variant in an individual with severe developmental delay, ... (more)
Pathogenic (Jul 01, 2018)	criteria provided, single submitter (ACMG Guidelines, 2015) Method: literature only	Tubulinopathies Allele origin: de novo	Institute of Human Genetics,Friedrich-Alexander-Universität Erlangen-Nürnberg Accession: SCV000898038.1 Submitted: (Oct 08, 2018)	Evidence details Publications PubMed (1) DOI: 10.1101/427948 Comment: A variant that is classified as pathogenic has been identified in the TUBA1A gene in a 51 months old born individual of female sex. The ... (more)
Pathogenic (Dec 03, 2018)	criteria provided, single submitter (ACMG Guidelines, 2015) Method: research	Lissencephaly 3 (Autosomal dominant inheritance) Allele origin: de novo	Broad Institute Rare Disease Group,Broad Institute Accession: SCV001164438.1 Submitted: (Oct 03, 2019)	Evidence details Comment: The heterozygous p.Arg214His variant in TUBA1A was identified by our study in one individual with lissencephaly. Trio exome analysis showed this variant to be de ... (more)
Pathogenic (Dec 01, 2018)	criteria provided, single submitter (Praxis fuer Humangenetik Tuebingen - Variant	not provided Allele origin: germline	CeGaT Praxis fuer Humangenetik Tuebingen Accession: SCV001247150.2 Submitted: (May 18, 2020)	Evidence details

推薦網站

ClinVar

NM_006009.4(TUBA1A):c.641G>A (p.Arg214His)

Interpretation:	**Pathogenic/Likely pathogenic**
Review status:	★★☆☆ criteria provided, multiple submitters, no conflicts
Submissions:	8 (Most recent: Jul 6, 2020)
Last evaluated:	Dec 3, 2018
Accession:	VCV000372542.8
Variation ID:	372542
Description:	single nucleotide variant

NM_006009.4(TUBA1A):c.641G>A (p.Arg214His)

Allele ID:	359970
Variant type:	single nucleotide variant
Variant length:	1 bp
Cytogenetic location:	12q13.12
Genomic location:	12: 49185725 (GRCh38) GRCh38 UCSC 12: 49579508 (GRCh37) GRCh37 UCSC

HGVS:

Nucleotide	Protein	Molecular consequence
NC_000012.11:g.49579508C>T		
NC_000012.12:g.49185725C>T		
NM_006009.4:c.641G>A MANE SELECT	NP_006000.2:p.Arg214His	missense

... more HGVS

Protein change:	R214H
Other names:	-
Canonical SPDI:	NC_000012.12:49185724:C:T

Lissencephaly
NM_006009.4(TUBA1A):c.641G>A (p.Arg214His)

- 大部分是de novo
- 顯性遺傳模式, 父母遺傳機會小
- 是否還有其他基因異常？

→prenatal exome sequencing

分析重點

1. 有無其他基因
2. NM_006009.4(TUBA1A):c.641是否有變異

WES：無lissencephaly相關基因

	A	B	C	D	E	F	G	H	
	Chr	**Gene**	**Ref**	**Alt**	**Genotype**	**Phenotype**	**ClinicSigr**	**Significan**	**H**
	chr3	GHRL|GH	G	T	0/1	Metabolic_syndrome~_susceptibility_to|Obesity~_age_at_onset_of	Pathogenic~_risk_fac		N
	chr4	SOD3	C	G	0/1	Superoxide_dismutase~_elevated_extracellular	Pathogenic		N
	chr5	FGFR4	G	A	1/1	Cancer_progression_and_tumor_cell_motility	Pathogenic		N
	chr18	PIGN	C	T	0/1	Multiple_congenital_anomalies-hypotonia-seizures_syndrome_1	Pathogenic		N
	chr17	MAPK7	G	A	0/1	Scoliosis~_isolated~_susceptibility_to~_1	Pathogenic		N
	chr1	FLG|FLG-	A	AC	0/1	not_provided	Pathogenic		N
	chr2	TRAF3IP1	C	G	0/1	Jeune_thoracic_dystrophy	Pathogenic		N
	chr11	ATM|C11c	G	T	0/1	Ataxia-telangiectasia_syndrome|not_provided	Pathogenic		N
)	chr17	TLK2	G	A	0/1	not_provided	Pathogenic		N
	chr16	IL4R	A	G	0/1	Acquired_immunodeficiency_syndrome~_slow_progression_to|Atopy~_re	Pathogenic~_protecti		N
2	chr13	BRCA2	G	T	0/1	Hereditary_cancer-predisposing_syndrome|not_provided	Pathogenic/Likely_pa		N
3	chr10	PTEN	A	T	0/1	Hereditary_cancer-predisposing_syndrome|PTEN_hamartoma_tumor_syn	Likely_pathogenic		N
4	chr15	DNAAF4|D	AT	A	0/1	Primary_ciliary_dyskinesia	Likely_pathogenic		N
5	chr4	ZGRF1	C	T	0/1	Speech-language_disorder_1	Likely_pathogenic		N
6	chr6	HFE|LOC	C	G	0/1	Alzheimer_disease|Hereditary_hemochromatosis|Familial_porphyria_cutar	Conflicting	Likely_ber	N
7	chr19	CD320	ACTC	A	0/1	Methylmalonic_aciduria_due_to_transcobalamin_receptor_defect|not_spe	Conflicting	Likely_ber	N
8	chr4	KLKB1	G	A	0/1	Prekallikrein_deficiency	Conflicting	Benign(1)-	N
9	chr12	CD4	C	T	0/1	Okt4_epitope_deficiency	Conflicting	Benign(1)-	N
0	chr14	GALC	GA	G	1/1	Abnormality_of_brain_morphology|Galactosylceramide_beta-galactosidase	Conflicting	Benign(4)-	N
	chr8	GATA4	C	A	1/1	Congenital_heart_disease|not_provided	Conflicting	Pathogeni	N
2	chr1	SPTA1	C	T	1/1	Hemolytic_anemia|Hereditary_pyropoikilocytosis|Elliptocytosis_2|Spheroc	Conflicting	Benign(4)-	N
3	chr1	SPTA1	G	A	0/1	Hemolytic_anemia|Hereditary_pyropoikilocytosis|Elliptocytosis_2|Spheroc	Conflicting	Benign(1)-	N
4	chr16	ABCC6	T	C	0/1	Pseudoxanthoma_elasticum|not_specified|not_provided	Conflicting	Benign(1)-	N
5	chr8	GATA4	T	C	1/1	Congenital_heart_disease	Conflicting	Benign(1)-	N
6									

須熟悉VCF格式：一般不列出正常點

GTACCTTGATTTCGTATTCTGAGAGGCTGCTGCTTAGC
GCGCGGGAATTACAGATAAATTAAAACTGCGACTGCGC
GACAGGCTGTGGGGTTTCTCAGATAACTGGGCCCCTGC
AAGGTAGTAGAGTCCCGGGAAAGGGACAGGGGGCCCAA
GATTTCCGAAGCTGACAGATGGGTATTCTTTGACGGGG
TGTGAACCCTGGGGAGGGGGGCAGTTTGTAGGTCGCGA
AGTGTCCGTGGGGGAATCCTCGTGATAGGAACTGGAAT
CGTCGGCTGGTCATGAGGTCAGGAGTTCCAGACCAG
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ACCCGGGAGGCGGAGGTTGCAGTGAGCCGAGATCGCGC
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TGTGGAAGAAGAGGTGCCAGGAATATGTCTGGGAAGGG
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GCTGCCGGCAGGGATGTGCTTGAGGAGGATCCAGAGAT

Raw VCF (variant call format), hg38

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##SnpEffVersion="4.3b (build 2016-11-06 07:07), by Pablo Cingolani"
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##SnpSiftCmd.1="SnpSift annotate /home/cc/snpEff/data/clinvar.vcf.gz /home/cc/gatk_output/DNA15064/DNA15064_snp_ann"
##fileDate=20161204
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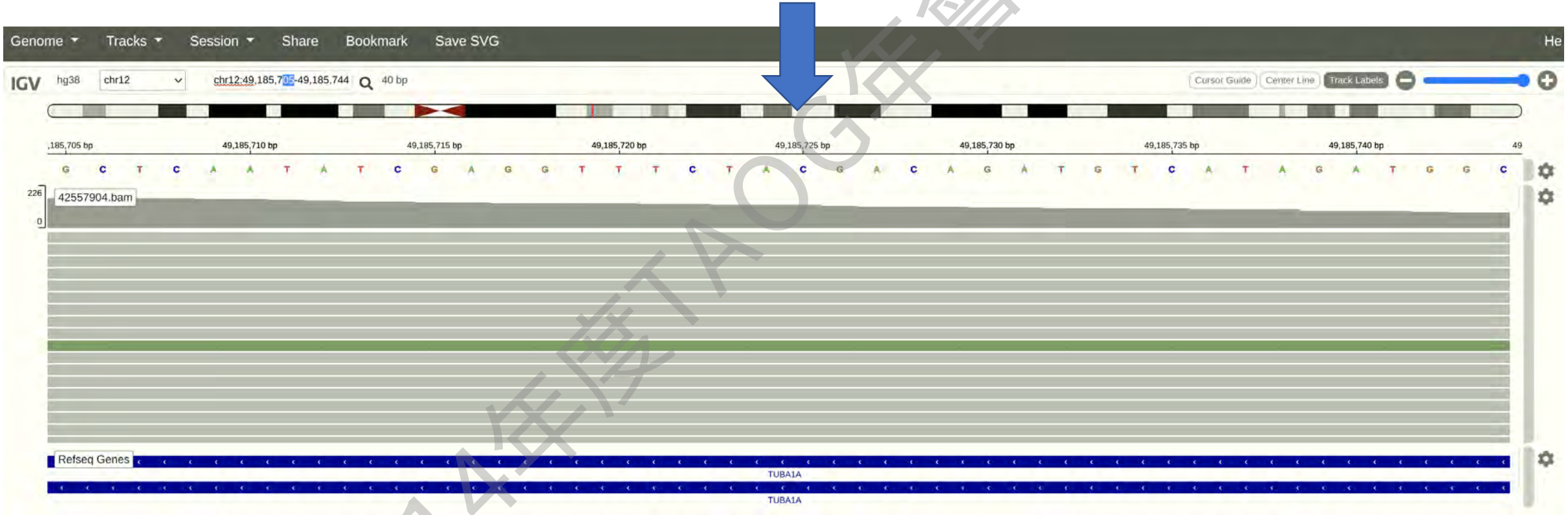
#CHROM  POS     ID      REF ALT QUAL FILTER  INFO  FORMAT  $sm
chr1    133160  rs371468694     G A 44.84 VQSRTrancheSNP99.90to100.00   .  GT:AD:DP:GQ:PL   0/1:1,3:4:18:73,0,18
chr1    777778  rs183634591     T A 40.74 PASS  GENEINFO=LOC100288069:100288069|LOC105378581:105378581 GT:AD:DP:GQ:PL   1/1:0,2:2:6:68,6,0
chr1    817341  rs3131972       A G 113.03  PASS  GENEINFO=FAM87B:400728  GT:AD:DP:GQ:PL   1/1:0,4:4:12:141,12,0
chr1    818802  rs3131969       A G 62.74 PASS  GENEINFO=FAM87B:400728  GT:AD:DP:GQ:PL   1/1:0,2:2:6:90,6,0
chr1    818812  rs3131968       A G 62.74 PASS  GENEINFO=FAM87B:400728  GT:AD:DP:GQ:PL   1/1:0,2:2:6:90,6,0
chr1    841742  rs2980319       A T 59.28 PASS  GENEINFO=LINC01128:643837 GT:AD:DP:GQ:PL   1/1:0,3:3:9:87,9,0
chr1    857100  rs2905036       C T 280.77  PASS  GENEINFO=LINC01128:643837 GT:AD:DP:GQ:PL   1/1:0,11:11:33:309,33,0
chr1    873251  rs11240779      G A 51.77 VQSRTrancheSNP99.90to100.00   GENEINFO=FAM41C:284593  GT:AD:DP:GQ:PL   0/1:3,3:6:71:80,0,71
chr1    873542  rs6594027       G A 40.74 PASS  GENEINFO=FAM41C:284593  GT:AD:DP:GQ:PL   1/1:0,2:2:6:68,6,0
chr1    876290  rs201930939     GCCCACACTCC     G 53.7  PASS  GENEINFO=FAM41C:284593  GT:AD:DP:GQ:PL   1/1:0,2:2:6:90,6,0
chr1    877371  rs4246500       T C 78.28 PASS  GENEINFO=FAM41C:284593  GT:AD:DP:GQ:PL   1/1:0,3:3:9:106,9,0
chr1    880282  rs4970339       G T 49.74 PASS  .  GT:AD:DP:GQ:PL   1/1:0,2:2:6:77,6,0
chr1    880301  rs4970338       G T 18.59 LowQual   .  GT:AD:DP:GQ:PL   1/1:0,1:1:3:45,3,0
chr1    883265  chr1:883265_G/T  G T 38.74 PASS  .  GT:AD:DP:GQ:PL   1/1:0,2:2:6:66,6,0
chr1    905950  chr1:905950_C/T  C T 28.79 LowQual   .  GT:AD:DP:GQ:PL   0/1:1,2:3:25:57,0,25
chr1    907932  chr1:907932_C/A  C A 33.77 PASS  .  GT:AD:DP:GQ:PL   0/1:3,2:5:62:62,0,86
chr1    911109  rs4970333       T C 60.77 PASS  GENEINFO=LOC284600:284600 GT:AD:DP:GQ:PL   0/1:2,3:5:51:89,0,51
chr1    915400  rs6657440       C T 38.74 PASS  GENEINFO=LOC284600:284600 GT:AD:DP:GQ:PL   1/1:0,2:2:6:66,6,0
```

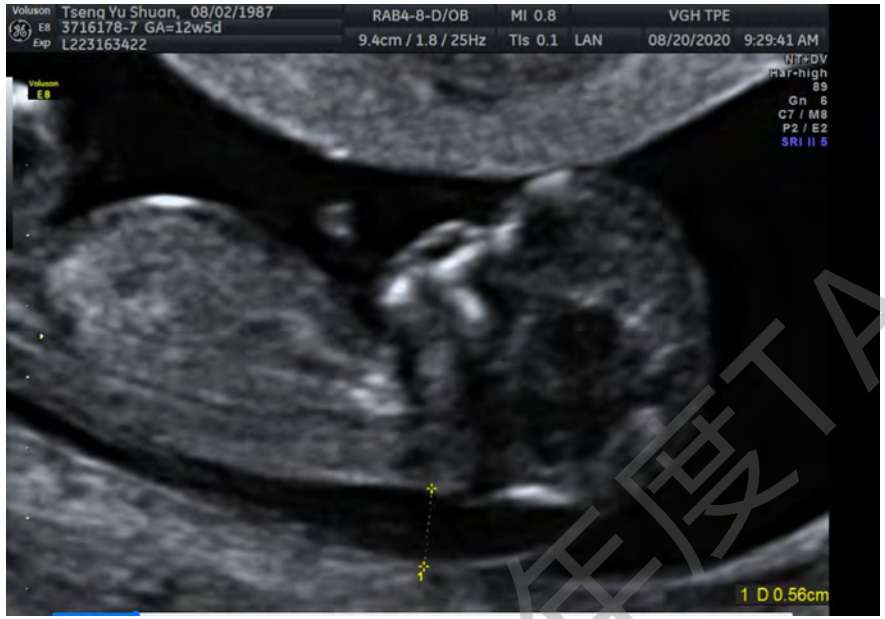
需用IGV確認
TUBA1A: NC_000012.12:g.49185725
→正常 且定序QC足夠

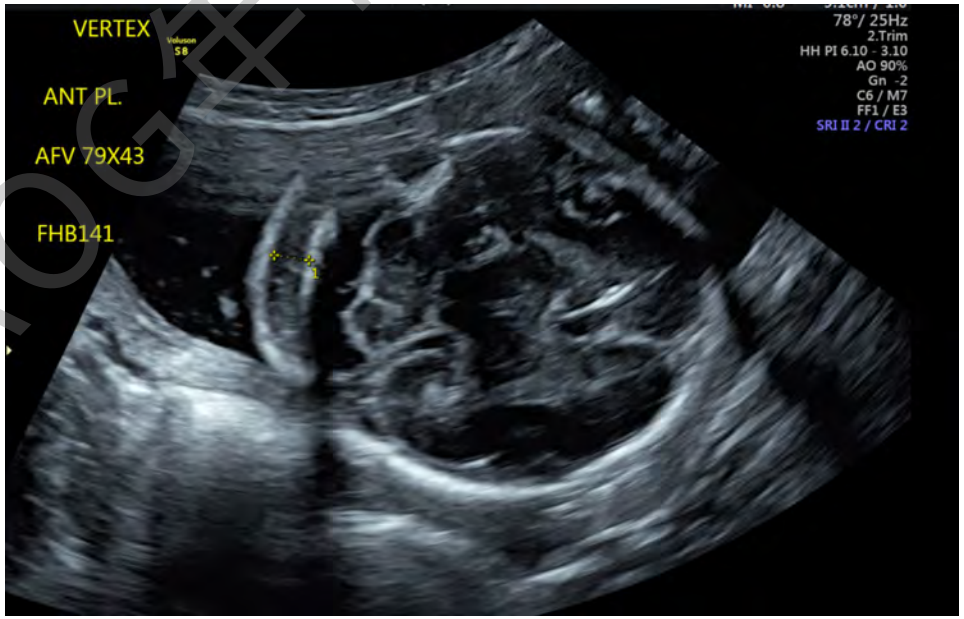


胎兒正常

案例

第二胎23周 : thickened NT (5.6mm) ;
no other abnormality,
做過羊水及SNP array, 都正常





→ 繼續懷孕?

染色體沒問題，但是基因呢？

1. 先收集資料

Ultrasound Obstet Gynecol 1998;11:391–400

Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation

A. P. Souka, R. J. M. Snijders, A. Novakov, W. Soares and K. H. Nicolaides

Table 1 Pregnancy outcome in 4116 chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation

Nuchal translucency (mm)	*Total* (*n*)	*Terminations*		*Intrauterine death*	*Postnatal death*	*Alive*
		Total	*Abnormal*			
95th centile–3.4	3423	49	36	47	29	3298 (96.3%)
3.5–4.4	448	23	14	9	4	412 (92.0%)
4.5–5.4	138	13	8	4	3	118 (85.5%)
5.5–6.4	48	13	7	4	0	31 (64.6%)
≥ 6.5	59	21	12	10	2	26 (44.4%)
Total	4116	119	77	74	38	3885 (94.4%)

初步預估異常機會　**7/13 = 54%**

2. 比對可能共病

Table 2 Fetal abnormalities and genetic syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation according to translucency thickness

	Fetal nuchal translucency thickness (mm)					*Pregnancy outcome*			
Fetal abnormality	*< 3.5*	*3.5–4.4*	*4.5–5.4*	*5.5–6.4*	*≥ 6.5*	*TOP*	*IUD*	*NND*	*Alive*
Anencephaly	4	1				5			
Encephalocele	3[1]				1	4			
Ventriculomegaly	6					5			1
Dandy–Walker cyst	1					1			
Holoprosencephaly	1					1			
Microcephaly	1								1
Facial cleft	2								2
Microphthalmia	1[7]								1
Laryngeal cyst	1								1
Cystic hygroma	1								1
Major cardiac defect	12	12	6	3	10	19	6	3	15
Diaphragmatic hernia	4	1	3	1		1		5	2
Exomphalos	2[2]	3[3,4]	1[5]	1[6]		5	1		1
Gastroschisis		1						1	
Bowel obstruction	2								2
Duodenal atresia		1							1
Hydronephrosis	2	2	1			1			4
Multicystic kidneys	4					3			1[7]
Polycystic kidneys					1	1			
Renal agenesis	1	1				1			1[7]
Megacystis	7	1				2	2		4
Spina bifida	3	1				2	1		1
Kyphoscoliosis				1		1			
Body stalk anomaly	1	3	1	1	4	10			
Diastomatomelia	1								1
Talipes	10	4	1			1			14
Akinesia deformation	2			1	3	6			
Jarcho–Levin syndrome	1		1			1		1	
Joubert syndrome	1					1			
Nance–Sweeney syndrome			1						1
Noonan syndrome					1				1
Smith–Lemli–Opitz syndrome	1		1	1		2		1	
Spinal muscular atrophy	1							1	
Thanatophoric dysplasia	1					1			
Trigonocephaly 'C'	1								1
VACTER association	2					1			1
Unspecified syndrome	3	1	1		1	2			4

3.檢查:染色體+基因

NM_006939.4(SOS2):c.791C>G (p.Thr264Arg) GRCh37:Chr14:50649248 GRCh38:Chr14:50182530	SOS2	T264R	Noonan s
NM_007373.4(SHOC2):c.807_808delinsTT (p.Gln269_His270delinsHisTyr) GRCh37:Chr10:112745489-112745490 GRCh38:Chr10:110985731-110985732	SHOC2		Noonan s anagen h
NM_005188.4(CBL):c.1096-2A>T GRCh37:Chr11:119148874 GRCh38:Chr11:119278164	CBL		Noonan s without ju
NM_002709.3(PPP1CB):c.166G>C (p.Ala56Pro) GRCh37:Chr2:28999830 GRCh38:Chr2:28776964	PPP1CB	A56P	Noonan s anagen h
CBL, IVS8AS, A-G, -2	CBL		Noonan s myelomo
NM_005188.3(CBL):c.1168G>T (p.Asp390Tyr) GRCh37:Chr11:119148948 GRCh38:Chr11:119278238	CBL	D390Y	Noonan s without ju
NM_005188.3(CBL):c.1144A>G (p.Lys382Glu) GRCh37:Chr11:119148924 GRCh38:Chr11:119278214	CBL	K382E	Noonan s without ju
NM_000267.3(NF1):c.4095_4096insTG (p.His1366fs) GRCh37:Chr17:29576122-29576123 GRCh38:Chr17:31249104-31249105	NF1	H1366fs	Neurofibr
NM_012250.6(RRAS2):c.208G>A (p.Ala70Thr) GRCh37:Chr11:14316397 GRCh38:Chr11:14294851	RRAS2	A35T, A70T	Noonan s 12
NM_004333.6(BRAF):c.741T>G (p.Phe247Leu) GRCh37:Chr7:140501331 GRCh38:Chr7:140801531	BRAF	F247L	not provic Noonan- syndrome
NM_006939.4(SOS2):c.791C>A (p.Thr264Lys) GRCh37:Chr14:50649248 GRCh38:Chr14:50182530	SOS2	T264K	Noonan s
NM_012250.6(RRAS2):c.70_78dup (p.Gly24_Gly26dup) GRCh37:Chr11:14380338-14380339 GRCh38:Chr11:14358792-14358793	RRAS2		Noonan s 12
NM_002834.5(PTPN11):c.1471C>G (p.Pro491Ala) GRCh37:Chr12:112926851 GRCh38:Chr12:112489047	PTPN11	P491A, P495A, P490A	Noonan s syndrome
NM_005188.3(CBL):c.1096-4_1096-1del GRCh37:Chr11:119148872-119148875 GRCh38:Chr11:119278162-119278165	CBL		Rasopath with or wi leukemia,
NM_004859.4(CLTC):c.1912_1916delinsAGA (p.Ala639fs) GRCh37:Chr17:57743970-57743974 GRCh38:Chr17:59666609-59666613	CLTC	A639fs, A643fs	Noonan s
NM_006767.4(LZTR1):c.1785+1G>C GRCh37:Chr22:21349017 GRCh38:Chr22:20994728	LZTR1		Noonan s

Noonan syndrome 相關基因

SOS2, SHOC2, CBL, PPP1CB, NF1, RRAS2, BRAF, PTPN11, CLTC, LZTR1, MRAS, RAF1, RIT1, KRAS, NRAS, MAP2K1, SOS1, MAPK1, GJB2, CDC42, MAP2K2, HRAS|LRRC56, , DYNC2H1, DYNLT2B, NEK1, IGFBP7, SHOC2|SMC3|PDCD4|BBIP1|RBM20|PDCD4-AS1|MIR548E|MIR4680|LOC111875823|LOC116216121, SPRED1, SLC7A9, ARVCF|COMT|CRKL|GP1BB|GSC2|SERPIND1|PI4KA|SEPTIN5|PRODH|RANBP1|SLC7A4|SLC25A1|TBX1|CLDN5|HIRA|UFD1|ZNF74|DGCR6|LZTR1|CLTCL1|ESS2|CDC45|P2RX6|SNAP29|DGCR2|TXNRD2|TSSK2|DGCR11|DGCR9|DGCR5|DGCR10|TRMT2A|ZDHHC8|MED15|DGCR8|GNB1L|MRPL40|RTN4R|RTL10|THAP7|KLHL22|DGCR6L|RIMBP3|SCARF2|C22orf39|TANGO2|LINC00895|LINC00896|AIFM3|LINC02891|USP41|CCDC188|LRRC74B|MIR185|THAP7-AS1|FAM230E|FAM230A|MIR649|GGTLC3|TMEM191B|FAM230J|MIR1286|MIR1306|MIR3618|SEPT5-GP1BB|MIR4761|LINC01311|FAM230F|FAM230G|LINC01637|MIR6816|HSERVPRODH|LOC108510655|SNORA77B|LOC110120888|LOC110121413|LOC112694764|LOC112694766|LOC112694767|LOC114004361|LOC116309126|LOC116309127"

4.分析及諮詢

Fetal WES：無NT異常相關基因

Gene	Ref	Alt	Filter	Quality	DP	Inheritance	Genotype	Zygosity	Phenotype	ClinicSign	Significar
TAB2|SUM	G	A	.~LowGQ)	1969~377	141~147~	149	0/1	heterozygc	Diabetes_mellitus~_insulin-dependent~_5	Pathogenic	
SOX10|PC	T	G	LowGQX;M	0	6		0/1	heterozygc	Waardenburg_syndrome_type_2E~_with_neurologic_ir	Pathogenic	
IRGM	C	T	LowGQX;M	134~640~	47~46~48		0/1	heterozygc	Inflammatory_bowel_disease_19	Pathogenic	
AR	C	A	LowGQX;M	0	6		0/1	heterozygc	not_provided	Pathogenic	
PRKCQ	G	A	.~LowGQ)	250~39~6	45~46~50	Heterogeneous|M	0|1		Inflammatory_bowel_disease_1	Pathogenic	
IL4R	A	G	PASS~Lo	53~123~3	13~12~11	NA	1/1	homozygo	Acquired_immunodeficiency_syndrome~_slow_progres	Pathogenic~_protecti	
AEBP1	C	A	LowGQX;M	0	7	Autosomal_reces	0/1	heterozygc	EHLERS-DANLOS_SYNDROME~_CLASSIC-LIKE~_2	Likely_pathogenic	
MYBPC3	C	A	LowGQX;M	0	4		0/1	heterozygc	not_provided	Likely_pathogenic	
TTN|TTN-A	C	A	LowGQX;M	0	10	Autosomal_domi	0/1	heterozygc	Familial_hypertrophic_cardiomyopathy_9	Likely_pathogenic	
FECH	A	G	.~PASS~F	3193~100	94~94~97	.	1/1	homozygo	Jaundice|Erythema|Increased_urinary_porphobilinogen|	Conflicting	Likely_patl
MEFV	C	G	.~LowGQ)	221~57~2	24~24~24	.	0/1	heterozygc	Familial_mediterranean_fever~_autosomal_dominant|Fa	Conflicting	Benign(3)-
MEFV	G	A	LowGQX;M	103~388~	32~32~32	.	0/1	heterozygc	Familial_Mediterranean_fever|not_specified|not_provide	Conflicting	Benign(1)-
MEFV	C	T	.~LowGQ)	483~106~	40~39~40	.	0/1	heterozygc	Familial_Mediterranean_fever|not_specified|not_provide	Conflicting	Benign(1)-
KLKB1	G	A	.~LowGQ)	2462~402	200~203~	.	0/1	heterozygc	Prekallikrein_deficiency	Conflicting	Benign(1)-
GALC	GA	G	PASS~.	67~5195	230~206	.	1/1	homozygo	Abnormality_of_brain_morphology|Galactosylceramide_	Conflicting	Benign(4)-
GATA4	C	A	PASS~.~F	665~2034	67~67~67	.	1/1	homozygo	Congenital_heart_disease|not_provided	Conflicting	Pathogeni
CYP21A2|	C	A	PASS~.~F	1135~399	116~119~	.	1/1	homozygo	Classic_congenital_adrenal_hyperplasia_due_to_21-hy	Conflicting	Benign(2)-
PIBF1	G	A	.~LowGQ)	1001~128	112~111~	AR	0/1	heterozygc	Joubert_syndrome|JOUBERT_SYNDROME_33|not_sp	Conflicting	Likely_patl
PCCA	G	T	LowGQX;M	474~3202	263~265~	AR	0/1	heterozygc	Propionic_acidemia|not_specified	Conflicting	Benign(3)-
OTOA	G	T	.	544	272	.	0|1		Deafness~_autosomal_recessive_22|not_specified|Rare	Conflicting	Likely_patl
NPHS1	G	A	.~LowGQ)	687~97~0	88~91~92	AR	0/1	heterozygc	Finnish_congenital_nephrotic_syndrome|Hereditary_ne	Conflicting	Benign(1)-
MYH2|MYI	A	G	.~LowGQ)	2507~403	182~183~	.	0/1	heterozygc	Myopathy~_proximal~_and_ophthalmoplegia|not_specif	Conflicting	Benign(2)-
SPTA1	C	T	.~PASS~F	7252~228	217~219~	.	1/1	homozygo	Hemolytic_anemia|Hereditary_pyropoikilocytosis|Elliptoc	Conflicting	Benign(4)-
TTN	C	A	LowGQX;M	0	10	.	0/1	heterozygc	Dilated_cardiomyopathy_1G|not_provided	Conflicting	Likely_patl
GATA4	T	C	.~LowGQ)	261~94~3	8~10~10	.	1/1	homozygo	Congenital_heart_disease	Conflicting	Benign(1)-
IER3IP1	A	G	.~LowGQ)	1379~221	111~113~	.	0/1	heterozygc	Epilepsy|Rolandic_epilepsy	Conflicting	Likely_ben
DUOX2	C	A	.~LowGQ)	1936~330	166~167~	.	0/1	heterozygc	Nongoitrous_Euthyroid_Hyperthyrotropinemia|Thyroid_(	Conflicting	Likely_ben
UGT1A|UC	C	A	LowGQX;M	162~1115	121~119~	.	0/1	heterozygc	Crigler-Najjar_syndrome~_type_II|Gilbert's_syndrome|n	Conflicting	Benign(2)-
UGT1A|UC	C	CAT	.~RefCall	149~0	17~23	.	0/1	heterozygc	Lucey-Driscoll_syndrome|Crigler-Najjar_syndrome~_typ	Conflicting	Benign(2)-
ACTN3	C	T	LowGQX;M	213~487~	20~17~21	.	1/1	homozygo	ACTININ~_ALPHA-3_POLYMORPHISM|ACTN3_defici	Conflicting	Benign(1)-

4.分析及諮詢

Mother WES：無特別異常基因

Gene	Ref	Alt	Filter	Quality	DP	Inheritance	Genotype	Zygosity	Phenotype	ClinicSigr	Significar	HGVS
GHRL|GH	G	T	LowGQX;I	293~1506	104~106~	108	0/1	heterozygc	Metabolic_syndrome~_susceptibility_to|Obesity~_age_at_ons	Pathogenic~_risk_fac		NC_0000
PLA2G7	**C**	**A**	**LowGQX;**	**788~4848**	**379~376~**	**Autosomal_rec**	**0/1**	**heterozyg**	**Platelet-activating_factor_acetylhydrolase_deficiency**	**Pathogenic~_risk_f**		**NC_0000**
IL4R	**A**	**G**	**.~LowGQ**	**925~315~**	**27~27~27**		**1|1**		**Acquired_immunodeficiency_syndrome~_slow_progress**	**Pathogenic~_protec**		**NC_0000**
PTEN	A	T	.~RefCall	130~0	252~307		0/1	heterozygc	Cowden_syndrome_1|Hereditary_cancer-predisposing_syndrc	Pathogenic		NC_0000
GATA6	G	T	LowGQX;I	0	6	Multifactorial_inl	0/1	heterozygc	Congenital_diaphragmatic_hernia|Abnormality_of_cardiovascu	Pathogenic		NC_0000
ABCD1	G	A	LowGQX;I	0	4	X-linked_recess	0/1	heterozygc	Adrenoleukodystrophy	Pathogenic		NC_0000
PRKCQ	G	A	.~LowGQ)	640~144~	60~65~66	Heterogeneous|	0/1	heterozygc	Inflammatory_bowel_disease_1	Pathogenic		NC_0000
FOXL2	G	T	LowGQX;I	1	3	Autosomal_dom	0/1	heterozygc	Blepharophimosis~_ptosis~_and_epicanthus_inversus	Pathogenic		NC_0000
COL2A1	C	T	LowGQX;I	0	8	Autosomal_rece	0/1	heterozygc	Stargardt_disease	Pathogenic		NC_0000
TULP1	A	C	.~RefCall	80~0	63~76	AR	0/1	heterozygc	Retinal_atrophy|Seizures|Dysarthria|Spastic_tetraparesis|Dysp	Pathogenic/Likely_pa		NC_0000
TTN|TTN-A	G	A	LowGQX;I	0	6	Autosomal_dom	0/1	heterozygc	Dilated_cardiomyopathy_1G|Limb-girdle_muscular_dystrophy	Likely_pathogenic		NC_0000
SCN5A	C	A	LowGQX;I	0	9	Autosomal_dom	0/1	heterozygc	Brugada_syndrome	Likely_pathogenic		NC_0000
MESP2	G	T	LowGQX;I	0	5	AR	0/1	heterozygc	not_provided	Likely_pathogenic		NC_0000
FECH	A	G	.~LowGQ)	1730~332	127~128~	.	0/1	heterozygc	Jaundice|Erythema|Increased_urinary_porphobilinogen|Autosc	Conflicting	Likely_pat	NC_0000
MEFV	C	G	.~LowGQ)	261~76~5	15~20~20	.	0/1	heterozygc	Familial_mediterranean_fever~_autosomal_dominant|Familial_	Conflicting	Benign(3)~	NC_0000
MEFV	G	A	LowGQX;I	99~438~5	38~37~38	.	0/1	heterozygc	Familial_Mediterranean_fever|not_specified|not_provided	Conflicting	Benign(1)~	NC_0000
MEFV	C	T	LowGQX;I	69~399~4	53~50~54	.	0/1	heterozygc	Familial_Mediterranean_fever|not_specified|not_provided	Conflicting	Benign(1)~	NC_0000
KLKB1	G	A	.~LowGQ)	3346~488	280~281~	.	0/1	heterozygc	Prekallikrein_deficiency	Conflicting	Benign(1)~	NC_0000
UGT1A|UC	T	G	LowDepth;	3	1	AR	0/1	heterozygc	Gilbert's_syndrome|Gilbert_syndrome~_susceptibility_to|not_s	Conflicting	Benign(1)~	NC_0000
AMPD1	C	T	.~LowGQ)	1147~221	86~88~89	AR	0/1	heterozygc	Muscle_AMP_deaminase_deficiency|not_provided	Conflicting	Likely_pat	NC_0000
PRSS1|TR	C	T	PASS~.	12~864	161~164	.	0/1	heterozygc	Recurrent_pancreatitis|Hereditary_pancreatitis|not_specified	Conflicting	Likely_ben	NC_0000
GALC	GA	G	.~PASS	7156~66	276~324	.	1/1	homozygo	Abnormality_of_brain_morphology|Galactosylceramide_beta-g	Conflicting	Benign(4)~	NC_0000
GATA4	C	A	PASS~.~F	1280~395	129~125~	.	1/1	homozygo	Congenital_heart_disease|not_provided	Conflicting	Pathogeni	NC_0000
CYP21A2|	C	A	PASS~.~F	1758~622	173~177~	.	1/1	homozygo	Classic_congenital_adrenal_hyperplasia_due_to_21-hydroxyl	Conflicting	Benign(2)~	NC_0000
PIBF1	G	A	.~LowGQ)	1410~255	113~114~	.	0/1	heterozygc	Joubert_syndrome|JOUBERT_SYNDROME_33|not_specified	Conflicting	Likely_pat	NC_0000
MYH2|MYI	A	G	.~LowGQ)	4091~692	278~272~	.	0/1	heterozygc	Myopathy~_proximal~_and_ophthalmoplegia|not_specified	Conflicting	Benign(2)~	NC_0000
SPTA1	C	T	.~LowGQ)	2433~269	254~257~	.	0/1	heterozygc	Hemolytic_anemia|Hereditary_pyropoikilocytosis|Elliptocytosis_	Conflicting	Benign(4)~	NC_0000
GATA4	T	C	PASS~Lo\	54~188~6	20~18~18	.	1/1	homozygo	Congenital_heart_disease	Conflicting	Benign(1)~	NC_0000
IER3IP1	A	G	.~LowGQ)	1539~246	130~130~	.	0/1	heterozygc	Epilepsy|Rolandic_epilepsy	Conflicting	Likely_ben	NC_0000
UGT1A|UC	C	A	LowGQX;I	253~1884	188~190~	.	0/1	heterozygc	Crigler-Najjar_syndrome~_type_II|Gilbert's_syndrome|not_spe	Conflicting	Benign(2)~	NC_0000
UGT1A|UC	C	CAT	.~RefCall	491~0	39~45	.	0/1	heterozygc	Lucey-Driscoll_syndrome|Crigler-Najjar_syndrome~_type_II|Gi	Conflicting	Benign(2)~	NC_0000
ACTN3	C	T	.~LowGQ)	222~54~5	26~28~28	.	0/1	heterozygc	ACTININ~_ALPHA-3_POLYMORPHISM|ACTN3_deficiency|S	Conflicting	Benign(1)~	NC_0000

4.分析及諮詢

Father WES : SDHA, C9異常

Gene	Ref	Alt	Filter	Quality	DP	Inheritance	Genotype	Zygosity	Phenotype	ClinicSigr	Significar	H
SLC6A19	G	A	LowGQX;I	299~56~1	121~128~	Autosomal_dom	0/1	heterozygo	Hyperglycinuria|Iminoglycinuria~_digenic	Pathogenic		N
TAB2|SUM	G	A	PASS~.~F	2065~660	198~199~202		1/1	homozygo	Diabetes_mellitus~_insulin-dependent~_5	Pathogenic		N
WFS1	C	T	LowGQX;I	0	10	Autosomal_rece	0/1	heterozygo	Diabetes_mellitus_AND_insipidus_with_optic_atrophy_AND_deafness	Pathogenic		N
PTPRJ	A	C	LowGQX;I	246~1325	105~99~1	Autosomal_dom	0/1	heterozygo	Carcinoma_of_colon	Pathogenic		N
GJB2	C	T	LowGQX;I	112~598~	43~43~44		0/1	heterozygo	Hearing_impairment|Mutilating_keratoderma|Keratitis-ichthyosis-deafness_syndi	Pathogenic		N
C9	**G**	**A**	**.~LowGQ**	**4724~763**	**367~367~**	**?**	**0/1**	**heterozyg**	**Complement_component_9_deficiency**	**Pathogenic**		**N**
IRGM	C	T	.~LowGQX	965~173~	72~72~74		0/1	heterozygo	Inflammatory_bowel_disease_19	Pathogenic		N
EEF2	G	T	LowGQX;I	0	5	Autosomal_dom	0/1	heterozygo	Spinocerebellar_ataxia_type_26	Pathogenic		N
SDHA	**C**	**T**	**.~LowGQ**	**3921~612**	**322~319~**	**AR/ AD/ Multifa**	**0/1**	**heterozyg**	**Rhabdomyosarcoma_(disease)|Mitochondrial_complex_II_deficiency|Leig**	**Pathogenic**		**N**
TTN	C	T	LowGQX;I	0	10		0/1	heterozygo	Noncompaction_cardiomyopathy	Pathogenic		N
PKD1|LOC	G	T	LowDepth;	1	2		0/1	heterozygo	Polycystic_kidney_disease~_adult_type	Pathogenic		N
IL4R	A	G	.~LowGQX	522~214~	16~17~17		1/1	homozygo	Acquired_immunodeficiency_syndrome~_slow_progression_to|Atopy~_resistan	Pathogenic~_protecti		N
VEGFA	G	GGACA	.~PASS	438~59	27~39		0/1	heterozygo	not_provided	Likely_pathogenic		N
LOXHD1	C	T	LowGQX;I	75~47~57	48~50~47	Autosomal_rece	0/1	heterozygo	Deafness~_autosomal_recessive_77	Likely_pathogenic		N
FECH	A	G	LowGQX;I	340~37~1	142~142~	.	0/1	heterozygo	Jaundice|Erythema|Increased_urinary_porphobilinogen|Autosomal_erythropoieti	Conflicting	Likely_patl	N
KLKB1	G	A	.~PASS~F	9392~289	278~280~	.	1/1	homozygo	Prekallikrein_deficiency	Conflicting	Benign(1)-	N
GALC	GA	G	PASS~.	70~6482	299~251	.	1/1	homozygo	Abnormality_of_brain_morphology|Galactosylceramide_beta-galactosidase_defi	Conflicting	Benign(4)-	N
GATA4	C	A	PASS~.~F	1688~546	162~161~	.	1/1	homozygo	Congenital_heart_disease|not_provided	Conflicting	Pathogeni	N
SHOX	G	C	LowDepth;	3	1	.	0/1	heterozygo	Short_stature~_idiopathic~_X-linked	Conflicting	Benign(1)-	N
CYP21A2|	C	A	.~PASS~F	8368~238	250~243~	.	1/1	homozygo	Classic_congenital_adrenal_hyperplasia_due_to_21-hydroxylase_deficiency|not	Conflicting	Benign(2)-	N
PCCA	G	T	LowGQX;I	825~4962	357~357~	.	0/1	heterozygo	Propionic_acidemia|not_specified	Conflicting	Benign(3)-	N
NPHS1	G	A	.~LowGQX	1252~202	113~110~	.	0/1	heterozygo	Finnish_congenital_nephrotic_syndrome|Hereditary_nephrotic_syndrome|not_pi	Conflicting	Benign(1)-	N
SPTA1	C	T	.~LowGQX	2902~456	234~238~	.	0/1	heterozygo	Hemolytic_anemia|Hereditary_pyropoikilocytosis|Elliptocytosis_2|Spherocytosis_	Conflicting	Benign(4)-	N
GATA4	T	C	.~LowGQX	1302~384	39~39~40	.	1/1	homozygo	Congenital_heart_disease	Conflicting	Benign(1)-	N
DUOX2	C	A	.~LowGQX	3772~625	292~290~	.	0/1	heterozygo	Nongoitrous_Euthyroid_Hyperthyrotropinemia|Thyroid_dyshormonogenesis_6|nc	Conflicting	Likely_ben	N
ACTN3	C	T	.~LowGQX	1291~435	39~39~39	.	1/1	homozygo	ACTININ~_ALPHA-3_POLYMORPHISM|ACTN3_deficiency|Sprinting_performa	Conflicting	Benign(1)-	N

胎兒uncertain significance (VUS) 中有一可能與Noonan syn 有關基因

SEC63	0/1	TA	T	.	33	138	.	Uncertain_significanc	Polycystic_liver_disease_1	2/90
SRD5A3|S	0/1	G	T	LowDepth	3	1	.	Uncertain_significanc	Congenital_disorder_of_glycosylation_type_1Q	0/90
TRDN	0/1	TA	T	.~RefCall	36~0	27~36	.	Uncertain_significanc	Catecholaminergic_polymorphic_ventricular_tachycardia	7/90
SEC63	1/2	C	A, CAA	.	1052	45	.	Uncertain_significanc	Polycystic_liver_disease_1	6/90
BRAF	**1/1**	**G**	**GA**	**.~PASS**	**2650~56**	**77~210**	**.**	**Uncertain_significa**	**Noonan_syndrome_with_multiple_lentigines|Cardio-facio-cu**	**40/90**
DNAJB6	0/1	G	A	PASS	0	3	.	Uncertain_significanc	Limb-girdle_muscular_dystrophy~_type_1E|Limb-Girdle_Muscula	0/90
ADAMTSL	0|1	C	G	LowGQX;M	143~870~	89~88~90	.	Uncertain_significanc	Geleophysic_dysplasia_1	13/90
PKHD1	0/1	TA	T	.~RefCall	506~0	143~195	.	Uncertain_significanc	Autosomal_recessive_polycystic_kidney_disease	1/90

但母親也有相同變異, 所以可排除

1	PALLD	0/1	G	A	LowGQX;M	167~996~(	87~90~91	.	Uncertain_significanc	Pancreatic_cancer_1	0/89
1	MANBA	0/1	C	T	LowGQX;M	0	4	.	Uncertain_significanc	Beta-D-mannosidosis	0/89
2	SEC63	0/1	TA	T	.	121	161	.	Uncertain_significanc	Polycystic_liver_disease_1	1/89
1	EYA4|TAR	0/1	C	T	LowGQX;M	0	8	.	Uncertain_significanc	Deafness~_autosomal_dominant_10|Dilated_cardiom	0/89
2	PAX4	0/1	TA	T	.	52	46	.	Uncertain_significanc	Maturity_onset_diabetes_mellitus_in_young	3/89
1	**BRAF**	**1/1**	**G**	**GA**	**.~PASS**	**2527~58**	**96~259**	**.**	**Uncertain_significa**	**Noonan_syndrome_with_multiple_lentigines|Card**	**39/89**
1	ADAMTSL	0/1	C	G	LowGQX;M	319~1649~	119~119~	.	Uncertain_significanc	Geleophysic_dysplasia_1	1/89
2	VPS13A	0/1	AT	A	.~RefCall	633~0	188~270	.	Uncertain_significanc	Choreoacanthocytosis	23/89
1	ESCO2	0/1	T	TAATA	.~PASS	1837~50	66~78	.	Uncertain_significanc	Roberts-SC_phocomelia_syndrome	29/89

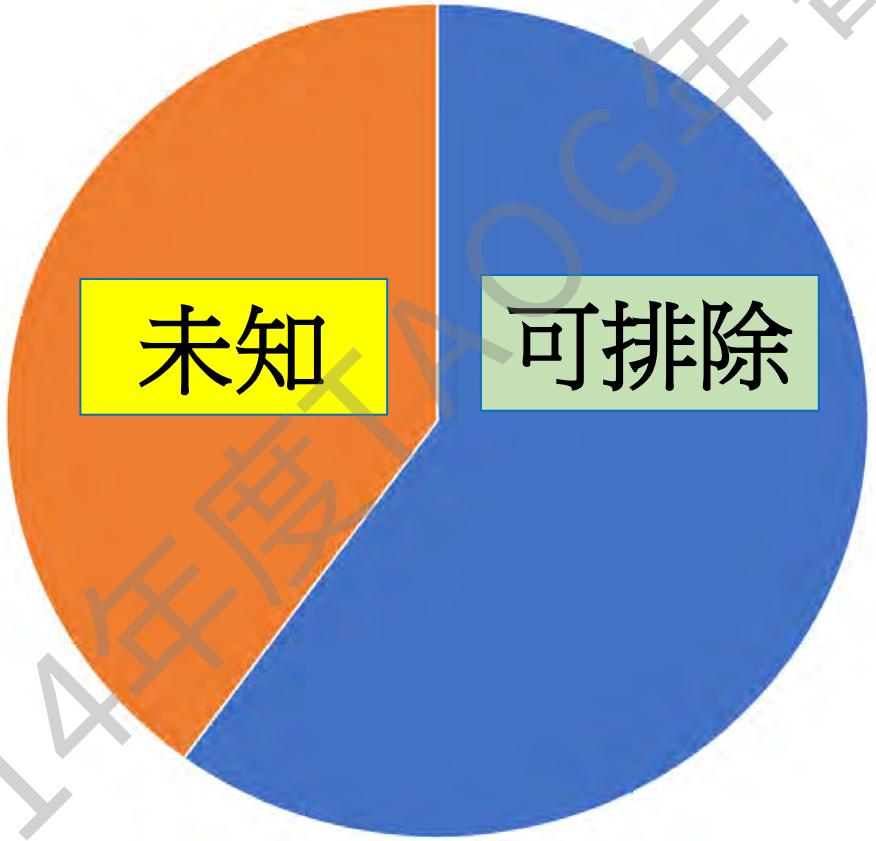
Trio WES可提供快速且更穩當分析

出生後兒科醫師檢查無異常

總結

產前診斷無法做到100%
→只能用排除法

後天因素
環境
飲食
心理
基因表現
Penetrance
Expressivity



Ultrasound
Amniocentesis
Array CGH
Single gene tests
2nd WES
3rd WGS

重要考量點及原則

- 了解檢測的限制
- 能為帶來受檢者益處
- 兼具廣度及深度，完整及精確
- 保持客觀 : 勿預設立場, 勿過度解讀
- 盡可能做到上限 : 區分是否為基因或非基因異常
- 說明全基因檢測結果，要顧及父母心理層面，區分是單基因或多因素疾病
- 產前檢測僅能用排除法，一般無法做到百分百確認
- 產前基因檢測不確定性高，證據力很重要，要說明清楚
- 讓病人知道檢測限制, 及結果失誤的可能性，以後有更新及再次修正說明之必要