

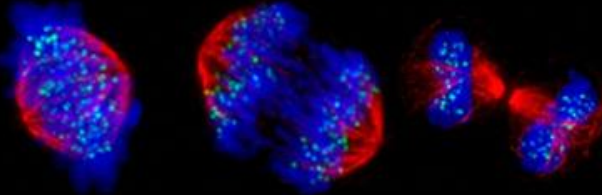


Molecular cytogenetic characteristics of CNVs in children with congenital heart defects.

Anastasiya Slepukhina

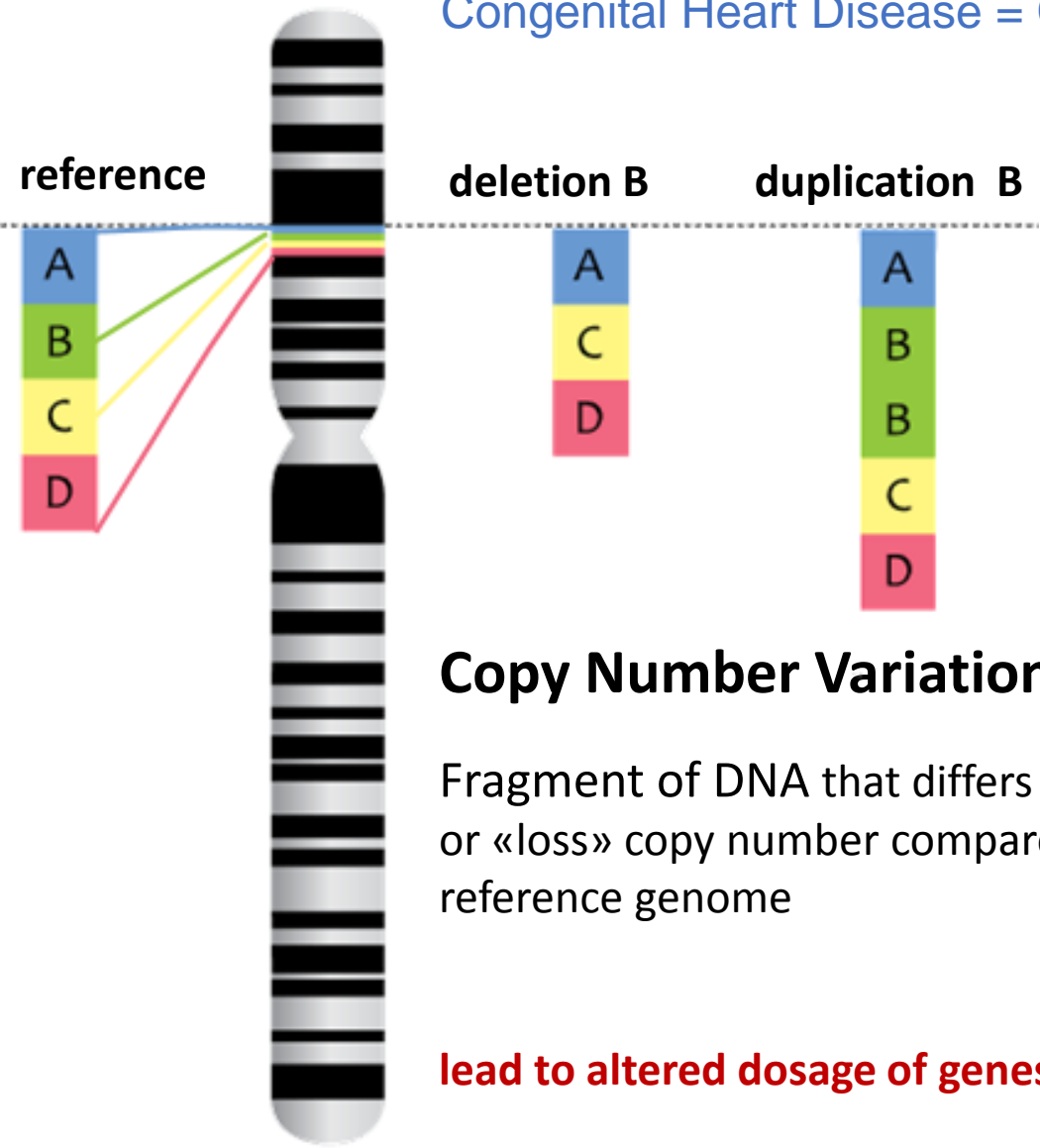
Institute of Chemical Biology and Fundamental Medicine
Siberian Branch of the Russian Academy of Sciences

Kemerovo, 2019



Genetics of Congenital Heart Diseases

Congenital Heart Disease = Congenital Heart Defect = CHD



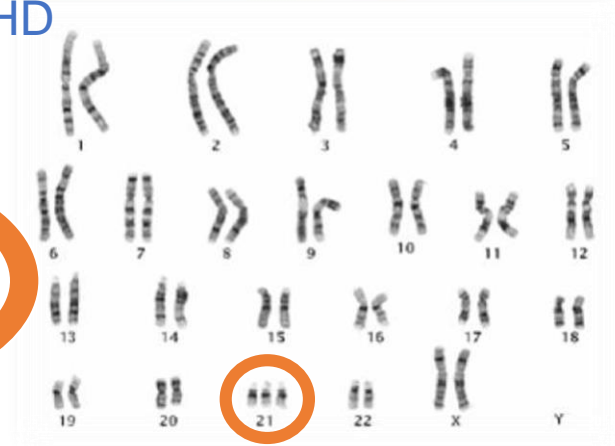
Copy Number Variation (CNV)

Fragment of DNA that differs in «gain» or «loss» copy number compared with reference genome

lead to altered dosage of genes

Aneuploidy

12-42%^{1,2}



¹ Hartman et al. 2011;

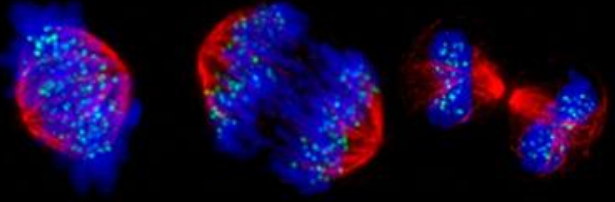
² Shih and Yang 2012, при пренатальном выявлении пороков

³ Fahed et al. 2013

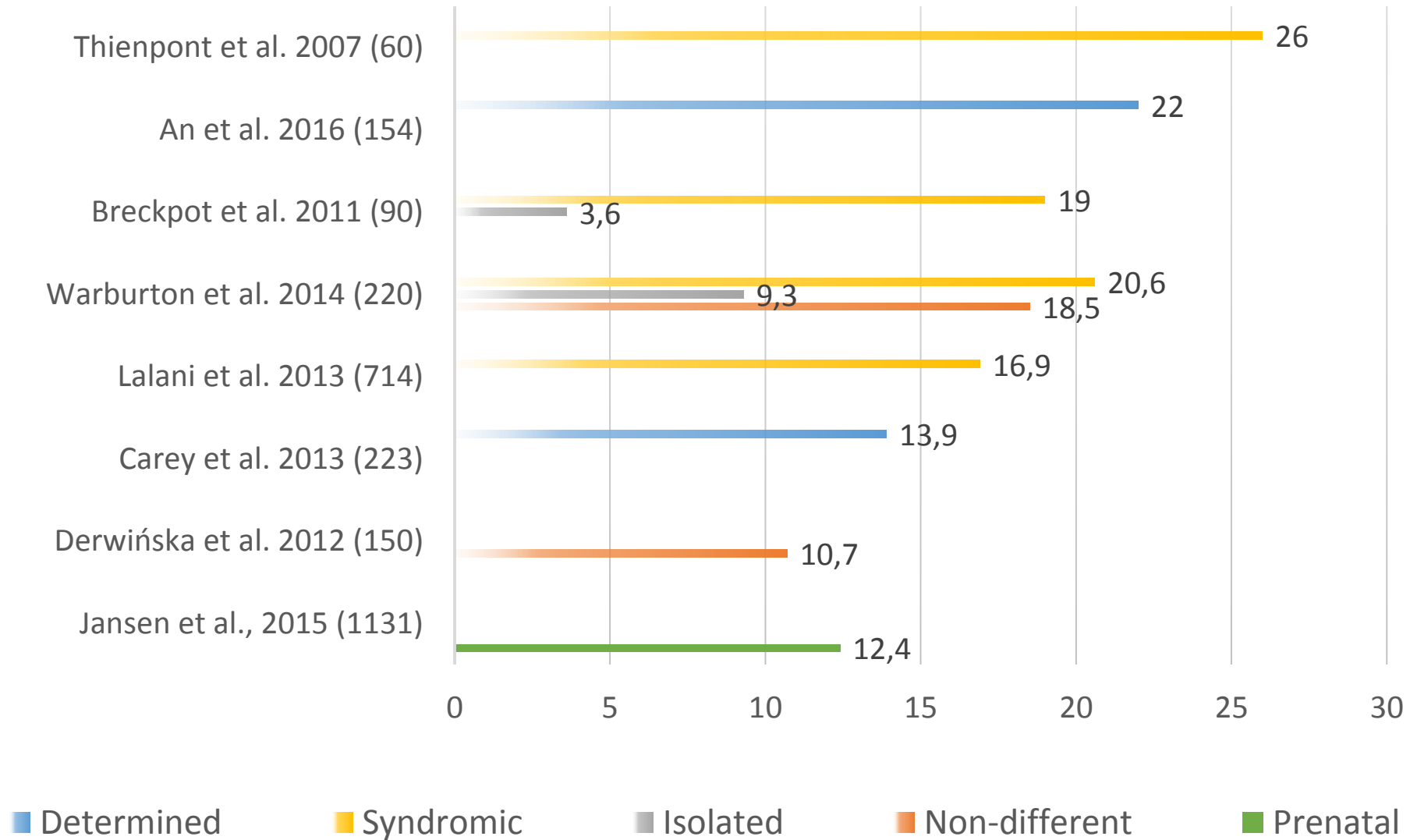
Point mutation

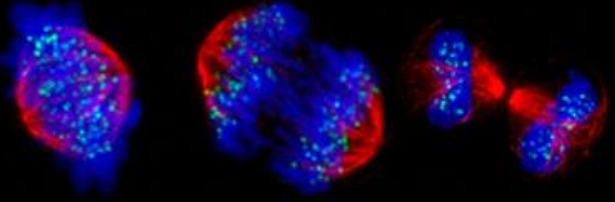
2-3%³

- GATA4
- MEF2A
- NKX2-5
- GATA6
- NOTCH1
- SFR



CNV and CHD (%)

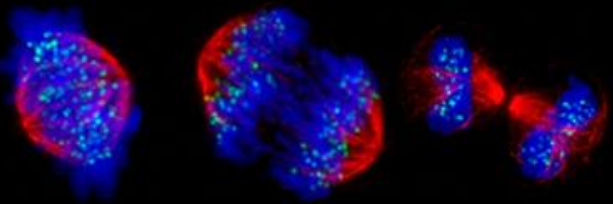




Clinical polymorphism

CNVs





Clinical significance CNV

1. Benign (polymorphic): described in a group of relatively healthy individuals

2. Pathogenic: known syndromes

3. CNVs with

Uncertain clinical significance :

- *likely benign*
- *likely pathogenic*
- *uncertain clinical significance*

Criteria:

- Database
- Type (gain or loss)
- Size
- Genome content
- Inheritance

Material and methods



83



Age:
from 2 days
to 6 years



Geneticist



Cardiologist

Surgeon



Approved LEC

Inclusion criteria:

- Congenital heart defect
- Multiple congenital anomalies, including microanomalies, faces dysmorphism, anatomical features of the structure of the body and internal organs, diseases
- Developmental delay, intellectual disability, behavioral problems

Exclusion criteria:

- Aneuploidy, balanced and non-balanced translocation



aCGH



+ verif.

RT PCR



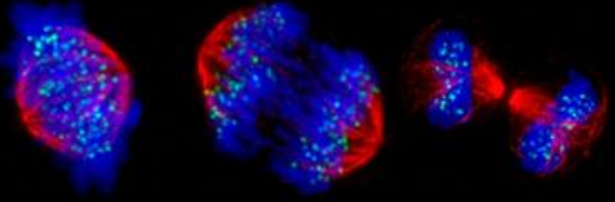
DGV

OMIM

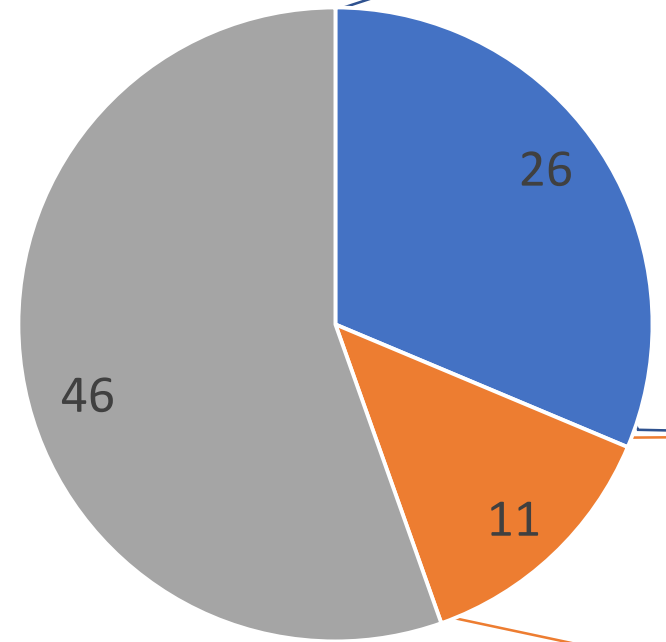
DECIPHER

ECARUCA

ISCA



Results



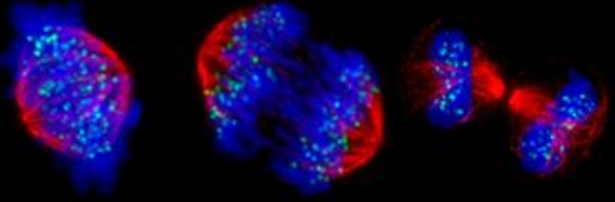
Pathogenic and Likely pathogenic CNVs:

- Microdeletions 22q11 6
- Microduplication 22q11 1
- Microdeletions 7q11.23 3
- Microdeletion 1p36 1
- Microdeletion 10q22-q23 1
- Another rare CNVs 14

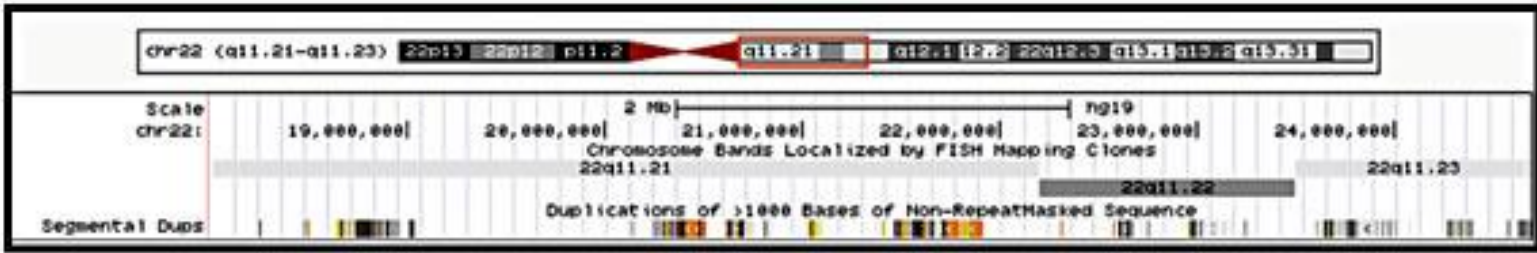
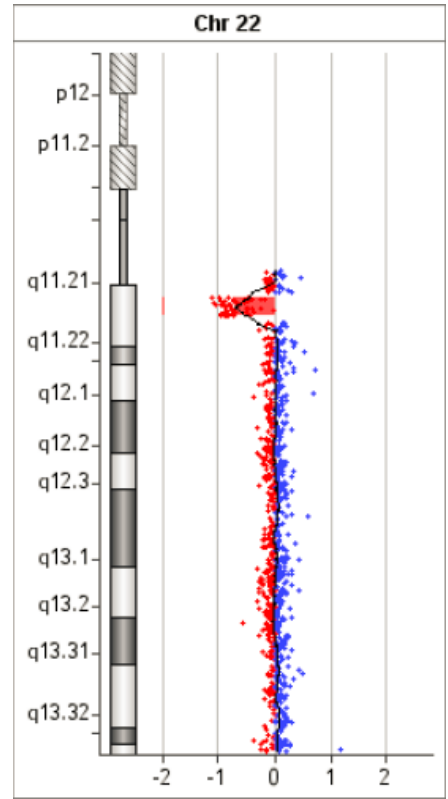


CNVs with uncertain clinical significance:




- Microdeletions 2
- Microduplications 9



Microdeletions 22q11 (6 patients)

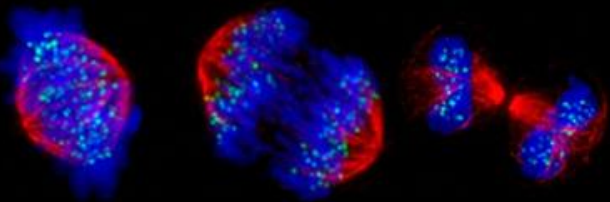


A B C D E F G H

-  2,47 M6 x 4
-  2,41 M6
-  1,39M5

Gene candidate

TBX1, a T-box transcription factor that promotes cell proliferation in the secondary heart field



Microduplication Xp22.31

Вариант	Размер, Мб
arr[hg18] Xq22.31(6562712-8075153)×3	1,52

Chapter 15

Retinoic Acid Signaling and Heart Development

Stéphane Zaffran, Karen Niederreither

Book Editor(s): Pascal Dollé, Karen Neiderreither

First published: 12 June 2015 | <https://doi.org/10.1002/9781118628003.ch15>



The Retinoids: Biology, Biochemistry, and Disease

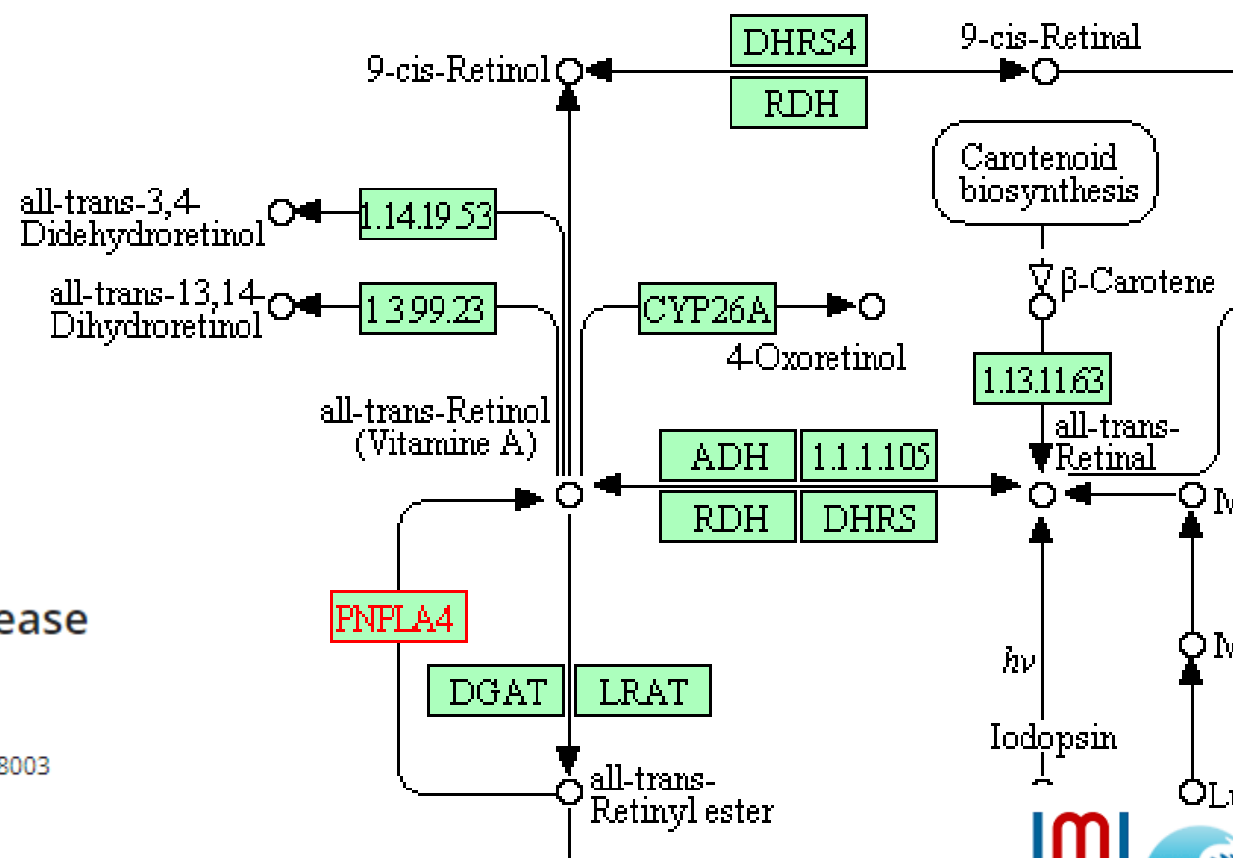
Editors(s): Pascal Dollé, Karen Neiderreither

First published: 12 June 2015

Print ISBN: 9781118627983 | Online ISBN: 9781118628003 | DOI: 10.1002/9781118628003

Copyright © 2015 John Wiley & Sons, Inc.

RETINOL METABOLISM IN ANIMALS



Microduplication 5q11.2

arr[hg18]5q11.2(50714334_51750120)×3

Gene

ISL1

Product

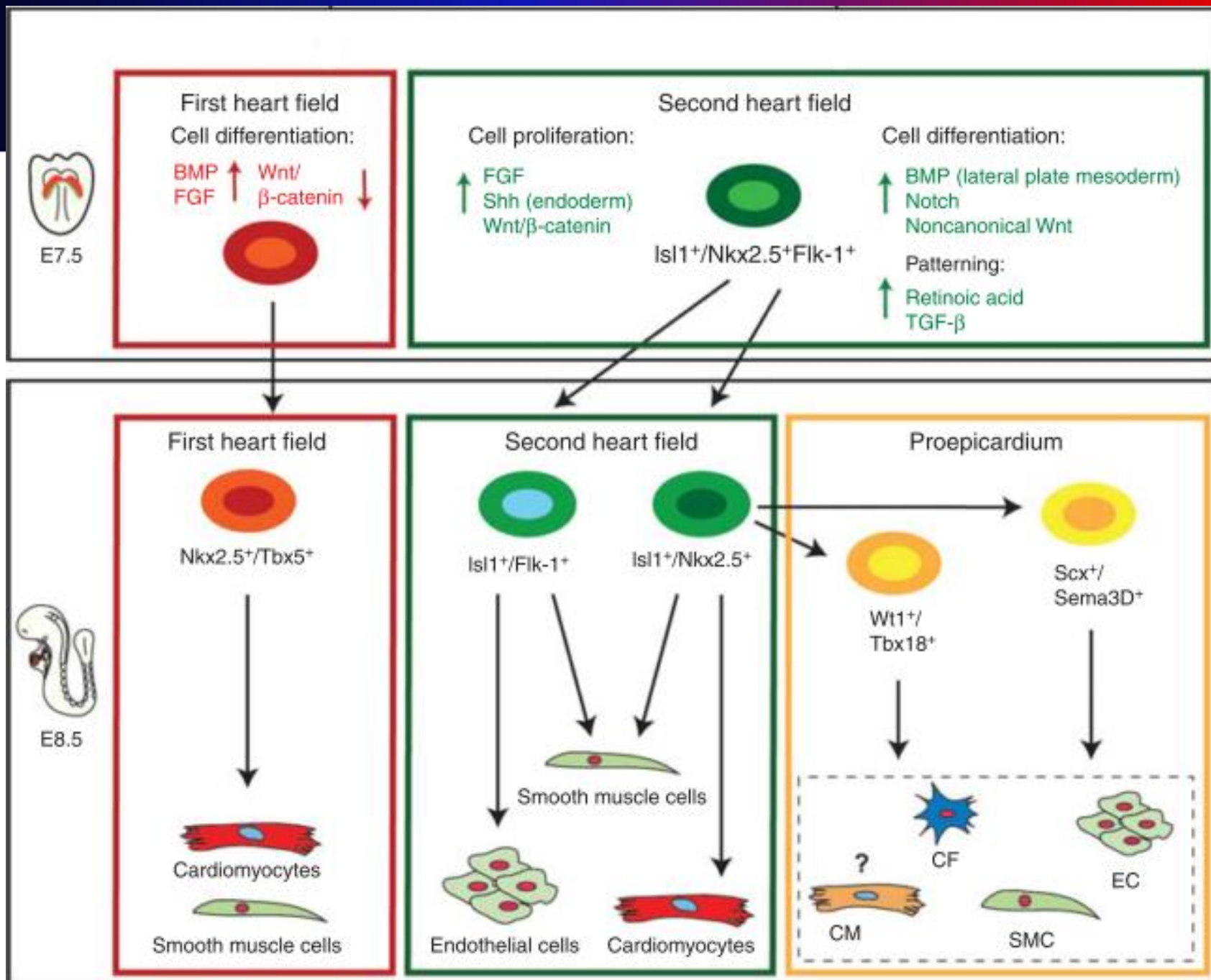
Transcription factor

Function

Induce cell differentiation in second heart field

Reference

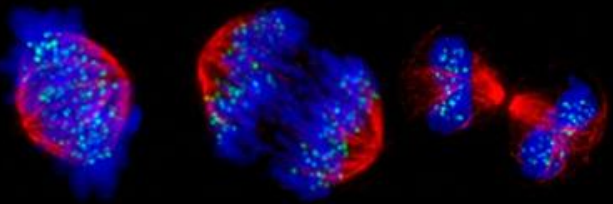
Quaranta et al, 2018





Over-Representation Analysis, GeneOntology

Gene Ontology	Deletion	Genes	Statistic
GO:0030054 cell junction	1p36	TPRG1L, FAAP20, GABRD, KLHL17, TMEM240, AGRN, PRKCZ, TP73	Gene set size=1357; Overlap=20; Expected Value=6,78; Enrichment Ratio=2,95; $p_{FDR}=0,00927$
	7q11.23	CLDN4, CLDN3, ARHGEF16 LIMK1, STX1A, EIF4H	
	22q11.2	CRKL, PI4KA, RANBP1, CLDN5, SCARF2, P2RX6	

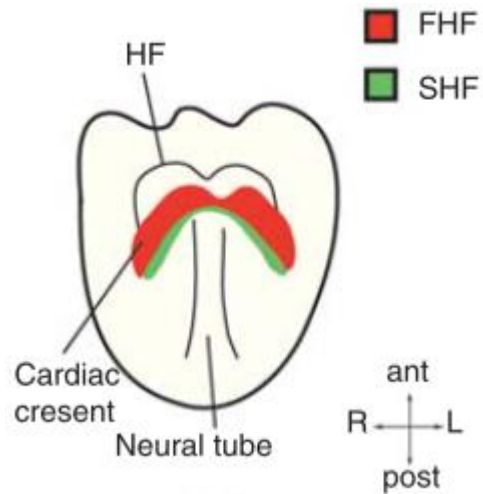
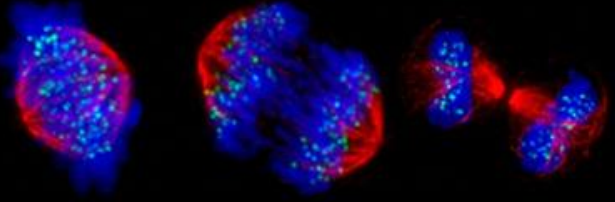


Conclusion

- Pathogenetically significant CNVs are found in 30% of patients with extracardiac pathology.
- CNV contains genes responsible for cardiogenesis.
- Cell junction is one of the basic biological processes characterized enrichment of genes from pathogenic microdeletions.



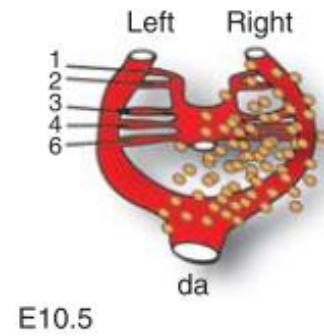
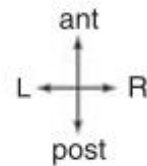
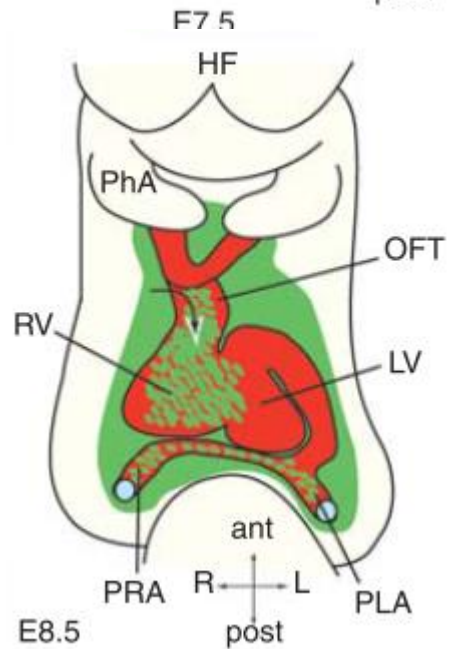
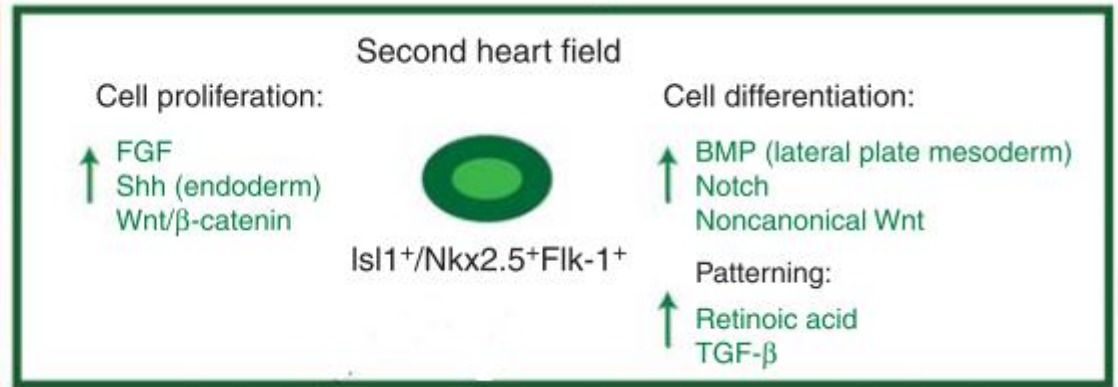
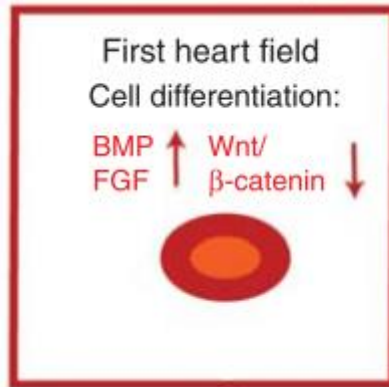
Формирование сердца



■ FHF
■ SHF

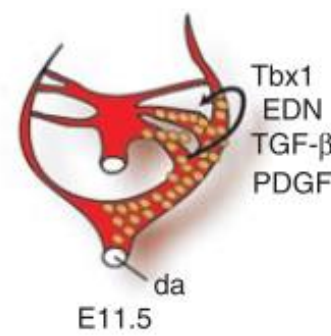


E7.5

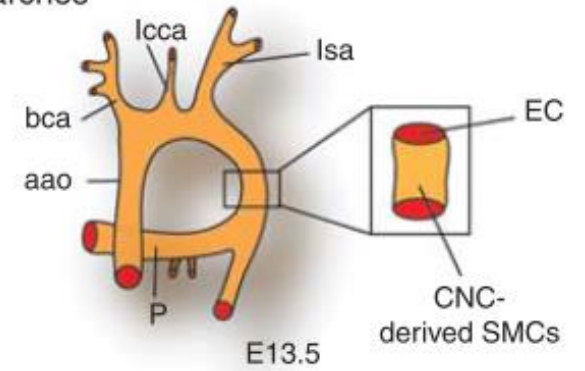


E10.5

Repatterning of the aortic arches



E11.5



E13.5