Isolated congenital heart defects:
Genetics

MaNaMa Clinical Genetics

February 11, 2025

UNIVERSITEIT GENT

No disclosures

fwo Research Foundation Flanders Opening new horizons

FILANTROPISCH CENTRUM PELICANO

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Overview

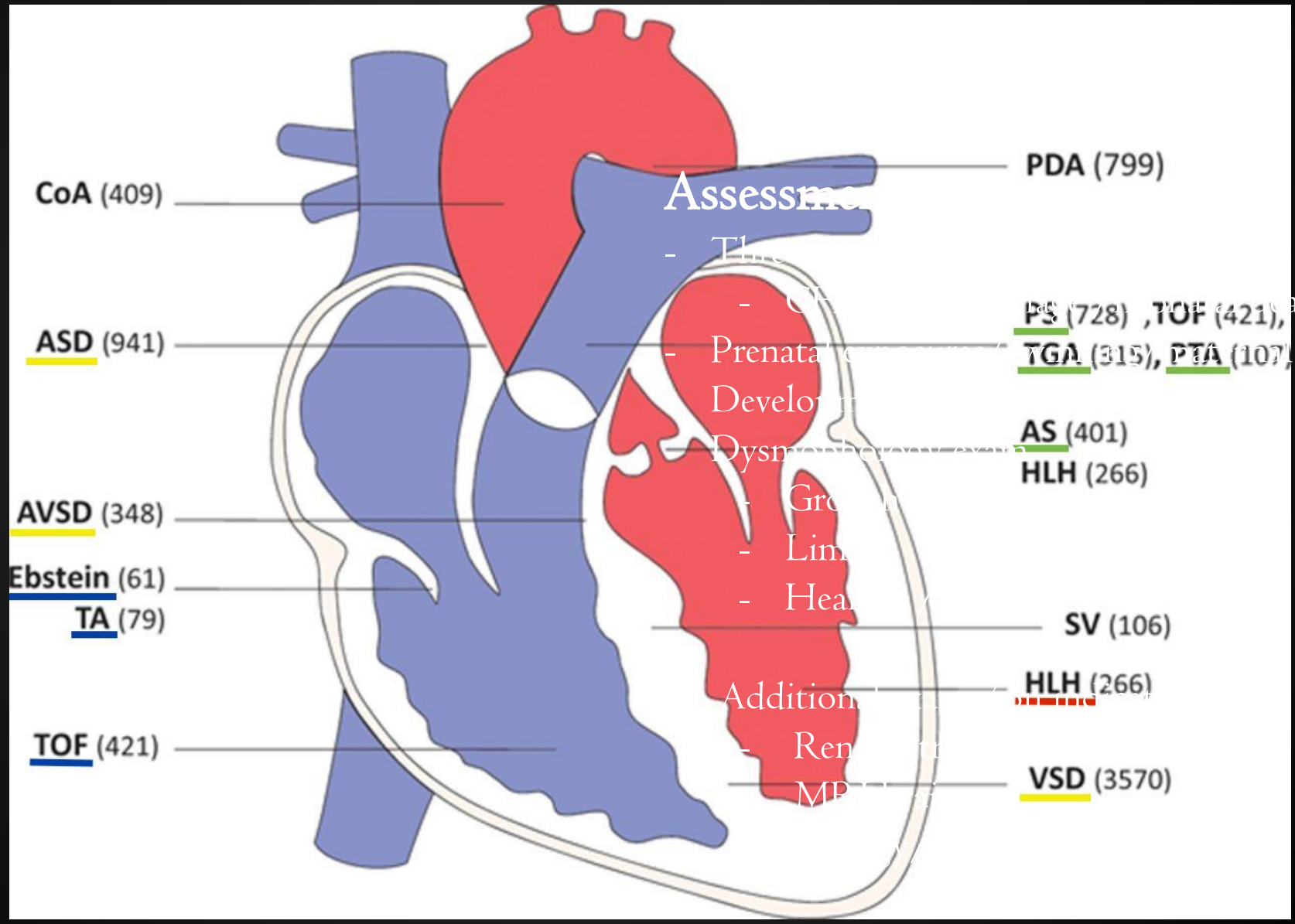
- Introduction
- Syndromic versus non-syndromic
- Environmental causes
- ‘Monogenic’ - ‘oligogenic’ - ‘multifactorial’
- Linking genes and environment
- Ghent/Utrecht/Groningen experience

Introduction

Congenital structural heart defects:

- May or may not require intervention
- Early or late(r)-onset presentation
- Minor defects are not uncommon (PFO, ASD, BAV)
- Require life-long follow-up due to secondary complications (valvular dysfunction, arrythmias, cardiomyopathy, liver function…)

Introduction



Assessm

- Th
- C
- Prenata
- Develo
- Dysm
- Gro
- Lim
- Hea

Addition

- Ren
- MR

ath
illness

/1000 000

SYNDROMIC VERSUS NON-SYNDROMIC CHD

Syndromic heart defects:

- CHD +

  ≥ I major anomaly

  or

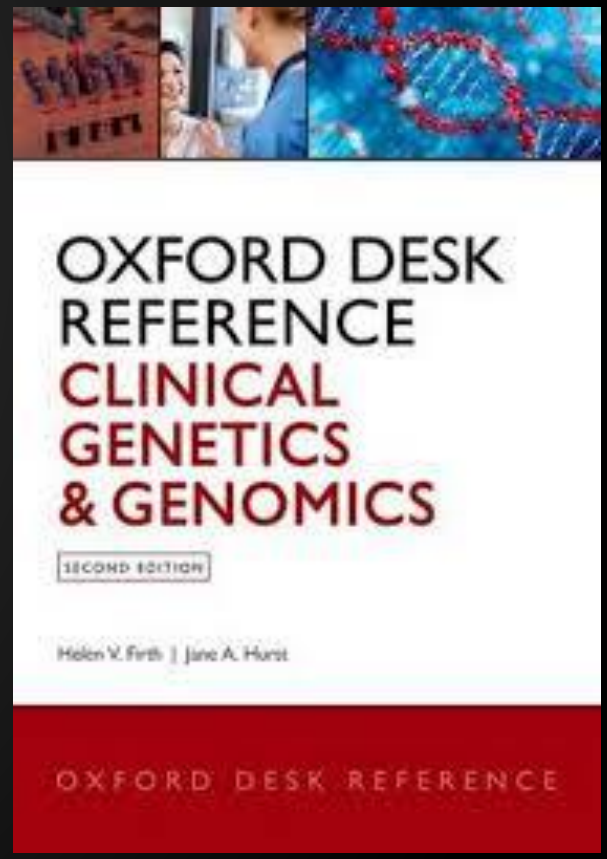
  ≥ 3 minor anomalies

Syndrome:

Disorder characterized by the variable occurence of **several anomalies**, often congenital and resulting from a **single cause** (genetically or environmentally) determined

SYNDROMIC VERSUS NON-SYNDROMIC CHD

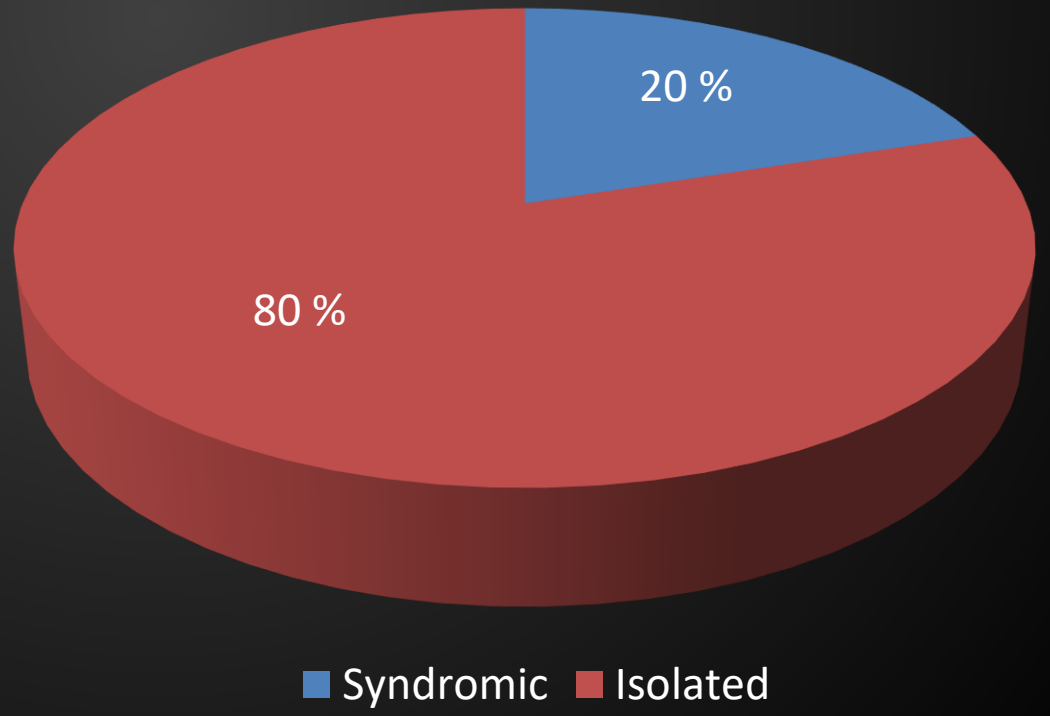
- How to determine whether it is syndromic or not?
  - Statistics:
    - chance to have major malformation A (eg CHD) = 8/1000
    - chance to have major malformation B (eg CP) = 8/1000
    - Incidence by chance = 64/1 000 000 (CP and CHD)
    - Real incidence: 1/5000
  - Experience



SYNDROMIC VERSUS NON-SYNDROMIC CHD

The most common congenital anomaly
Prevalence 8/1000 live births.

aneuploidy
copy number variations
monogenic disorders
environmental teratogens
unknown



SYNDROMIC VERSUS NON-SYNDROMIC CHD

copy number variations
monogenic disorders
environmental teratogens

Sporadic
does not mean
Non-Mendelian

Largely unknown

Genetic heterogeneity

Incomplete penetrance

Polygenic

Somatic variaton

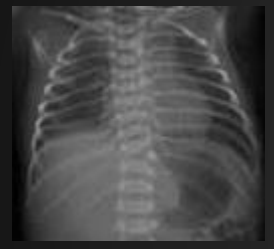
Epigenetics

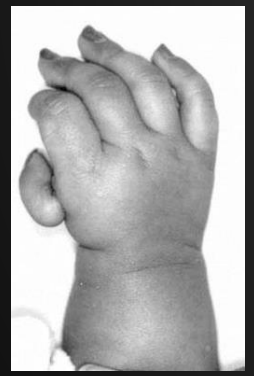
Multifactorial

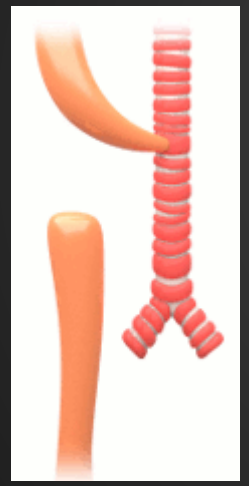
Nongenetic factors

SYNDROMIC VERSUS NON-SYNDROMIC CHD

Vertebra
Anal
Cardiac
Tracheo-
Esophageal
Renal
Limbs







http://www.nature.com/naturegenetics

Mutations in a new member of the chromodomain gene family cause CHARGE syndrome

Lisenka E L M Vissers[1], Conny M A van Ravenswaaij[1], Ronald Admiraal[2], Jane A Hurst[3], Bert B A de Vries[1], Irene M Janssen[1], Walter A van der Vliet[1], Erik H L P G Huys[1], Pieter J de Jong[4], Ben C J Hamel[1], Eric F P M Schoenmakers[1], Han G Brunner[1], Joris A Veltman[1] & Ad Geurts van Kessel[1]

THE 'SYNDROMIC' SPECTRUM

(Nearly) isolated

Full spectrum

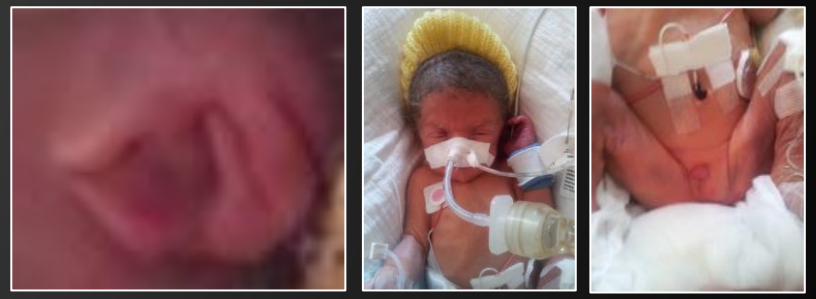
L p25 → p3, OFC p10

A. Pulmonalis stenosis, VSD

Hearing loss (SOM)

Borderline NMD, normal education

CHD7
c.6955C>T; p.Arg2319Cys dn



30ww (T2) 1228g

Choioretinal coloboma

Aortic valve hypoplasia, CoA

Hypoplasia external genitalia

Facialis paralysis

Esophageal atresia

CHD7
c.5428C>T; p.Arg1810* dn

Environmental causes of (S)CHD

Teratogen	Associated risk	Defect
Alcohol	Up to 30%	VSD, ASD, TOF
Anticonvulsants	1.8%	
Lithium	Small	Ebstein, TA, ASD
Retinoic acid	10-20%	Conotruncal
Rubella	35%	PDA, PPAS, Septal defects

Fetal alcohol syndrome

- IUGR / Low W for H
- Facial features

Fetal alcohol syndrome

- IUGR / Low W for H
- Facial features
- CNS abnormalities
  - Microcephaly
  - Structural (CCA, Cerebellar hypoplasia)
  - Impaired motor skills (coordination, gait, fine motor skills)
- Behavioural
- Confirmed exposure

Fetal alcohol syndrome

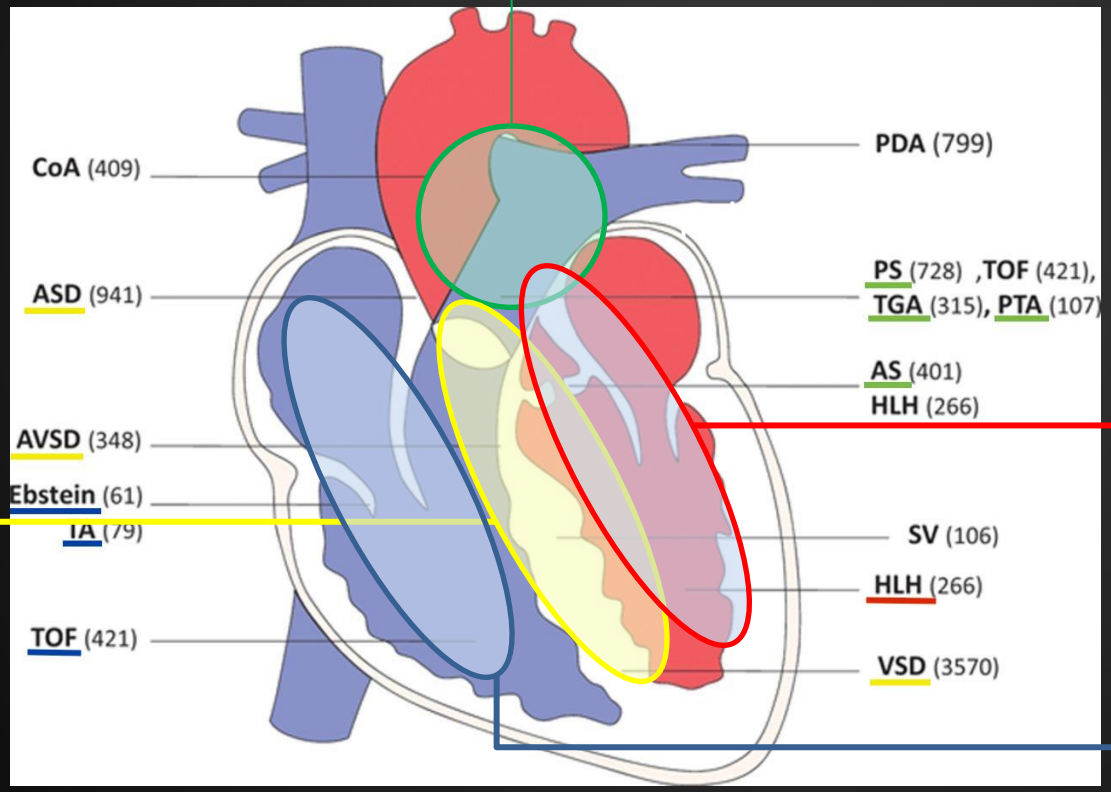
Environmental causes of CHD

Maternal condition	Associated risk	Defect
Diabetes	3-5%	VSD, coA, TGA, conotruncal, L-isomerism, CMP
Phenylketonuria	15%	TOF, CoA
SLE	20-40%	AV block

'MONOGENIC' CAUSES OF CHD

Adapted from Morton et al,
Nature reviews cardiology 2021

Conotruncal
TBX1, CHD7, GJA5, CHD1L, NOTCH1,
ZFPM2, GATA4, GATA6, VEGF pathway



Septal
NKX2-5, GATA4,
TBX5

Left-sided obstruction
GATA5, NOTCH1, ROBO4, SMAD6, MYH6

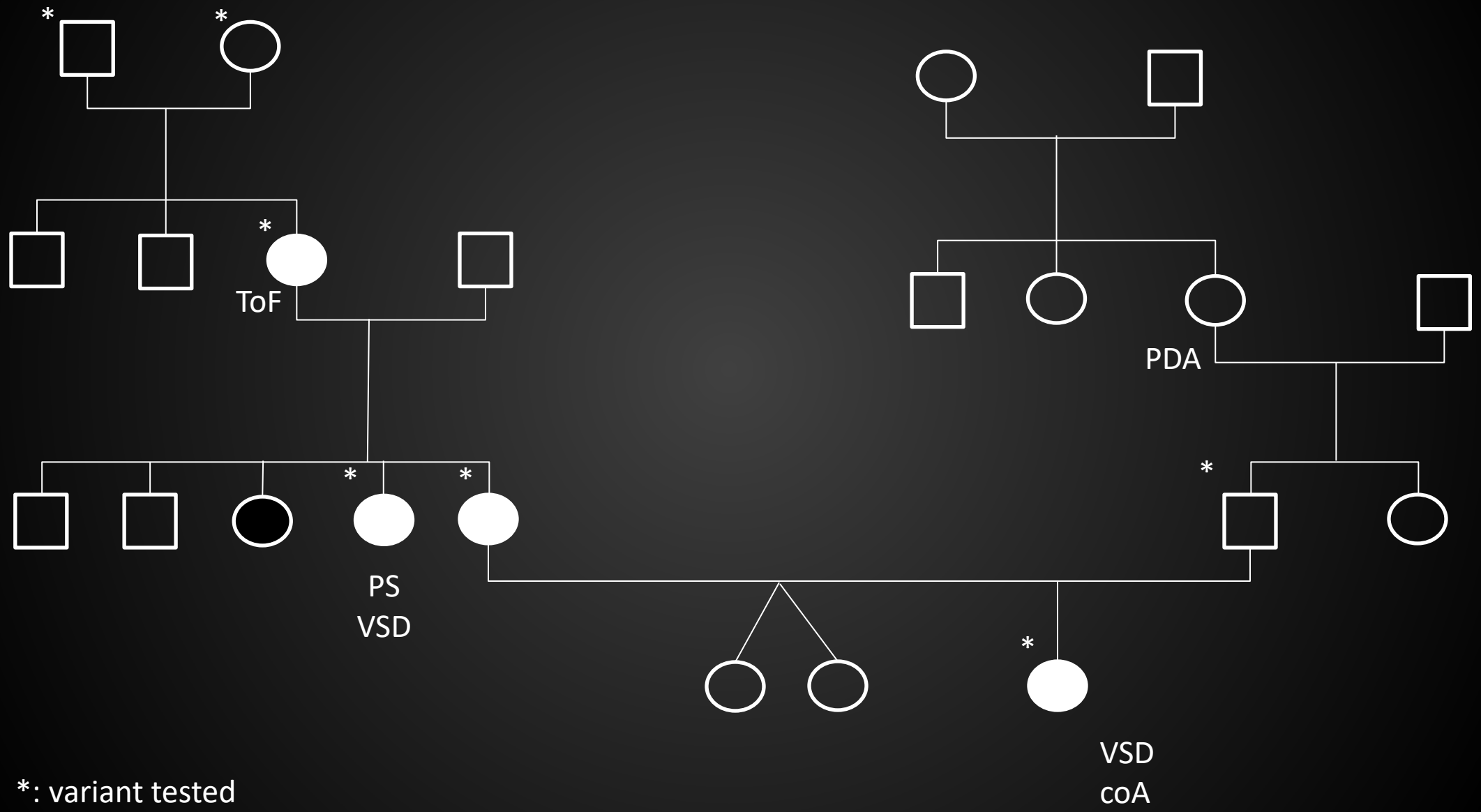
Right-sided obstruction
RASopathies, WNT5A, ROR2,
DVL1, DVL3, JAG1, NOTCH2

Each gene 'resolves' < 0.5% of isolated heart defects
Recessive defects underrepresented?

Left-right patterning

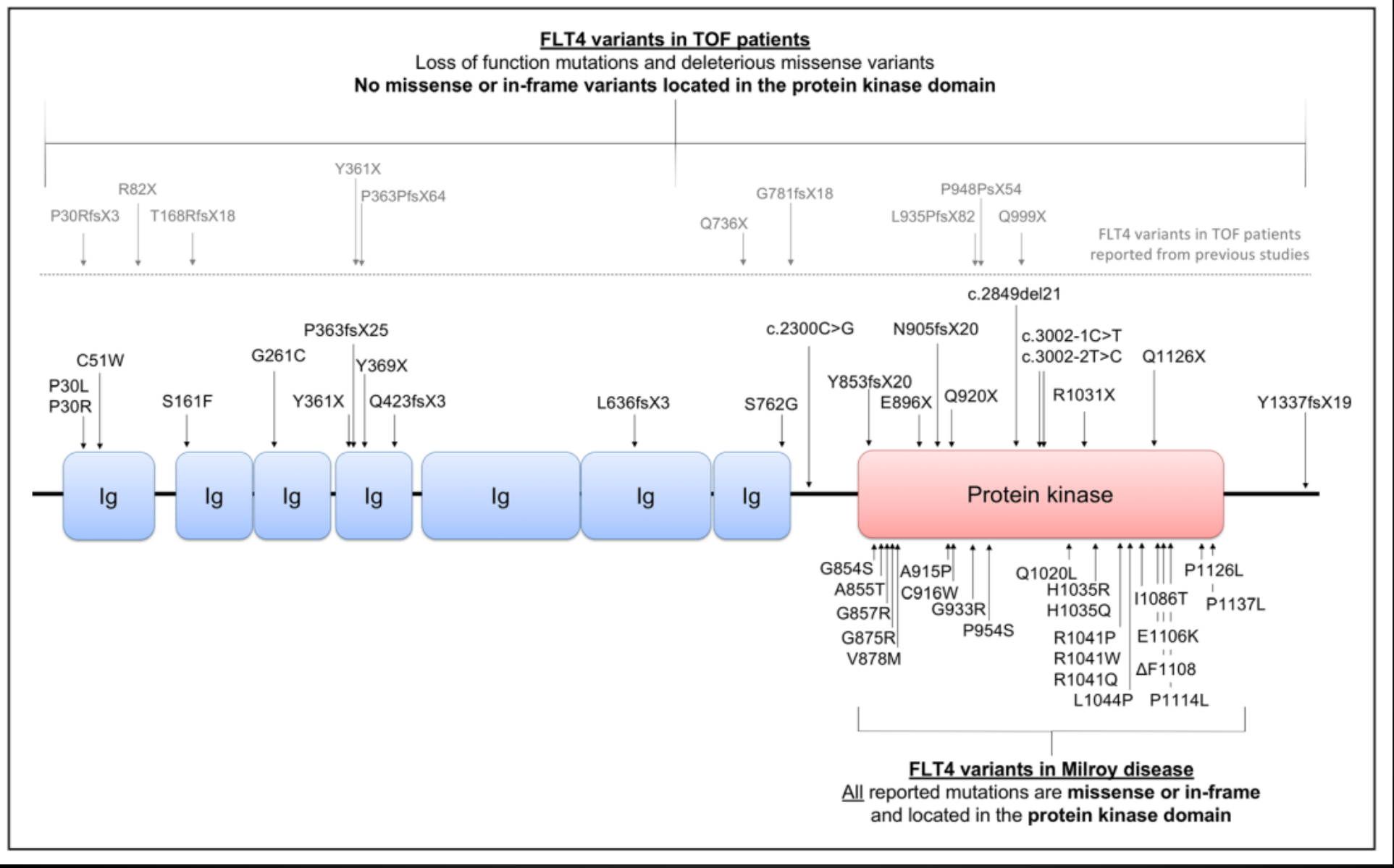
Ciliary genes, NODAL, FOXH1, ZIC3, SMAD2

Variable expressivity (Verlee et al, EJHG 2025)



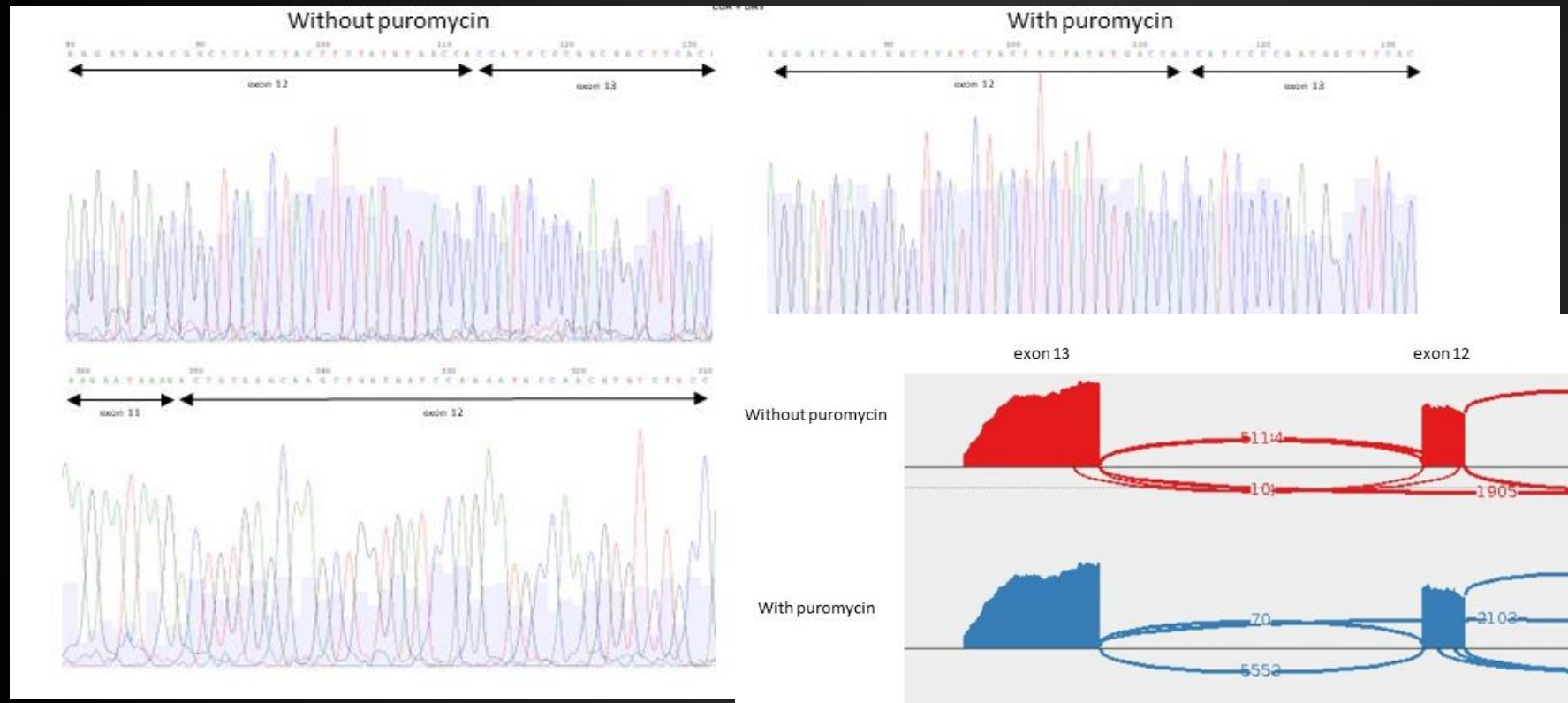
*: variant tested

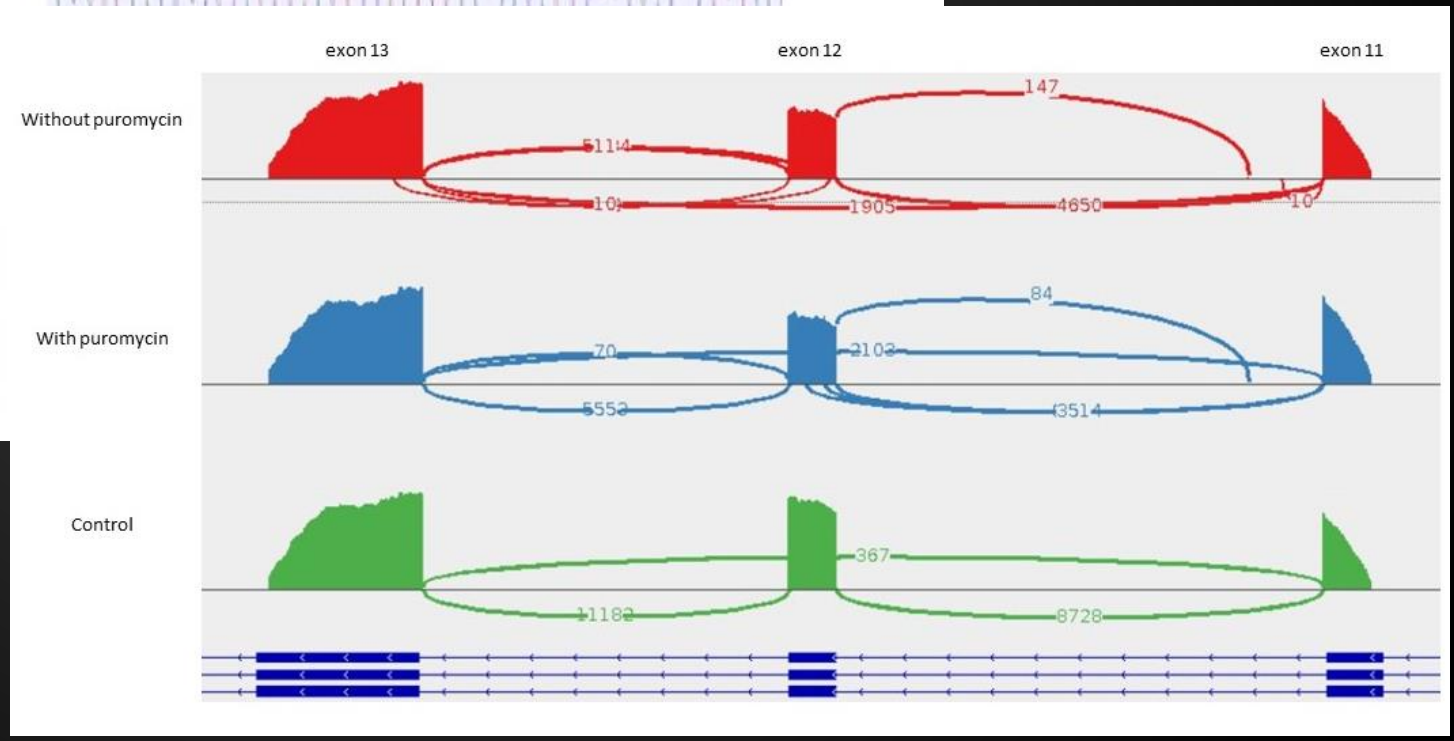
Black symbol: FLT4 (NM_182925.4) c.1657+6T>C present



Page et al, 2018: Circulation research

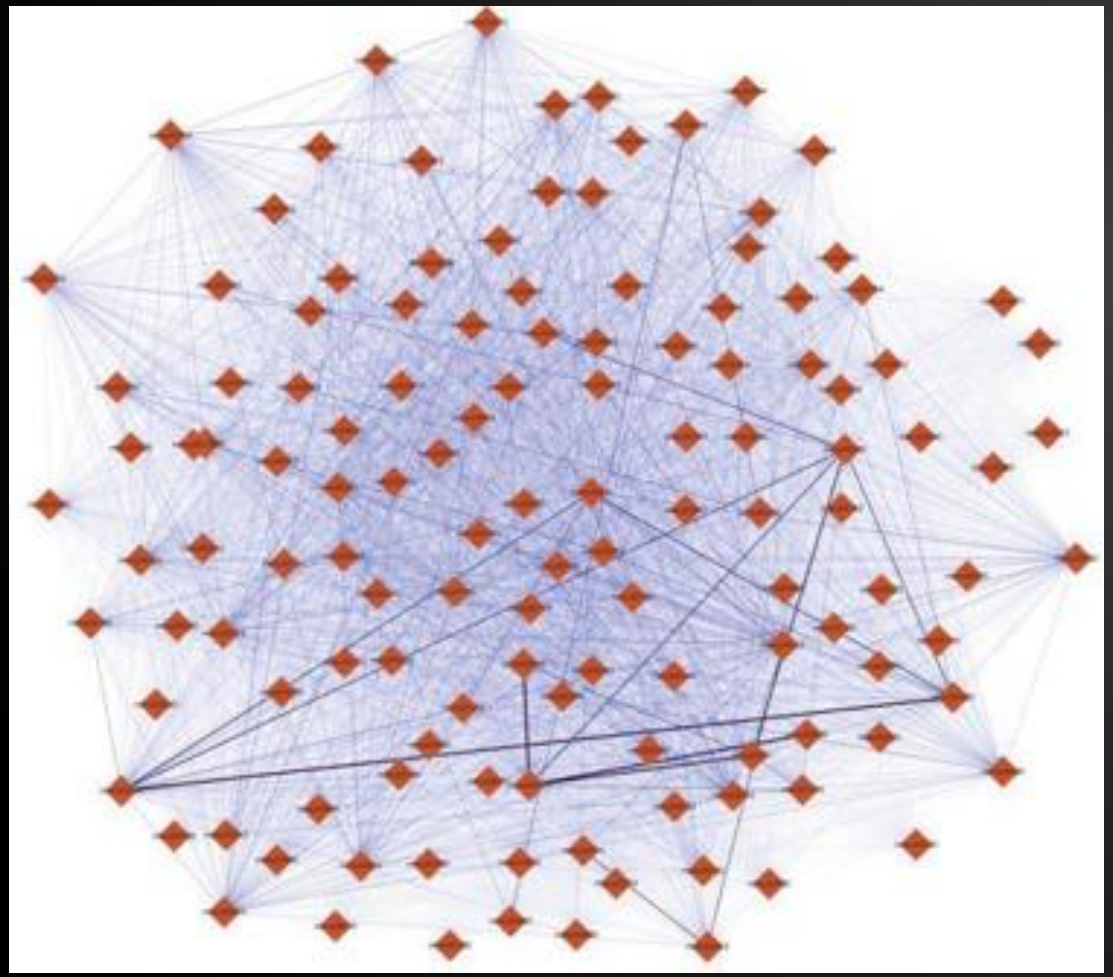
Whole Exome Sequencing Reveals the Major Genetic Contributors to Nonsyndromic Tetralogy of Fallot

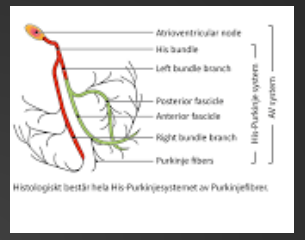

Without puromycin
With puromycin
exon 12
exon 13
exon 11
exon 12


exon 13
exon 12
exon 11
Without puromycin
With puromycin
Control
147
5114
10
1905
4650
10
84
70
2102
5552
3514
367
11182
8728

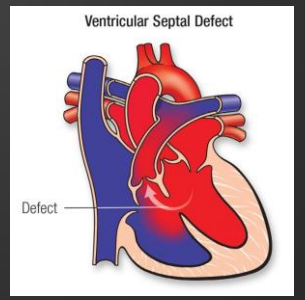
‘MONOGENIC’ CAUSES OF CHD

- Same variants in genes may cause diverse phenotypes: E.g. NKX2-5

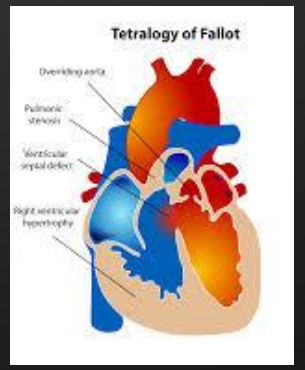




Arrythmias



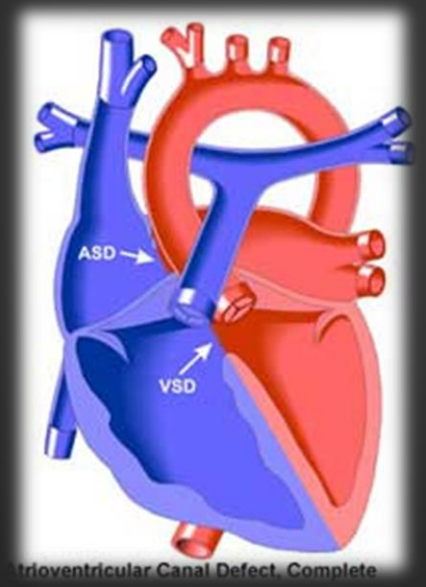
Septal defects



Contruncal defects

‘MONOGENIC’ CAUSES OF CHD

- Genetic heterogeneity:
  Several genes may underlie a same phenotype



AVSD

CRELD1

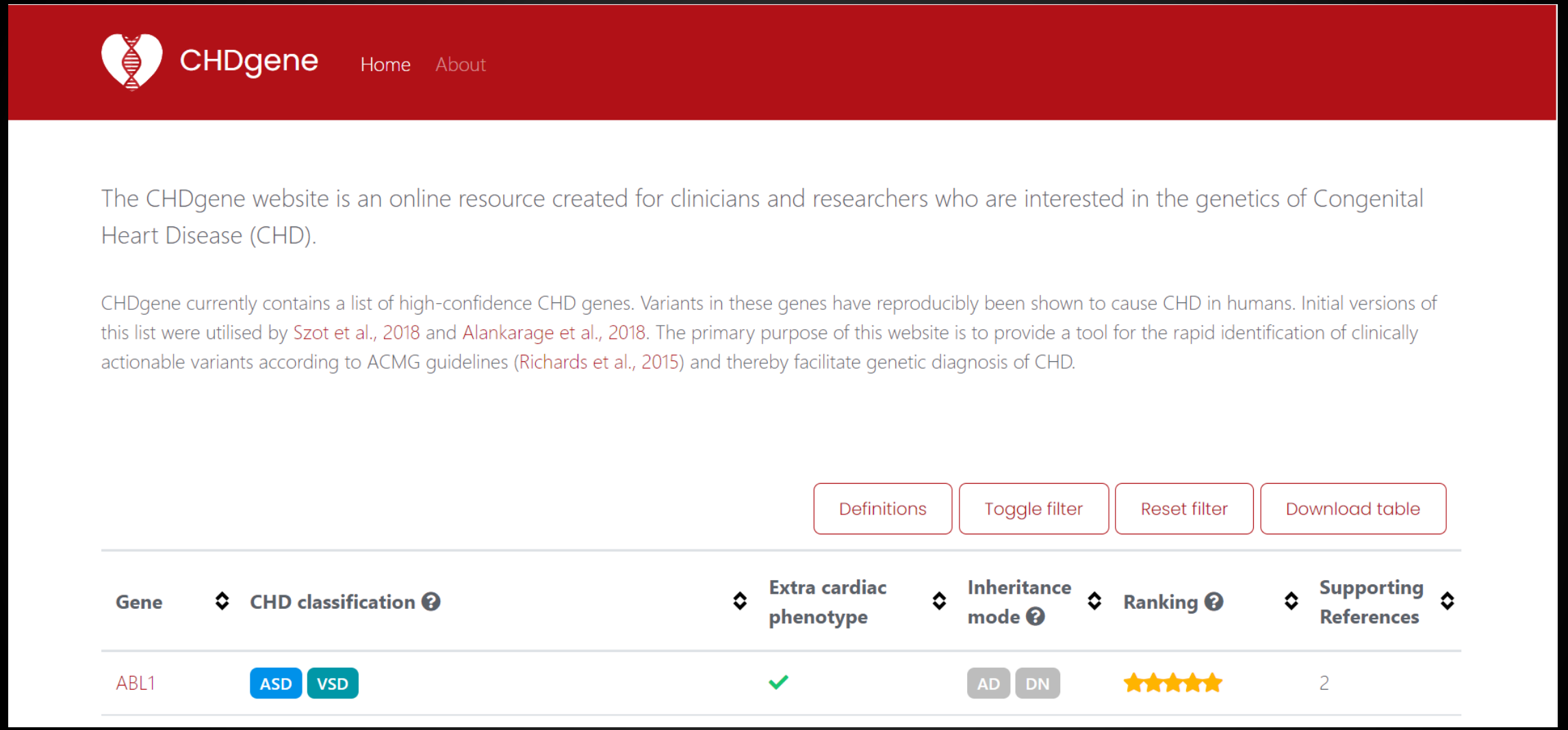
MDM4

GJA1

GATA6

GATA4

‘MONOGENIC’ CAUSES OF CHD

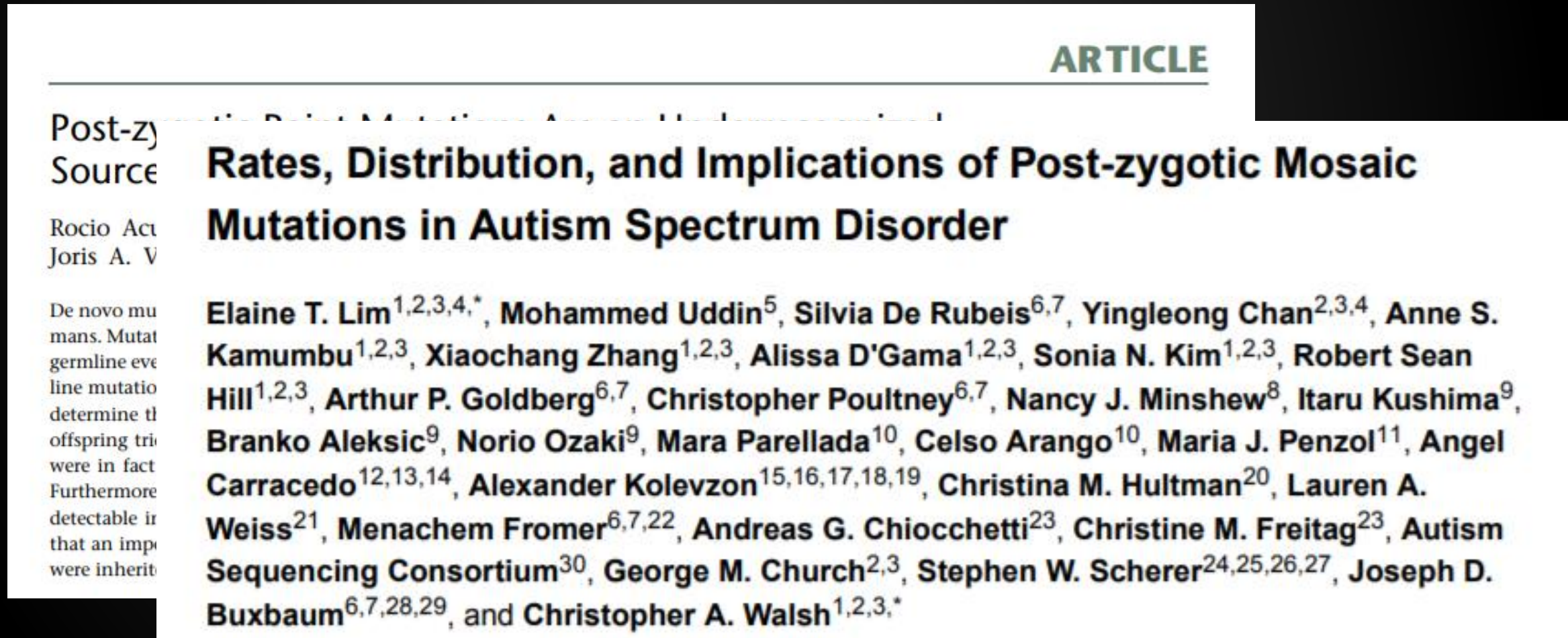


http://chdgene.victorchang.edu.au/

Yang et al, 2022. Circ Genom Precis Med.: 139 genes

‘MONOGENIC’ CAUSES OF CHD

- Mosaicism



ARTICLE

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Rates, Distribution, and Implications of Post-zygotic Mosaic Mutations in Autism Spectrum Disorder

Elaine T. Lim[1,2,3,4,*], Mohammed Uddin[5], Silvia De Rubeis[6,7], Yingleong Chan[2,3,4], Anne S. Kamumbu[1,2,3], Xiaochang Zhang[1,2,3], Alissa D'Gama[1,2,3], Sonia N. Kim[1,2,3], Robert Sean Hill[1,2,3], Arthur P. Goldberg[6,7], Christopher Poultney[6,7], Nancy J. Minshew[8], Itaru Kushima[9], Branko Aleksic[9], Norio Ozaki[9], Mara Parellada[10], Celso Arango[10], Maria J. Penzol[11], Angel Carracedo[12,13,14], Alexander Kolevzon[15,16,17,18,19], Christina M. Hultman[20], Lauren A. Weiss[21], Menachem Fromer[6,7,22], Andreas G. Chiocchetti[23], Christine M. Freitag[23], Autism Sequencing Consortium[30], George M. Church[2,3], Stephen W. Scherer[24,25,26,27], Joseph D. Buxbaum[6,7,28,29], and Christopher A. Walsh[1,2,3,*]

‘MONOGENIC’ CAUSES OF CHD

- Mosaicism

< 1%

Am J Med Genet A. 2015 Nov;167A(11):2674-83. doi: 10.1002/ajmg.a.37270. Epub 2015 Aug 6

Mosaic partial deletio

Duffy EA[1], Pretorius PR[1,2], Lerach

Original Article

Molecular

SHORT REPORT

Somatic NKX2-5 mutat
disease in complex con

S M Reamon-Buettner, J Borlak

J. Breckpot[a] B. Thienpont[a,d] M. Gewillig[b]
K. Devriendt[a]

Published in final edited form as:

Hum Genet. 2018 February ; 137(2): 183–193. doi:10.1007/s00439-018-1871-6.

Robust identification of mosaic variants in congenital heart disease

Kathryn B. Manheimer[1], Felix Richter[1], Lisa J. Edelmann[2], Sunita L. D’Souza[3], Lisong Shi[2], Yufeng Shen[16,17], Jason Homsy[5,18], Marko T. Boskovski[19], Angela C. Tai[5], Joshua Gorham[5], Christopher Yasso[5], Elizabeth Goldmuntz[6,7], Martina Brueckner[8,9], Richard P. Lifton[8,10,11,12,13], Wendy K. Chung[14,15], Christine E. Seidman[5,20,21], J. G. Seidman[5], and Bruce D. Gelb[1,2,4]

From 'monogenic' to 'Oligogenic' CHD

CHD Gene $1^{+/-}$

X

CHD Gene $2^{+/-}$

CHD gene	Modifyer gene	CHD Increase / decrease	Reference
Gata4	Gata5, Tbx5	↑	Laforest et al, 2011 Maitra et al, 2009
Jag1	Notch2	↑	McCright et al, 2002
Nkx2-5	Nipbl	↑	Santos et al, 2016
Nkx2-5	Smad1	↓	Pral et al, 2007

From 'monogenic' to 'Oligogenic' CHD

Evidence in human disease

- Case reports

From 'monogenic' to 'Oligogenic' CHD

Evidence in human disease

- Case reports
- Risk for CHD in first degree family members of 22q11.2 microdeletion carriers

	RR [CHD] in 1st degree FM without 22q11.2 microdeletion
22q11.2 with CHD	4
22q11.2 without CHD	1

Digilio et al, 2005; Swaby et al, 2011

From 'monogenic' to 'Oligogenic' CHD

Evidence in human disease

- Case reports
- Risk for CHD in first degree family members of 22q11.2 microdeletion carriers
- GnomAD: intolerance for LOF variants in CHD genes (Sifrim et al, Nat Genet. 2016)

  pLi [CHD genes]: 0.59 ± 0.03

  pLi [all genes]: 0.30 ± 0.003

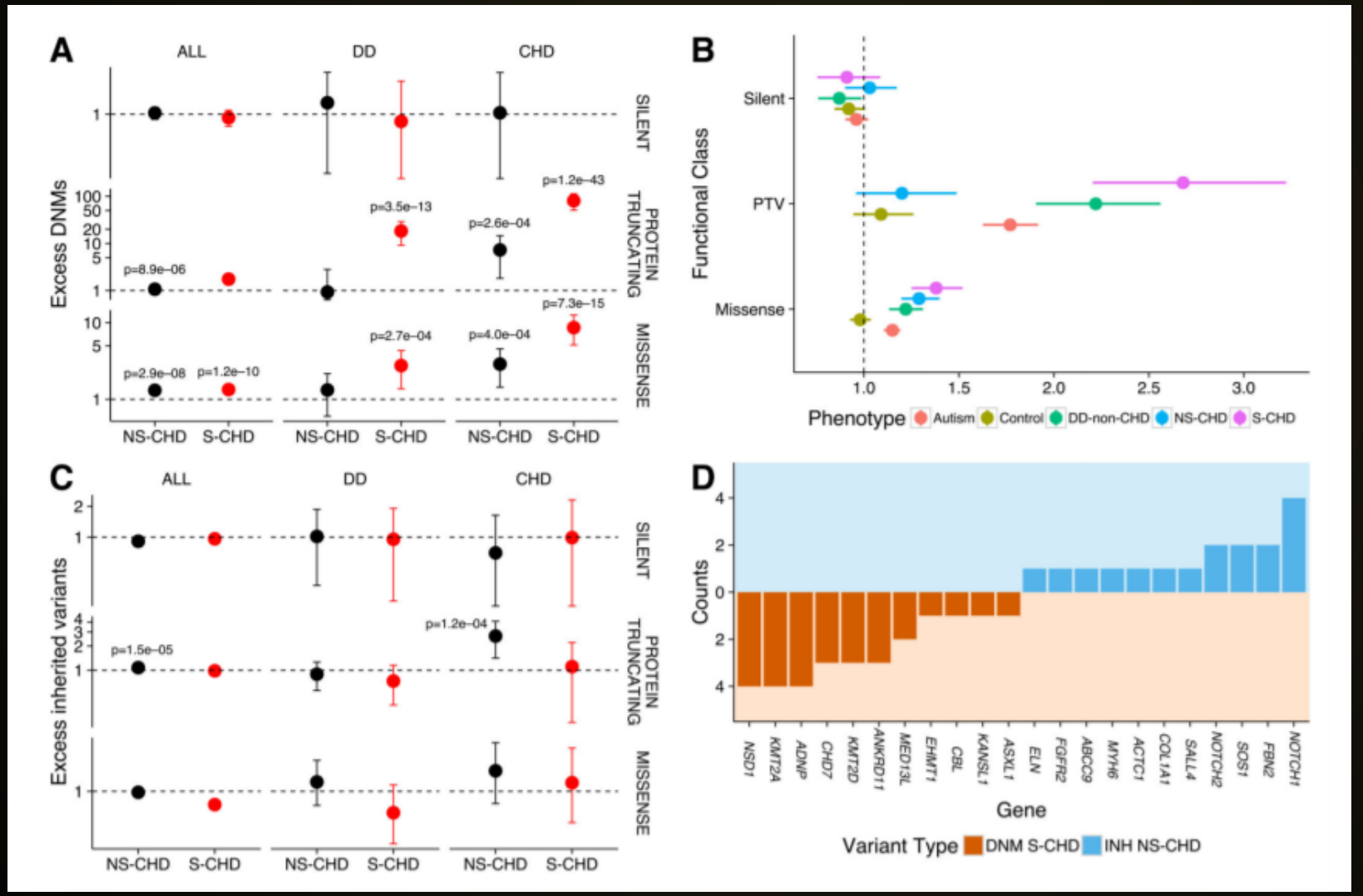
$P=3x10^{-22}$

BUT: CHD incidence 0.8% while

1.9% of control individuals has a LOF variant in CHD gene

'Oligogenic' causes of CHD

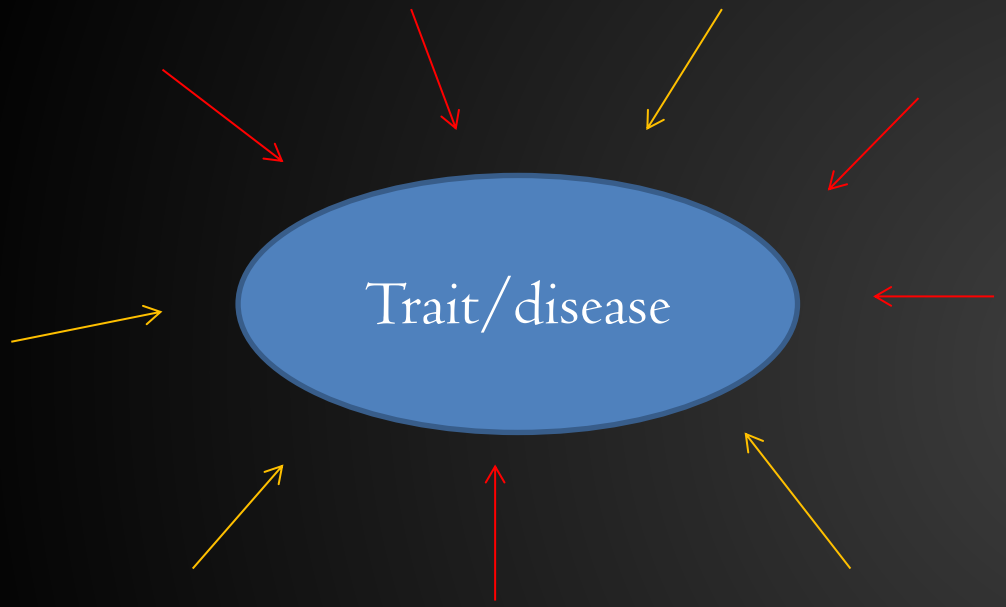
- Mutational burden studies: Genetic landscape for S-CHD and NS-CHD



Sifrim et al,
Nat Genet, 2016

- S-CHD : 518
- NS-CHD: 847

‘Oligogenic’ to ‘Multifactorial’ CHD



Environmental
Genetic

Congenital anomalies
- CP/L
- Clubfoot
- Neural tube defects

Brain development
Diabetes mellitus
CV risk factors

Note: variability in monogenic traits...

'Oligogenic' to 'Multifactorial' CHD

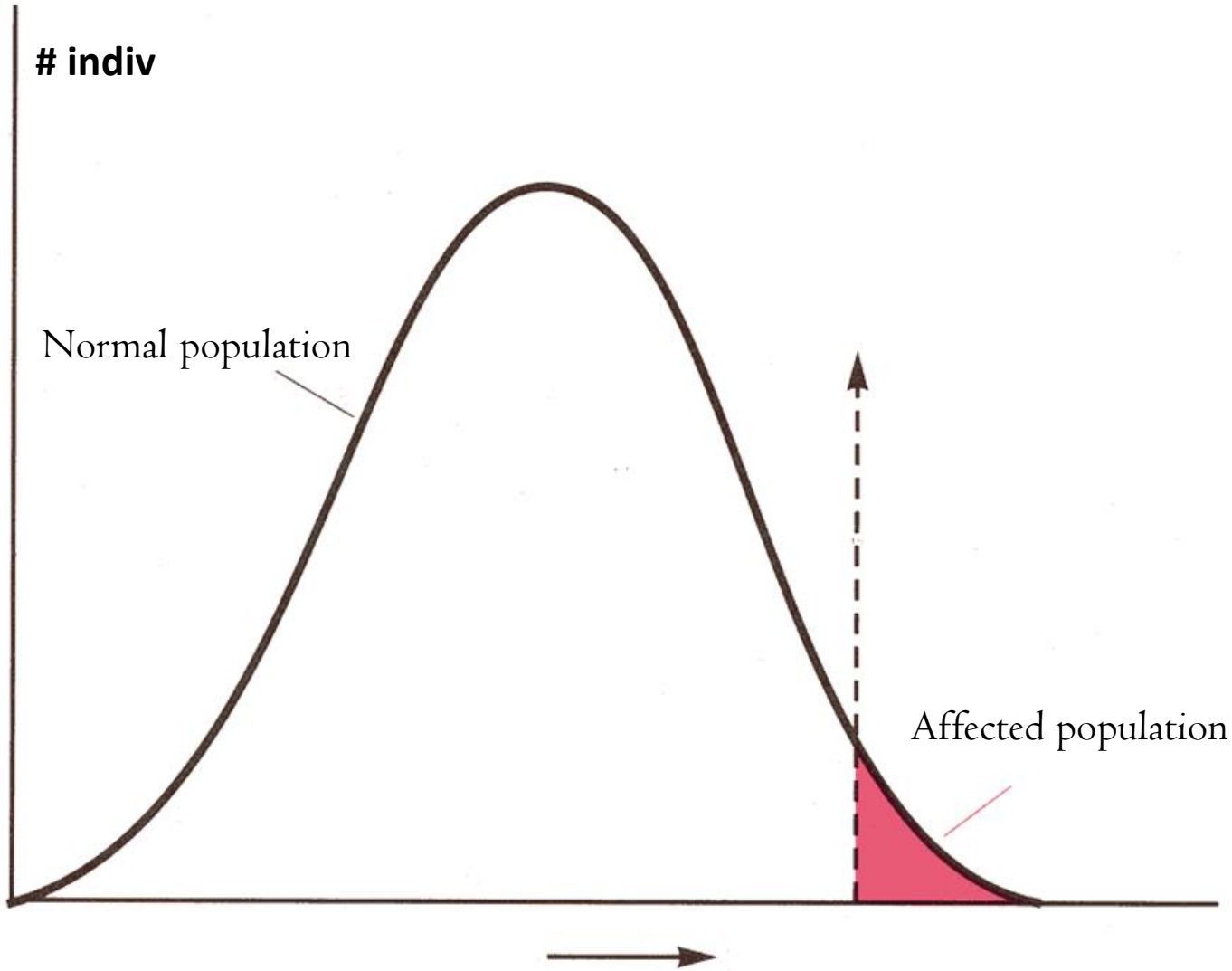
- Risk first degree family member ~ (population risk)$^{1/2}$
  [Population risk 1/1000 ~ 1st degree family member risk 3%]

- Exponential decrease in reoccurrence risk for further degree relatives

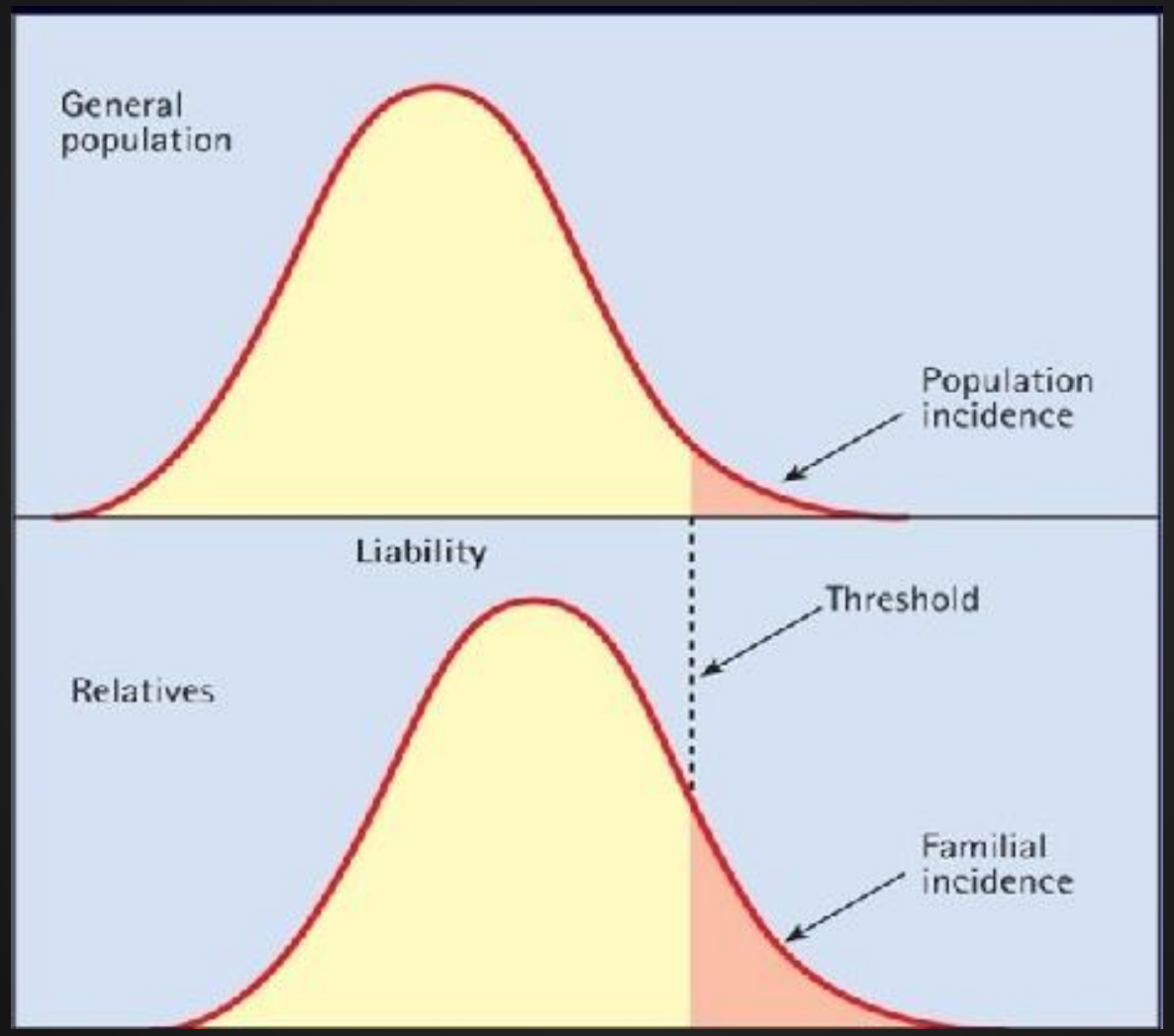
- Risk ~ several relatives affected
  more severe disease

- Risk ↑ ~ consanguinity

'Oligogenic' to 'Multifactorial' CHD



‘Oligogenic’ to ‘Multifactorial’ CHD



‘Oligogenic’ to ‘Multifactorial’ CHD

monozygote	dizygote	pathogenesis
		genetic
		genetic and environment
		environment

LINKING GENES AND ENVIRONMENT ?

- *Transcription factors:*
  GATA4 – GATA5 - GATA6 – NKX2.5 – GDF1 – GJA5 – ZIC3 – TFAP2B…
- *Cilia:*
  DNAH6 – DNAI1 – DNAH5…
- *Cell signaling*
  Notch, TGFβ, VEGF, Ras-Mapk…
- *Chromatin remodeling*
  ANKRD11, CHD7, CHD4, KMT2A, KMT2D, …
- *Cardiac contractile apparatus*
  MYH6…

Disturbed gene expression ?

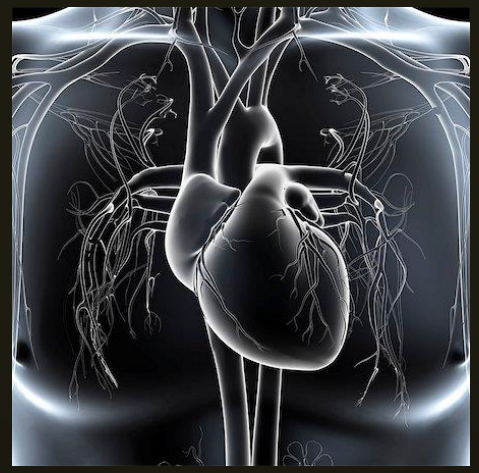
LINKING GENES AND ENVIRONMENT ?

Environment

Epi-genetics

Genes

Drugs
Medication
Alcohol
Tobacco
Folic acid
Infection
Twinning
(Maternal age)
(Paternal age)
…

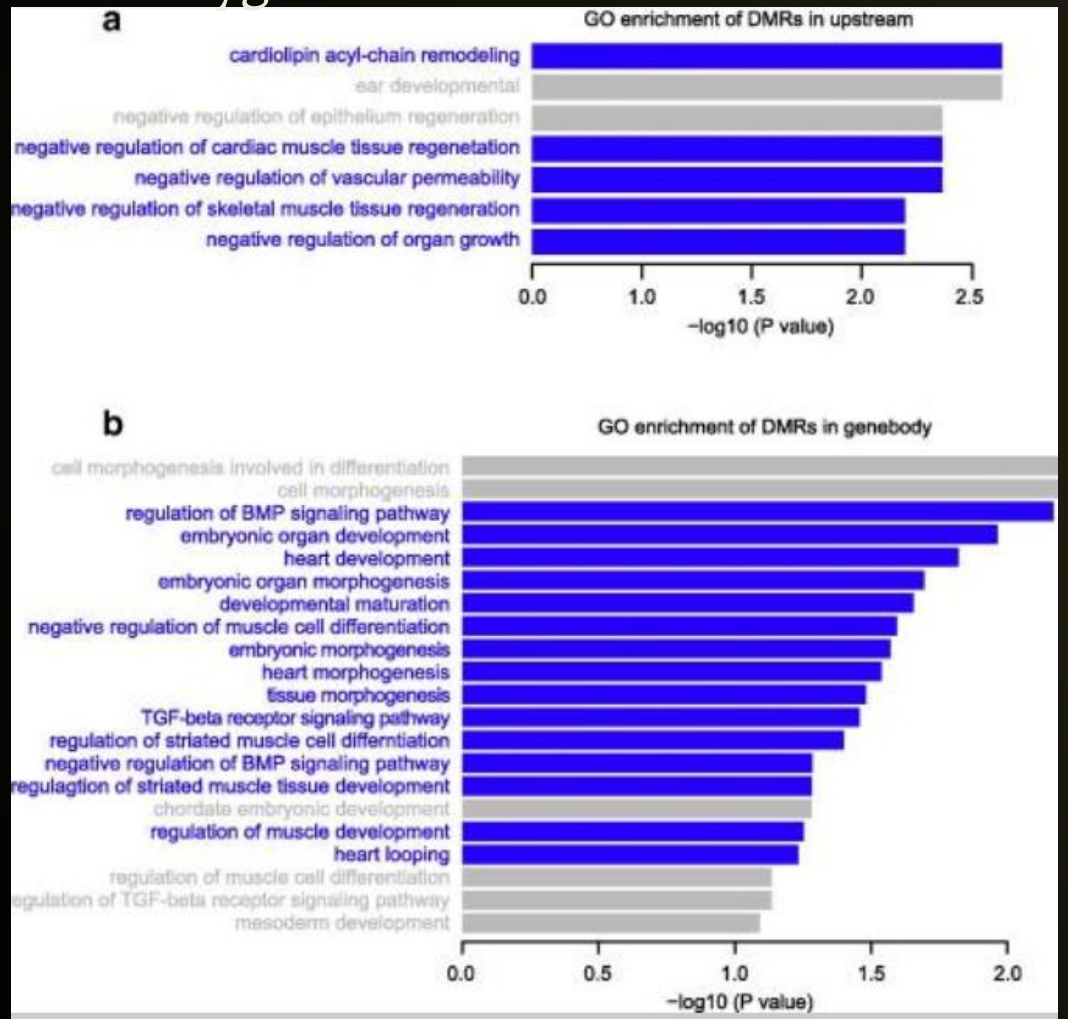


Major genes
Polygenic risk scores

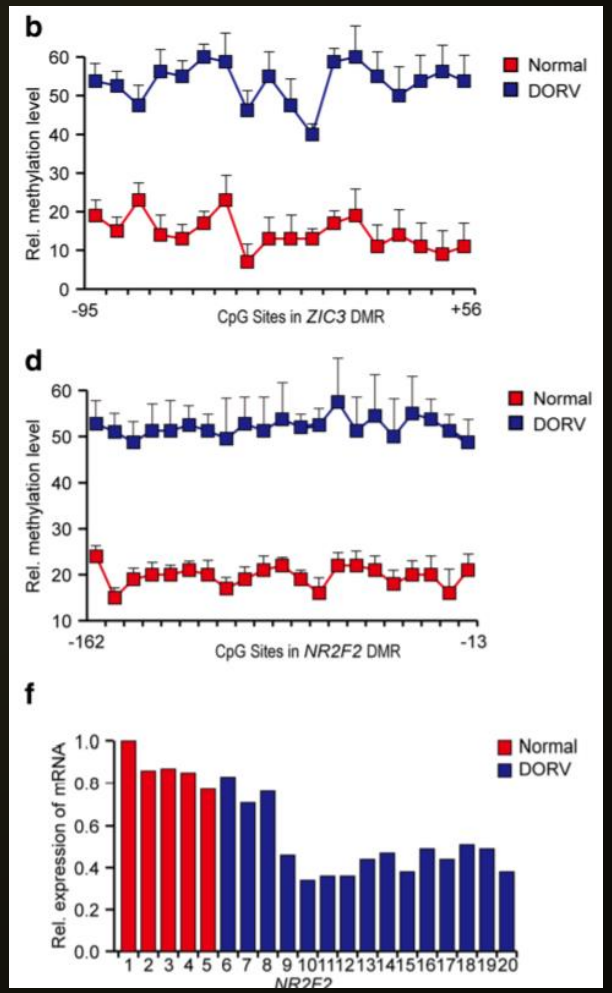
LINKING GENES AND ENVIRONMENT ?

Methylation differences

Monozygotic twin discordant for DORV

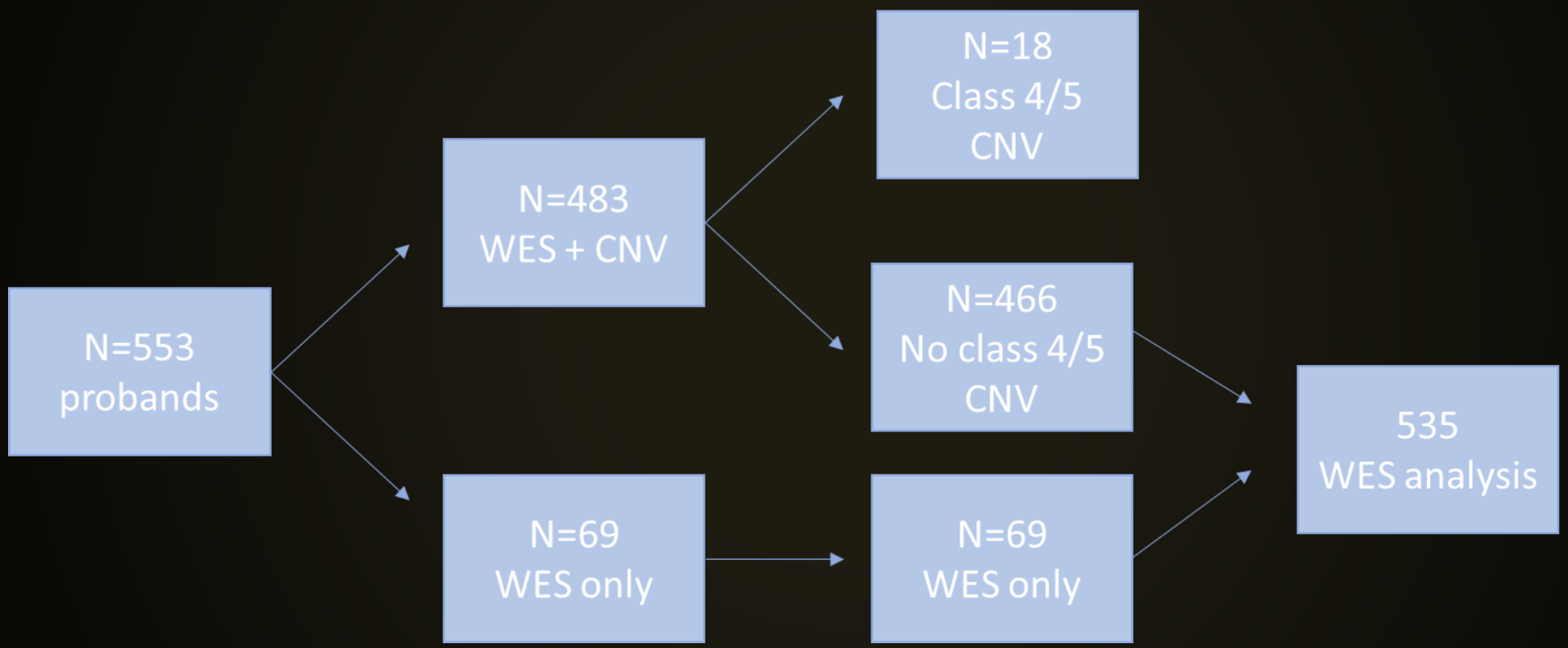


DORV samples



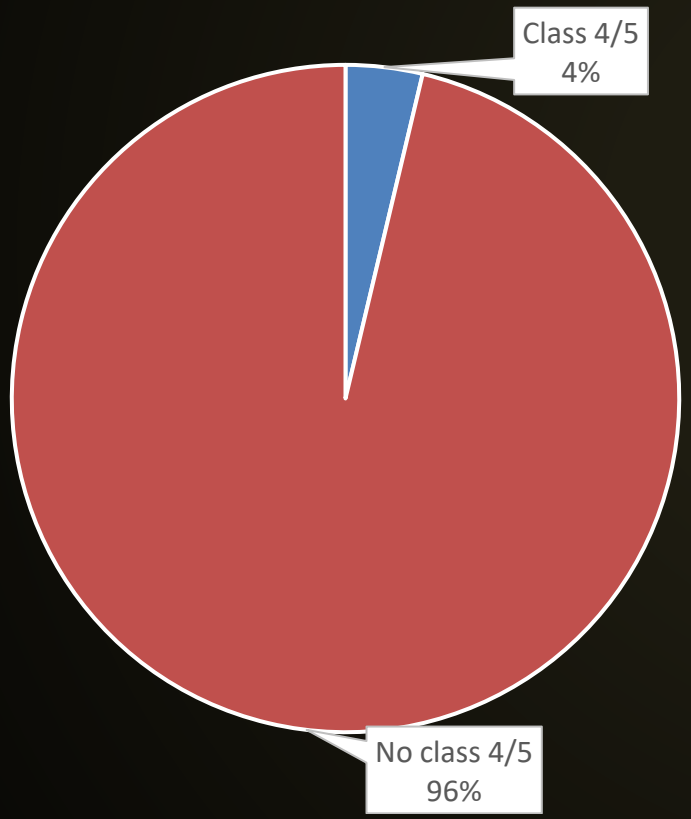
Lyu et al, 2018

The Ghent Diagnostic experience

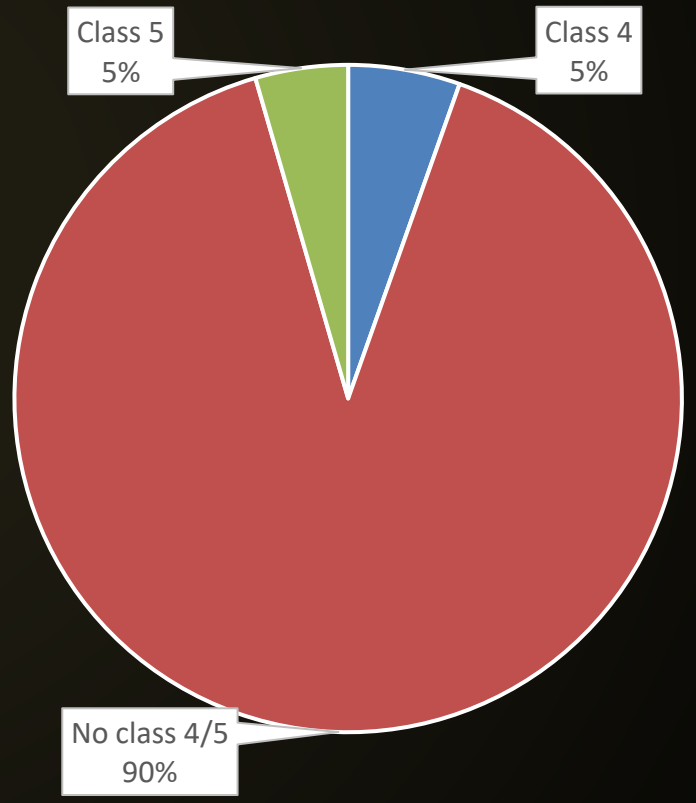


The Ghent Diagnostic experience

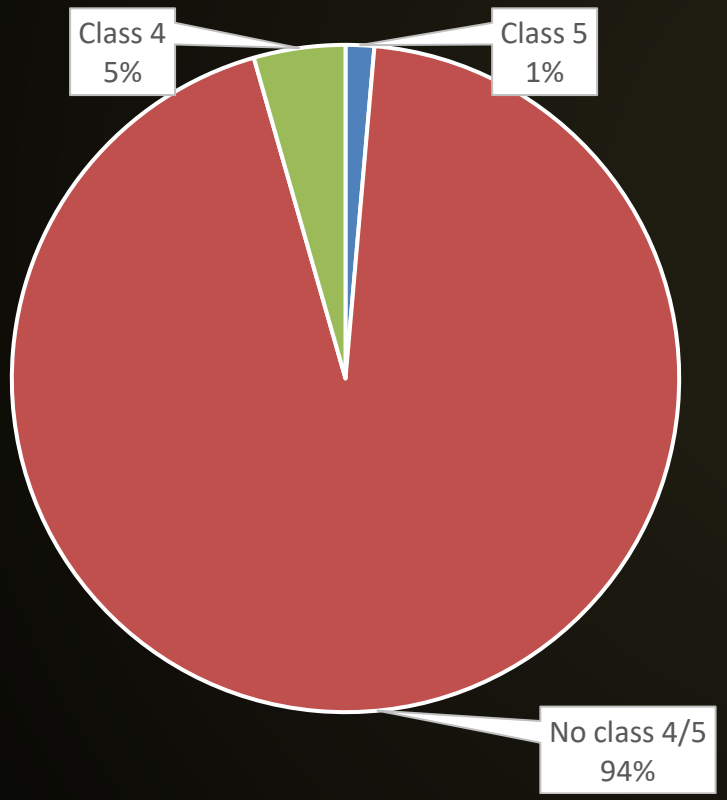
CNV analysis (n=484)



ES-CHD analysis (n=535)

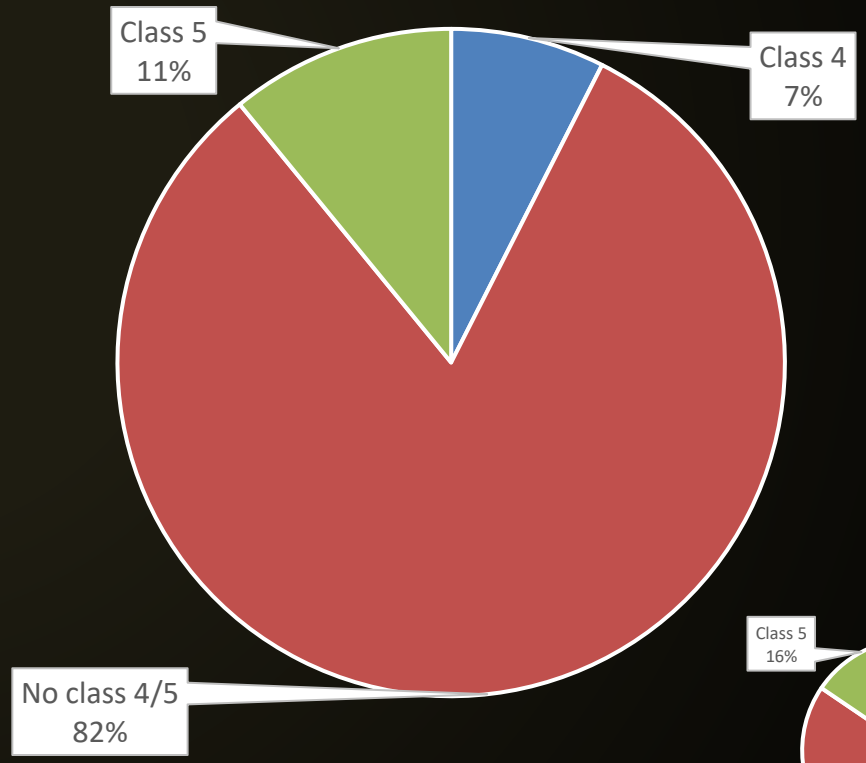


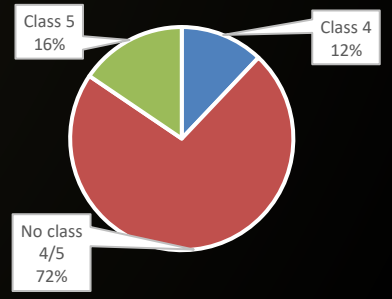
ES-CHD analysis NS (n=361)



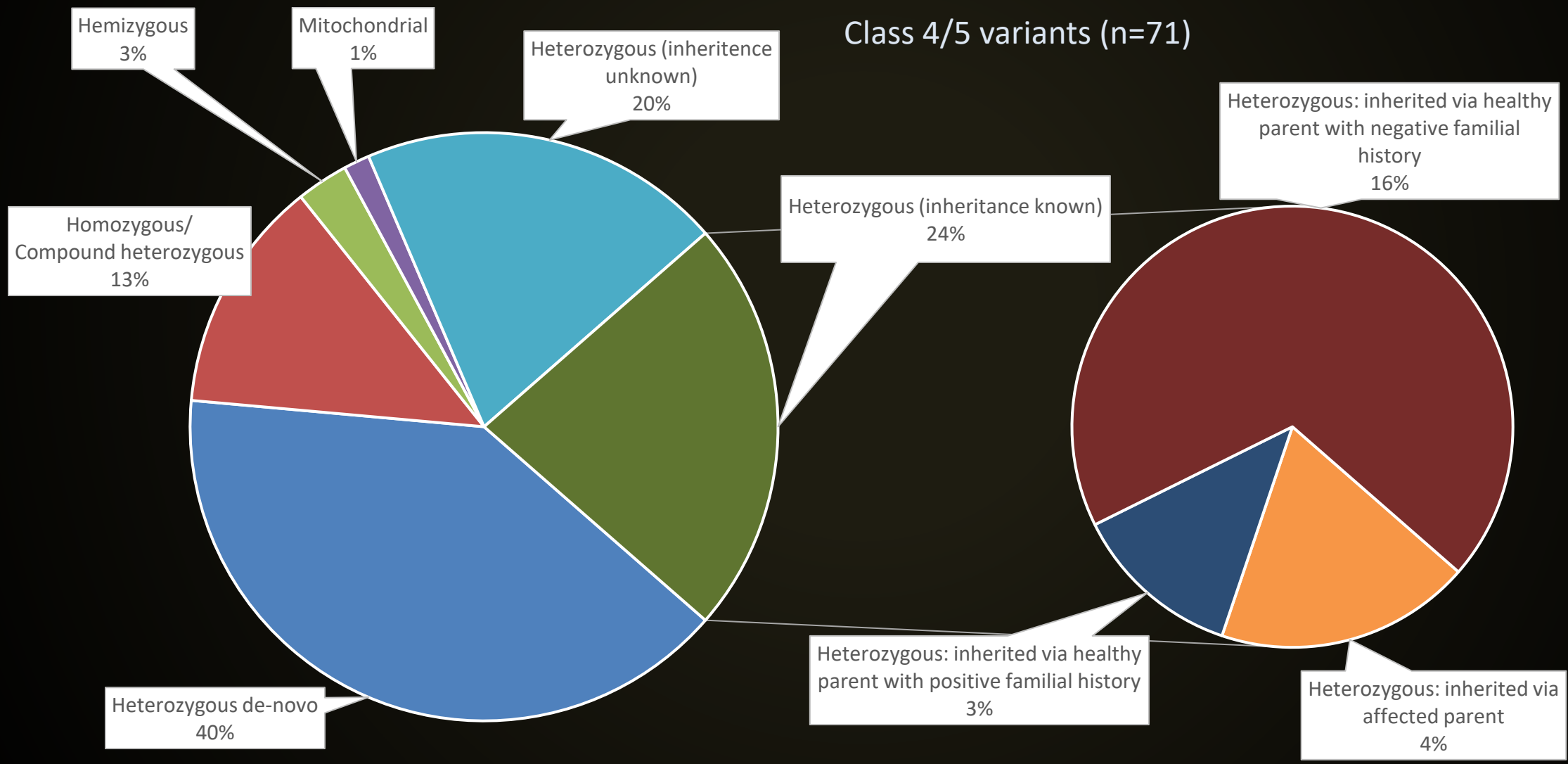
Mendeliome → + 0.3%

ES-CHD analysis S (n=174)





Mendeliome → + 10%

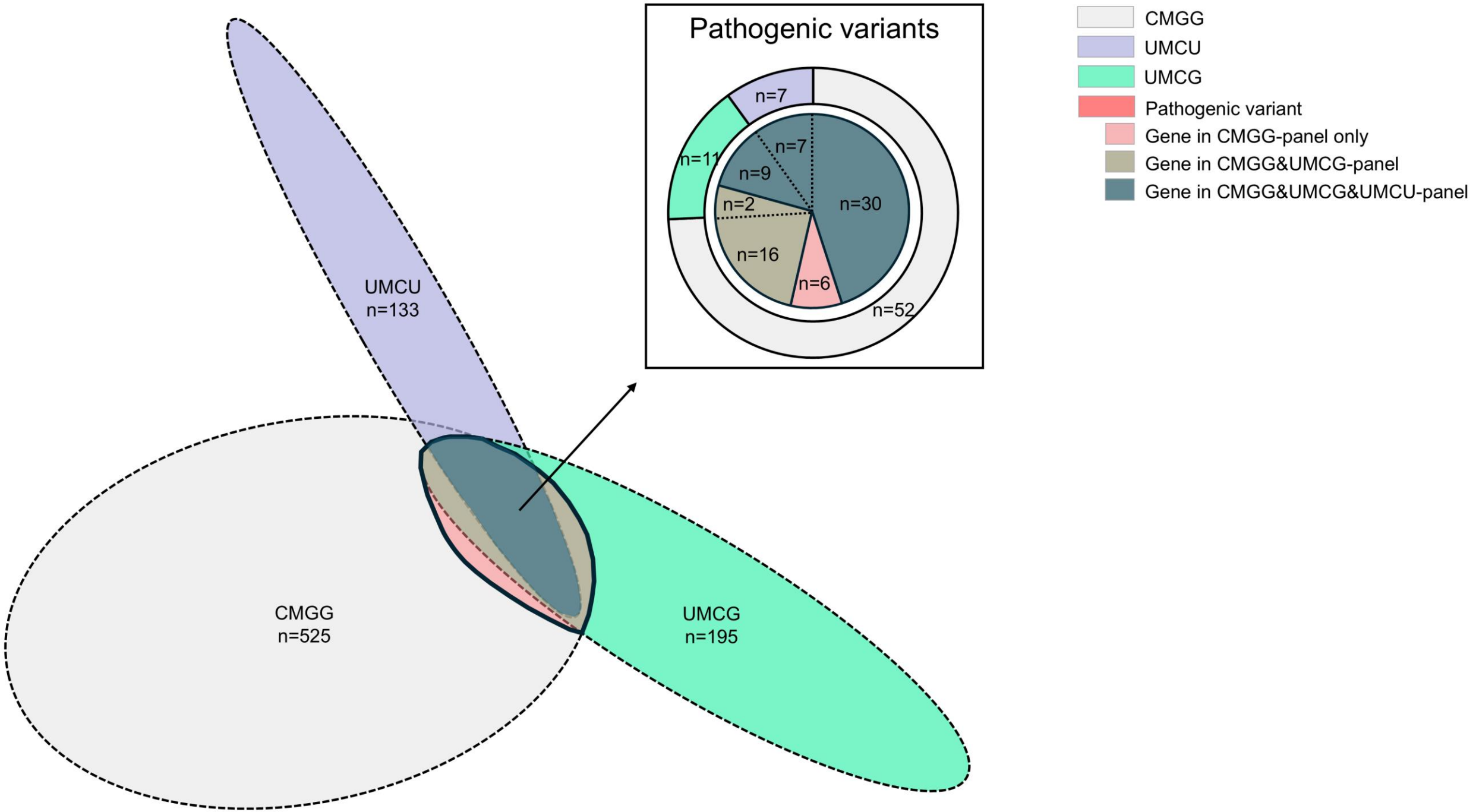

Class 4/5 variants (n=71)
Hemizygous
3%
Mitochondrial
1%
Heterozygous (inheritence unknown)
20%
Heterozygous: inherited via healthy parent with negative familial history
16%
Homozygous/ Compound heterozygous
13%
Heterozygous (inheritance known)
24%
Heterozygous de-novo
40%
Heterozygous: inherited via healthy parent with positive familial history
3%
Heterozygous: inherited via affected parent
4%

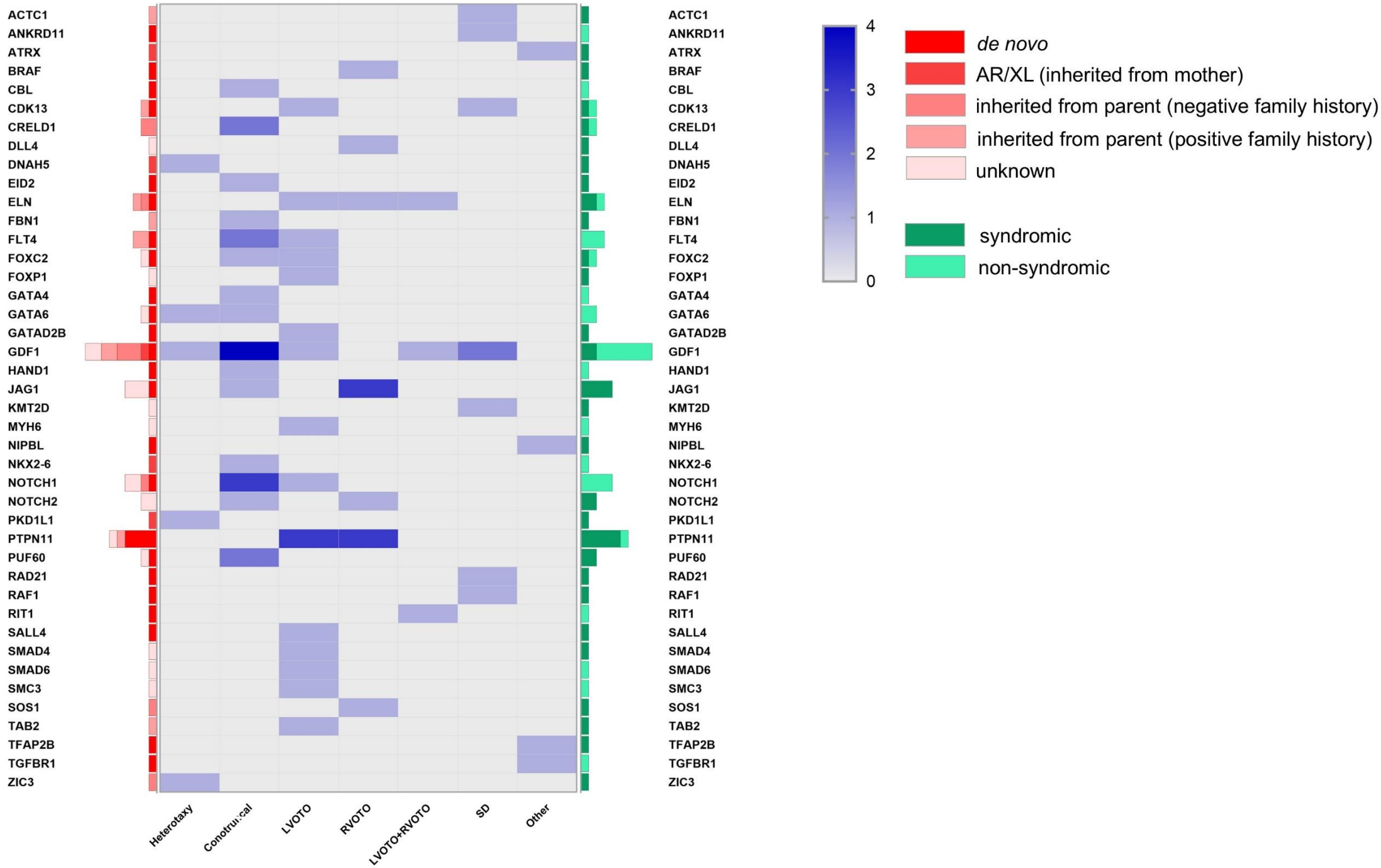
	Overall
No incidental findings	548/560 (97,9%)
Incidental findings in CMP-related genes	8/560 (1,4%)
Other	4/560 (0,7%)

THE GHENT-UTRECHT-GRONINGEN EXPERIENCE

CMGG (525 probands; 472 genes), the UMCG (195 probands; 345 genes) and the UMCU (133 probands; 55 genes)

Center	# genes in CHD panel	# of probands
Ghent	472	525
Utrecht	55	133
Groningen	345	195


Pathogenic variants
n=7
n=11
n=7
n=9
n=2
n=30
n=16
n=6
n=52
UMCU
n=133
CMGG
n=525
UMCG
n=195
CMGG
UMCU
UMCG
Pathogenic variant
Gene in CMGG-panel only
Gene in CMGG&UMCG-panel
Gene in CMGG&UMCG&UMCU-panel


ACTC1
ANKRD11
ATRX
BRAF
CBL
CDK13
CRELD1
DLL4
DNAH5
EID2
ELN
FBN1
FLT4
FOXC2
FOXP1
GATA4
GATA6
GATAD2B
GDF1
HAND1
JAG1
KMT2D
MYH6
NIPBL
NKX2-6
NOTCH1
NOTCH2
PKD1L1
PTPN11
PUF60
RAD21
RAF1
RIT1
SALL4
SMAD4
SMAD6
SMC3
SOS1
TAB2
TFAP2B
TGFBR1
ZIC3
Heterotaxy
Conotruncal
LVOTO
RVOTO
LVOTO+RVOTO
SD
Other
4
3
2
1
0
de novo
AR/XL (inherited from mother)
inherited from parent (negative family history)
inherited from parent (positive family history)
unknown
syndromic
non-syndromic

CURRENT STATUS

CHD: Overall diagnostic yield (until know)

- CNV + ES (exome seq – genpanel 471 (candidate) genes: ~15%
- ES: +0.3%

Syndromic CHD

- CNV + Panel: 22%
- ES: +10%

Non-syndromic CHD

– ES: 6%

Variants in genes associated with S-CHD

(JAG1, TGFBR1, PUF60, SALL4, ANKRD11, RPS11, NOTCH2, FOXP1, GATAD2B, ZIC3, …)

Isomerism genes

Higher uptake in families with multiple affected members

→Not recognized?

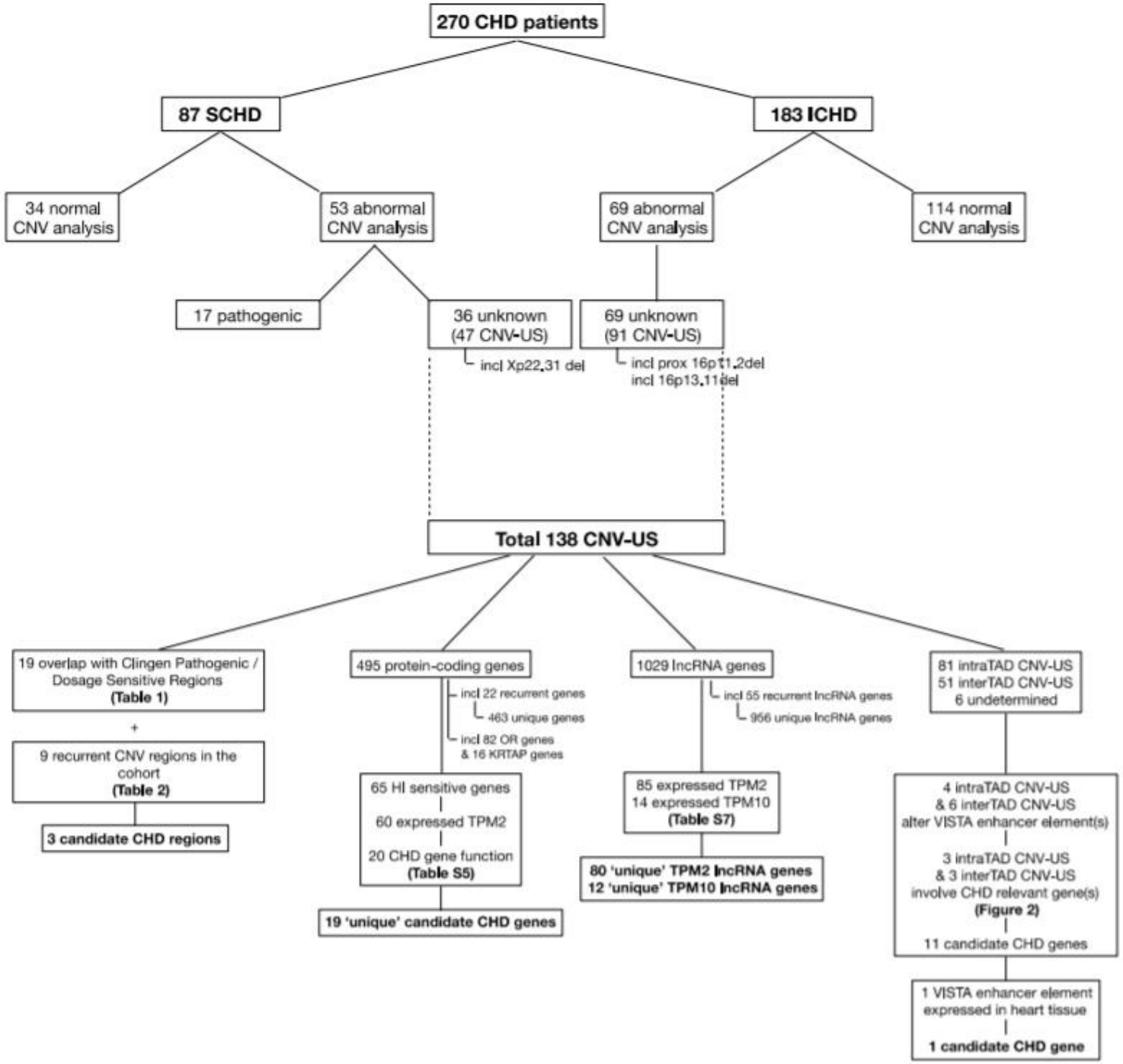
→Young age?

Counseling !

NON-CODING ?

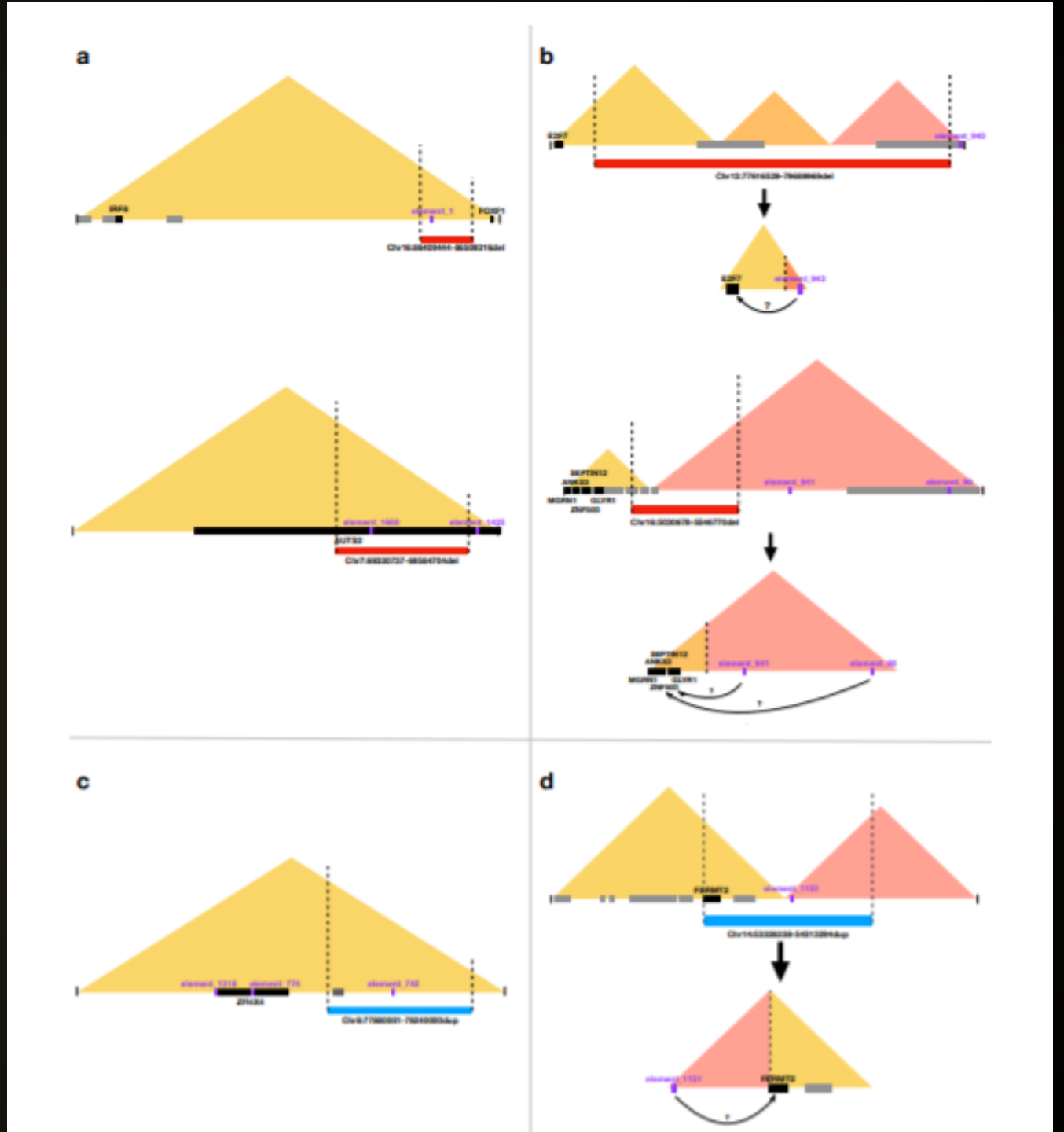
273 CNV analysis

Meerschaut et al, Genes, 2021



273 CNV analysis

Meerschaut et al, Genes, 2021



And Finally …

‘Recurrence risks’ in molecularly uninvestigated NS CHD

Recurrence risk

Lesion	Siblings, %	Offspring, %	
		Father affected	Mother affected
(T)APVR	NR	3.7	
ASD	1.7-3	1.5-5.7	4-6
VSD	1.6-3.8	2.9-7.5	2.9-7.1
AVSD	3-6.5	1-4.5	11.5-14
Left-sided obstruction	1.25-11	5.9-7.4	5.9-14.3
TOF	2.5-6.5	1.5-3.8	2.5-18.2
TGA	1-3	1.5	
Truncus arteriosus	5-9.5	NR	
Ebstein anomaly	13.3	NR	6
Pulmonary valve anomaly	5.4	2-3.5	4-6.5
PDA	3	2-2.5	3.5-4

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defects; NR, not reported; PDA, persistent ductus arteriosus; (T)APVR, (total) abnormal pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Muiño et al, 2020

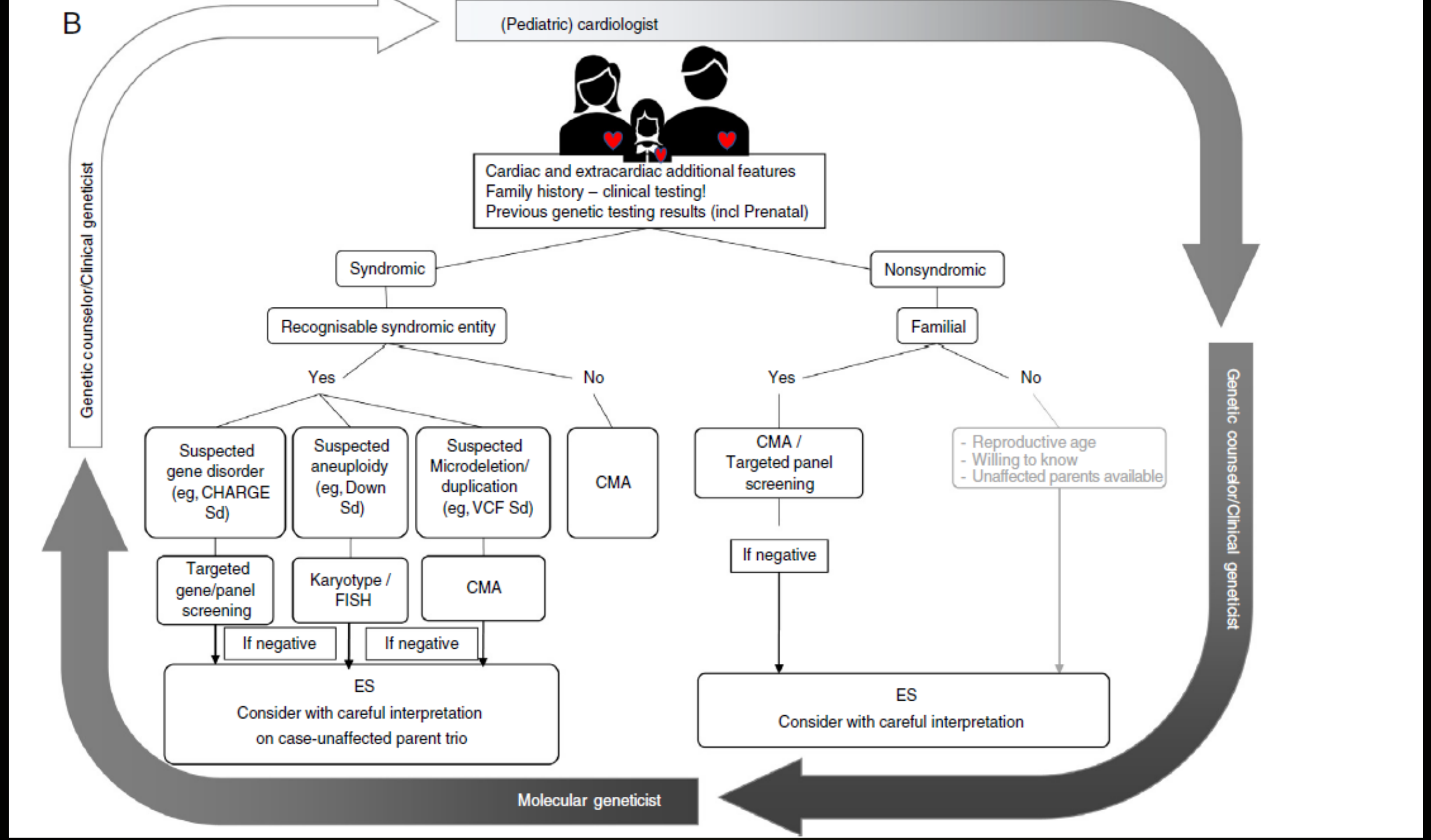
*J. De Backer et al. / Rev Esp Cardiol. 2020;**xx(x)**:xxx–xxx*

Can genetics offer any benefit to my patients/their families?

- Medical/paramedical management?
  - Risk prediction
  - Preventive treatment
- Family planning?
  - Siblings
  - Offspring

Yes → Refer patient/family for counseling

No → Stop! (unless in research setting)


B
(Pediatric) cardiologist
Genetic counselor/Clinical geneticist
Cardiac and extracardiac additional features
Family history – clinical testing!
Previous genetic testing results (incl Prenatal)
Syndromic
Nonsyndromic
Recognisable syndromic entity
Familial
Yes
No
Yes
No
Suspected gene disorder (eg, CHARGE Sd)
Suspected aneuploidy (eg, Down Sd)
Suspected Microdeletion/ duplication (eg, VCF Sd)
CMA
CMA / Targeted panel screening
- Reproductive age
- Willing to know
- Unaffected parents available
Targeted gene/panel screening
Karyotype / FISH
CMA
If negative
If negative
If negative
ES
Consider with careful interpretation
on case-unaffected parent trio
ES
Consider with careful interpretation
Genetic counselor/Clinical geneticist
Molecular geneticist

THANK YOU!

Bert.Callewaert@Ugent.be