22q11 deletions-syndrom

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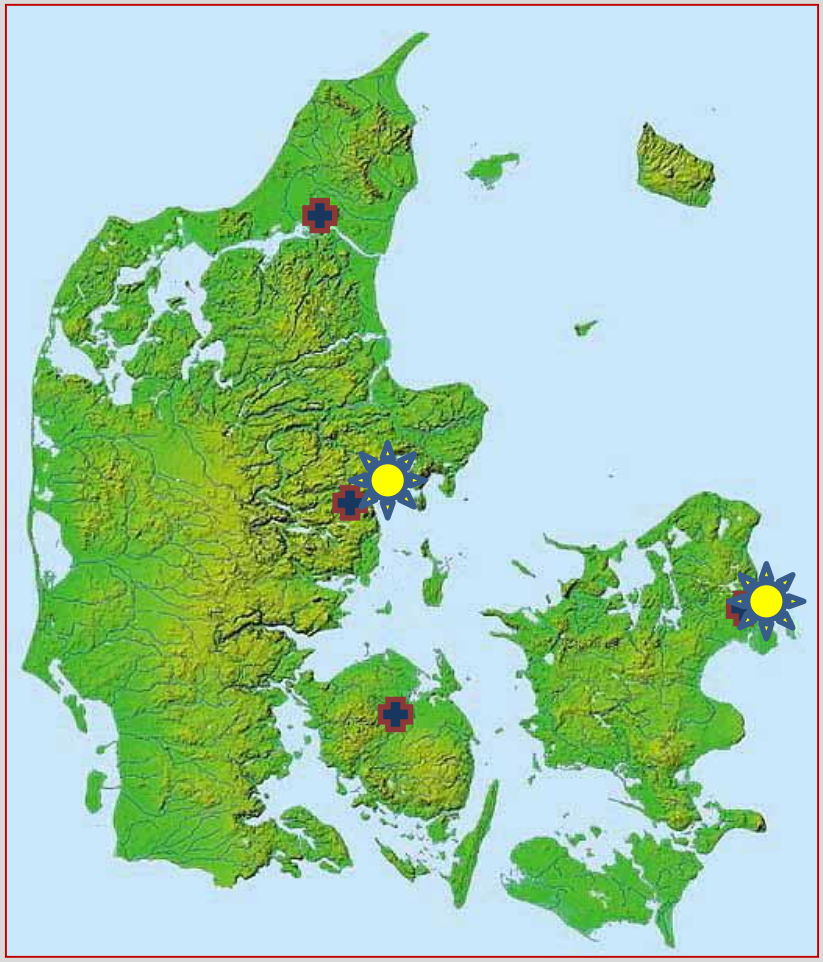
Sjældne-landskabet

- **To landdelscentre**
  - **Center for Sjældne Sygdomme, AUH & RH**
    - Helhedsorienteret indsats
- Højt specialiserede funktioner
  - Specialafdelinger
    - Organspecifik



22q11 deletions-syndrom

- 1:4.000

- Tidligere benævnelser
  - DiGeorge syndrom
  - CATCH 22
  - Shprintzen syndrom
  - Velo-Cardio-Facialt syndrom
  - Conotruncal Anomalies-Face syndrom

Hvad karakteriserer sjældne sygdomme?

- **Ofte arvelig/genetisk**
  - omtrent halvdelen debuterer i barnealderen
- **Kroniske**
  - de fleste kan ikke helbredes
  - kan være fremadskridende og med kortere livslængde
- **Komplekse**
  - ofte symptomer fra mindst 2 organsystemer, og dermed behov for indsats fra flere specialer
- **Diagnostik og behandling** kan være kompliceret
- **Velkoordineret indsats** nødvendig
  - tværfaglig
  - multidisciplinær

Kompleks fænotype

- **Meget variabel**

- 180 symptomer og misdannelser beskrevet
  - Somatik
  - Kognition
  - Adfærd & psyke

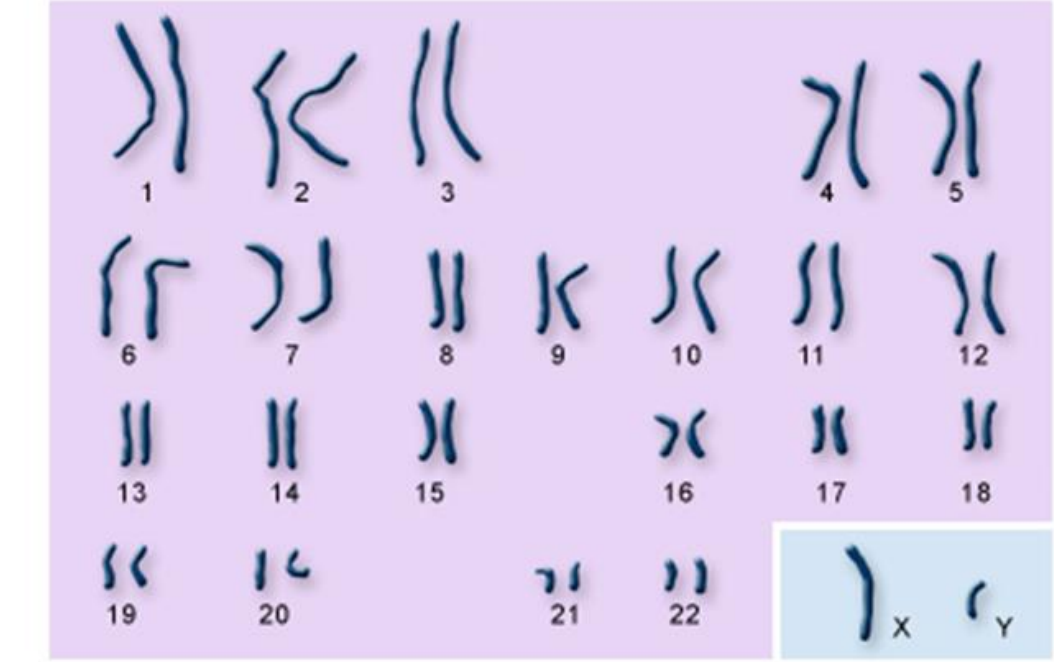
- Ingen obligatoriske fund

Box 1. Common features of the 22q11 deletion syndrome

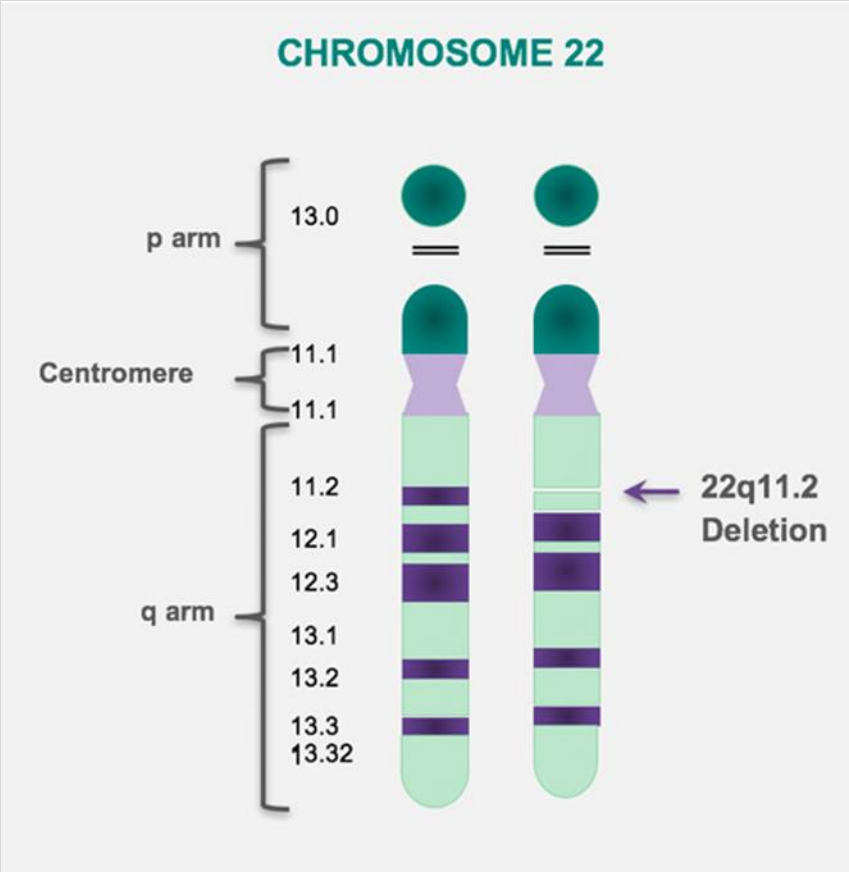
Congenital heart disease
Immunodeficiency
Hypocalcemia
Palate anomalies
Velopharyngeal dysfunction and other speech disorders
Feeding disorders and growth retardation
Otorhinolaryngologic issues
Dysmorphic facies
Renal anomalies
Skeletal anomalies
Cognitive or learning disabilities
Behavioral or psychiatric disorders

Mc Donald-McGinn & Sullivan. Medicine 2011 Goldmuntz. Clin Perinatol 2005;32:963-978

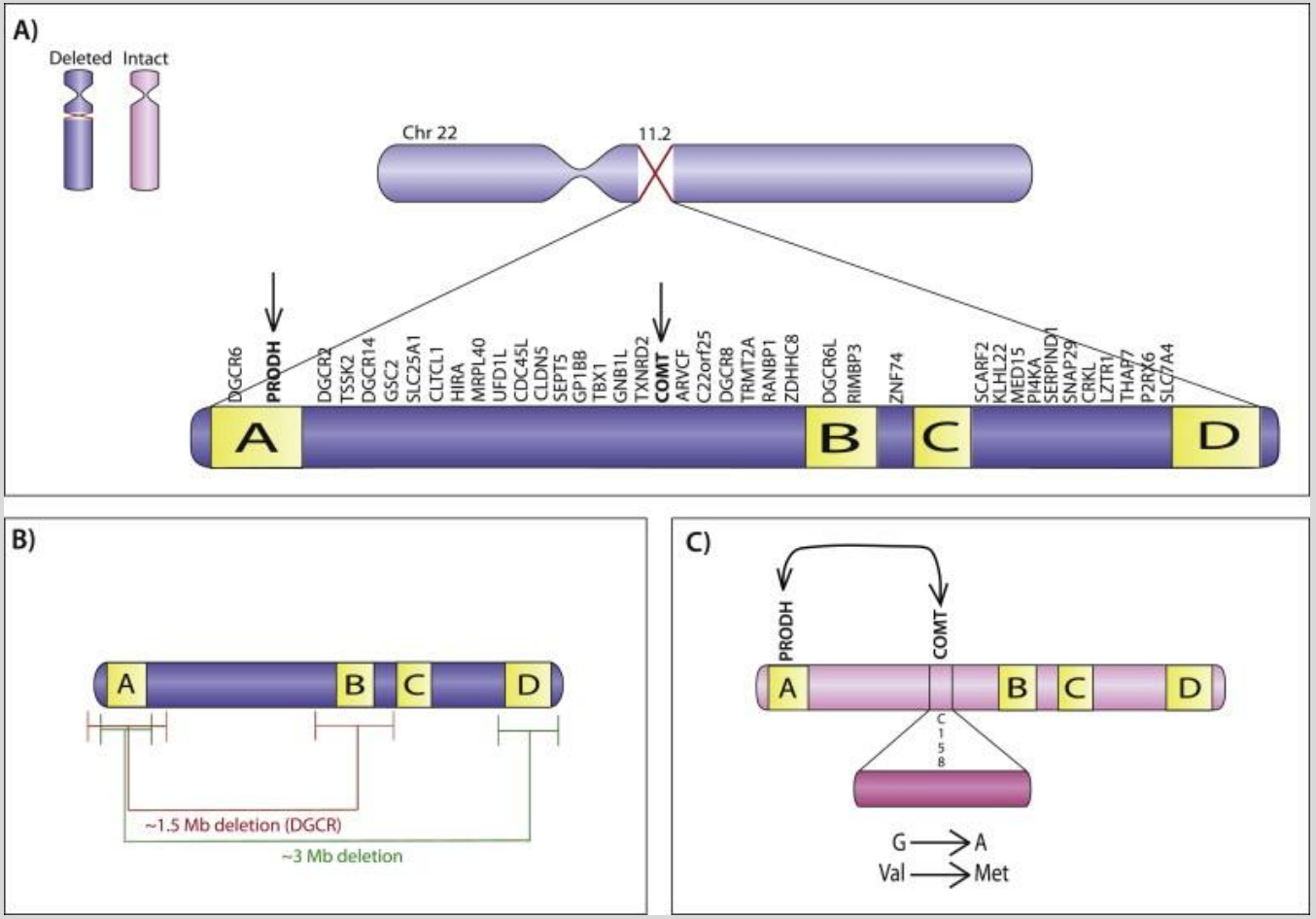
En genetisk sygdom



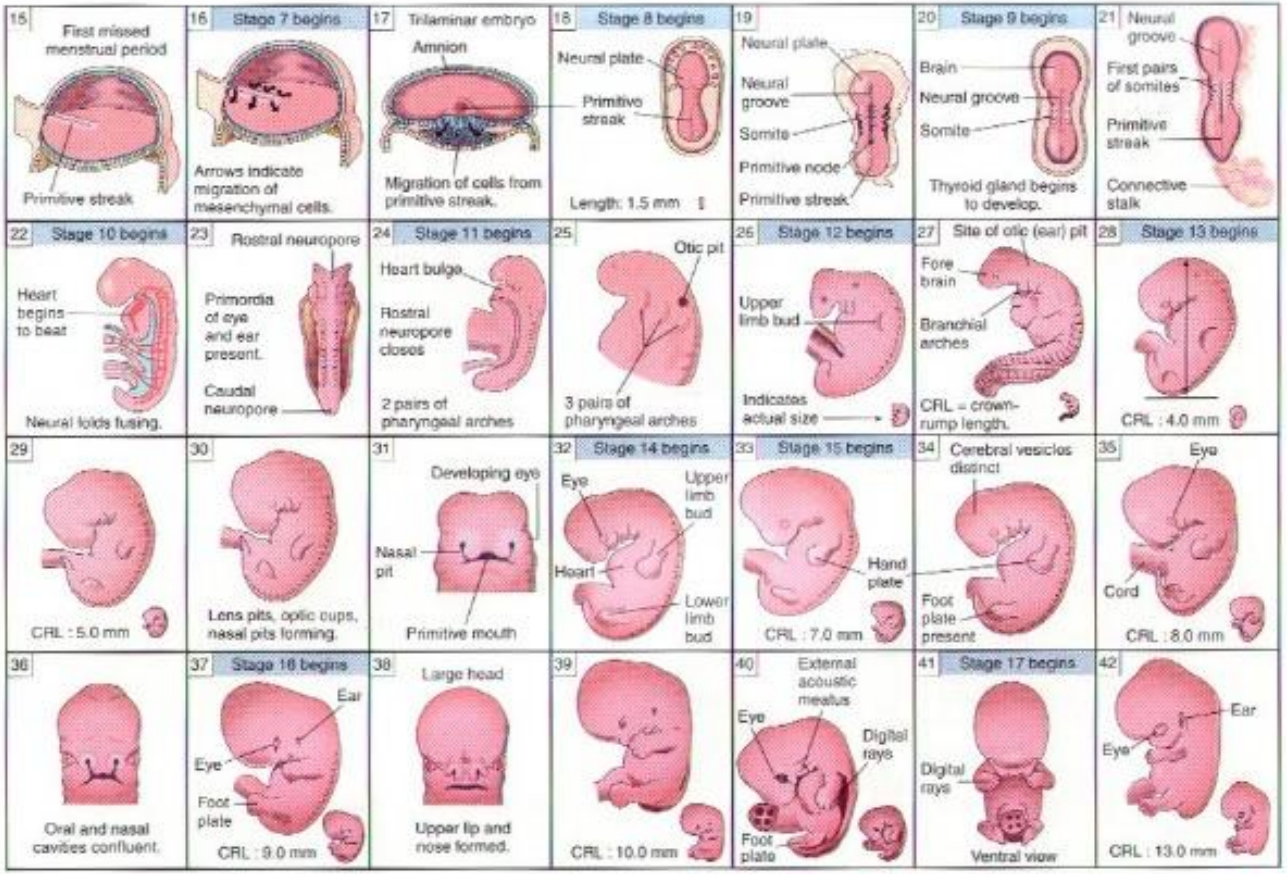
22q11.2 deletion



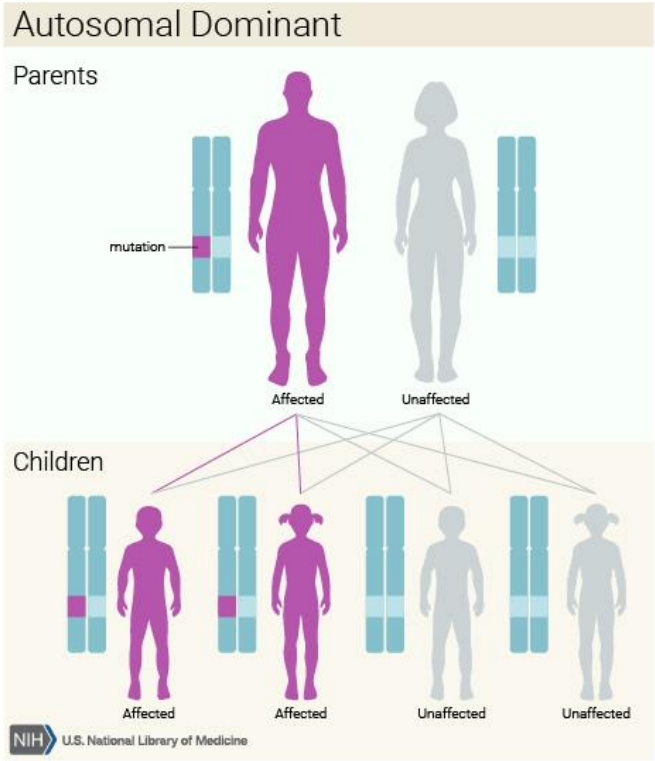
22q11.2


A)
Deleted
Intact
Chr 22
11.2
DGCR6
PRODH
DGCR2
TSSK2
DGCR14
GSC2
SLC25A1
CLTCL1
HIRA
MRPL40
UFD1L
CDC45L
CLDN5
SEPT5
GP1BB
TBX1
GNB1L
TXNRD2
COMT
ARVCF
C22orf25
DGCR8
TRMT2A
RANBP1
ZDHHC8
DGCR6L
RIMBP3
ZNF74
SCARF2
KLHL22
MED15
PI4KA
SERPIND1
SNAP29
CRKL
LZTR1
THAP7
P2RX6
SLC7A4
A
B
C
D
B)
A
B
C
D
~1.5 Mb deletion (DGCR)
~3 Mb deletion
C)
PRODH
COMT
A
B
C
D
C
1
5
8
G → A
Val → Met

Timetable Of Human Prenatal Development

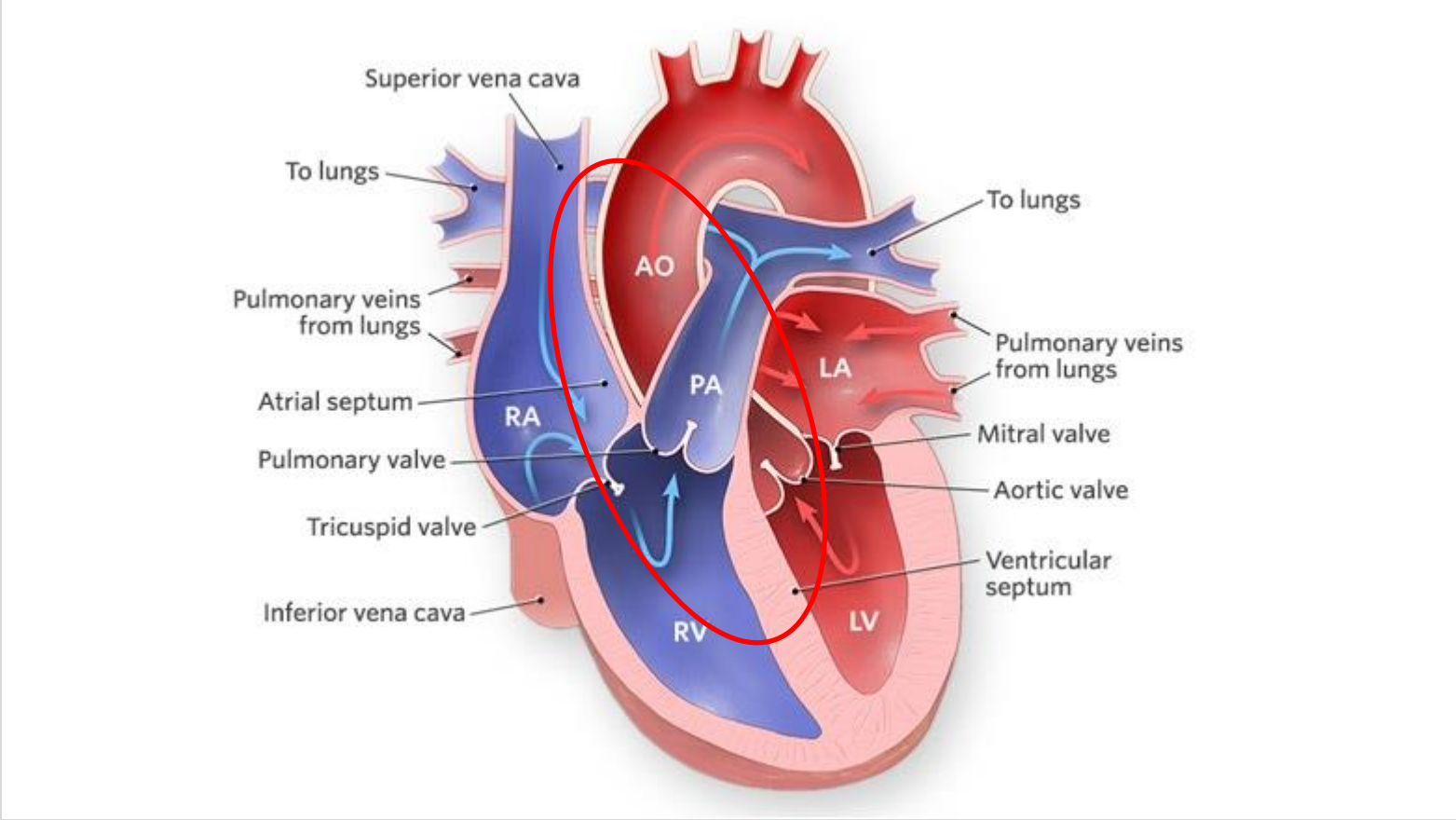


En arvelig sygdom



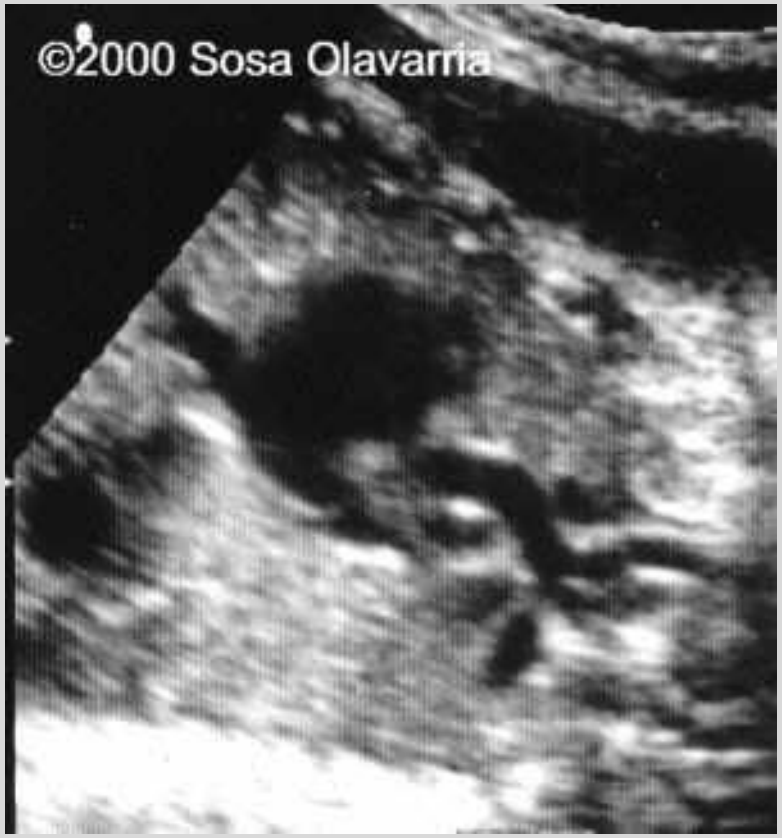
- Lige hyppigt hos begge køn
- 85 % nyopståede
- 15 % arvet fra mor eller far

Det normale hjerte

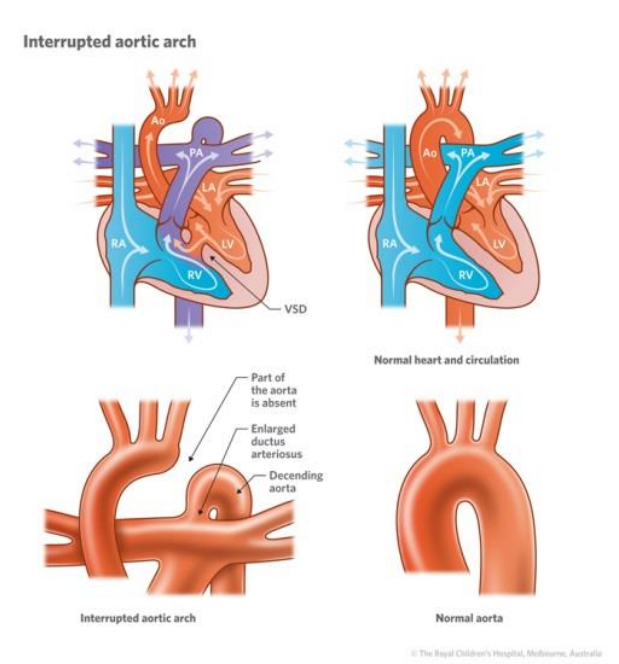


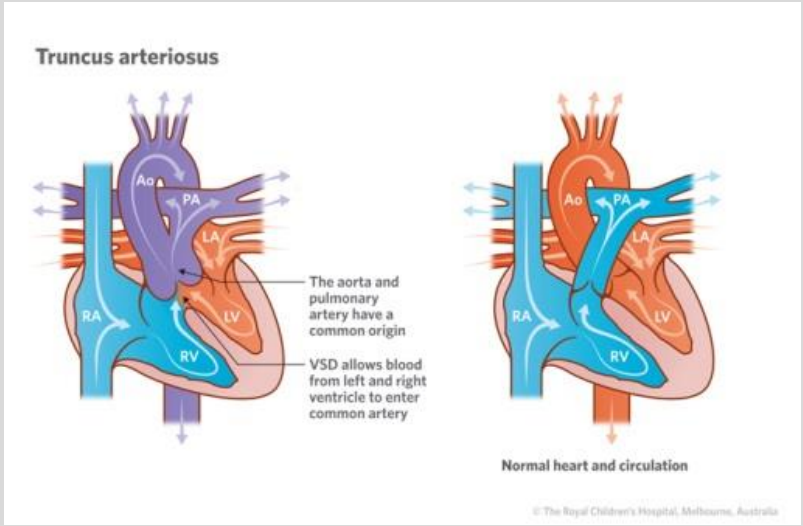
22q11 ds

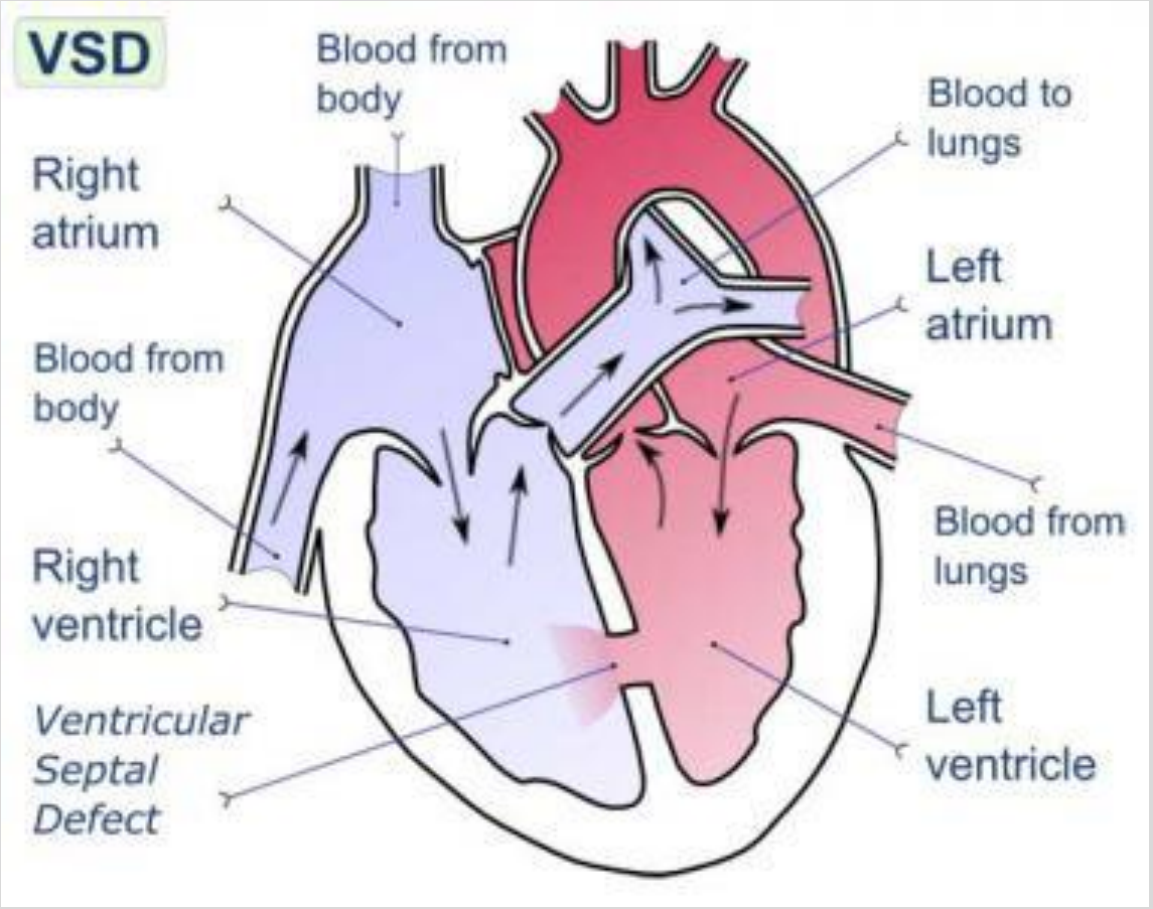
- Medfødt hjertefejl hos 75%
  - Steno-Fallots tetralogi
  - Truncus arteriosus
  - Afbrudt aortabue
  - VSD



Medfødte hjertefejl






VSD
Blood from body
Blood to lungs
Right atrium
Left atrium
Blood from body
Blood from lungs
Right ventricle
Left ventricle
Ventricular Septal Defect

Forekomst af 22q11ds ved medfødt hjertefejl

- Medfødt hjertefejl i DK, 2002-2008
  - I: 8,6 ud af 1.000
  - P: 2.500 nyfødte
    - 22q11 hos 2%
      - VSD
      - Fallot's tetralogi
      - Coarctatio
      - Truncus arteriosus

TABLE I. Prevalence of 22q11.2 Deletions in Cardiovascular Malformations as Listed in ICD-10

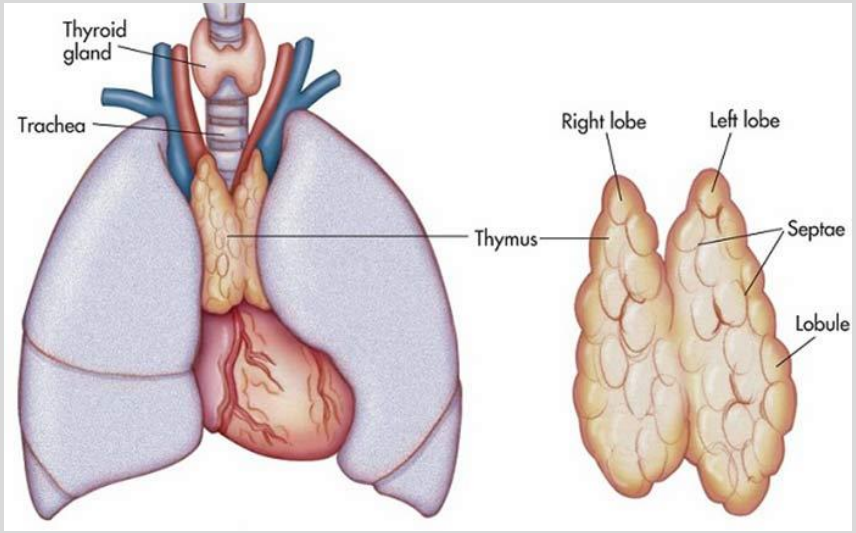
	NPR	22q11.2 deletion tests			
ICD-10 code	N registered	N tests	% (95% CI) tests	N del	Prevalence (% (95% CI))
Q20.0: common arterial trunk (TA)	48	43	90 (77–97)	5	12 (4–26)
Q20.1: double outlet right ventricle (DORV)	90	82	91 (83–96)	2	2 (0–9)
Q20.2: double outlet left ventricle	8	6	75 (35–97)	0	—
Q20.3: tranposition of great vessels (complete)	189	162	86 (80–90)	0	—
Q20.4: double inlet ventricle	61	51	84 (72–92)	1	2 (0–12)
Q20.5: ventricular inversion	18	16	89 (65–99)	0	—
Q20.6: isomerism of atrial appendages	10	10	100 (69–100)	0	—
Q20.8: other malformations of chambers and connections	6	4	67 (22–96)	0	—
Q20: congenital malformations of chambers and connections	**430**	**374**	**87 (84–90)**	**8**	**2 (1–4)**
Q21.0: ventricular septal defect (VSD)	904	775	86 (83–88)	15	2 (1–3)
Q21.1: atrial septal defect (ASD)	535	450	84 (81–87)	3	1 (0–2)
Q21.2: atrioventricular septal defect	184	163	89 (83–93)	0	—
Q21.3: tetralogy of Fallot (TOF)	210	194	92 (88–96)	15	8 (5–13)
Q21.4: aortopulmonary septal defect	8	7	88 (47–99)	0	—
Q21.8: other malformations of cardiac septa	3	2	67 (9–99)	0	—
Q21: congenital malformations of cardiac septa	**1,844**	**1,591**	**86 (85–88)**	**33**	**2 (1–3)**
Q22.0: pulmonary valve atresia	52	45	87 (74–94)	3	7 (2–19)
Q22.1: congenital pulmonary valve stenosis	178	162	91 (86–95)	1	1 (0–4)
Q22.2: congenital pulmonary valve insufficiency	2	1	50 (1–99)	0	—
Q22.3: other congenital malformations of pulmonary valve	1	1	100 (3–100)	0	—
Q22.4: congenital tricuspid stenosis	18	10	56 (31–78)	0	—
Q22.5: Ebstein's anomaly	14	12	86 (57–98)	0	—
Q22.6: hypoplastic right heart syndrome	22	18	82 (60–95)	0	—
Q22.8: other congenital malformations of tricuspid valve	11	9	82 (48–98)	0	—
Q22: congenital malformations of pulmonary and tricuspid valves	**298**	**258**	**87 (83–90)**	**4**	**2 (1–4)**
Q23.0: congenital stenosis of aortic valve	88	71	81 (71–88)	2	3 (0–11)
Q23.1: congenital insufficiency of aortic valve	16	14	88 (62–98)	0	—
Q23.2: congenital mitral stenosis	5	5	100 (48–100)	0	—
Q23.3: congenital mitral insufficiency	21	18	86 (64–97)	0	—
Q23.4: hypoplastic left heart syndrome	98	51	52 (42–62)	1	2 (0–12)
Q23.8: other congenital malformations of aortic and mitral valves	11	7	64 (31–89)	0	—
Q23: congenital malformations of aortic and mitral valves	**239**	**166**	**69 (64–75)**	**3**	**2 (0–6)**
Q24.0: dextrocardia	5	3	60 (15–95)	0	—
Q24.2: cor triatriatum	3	2	67 (9–99)	0	—
Q24.3: pulmonary infundibular stenosis	11	11	100 (72–100)	0	—
Q24.4: congenital subaortic stenosis	24	19	79 (58–93)	0	—
Q24.5: malformation of coronary vessels	9	7	78 (40–97)	0	—
Q24.6: congenital heart block	8	5	63 (24–91)	0	—
Q24.8: other specified congenital malformations of heart	7	5	71 (29–96)	0	—
Q24: other congenital malformations of heart	**67**	**52**	**78 (67–88)**	**0**	**—**
Q25.0: patent ductus arteriosus	262	213	81 (76–86)	1	0 (0–3)
Q25.1: coarctation of aorta	207	178	86 (81–90)	1	1 (0–4)
Q25.2: atresia of aorta (IAA)	45	36	80 (65–90)	8	22 (11–40)
Q25.3: stenosis of aorta	17	13	76 (50–93)	0	—
Q25.4: other congenital malformations of aorta	25	23	92 (74–99)	3	15 (4–39)
Q25.5: atresia of pulmonary artery	32	30	94 (79–99)	2	7 (1–24)
Q25.6: stenosis of pulmonary artery	48	43	90 (77–97)	1	2 (0–14)
Q25.7: other congenital malformations of pulmonary artery	7	6	86 (42–99)	1	17 (1–64)
Q25.8: other congenital malformations of great arteries	15	12	80 (52–96)	3	25 (7–57)
Q25: congenital malformations of great arteries	**658**	**554**	**84 (81–87)**	**20**	**4 (2–6)**
Q20-Q25 Diagnose-based numbers	**3,536**	**2,995**	**85 (83–86)**	**68**	**2.3 (1.8–2.9)**
Q20-Q25 Individual-based numbers	**2,952**	**2,478**	**84 (83–85)**	**46**	**1.9 (1.4–2.5)**

The ICD-10 does not facilitate further subdivision of diagnoses.

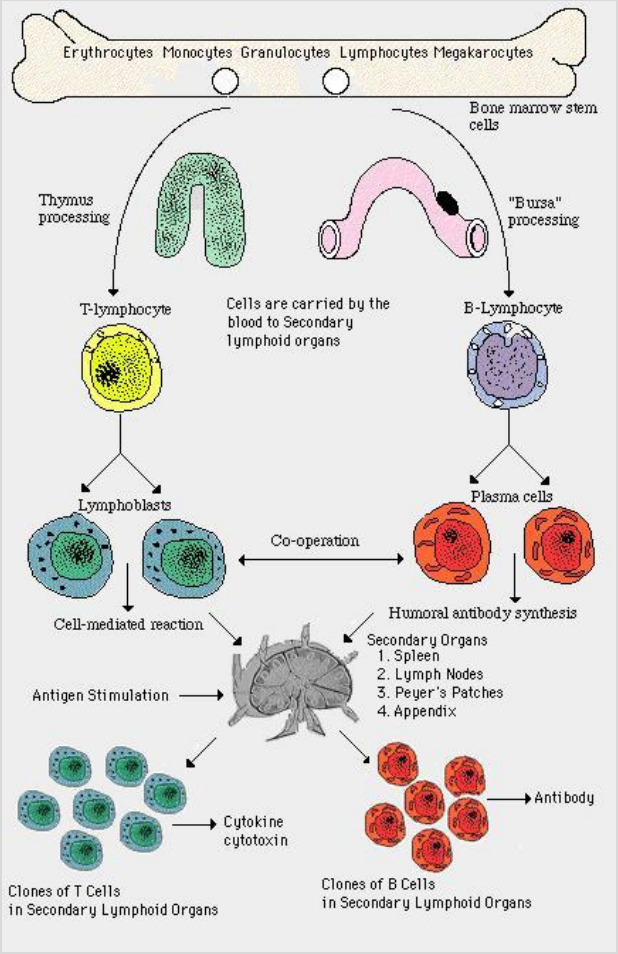
Agergaard et al. Am J Med Genet 2012

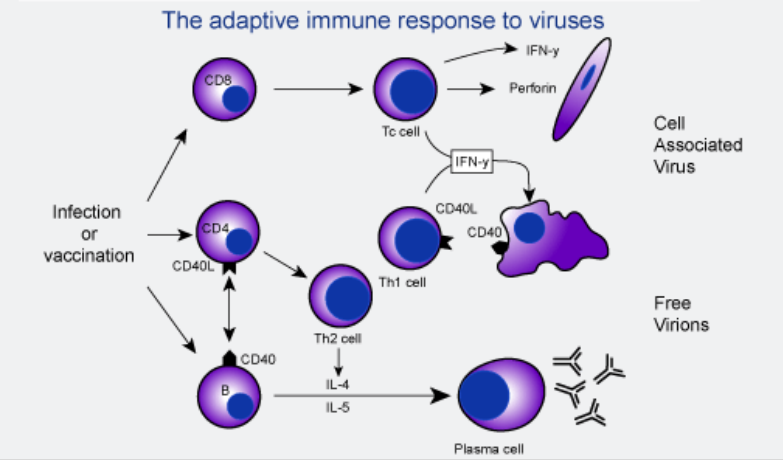
Immundefekt

- Thymus mangler eller er lille (hos 50%)
- Høj forekomst af abnormt immunapparat
  - T-celle defekt
- Klinisk immundefekt hos ret få
- Vaccinationer



Immunapparatet





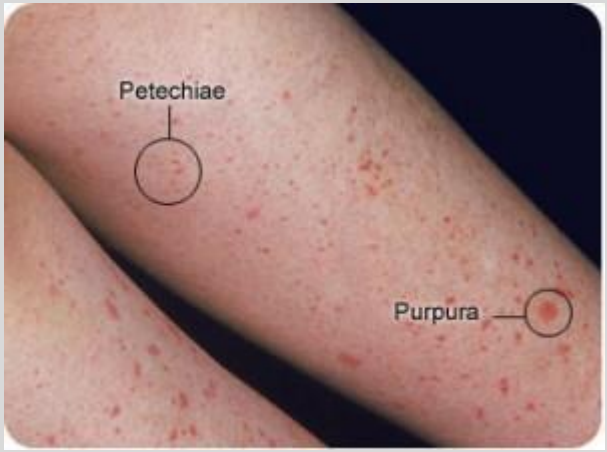
- Blodprøver
  - Lymfocytter
  - Antistoffer
  - Effekt af vaccine

Autoimmun sygdom

TABLE I. Demographic characteristics of the 11 patients with pDGS and autoimmune diseases

Patient no.	Sex	Disease	Age at disease (y)
1	F	Hypothyroidism	8
2	M	Hypothyroidism	7
3	F	Hypothyroidism, vitiligo	11
4	M	ITP	4
5	F	ITP	6
6	F	ITP, autoimmune neutropenia, AIHA	7
7	F	ITP, AIHA	5
8	M	Autoimmune neutropenia	0.7
9	F	Monoarticular arthritis, ANA^+	4
10	F	Polyarticular JIA	3
11	F	Psoriasis	5

ANA, Antinuclear antibodies; *F*, female; *ITP*, immune thrombocytopenic purpura; *JIA*, juvenile idiopathic arthritis; *M*, male.

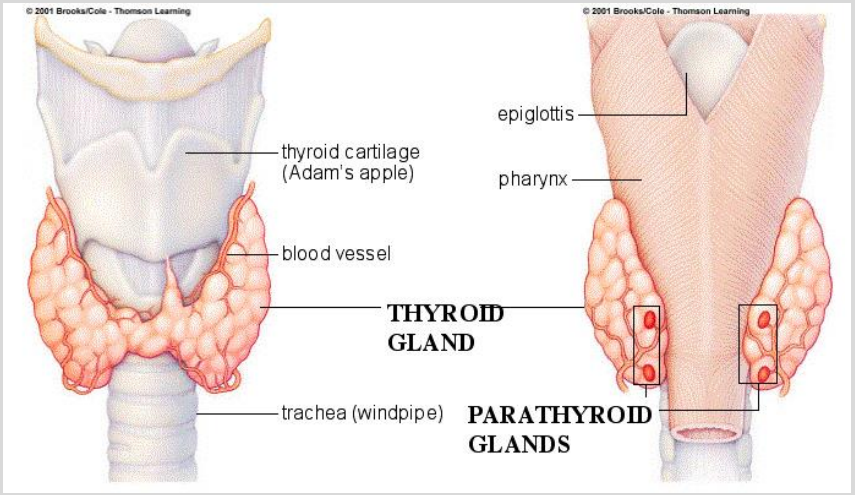


- 10 %
  - ITP 4 %
    - Lavt antal blodplader
  - Lavt stofskifte
  - Gigt
  - Cøliaki
    - glutenallergi

Tison et al. J Allergy Clin Immunol 2011;128:1115-16

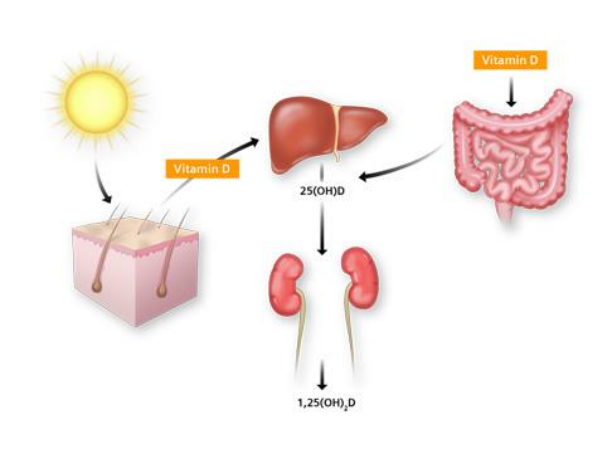
Hypocalcæmi (lavt kalk)

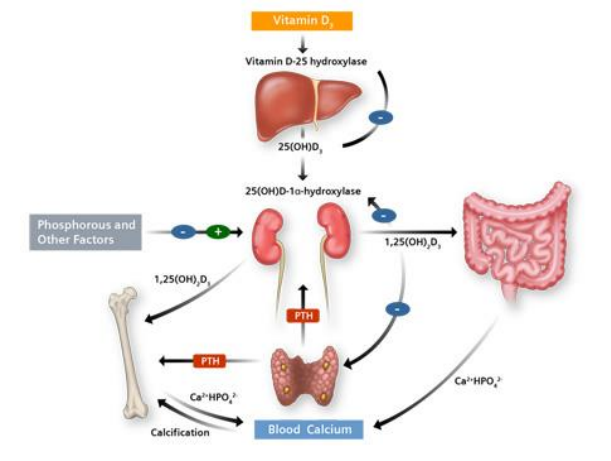
- Hos 50%
  - Sitren
- Abnorm parathyroidea-funktion
- Nyfødte
  - Kramper
- Sjældent kronisk
- Intermitterende
  - Akut sygdom
  - Pubertet
  - Graviditet



Behandling af lavt kalk

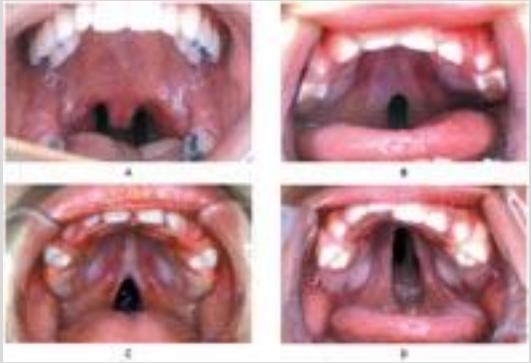
- Behandling
  - Kalk
    - 600 – 1200 mg/dag
  - D-vitamin
    - 10 – 20 µg
    - Evt aktiveret D-vitamin
  - Magnesium
  - Motion





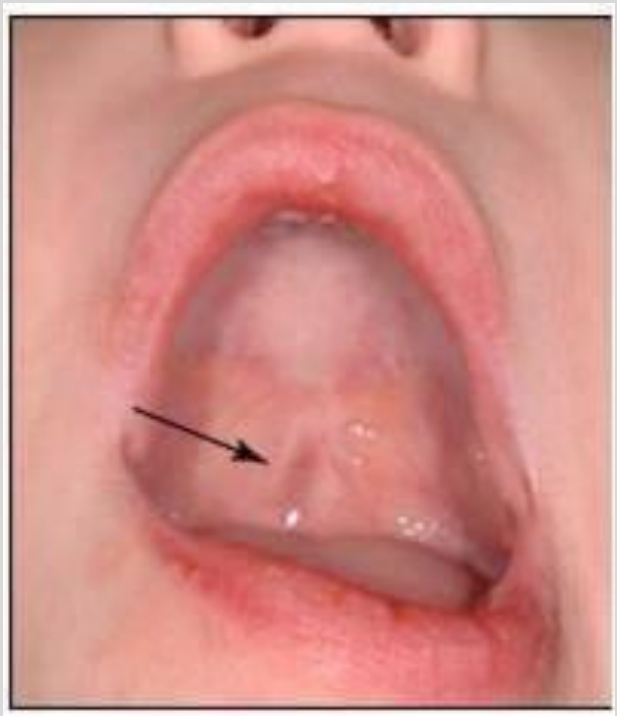
Ganen

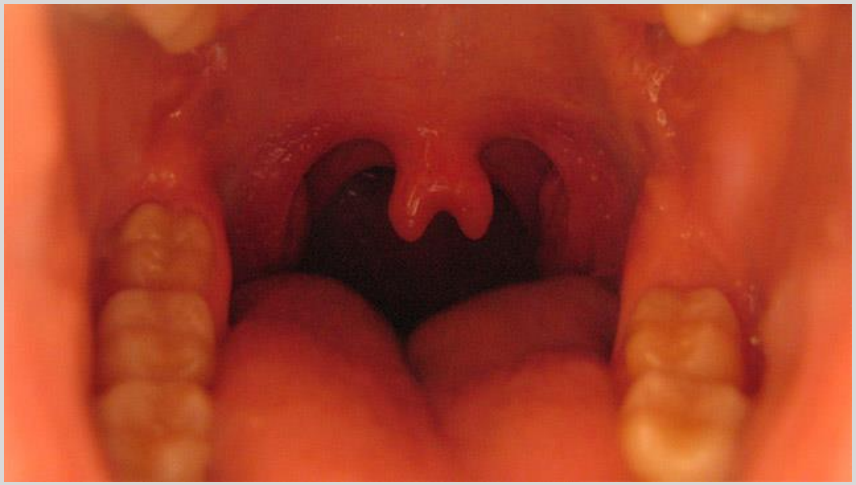
- Ganeanomalier
  - Veloinsufficiens 60%
    - Nedsat lukke
    - Nedsat bevægelighed
  - Submukøs eller isoleret ganespalte
    - 14-32 %



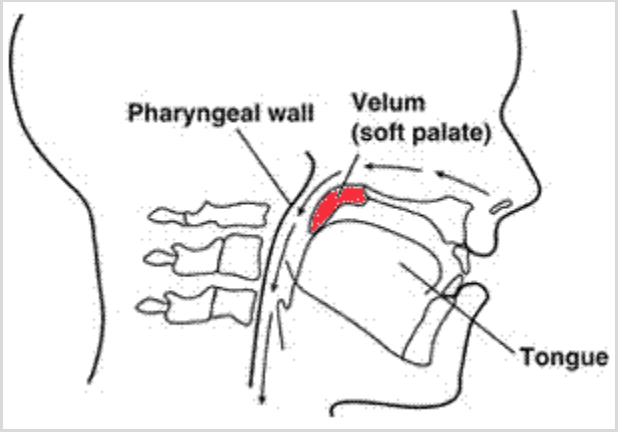
- Vanskeligheder
  - Die/spise
  - Synke
  - Udtale (hypernasal)

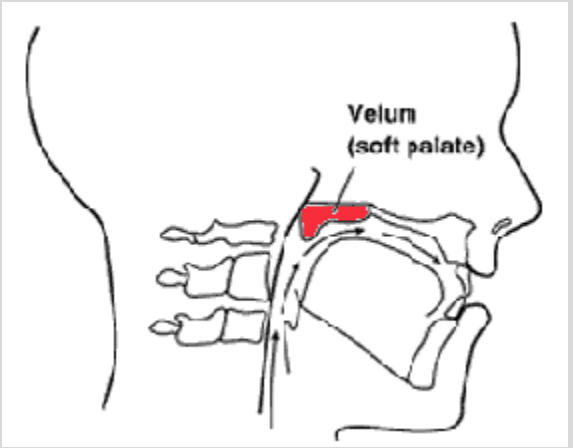
Ganen



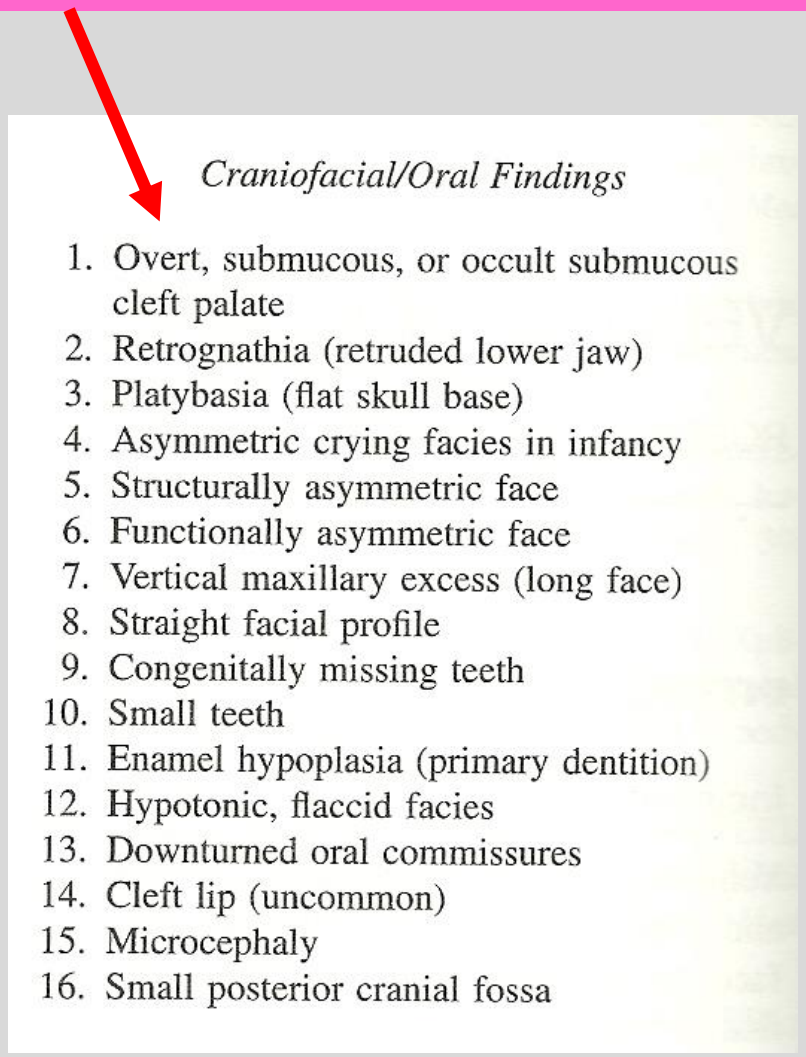


Ganefunktion





Sprog & tale

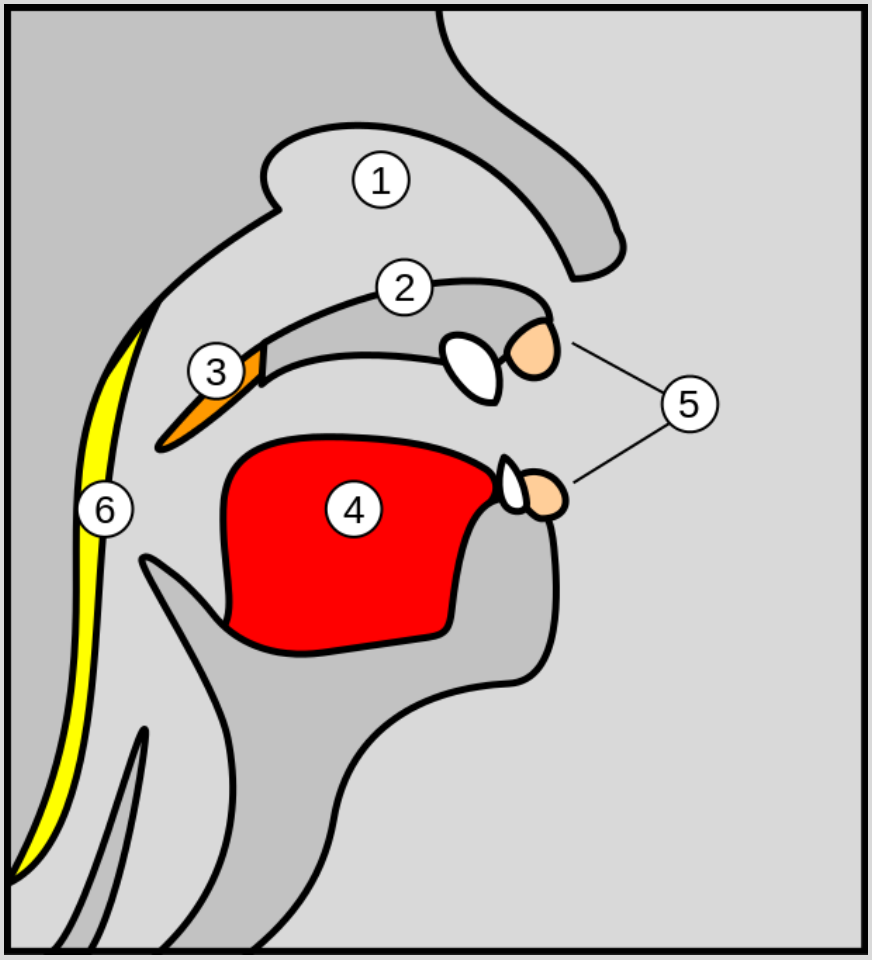


Craniofacial/Oral Findings

1. Overt, submucous, or occult submucous cleft palate
2. Retrognathia (retruded lower jaw)
3. Platybasia (flat skull base)
4. Asymmetric crying facies in infancy
5. Structurally asymmetric face
6. Functionally asymmetric face
7. Vertical maxillary excess (long face)
8. Straight facial profile
9. Congenitally missing teeth
10. Small teeth
11. Enamel hypoplasia (primary dentition)
12. Hypotonic, flaccid facies
13. Downturned oral commissures
14. Cleft lip (uncommon)
15. Microcephaly
16. Small posterior cranial fossa

- ganespalte, ubevægeligt ganesejl
- ”åbent snøvl” (hypernasal tale)
- forsinket sprog og sprog-forståelse

Taleforbedrende operation



Tænder

Craniofacial/Oral Findings

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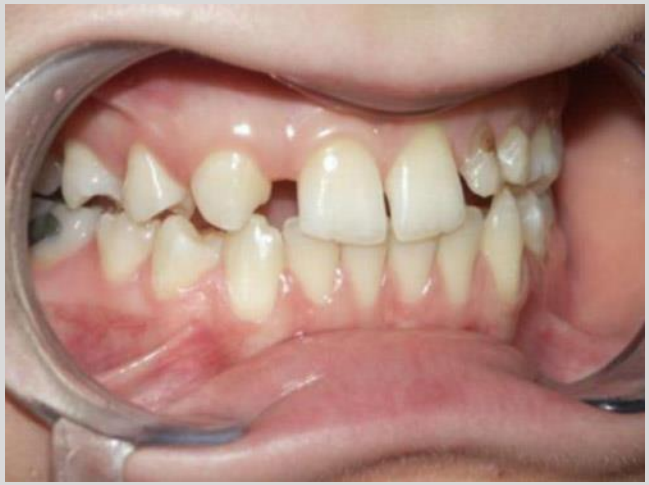


Vækst

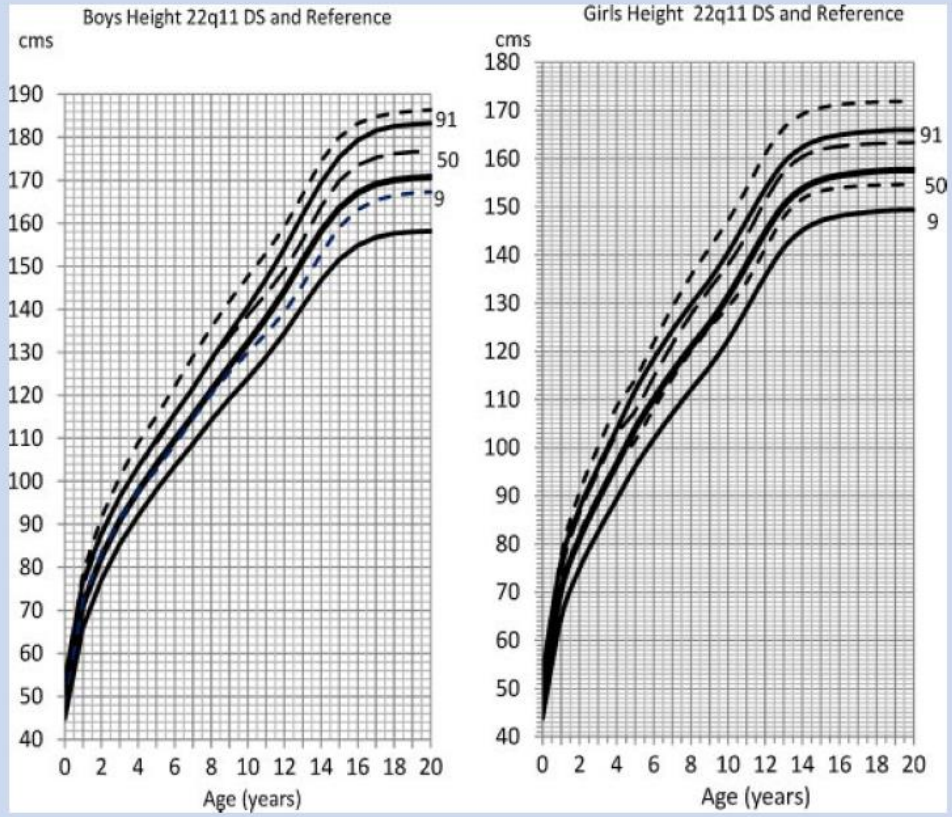


FIG. 1. Boys and girls height. Birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

Habel et al. Am J Med Genet 2012.

Hovedomfang

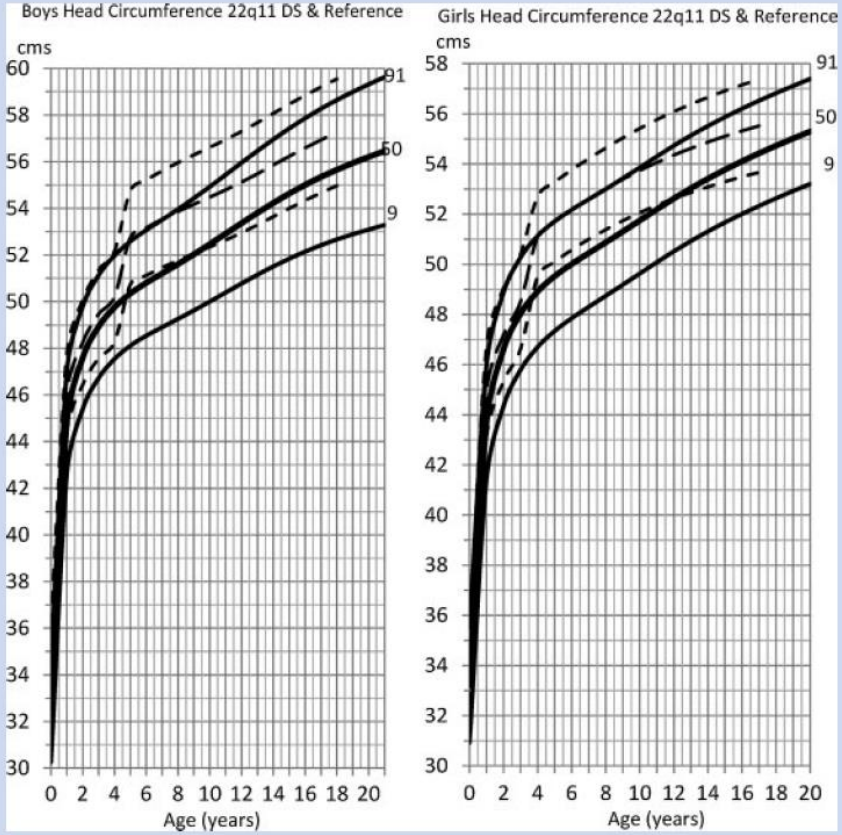


FIG. 4. Boys and girls head circumference birth to 20 years. 9th, 50th, and 91st centile lines for 22q11 DS (solid) and composite Reference (dashed).

Habel et al. Am J Med Genet 2012

Ansigtstræk

FIGURE 7. Case 3. Dysmorphic facial features of child mentioned in case. The affected child had several features common to children with chromosome 22q11.2 deletion syndrome, including hooded eyes, a bulbous nasal tip, a small chin, and a crumpled ear helix. (Photographs used with consent.)

McDonald-McGinn & Sullivan. Medicine 2011

Ansigtstræk

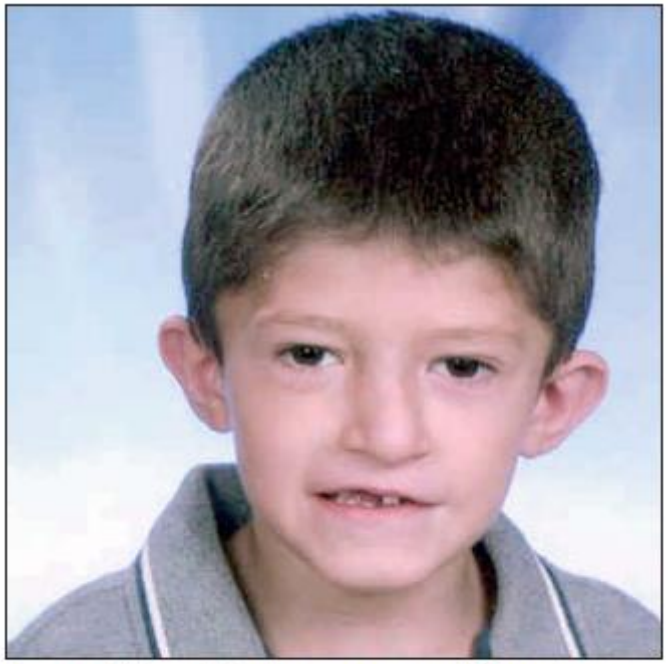


Figure 1: **Facial dysmorphia in chromosome 22q11.2 deletion syndrome**
In this patient, a slightly bulbous nose tip and hooded eyes are the primary features.

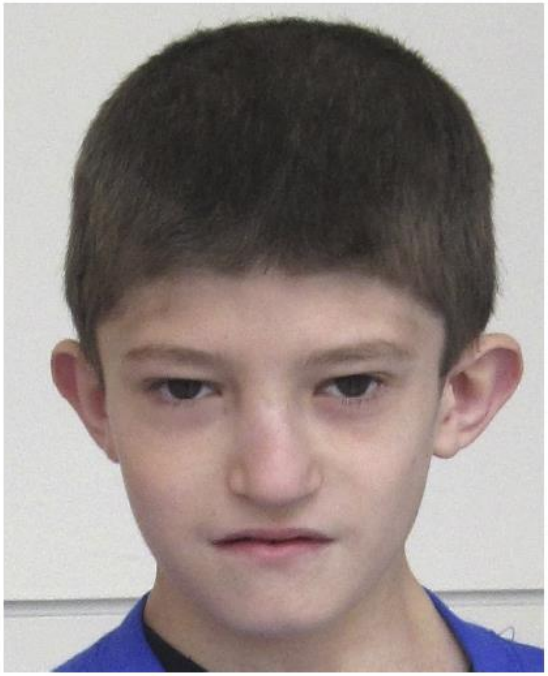
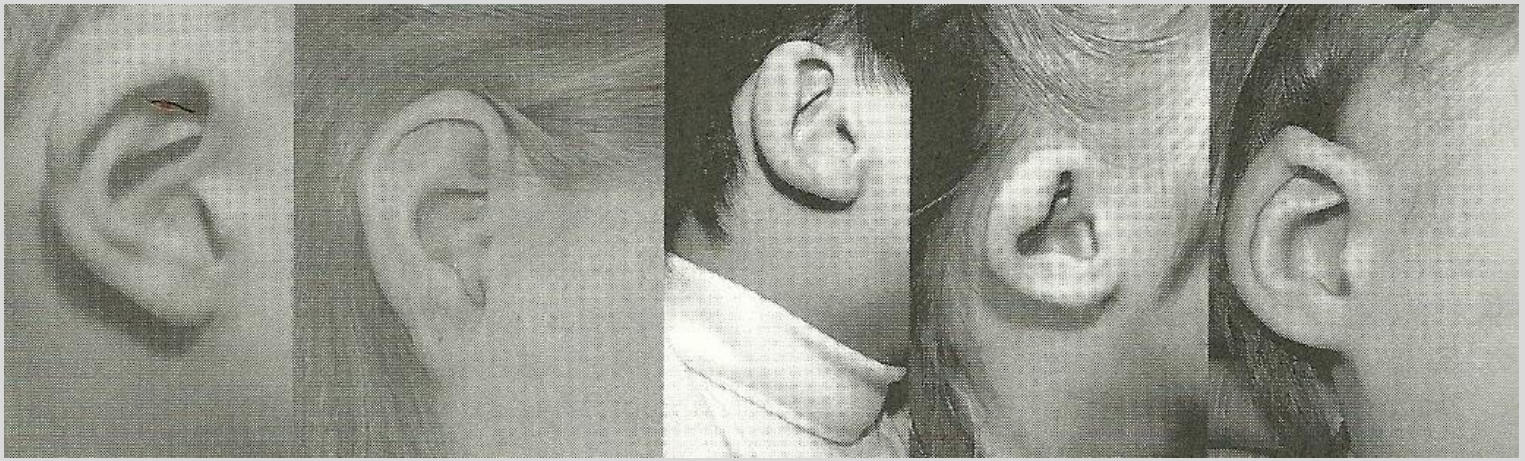


Figure. Mild dysmorphic facial features of a boy aged 11 years with 22q11.2DS, including a short forehead, hooded eyelids with upslanting palpebral fissures, malar flatness, bulbous nasal tip with hypoplastic alae nasi, and protuberant ears.

Bassett et al. J Pediatr 2011

Kobrynski & Sullivan. Lancet 2007

Ydre øre



Hørelse

- Omkring 50 % har let nedsat hørelse
  - Konduktivt
  - Perceptivt
  - Høreapparat

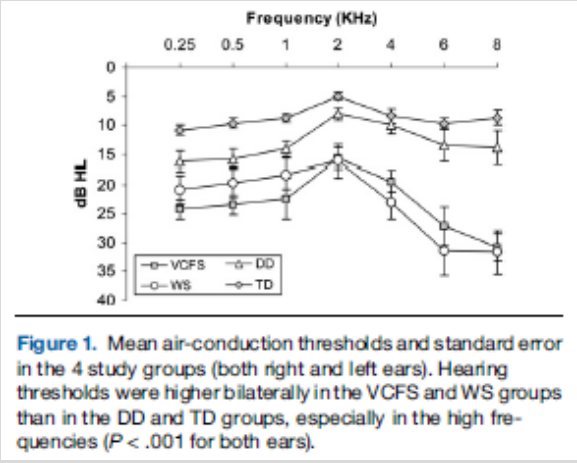


Figure 1. Mean air-conduction thresholds and standard error in the 4 study groups (both right and left ears). Hearing thresholds were higher bilaterally in the VCFS and WS groups than in the DD and TD groups, especially in the high frequencies ($P < .001$ for both ears).

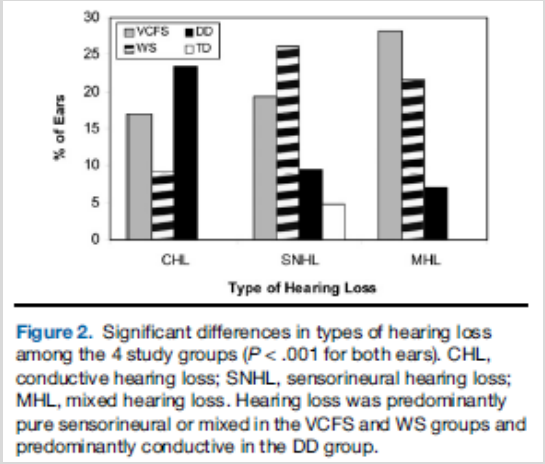
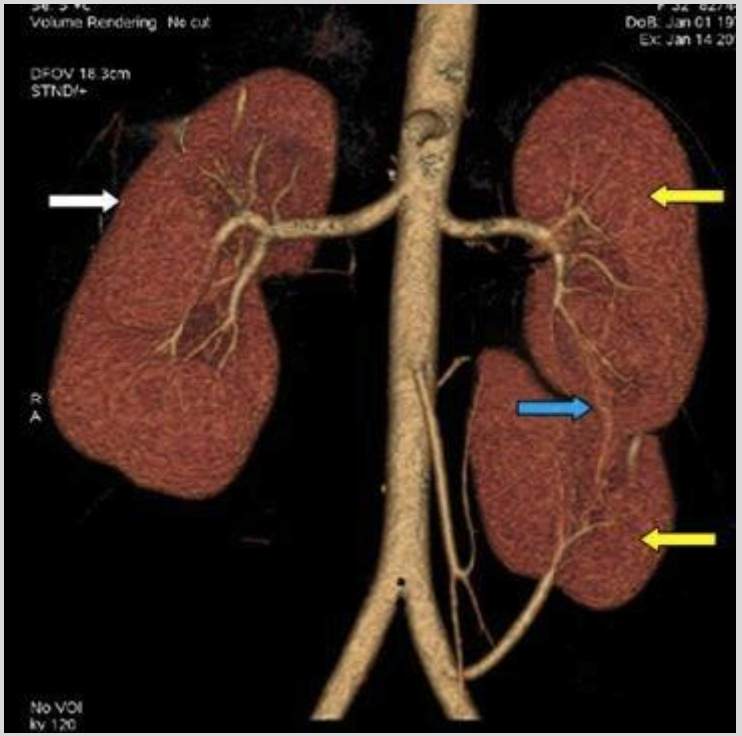


Figure 2. Significant differences in types of hearing loss among the 4 study groups ($P < .001$ for both ears). CHL, conductive hearing loss; SNHL, sensorineural hearing loss; MHL, mixed hearing loss. Hearing loss was predominantly pure sensorineural or mixed in the VCFS and WS groups and predominantly conductive in the DD group.

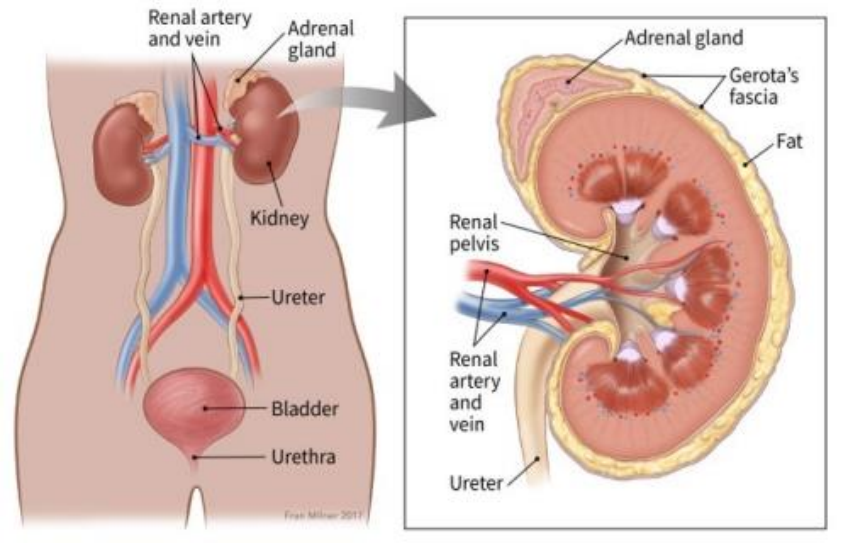
Zarchi et al. J Pediatr 2011;158:301-306

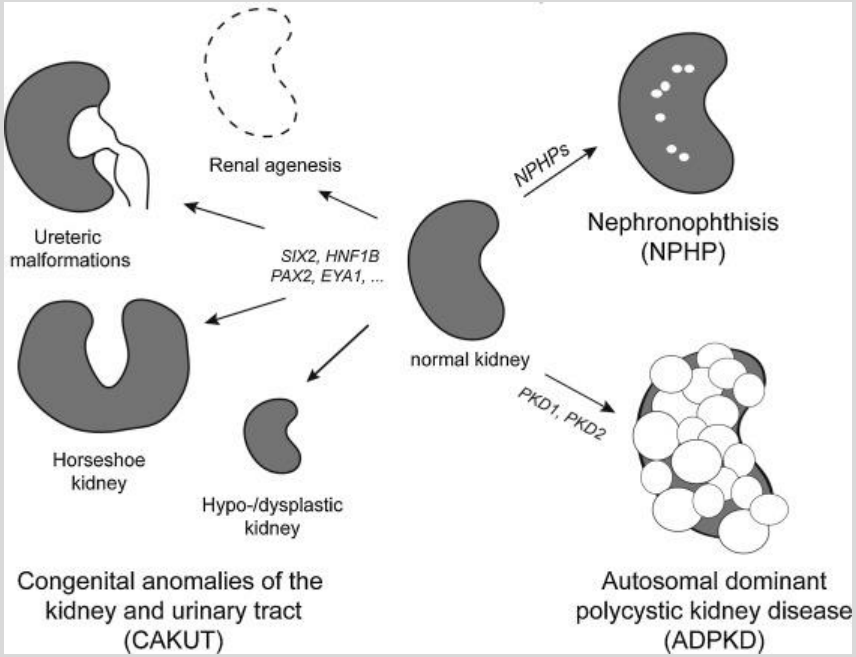
Urinveje

- Urinvejsmisdannelser hos 30%
  - Ensidigt manglende nyreanlæg
  - Misdannede nyrer
  - Dobbeltanlæg
  - Kønsorganer
    - Non-descensus 7 %



Nyrer

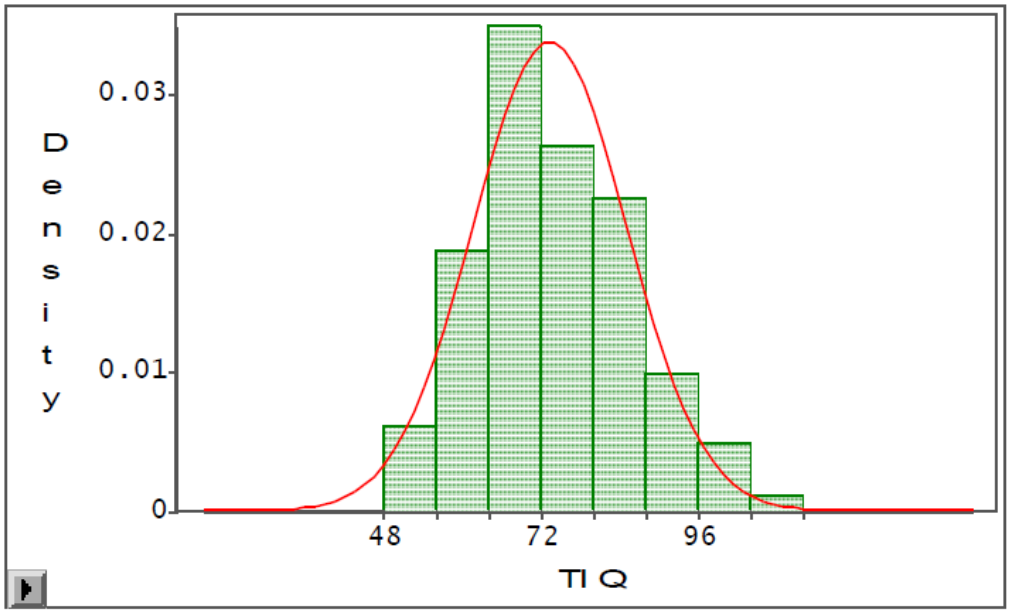

Renal artery and vein
Adrenal gland
Kidney
Ureter
Bladder
Urethra
Adrenal gland
Gerota's fascia
Fat
Renal pelvis
Renal artery and vein
Ureter


Renal agenesis
Ureteric malformations
SIX2, HNF1B
PAX2, EYA1, ...
NPHPs
Nephronophthisis (NPHP)
normal kidney
PKD1, PKD2
Horseshoe kidney
Hypo-/dysplastic kidney
Congenital anomalies of the kidney and urinary tract (CAKUT)
Autosomal dominant polycystic kidney disease (ADPKD)

Indlæring, adfærd og psyke

- Mennesker med 22q11ds har en distinkt, men dynamisk og udviklende kognitiv, adfærdsmæssig og social fænotype

IQ



-Wide variability

-Mean TIQ around 70

- In a subgroup,
  VIQ > PIQ

Swillen et al., 1997, 1999; Desmedt & Swillen , 2007

IQ

Table 1. Demographics of All Groups

	Controls (n = 47)		Siblings (n = 29)		VCFS (n = 88)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***p***
Age, yr	10.0	2.4	12.2	1.9	11.0	2.6	.001
Gender	20 F	27 M	16 F	13 M	39 F	48 M	.522
SES[a]	42.7	13.9	47.9	11.7	49.6	11.8	.021
WISC-III VCI	96.4	13.1	103.5	13.2	77.7	14.0	.001
WISC-III POI	98.0	12.0	104.6	14.8	71.8	11.5	.001

VCFS, velocardiofacial syndrome; SES, socioeconomic status; WISC-III; Wechsler Intelligence Scale for Children-Third Edition; VCI, Verbal Comprehension Index; POI, Perceptual Organization Index. [a]Hollingshead Index.

Roizen et al. J Dev Behav Pediatr 2007;28:119-24

Tidlige milepæle

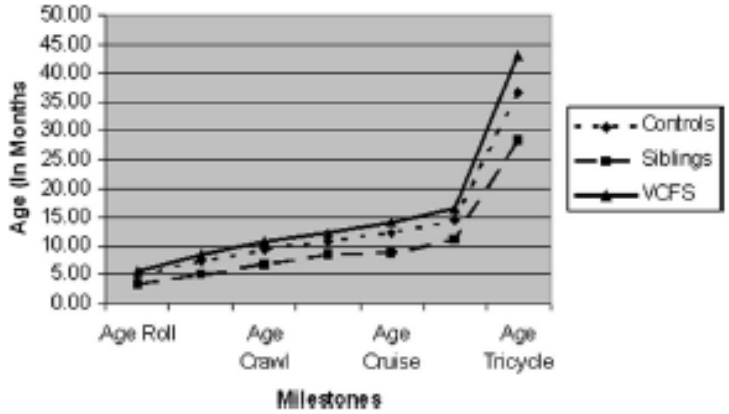


Figure 1. Gross motor milestones in total sample. VCFS, velocardiofacial syndrome.

Roizen et al. J Dev Behav Pediatr 2007;28:119-24

Tidlige milepæle

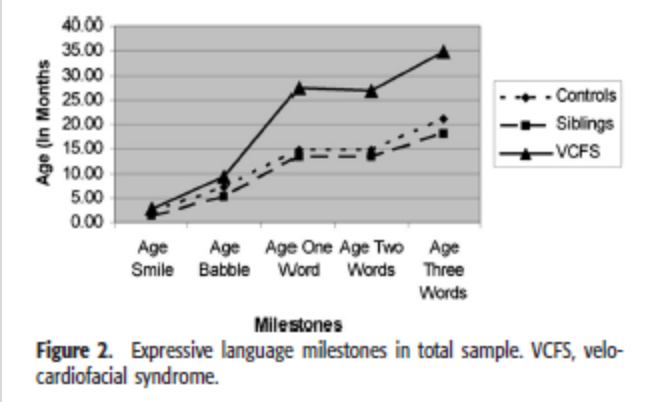


Figure 2. Expressive language milestones in total sample. VCFS, velocardiofacial syndrome.

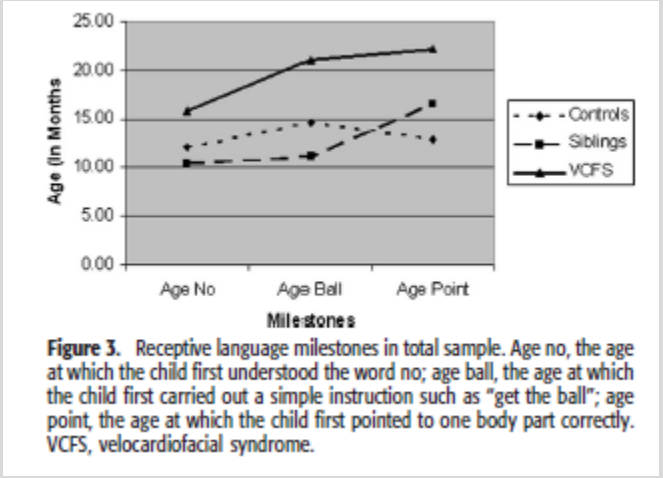


Figure 3. Receptive language milestones in total sample. Age no, the age at which the child first understood the word no; age ball, the age at which the child first carried out a simple instruction such as "get the ball"; age point, the age at which the child first pointed to one body part correctly. VCFS, velocardiofacial syndrome.

Roizen et al. J Dev Behav Pediatr 2007;28:119-24

Cognitive challenges

- Learning & neurocognitive profile in 22q11
  - problems with abstract thinking, problem-solving
  - problems with integrating new information
  - academic problems: arithmetics and reading comprehension
  - poor attention and concentration , (ADD; problems with starting, initiating,…)
  - deficits in visual-perceptual abilities
  - good reading skills and good auditory memory

(Swillen et al., *Child Neuropsychology*, 1999; 2005; Desmedt et al., 2007; 2008)

Psykiatri

- Hos 10 – 30 % afhængig af alder

- Børn
  - ADD
    - 5-45 %
  - ASD
    - 25-50%
  - Angst
    - 20-50 %
  - OCD
    - 4-33 %
- Unge og voksne
  - Angst
  - Depression
    - 12 %
  - Bipolære lidelser
    - 64%
  - Schizofreni
    - 10-30 %
    - 1-2% af alle med schizofreni

Adfærd og psykiatri

- ADHD 3-46%
- ASD 20-50%
  - Sky
  - Tilbageholdende
  - Behov for rutiner
  - Stereotyp adfærd
  - Social afkodning og interaktion
  - Sociale regler

Psychiatry Research 177 (2010) 211–215

Contents lists available at ScienceDirect

Psychiatry Research

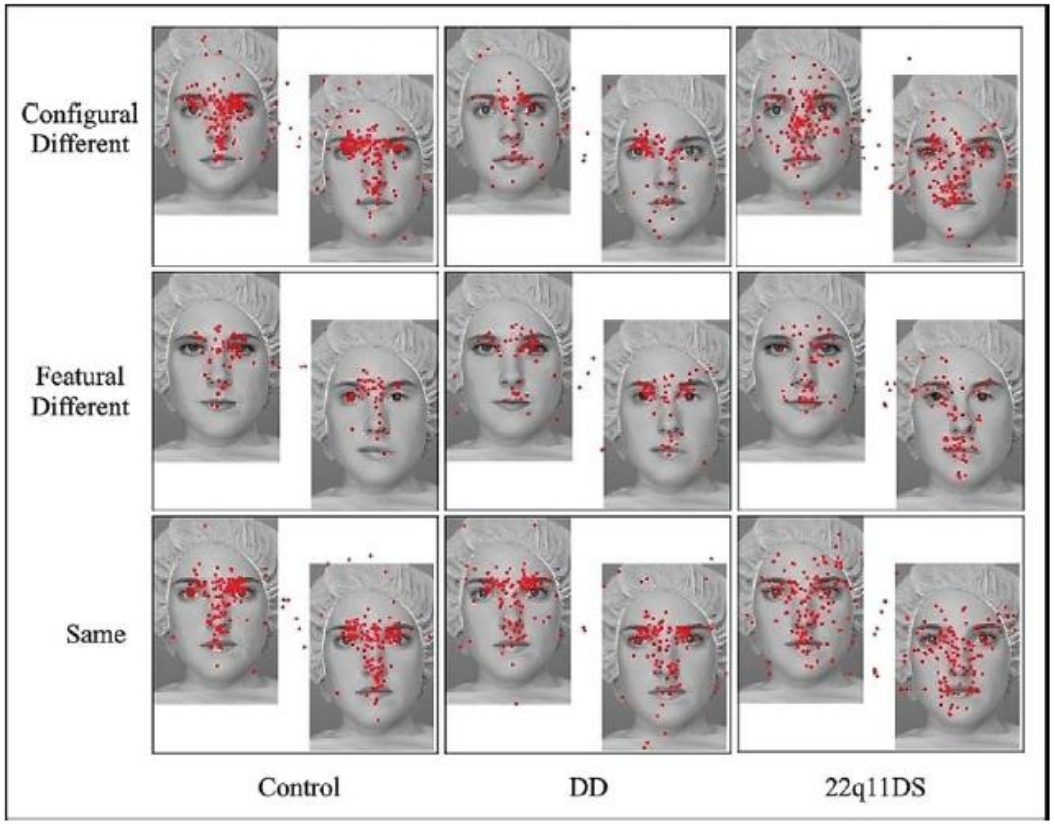
journal homepage: www.elsevier.com/locate/psychres

Visual scanning of faces in 22q11.2 deletion syndrome: Attention to the mouth or the eyes?

Linda Campbell [a,b,c,*], Kathryn McCabe [a,b], Kate Leadbeater [a], Ulrich Schall [a,b,c], Carmel Loughland [a,b,c], Dominique Rich [d]

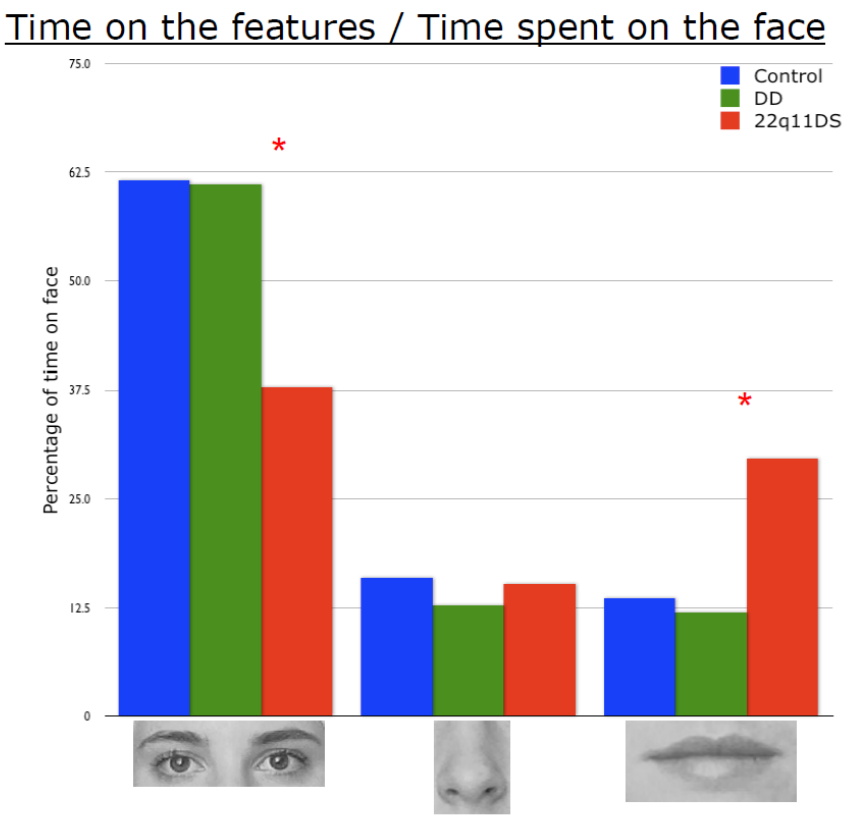
[a] Priority Research Centre for Brain and Mental Health, University of Newcastle, NSW, Australia
[b] Schizophrenia Research Institute Australia (SRI), Sydney, NSW, Australia
[c] Hunter Medical Research Institute, Australia
[d] Centre for Brain and Mental Health Research, University of Newcastle, Australia

FIGURE 2 Participants' fixations on an example image from each of the three conditions.



Glaser et al. J Am Acad Child Adolesc Psychiatry 2010

Time spent on the facial features



Ages: 8-15
VCFS: N=26
DD: N=17
Control: N=22

Mistanke om 22q11ds – hvornår?

	Frequency of deletion
Any cardiac lesion	1%
Conotruncal cardiac anomaly	7–50%
Interrupted aortic arch	50–60%
Pulmonary atresia	33–45%
Aberrant subclavian	25%
Tetralogy of Fallot	11–17%
Velopharyngeal insufficiency	64%
Velopharyngeal insufficiency post-adenoidectomy	37%
Neonatal hypocalcaemia	74%
Schizophrenia	0–6%

Table 2: Frequency of the chromosome 22q11.2 deletion

Kobrynski & Sullivan. Lancet 2007

22q11-deletionssyndrom

Overlæge Charlotte Olesen, læge Peter Agergaard, audiologopæd Maria Boers, overlæge Stense Farholt, professor Carsten J. Heilman, specialtandlæge Lut Hvidkjær, overlæge Kurt Kristensen, 1. reservelæge Marlene B. Lauritsen, psykolog Jytte Lunding, overlæge Bent W. Nielsen, professor Flemming Skovby, overlæge Nana Thrane, læge Ida Vogel & professor John R. Østergaard

OVERSIGTSARTIKEL

Århus Universitets-hospital, Skejby, Børneafdelingen

RESUME

22q11-deletionssyndrom (22q11DS) forekommer hos 1/2.000-4.000 levendefødte og er således et af de hyppigst forekommende syndromer med kendt genetisk baggrund. Fænotypen er overordentlig variabel og omfatter anomalier af næsten alle organer og funktioner. I denne oversigtsartikel gennemgås historie, genetik og fænotypiske manifestationer, hvorefter der angives anbefalinger vedrørende undersøgelse, opfølgning og behandling af børn og unge med 22q11DS.

22q11-deletionssyndrom (22q11DS) forekommer hos 1/2.000-4.000 levendefødte og er således et af de hyppigst forekommende syndromer med kendt genetisk baggrund [1, 2]. Fænotypen er overordentlig variabel og omfatter anomalier af næsten alle organer og funktioner. Syndromet er beskrevet af og navngivet efter forskellige eksperter på baggrund af typiske manifestationer. I det følgende gennemgås historie, genetik og fænotypiske manifestationer, hvorefter der angives anbefalinger vedrørende undersøgelse, opfølgning og behandling af børn og unge med 22q11DS.

SØGESTRATEGI

Der blev søgt i Medline Pubmed og Cochranedatabasen. Søgeord: *22q11 deletion-, DiGeorge-, Caylor-, Kanouchi-, Sphrintzen-,* og *Velo-cardio-facial syndrome*. Fra abstrakter valgte vi til gennemgang »klassiske« artikler, oversigtsartikler og nye originalarbejder inden for nedenstående områder. Vi har valgt at præsentere de nyeste og/eller største studier i denne oversigtsartikel.

HISTORIE

Angelo DiGeorge (pædiatrisk endokrinolog) beskrev i 1968 tre børn med letal T-celleimmundefekt og glandula parathyroidea-hypoplasi. Han tilskrev disse fund en abnorm udvikling af tredje og fjerde brankiebue, og denne samling af fund er kendt som *DiGeorges syndrom* [3]. Umiddelbart forinden beskrev *Glen Cayler* patienter med konotrunkale hjertemisdannelser og

Olesen et al. Ugeskr Læger 2010

Mere viden

- www.22q11.dk
- https://www.ncbi.nlm.nih.gov/books/NBK1523/
- https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/sjaeldne-sygdomme/sjaeldne-sygdomme/deletion-syndrom-22q11/
- www.ncbi.nlm.nih.gov/pubmed
- www.ncbi.nlm.nih.gov/omim
- www.orpha.net
- www.sst.dk/publ/publ2001/handicap
- http://sjaeldnediagnoser.dk/national-strategi/
- Center for Sjældne Sygdomme, AUH & RH