“Multidisciplinary care and research in genetic syndromes/CNV: 22q11 DS”

“Developmental trajectories in 22q11 DS across life span”

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https://www.kuleuven.be/labbehaviourandneurodevelopment

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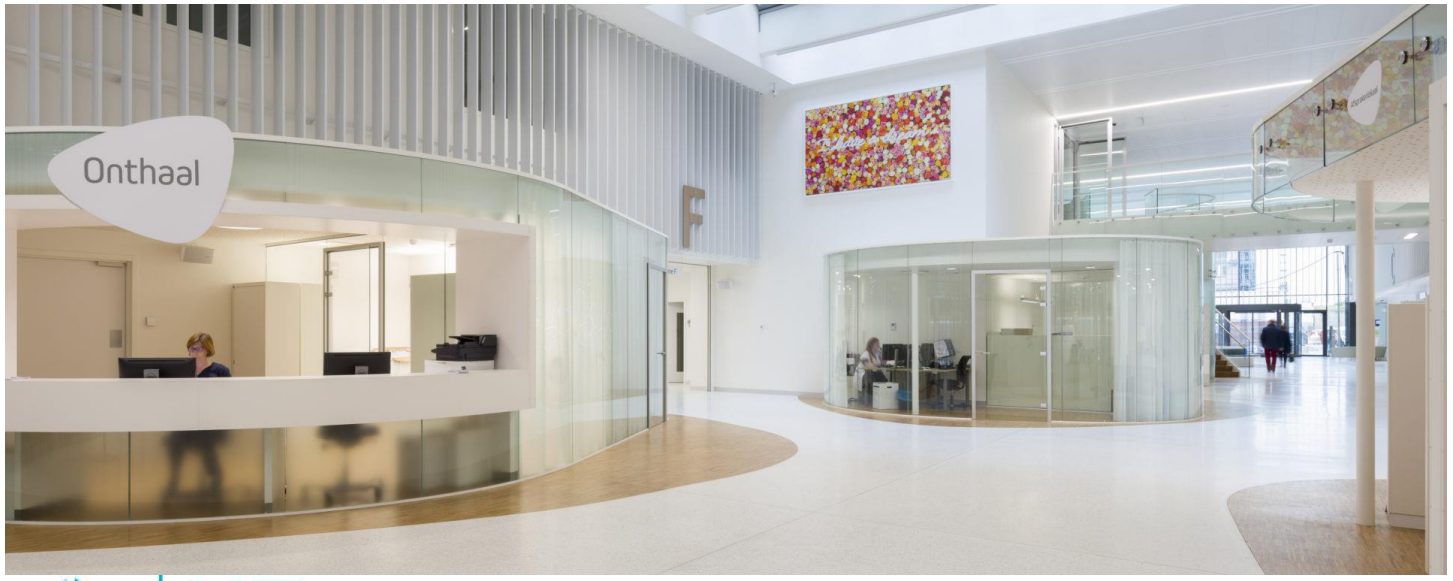

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Centre for Human Genetics Leuven
University Hospital Gasthuisberg/KU Leuven

- Persons with genetic syndromes /developmental disabilities (MCA/ID), so called rare diseases (CNVs)
- Multidisciplinary team
- Holistic approach & focus:
  - Child and family
  - Medical and developmental/ behavioural concerns

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Rare diseases (MCA/ID)/Copy Number Variations (CNVs)

The specific aspect is the rareness of rare diseases: by definition they are varied, complex and progressive conditions that may generate multiple disabilities and require access to state-of-the-art specialists' knowledge and attention at times that are not always predictable – but also a holistic and personalised approach to care that takes the individual case and its context into account.

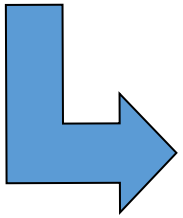
Prof. Dr. Herman Van den Berghe
(1933-2017)

50 JAAR 1966-2016

CME
Centrum Menselijke Erfelijkheid
Leuven

Rare diseases (MCA/MR; CNVs): e.g. 22q11.2 DS

- have needs in many areas: medical, cognitive, behavioural, social-emotional, practical/every day life, …
- the combination of these multiple needs implicates:
    - the need for a holistic, personalized, coordinated and continued care
    - the need for an expert multidisciplinary team, both in clinical practice AND in research



Since the early nineties, **multidisciplinary expert network/teams** have been established (e.g. 22q11 DS, NF1, PWS, Noonan, SMS, PMS,….)

In Leuven, the multidisciplinary 22q11 DS consultation started in 1994 (~450 patients)

How did we start in 1994 ?

"Combined consultations" @CME

MEDICAL CONCERNS

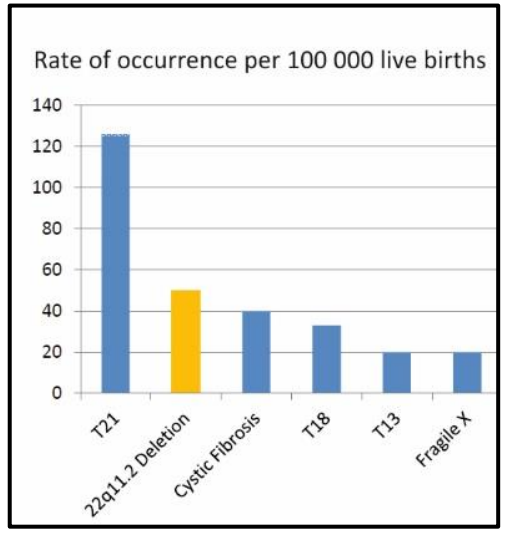
Clinical genetics
Pediatrics
Pediatric Cardiology
Pediatric ENT specialist
Feeding specialist

In 22q11 DS…

DEVELOPMENTAL/ BEHAVIORAL CONCERNS

Developmental and behavioral specialists focusing on motor, language, development, behaviour and social emotional development
Clinical & educational psychologist @ Clinical Genetics – Pediatrics/NDD (COS) MDT team

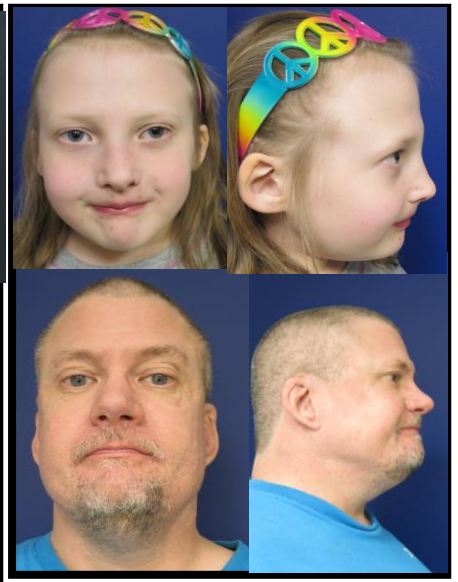
Why should you be interested in 22q11.2 DS syndrome?*

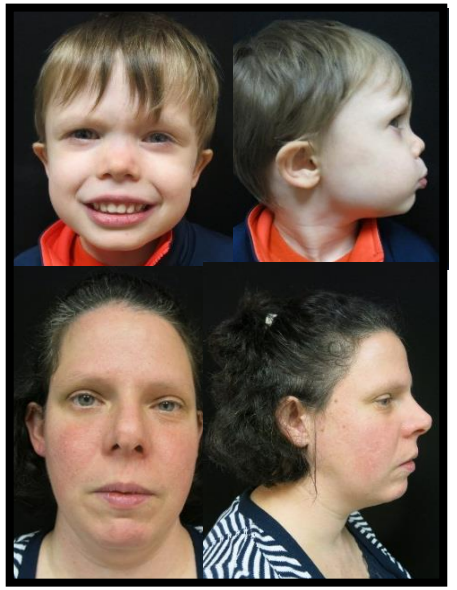


- It is the **most common microdeletion** syndrome.
- Because of phenotypic variability, clinically not well recognised.
- **Complex phenotype**.
- Behavioural phenotype
  - Almost all have **learning problems**
  - Most have a **borderline to mild-moderate ID**
  - About 30% are diagnosed with Attention Hyperactivity Disorder, particularly ADD
  - About 30% are diagnosed with anxiety disorder
  - About 20-40% are diagnosed with an autism spectrum disorder.
  - Third highest known **risk factor for psychosis**
- Frequently in contact with medical specialists, (child)psychiatrists, clinical psychologists, special educators, speech-language therapists…..

**Also known as velo-cardio-facial syndrome, Shprintzen syndrome, DiGeorge syndrome, Conotruncal anomaly syndrome, Cayler syndrome, Sedlackova syndrome, CATCH-22,…..*

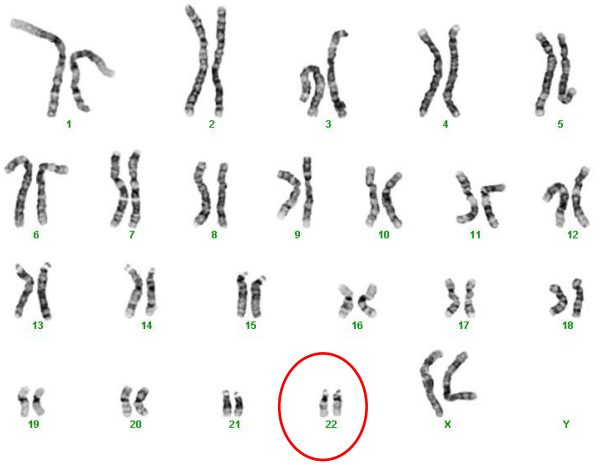
What is 22q11.2 DS ?

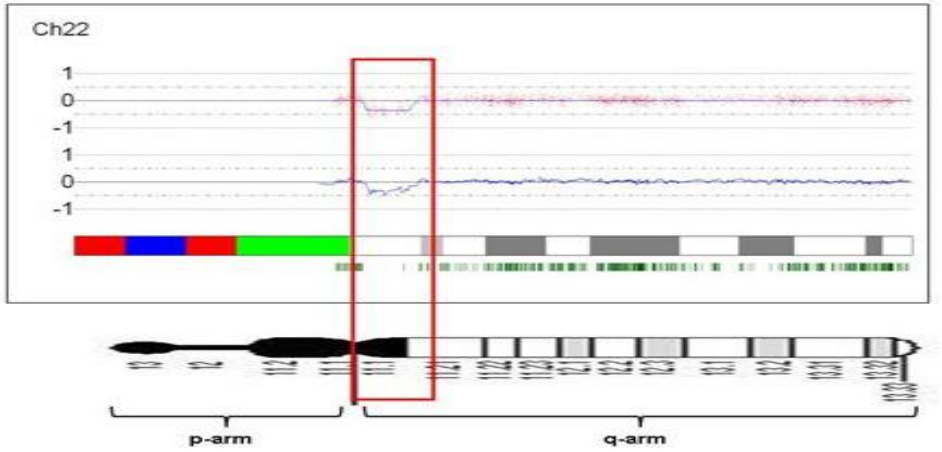


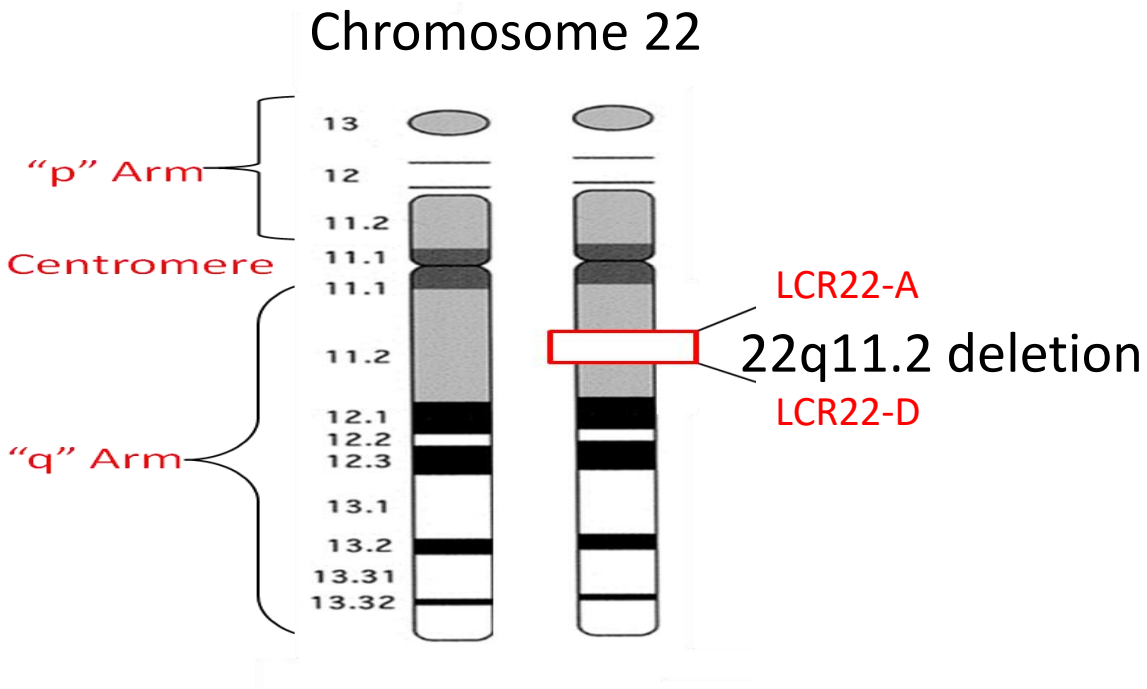


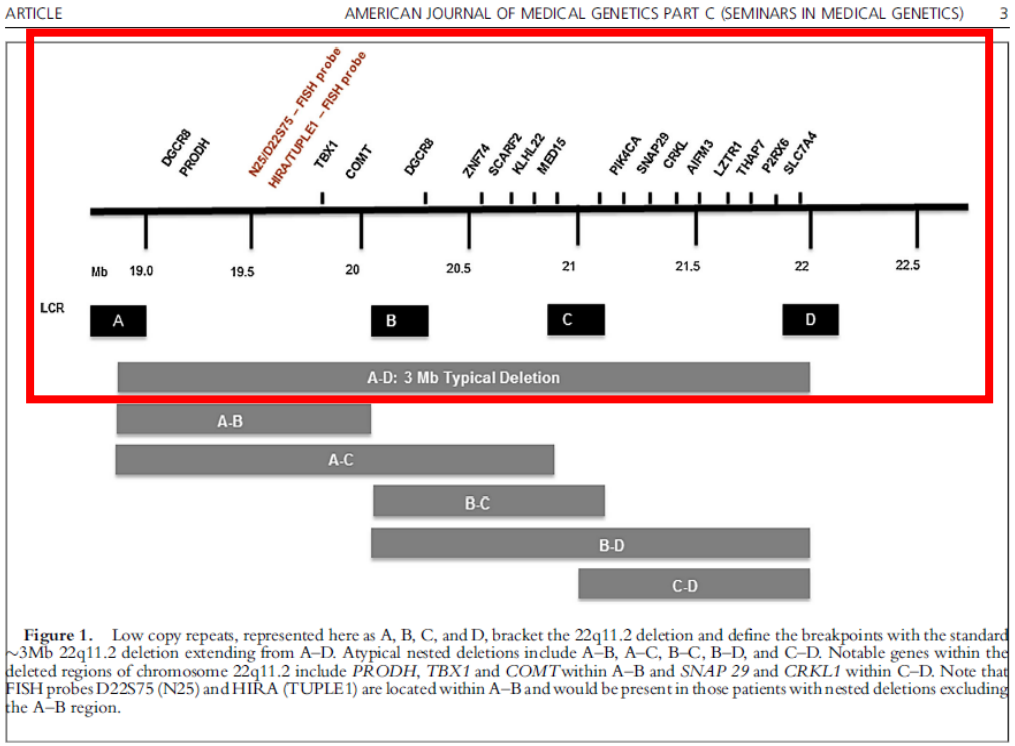
McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, Zackai EH, Emanuel BS, Vermeesch JR, Morrow BE, Scambler PJ, Bassett AS. **22q11.2 deletion syndrome**. *Nat Rev Dis Primers.* **2015** Nov 19;1:15071. doi: 10.1038/nrdp.2015.71. PMID: 27189754; PMCID: PMC4900471.

What is 22q11.2 DS ?



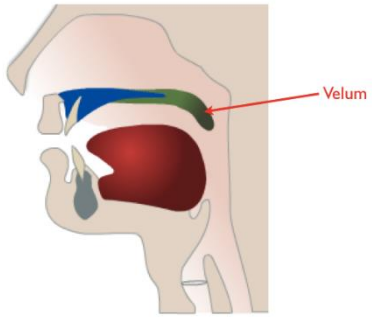


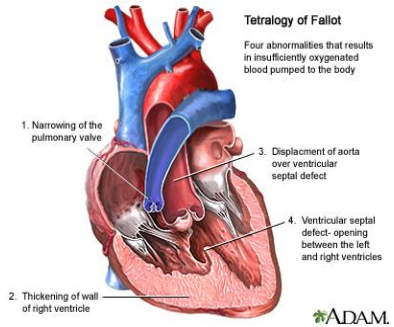


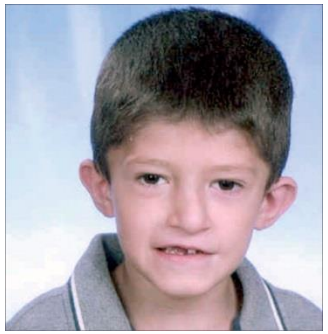


22q11.2 deletion syndrome (22q11.2 DS)

Velo-Cardio-Facial Syndrome







1/2 000 -1/4000 life births (90% *de novo*)

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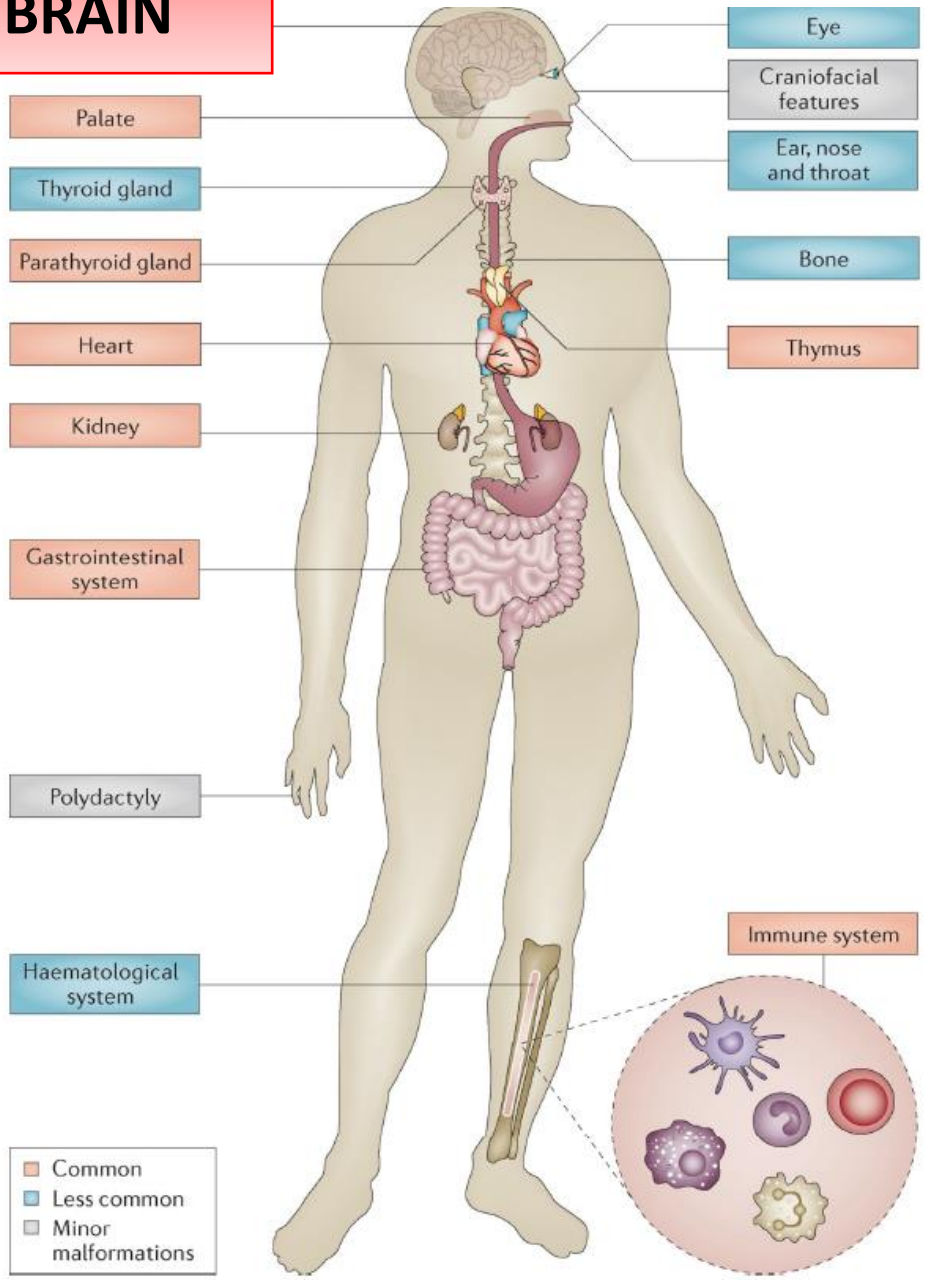
Multi-System Involvement in 22q11.2 DS

BRAIN



Major Common System Involvement:

- **Brain**
- Palate
- Thymus
- Parathyroid
- Heart
- Gut
- Kidney

Less Common but Significant Systems:

- Eye
- ENT
- Thyroid
- Hematologic
- Autoimmune (JRA)
- Skeletal (Scoliosis)
- GI (Imperforate anus, Intestinal malrotation, Hirschsprung's)

Minor Malformations that may contribute to Dx

- Craniofacial features (asymmetric crying facies; auricular anomalies; hooded eyelids; nasal dimple/crease)
- Polydactyly (pre and post axial of hands; postaxial of feet
- Cervical and thoracic vertebral anomalies

Risk factors

Genes ↔ Environment

22q11.2 DS

Development (cognition and behavior)

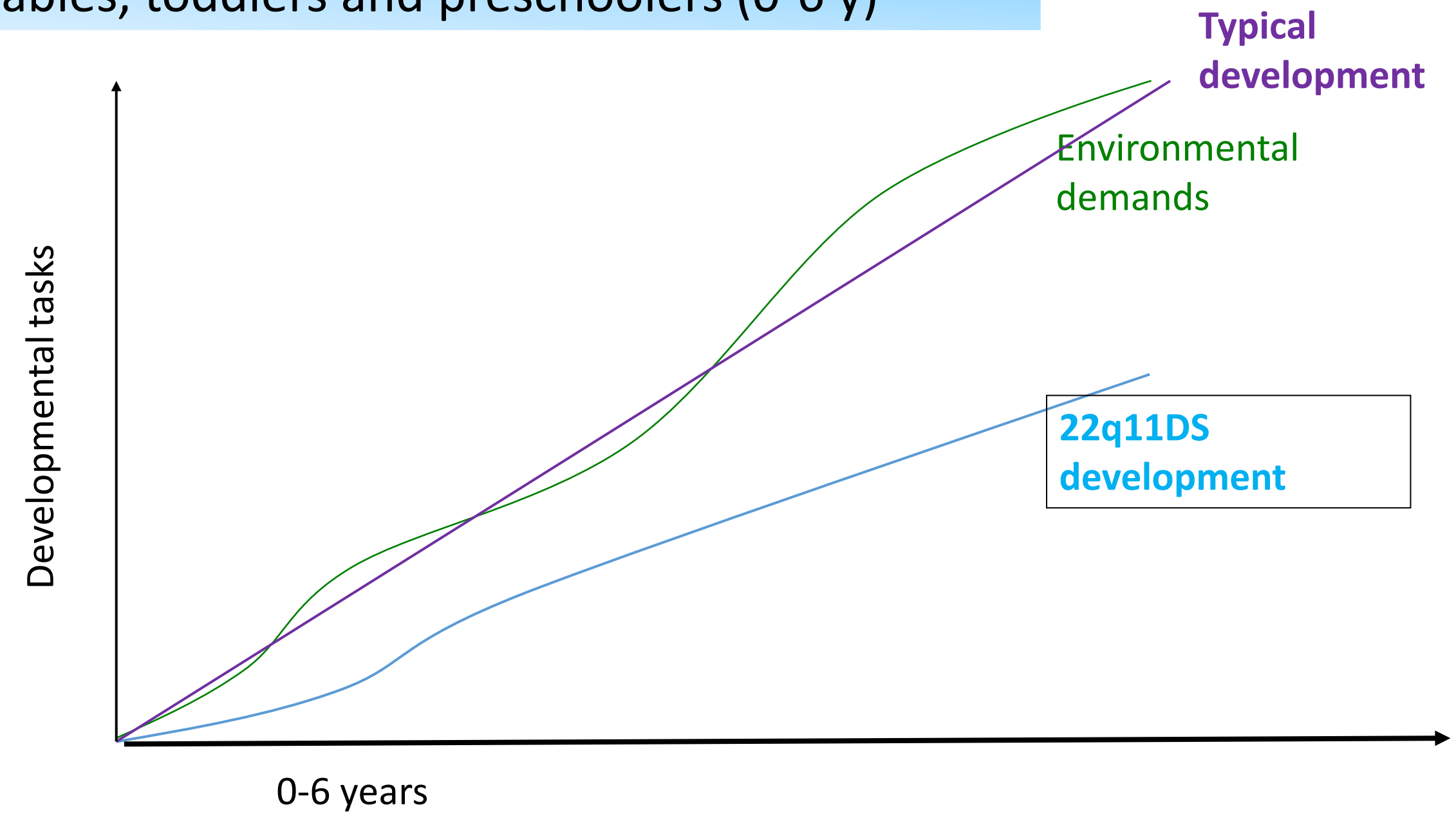
Protective factors

Time/development itself

Developmental trajectories in 22q11 DS

- **1. Babies, toddlers and preschoolers (0-6y)**
  - Medical/developmental concerns/needs
- **2. Primary school (6-12y)**
  - Cognitive and educational challenges
- **3. Adolescence (13-18y)**
  - Cognitive and educational challenges
- **4. Psychological/psychiatric challenges in 22q11 DS**

1. Babies, toddlers and preschoolers (0-6 y)



Babies/infants with 22q11 DS (0-1y)

MEDICAL CONCERNS

Heart
Feeding
Low calcium
Immune system
Low muscle tone
Constipation

DEVELOPMENTAL CONCERNS

Slow growth and weight gain
Hypotonia/motor delay
Speech and language delay

Toddlers with 22q11 DS (1-2y)

MEDICAL CONCERNS

Heart
Feeding/hypernasal speech
Recurrent infections
Low muscle tone
Constipation

DEVELOPMENTAL CONCERNS

Mild to moderate delays in all areas of development:
-Gross and fine motor
-General cognition
-Speech/language

Infants & toddlers with 22q11 DS (0-3y)

- Investigations/Diagnosis
  - Psychomotor assessment (BSID-II, PMDS-2) @ 1y and 2y
  - Speech/language assessment (@ 2y; check hearing !)
  - @ 3y check vision !

- **Guidance/support**
- Early intervention (preferably guidance @ home)
  - Physiotherapy/occupational therapy
  - Speech/language therapy (communication !)

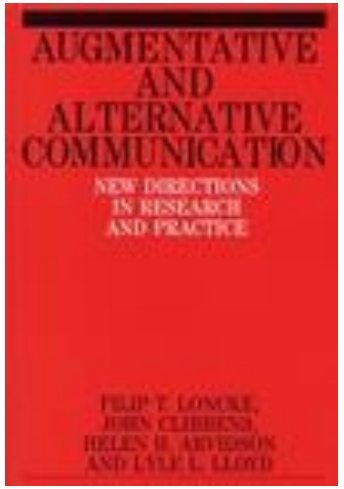
Physiotherapy and occupational therapy

Language therapy :
“TOTAL COMMUNICATION APPROACH”

Augmentative and alternative communication (AAC)

e.g. SMOG/SWSS (Speaking With Support of Signs)

Filip Loncke (University of Gent, University of Virginia)



Preschoolers with 22q11 (3-6 y)

MEDICAL CONCERNS

Surgical correction of VPI
Kidney problems/urinary tract problems
Recurrent ear infections
Low muscle tone
Eye/vision problems **(eye exam @ 3 !)**
Sleep problems !

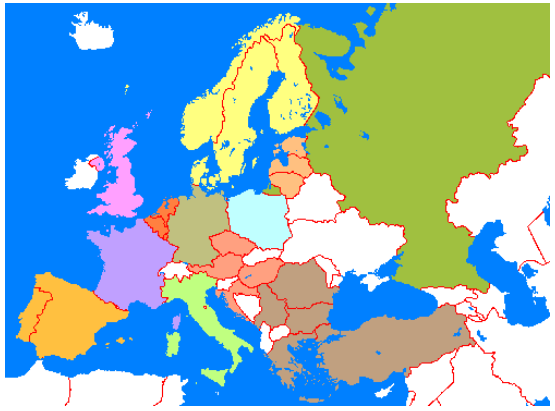
DEVELOPMENTAL CONCERNS

Mild to moderate delays in all areas of development:
-Gross and fine motor
-General cognition (DD, pre-arithmetic skills, visual-perceptual skills)
-Speech/language

Good **visual-perceptual processing and visual-spatial insight** are important for:

- Motor skills

- Academic skills: pre-arithmetic skills, mathematics, geography,



- Daily living skills

- Social communication skills

Visual-perceptual skills in 22q11 DS:

- need more time to process visual information

Visual-perceptual skills in 22q11 DS:

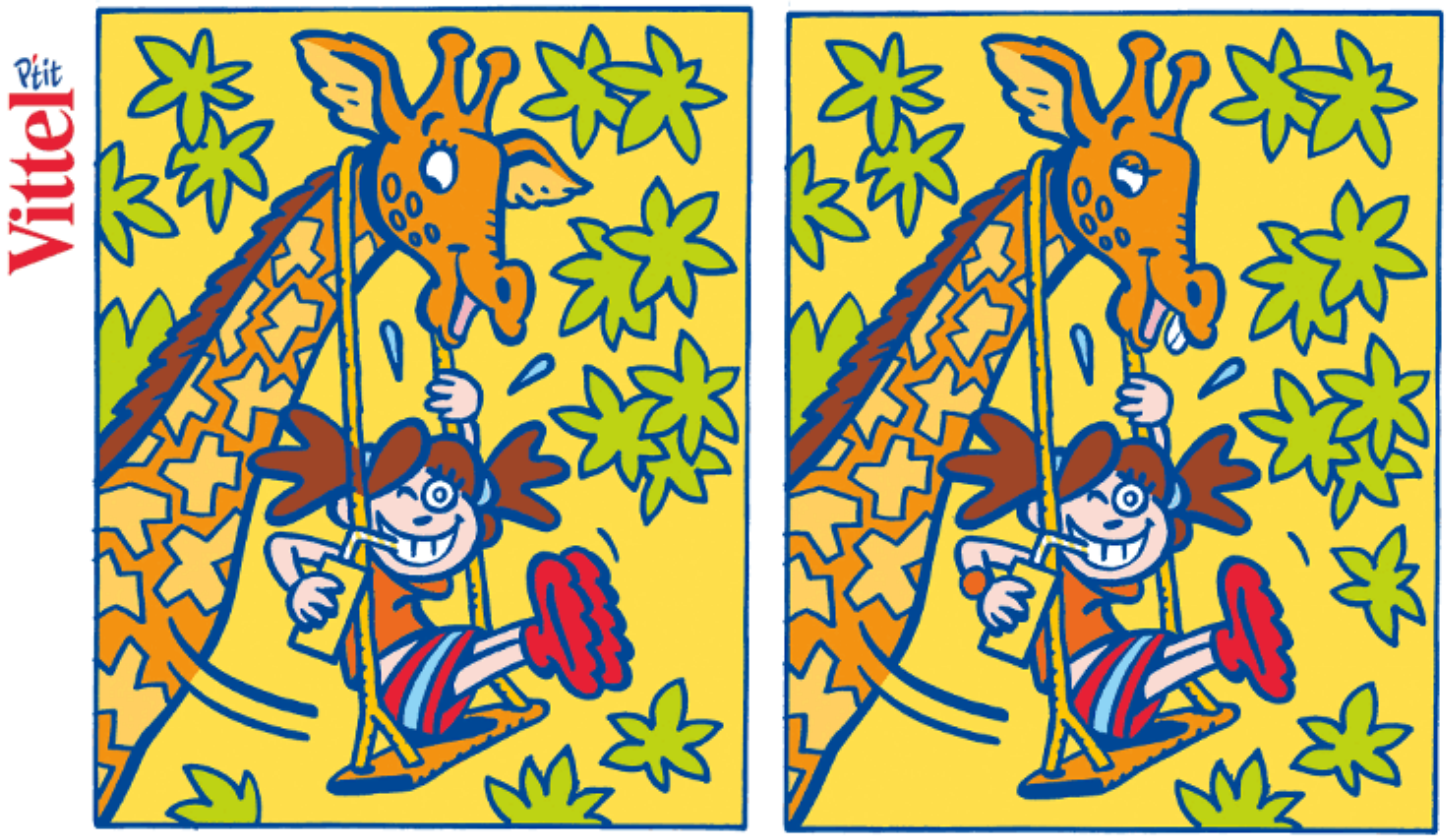
- problems with recognizing objects when presented in unconventional way

Conventional

Unconventional

Visual-perceptual skills in 22q11 DS:

- Problems in tasks with many visual stimuli (complex visual)

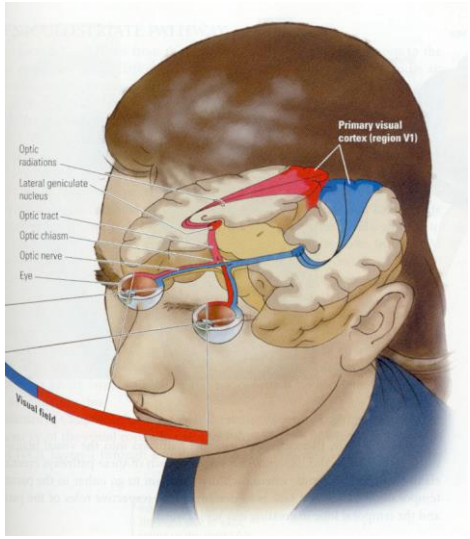


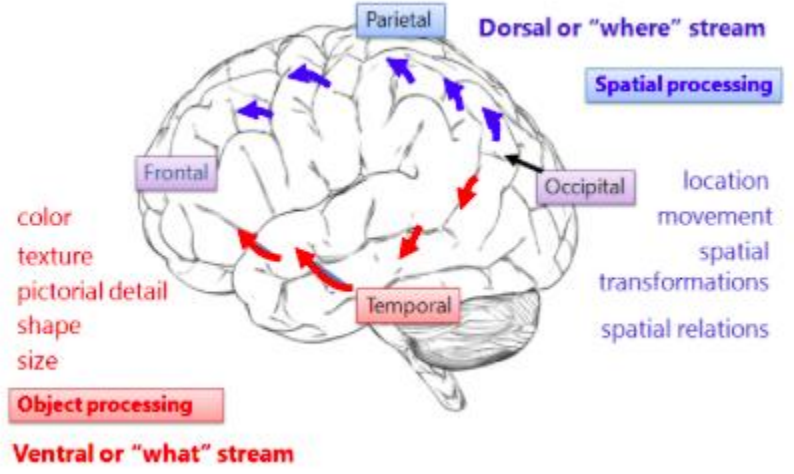
Visual perceptual problems in 22q11 DS

(both in children with problems with vision, and in children with normal vision)

- Need **more time for visual information processing**
- **Misinterpretation of objects** (presented in **unconventional way)**
- Problems with **visuo-motor integration**
- Problems with **spatial insight, spatial orientation, perceptual organization**

➡ Cortical visual impairment (CVI) = visual perception disorder caused by a lesion in the brain





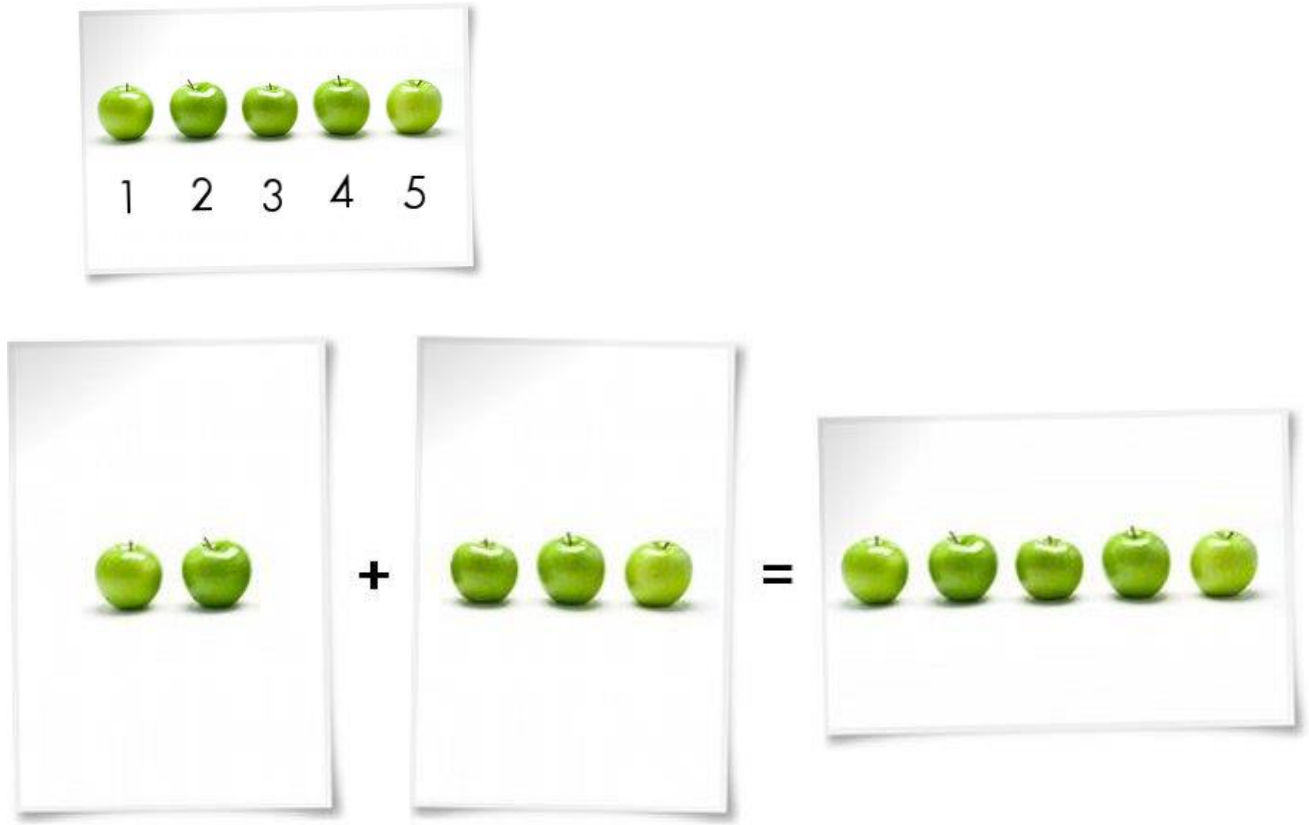
Recommendations vision and visual perception

- Eye exam from age 3 on (to exclude or diagnose vision problem)
- Be alert for signals of visual perceptual problems
- Observe visual perception: at home, in class, during play etc…

- In case there are several elements present/suggestive of visual-perceptual problems:
  - Specific CVI- assessment (CVI= cortical visual impairment) from 4 years on

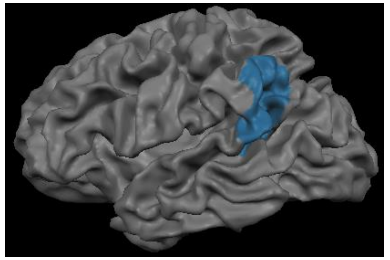
Pre-arithmetics and mathematical skills in 22q11 DS

- Problems with number sense, awareness of “amount”

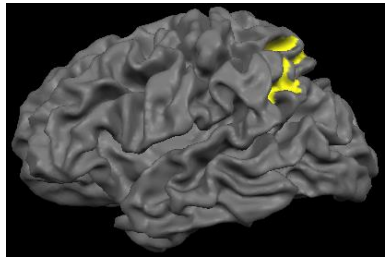


Dehaene et al. (2003) model

- Number processing and arithmetic:
  - Two anatomically and functionally distinct systems:

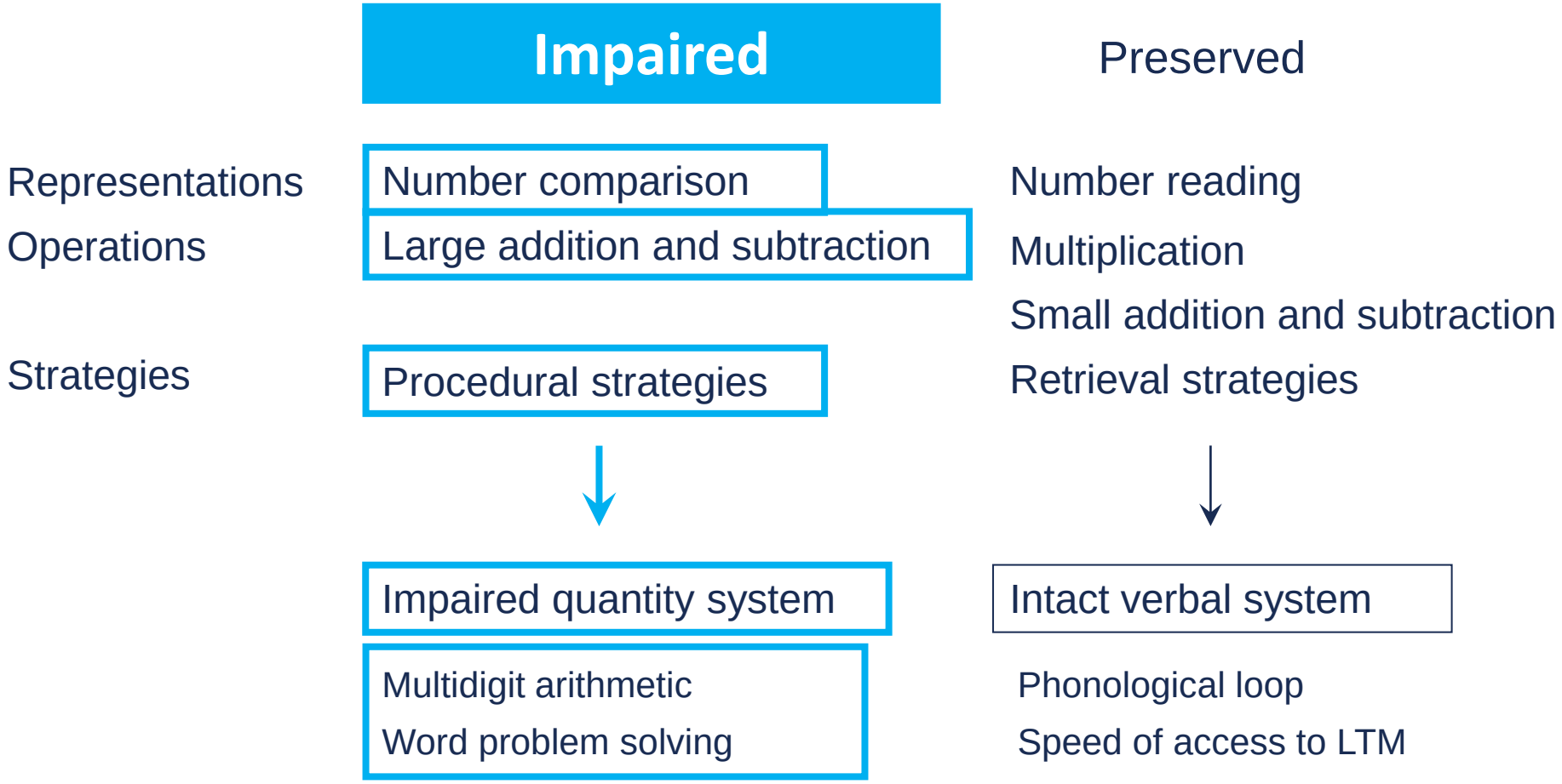


Verbal System
Left angular gyrus
Verbal representation of number
Multiplication
Retrieval strategies



Quantity System
Intraparietal sulcus
Quantity representation of number
Subtraction
Procedural strategies

In 22q11DS:



De Smedt & Swillen, 2009, *Cortex*

Preschoolers with del22q11 (3-6 y)

- **Guidance/support/ Remediation**

Appropriate assessment/diagnosis → appropriate education + support

  - Mainstream + support (speech, motor, cognitive, play, social skills)
  - Special education
- Stimulation and adaptation
- Anticipatory guidance
- In case of CVI: adaptation of visual learning material + learn visual scanning and strategies

- Encouragement/development of social and daily living skills
- If major concerns about social/emotional/peer-related issues → referral to child psychologist/child psychiatrist

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RESEARCH REVIEW

WILEY AMERICAN JOURNAL OF medical genetics PART A

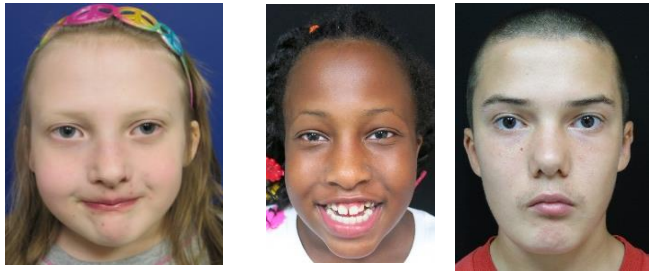
Neurodevelopmental outcome in 22q11.2 deletion syndrome and management

Ann Swillen[1] | Edward Moss[2] | Sasja Duijff[3]

TABLE 1 Treatment recommendations for improving neurodevelopmental outcome in 22q11 DS during infancy and early childhood (0–6y)

Developmental area	Developmental features	Treatment recommendations
Motor development	Hypotonia and neuromotor deficits	Physiotherapy, occupational therapy, and sensory integration therapy from early age on
Feeding	Poor sucking, nasal reflux, and oral motor coordination problems	Medical guidance/monitoring of feeding problems Feeding advice (feeding specialist with expertise in 22q11 DS)
Speech and language	Impaired speech and language development, hypernasality, high-pitched voice, and compensatory speech	Speech and language therapy, total communication approach (verbal, non-verbal, and sign language in combination with oral speech) (Solot et al., 2001) In the case of severe hypernasality, a pharyngoplasty is sometimes required
Neurodevelopment/ Cognitive development	Varying degree of impairment (from borderline development to mild–moderate ID)	Educational monitoring Early childhood specialist Anticipatory guidance
Social–emotional development and social skills	Emotionally reactive Problems with regulation of emotion and behavior Socially withdrawn, poor peer relations, self-directed behavior Social anxiety and general anxieties	Provide a secure and highly structured environment Infant mental health intervention Play therapy (structured play to promote social play) Structured (social) group experience
Attention	Easily distracted, impulsiveness	Structured (learning) environment Environment free from stimuli Use visual aids to improve sustained attention (sand timer; time-timer, etc.)

2. Primary school (6-12y)



Normal development

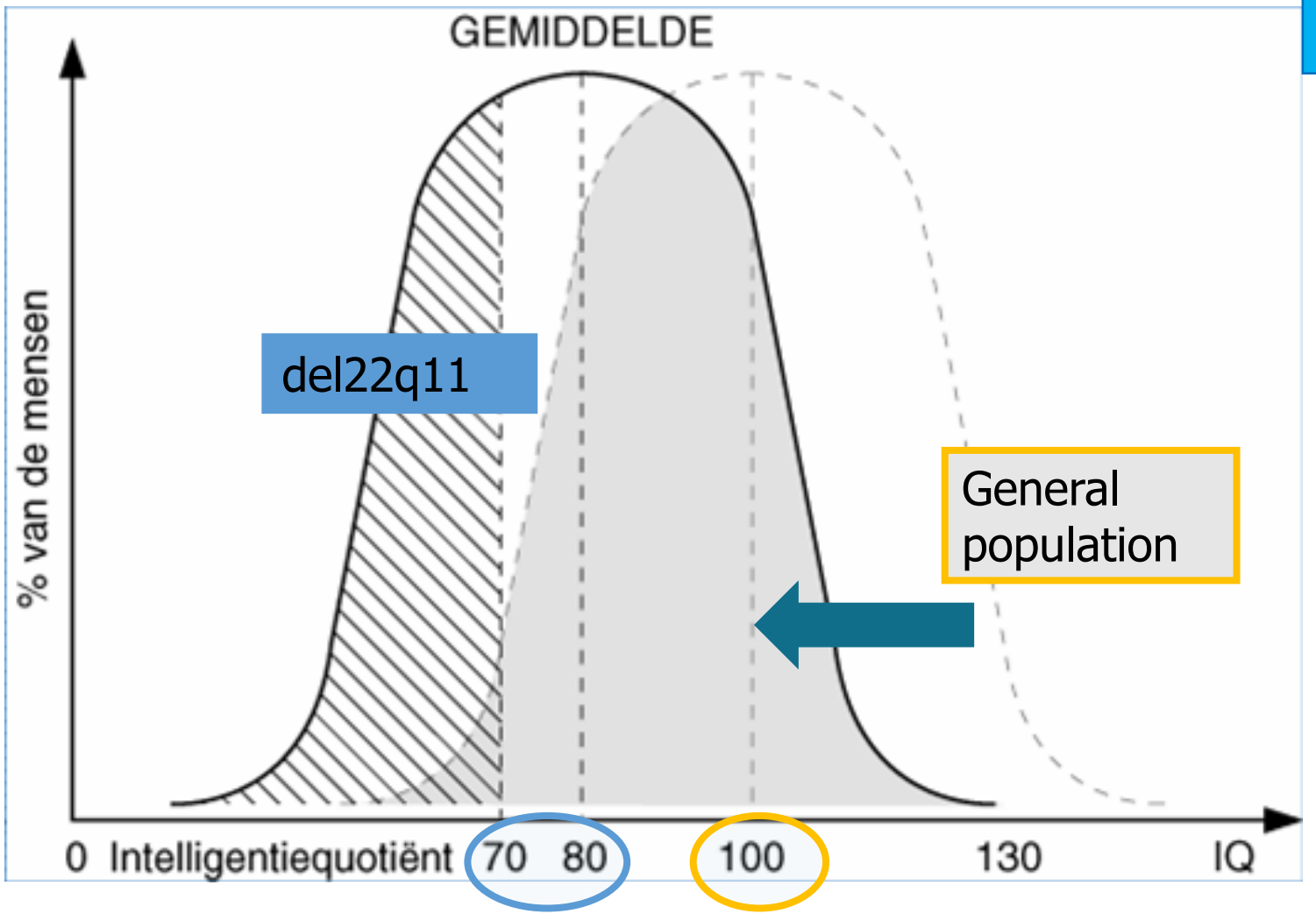
Environmental demands

22q11DS development

7-12 13-18 Adults

Cognitive shift in 22q11 DS

7- 10/12y



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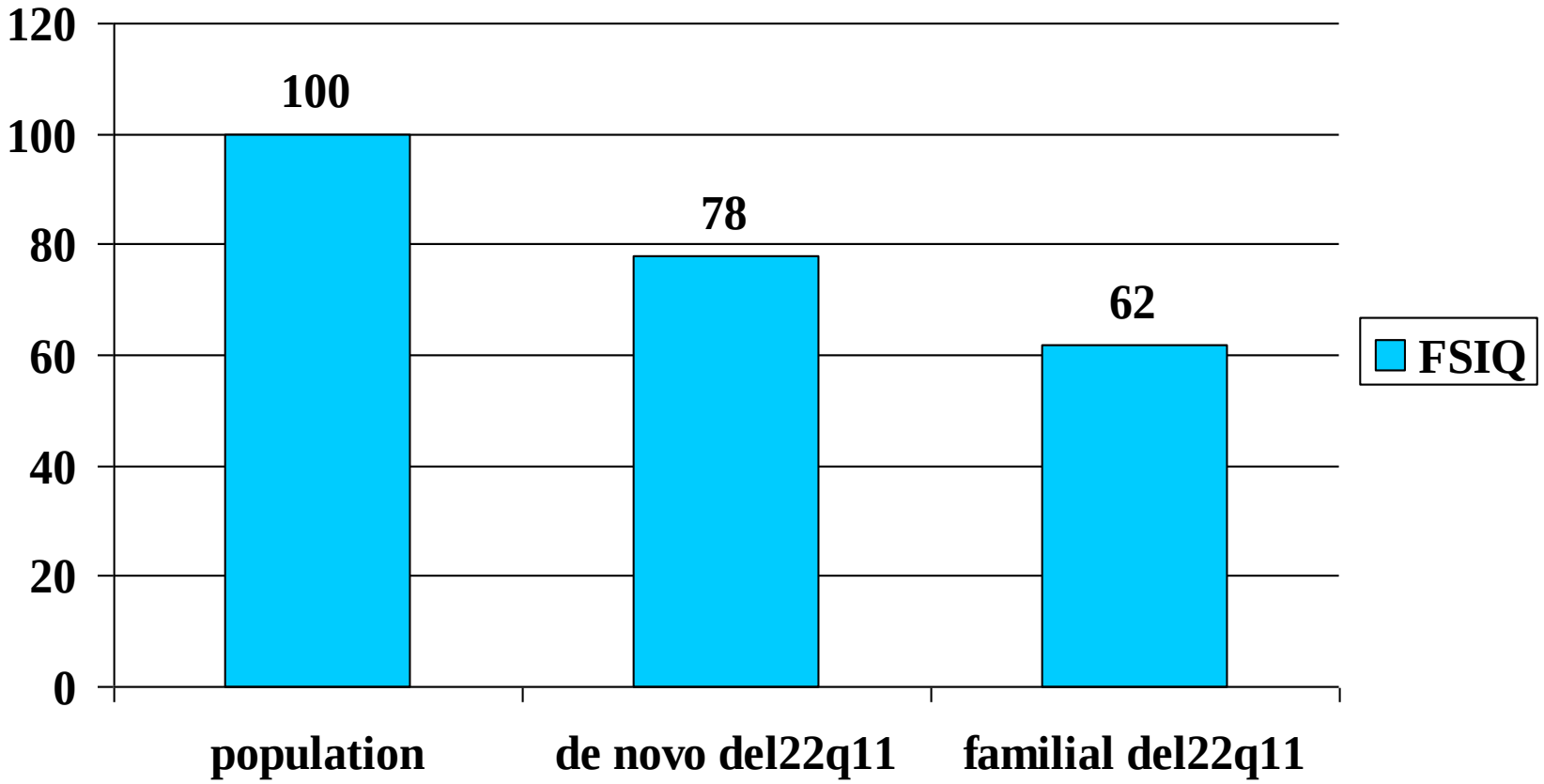
Intelligence in 22q11 DS (de novo vs. familial deletion)



Swillen et al, 1997, *Journal of Medical Genetics,* 34: 453-458

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Journal of Intellectual Disability Research doi: 10.1111/j.1365-2788.2007.00955.x

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Intellectual abilities in a large sample of children with Velo–Cardio–Facial Syndrome: an update

B. De Smedt,[1,2] K. Devriendt,[2] J.-P. Fryns,[2] A. Vogels,[2] M. Gewillig[3] & A. Swillen[2,4]

1 *Centre for Disability, Special Needs Education and Child Care, University of Leuven, Belgium*
2 *Centre for Human Genetics, University of Leuven, Belgium*
3 *Pediatric Cardiology, University Hospital Gasthulsberg of Leuven, Belgium*
4 *Faculty of Kinesiology and Rehabilitation Sciences, University of Leuven, Belgium*

Table 1 Group means (SD)

			P
Deletion	*De novo* ($n = 92$)	Familial ($n = 11$)	
FSIQ	74.50 (11.69)	65.00 (8.45)	0.01
VIQ	79.79 (13.91)	69.27 (11.53)	0.02
PIQ	73.42 (10.89)	66.09 (8.84)	0.03
Sex	Female ($n = 47$)	Male ($n = 56$)	
FSIQ	73.19 (10.40)	73.73 (12.84)	0.82
VIQ	78.87 (12.27)	78.50 (15.43)	0.89
PIQ	72.28 (10.38)	72.95 (11.39)	0.76
CHD	Yes ($n = 55$)	No ($n = 48$)	
FSIQ	74.38 (11.84)	72.46 (11.65)	0.41
VIQ	79.05 (14.23)	78.23 (13.89)	0.77
PIQ	73.56 (10.77)	71.58 (11.05)	0.36
Psychiatric	Non-ADHD ($n = 76$)	ADHD ($n = 27$)	
FSIQ	73.32 (12.32)	73.96 (10.10)	0.81
VIQ	78.30 (14.78)	79.70 (11.76)	0.66
PIQ	72.97 (11.18)	71.70 (10.19)	0.61
	Non-ASD ($n = 84$)	ASD ($n = 19$)	
FSIQ	74.56 (11.83)	68.74 (10.26)	0.05
VIQ	79.32 (14.51)	75.79 (11.43)	0.32
PIQ	73.71 (10.90)	67.89 (9.78)	0.03

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CHD, congenital heart defect; FSIQ, full-scale IQ; PIQ, performance IQ; SD, standard deviation; VIQ, verbal IQ.

Possible factors that contribute to wide variability in intelligence in 22q11 DS ?

- *De novo* versus *familial deletion* (Swillen et al., 1997; 2007)
- Gender differences ? (Swillen et al., 2007; Antshel et al., 2008)
- No effect of congenital heart defect
- Effect of diagnosis ASD on IQ ? ⟷ No effect psychiatric diagnosis (Vorstman et al., 2006)
- Effect of SES (Ousley et al., 2012), parental IQ and siblings IQ (Kates et al., 2014)

- Size of deletion ? Smaller deletions A-B +/- 5 IQ points > compared to A-D deletions
- Genetic polymorphisms ? COMT, PRODH
- Modifying genes ?
- Other environmental influences (therapy/remediation,…)

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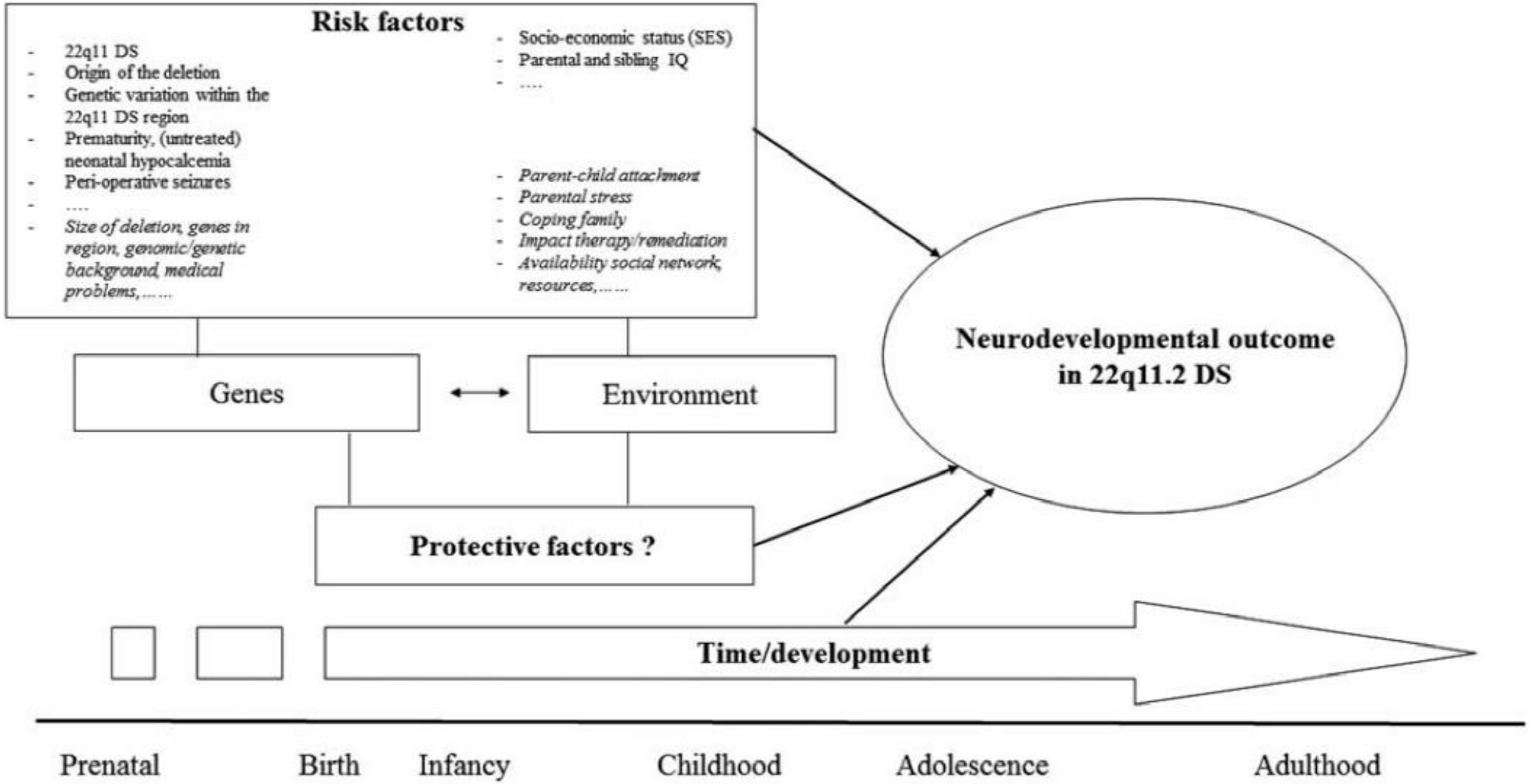

FIGURE 1 Possible factors contributing to neurodevelopmental outcome in 22q11.2 DS. Neurodevelopmental outcome in 22q11.2 DS is the result of the dynamic interaction of multiple factors: person-specific risk and protective factors, family and environmental risk and protective factors, and time/development itself. These factors act as independent, cumulative and synergistic influences

Cognitive challenges in 22q11 DS (7-12 y)

- academic problems: **arithmetics and reading comprehension**
- good (technical) reading skills and good verbal (STM) memory but problems with comprehension

- problems with abstract thinking/ problem-solving
- problems with integrating new information
- **poor attention and concentration (ADD)**
- **problems with starting, initiating,…**
- **deficits in visual-perceptual abilities**

- **But diverse cognitive trajectories !**

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

Practice and management (learning)

- **no standards for advise/intervention**
- USE RECENT COGNITIVE/NEUROPSYCHOLOGICAL ASSESSMENT & ADAPTIVE SKILLS !

→ individualized educational plan (IEP)

- remedial teaching (arithmetics, reading comprehension) or special needs school
- **structured and quite learning environment**
- be aware of medical problems (hearing, cardiac, fatigue,….)
- be aware of slower tempo
- if visual-perceptual problems are present:
  - adaptation of material, and visual training: learn visual strategies

3. from early adolescence on (13-18y)

Cognitive and educational challenges from early adolescence on (13-18y)

- **Learning problems increase with age**

- Stable learning trajectory
- “Growing into deficit”
- In subgroup, verbal decline >>

American Journal of Medical Genetics Part C (Seminars in Medical Genetics)

ARTICLE

Developmental Trajectories in 22q11.2 Deletion

ANN SWILLEN AND DONNA McDONALD-McGINN

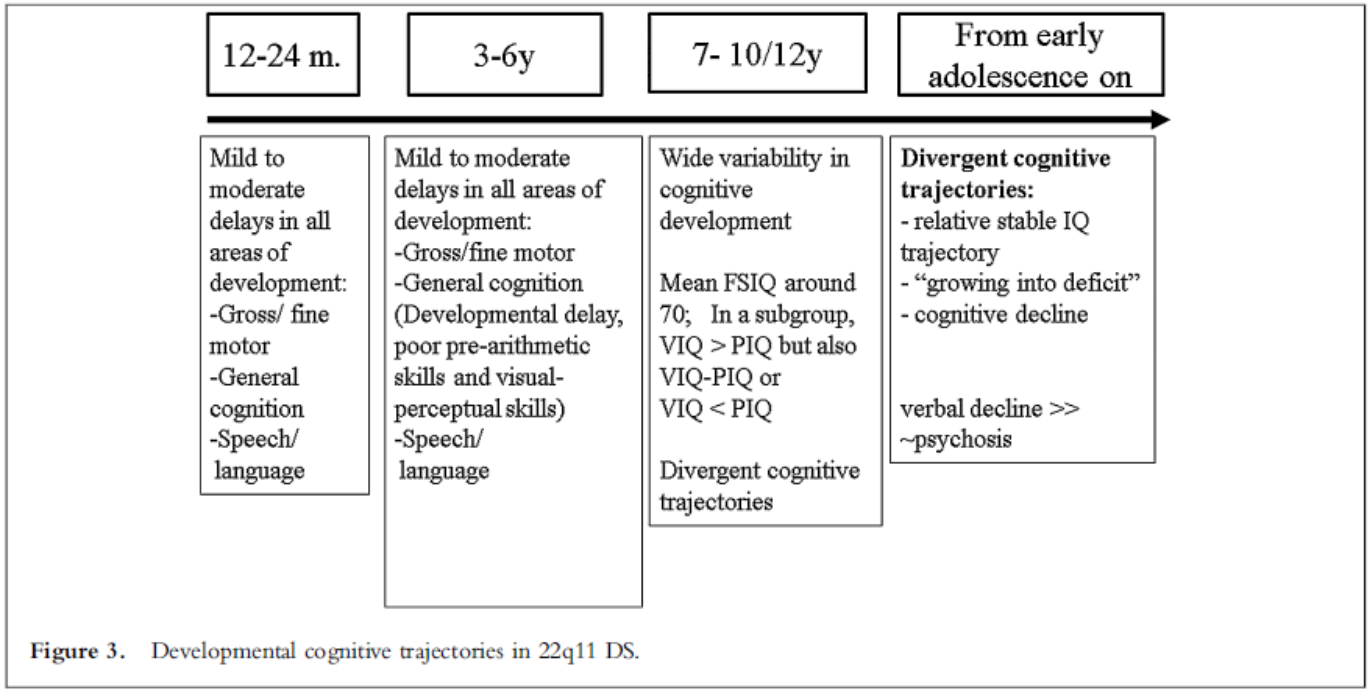

Figure 3. Developmental cognitive trajectories in 22q11 DS.

Recommendations and support for adolescents

- Offer **structure and security**
- « **Match** » **abilities – school/work environment**
- **Be alert for and pay attention regarding bullying**
- School
  - **Psychoeducation** teachers/pupils
  - Adapt curriculum/ extra support, facilities; part-time school (cfr. fatigue)
- Work:
  - **Psychoeducation**
  - Part-time jobs ! (cfr. fatigue, medical problems)
  - Jobcoach
  - Volunteers'work

Developmental Tasks during Adolescence and (Young) Adulthood

- Separate from parents, building identity
- Develop a healthy self-image
- Set & achieve education & vocational goals

- Financial independence
- Independent living
- Partnership - marriage
- Participate in community life
- Be happy – intact mental health

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« Changing Parenting » during adolescence

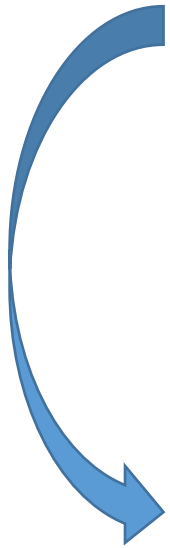
- From dependency to more independency
- Step-wise more independency, responsibilities

In families with children with disabilities:

- Over-protective
- Under- or overestimating difficulties/deficits

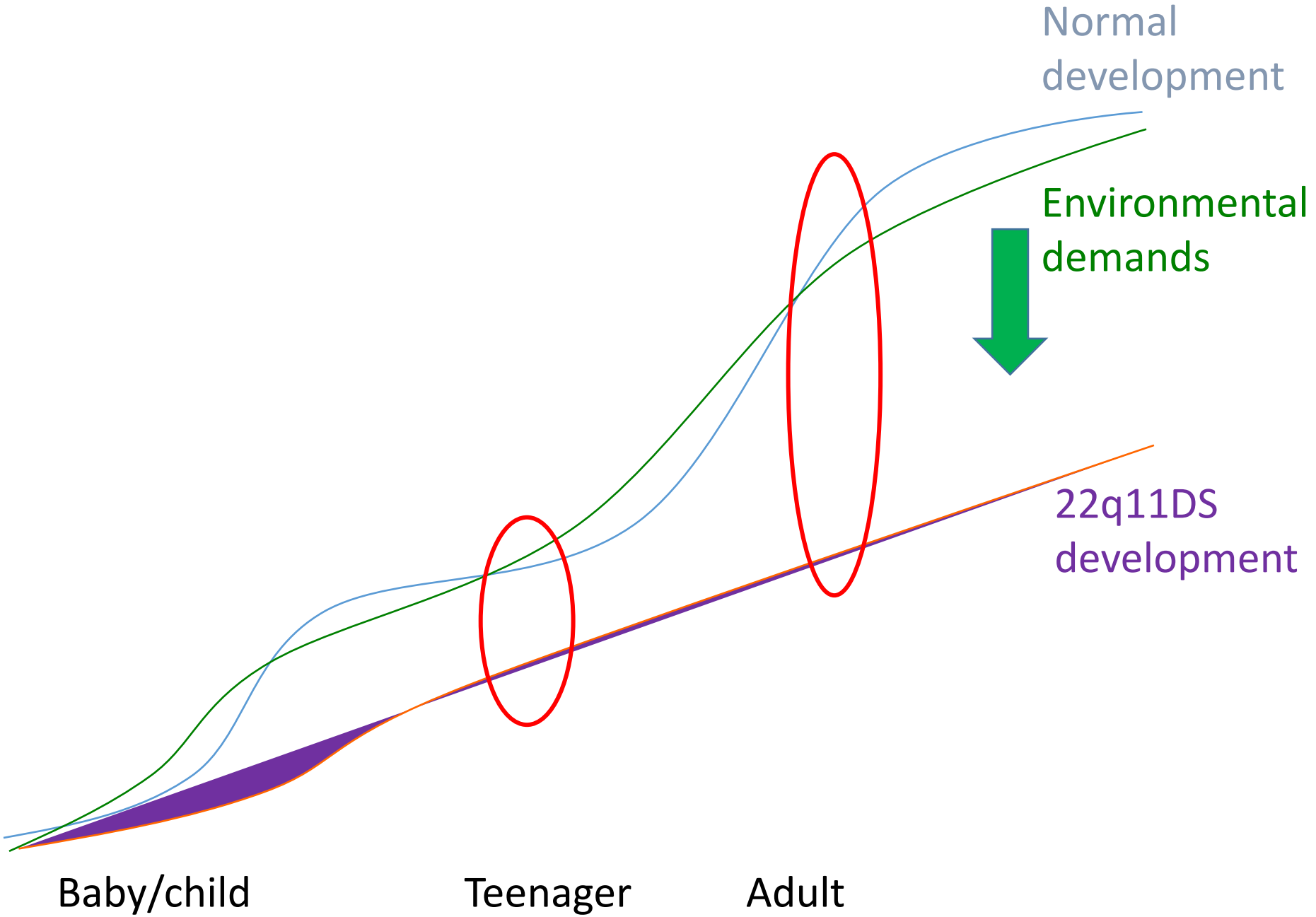
Psycho-social challenges (13-18y, 18+)

- Psycho-socially:
  - Shy, withdrawn behaviour
  - Emotional vulnerable and mood swings
  - Social and communication impairments:
    - Poor relations with peers
    - Poor verbal and non-verbal communication



Dependent

Poor self-concept/low self-esteem


Normal development
Environmental demands
22q11DS development
Baby/child
Teenager
Adult

Support for teenagers

- **Talk** to your child/teenager, **explain (psycho-education !)**
- Encourage the development of a **REALISTIC self-concept** (= crucial !)
- **Encourage and practice social skills**
- Encourage and **practice daily living skills** (including basic safety skills)
- **Hobby** ! (music, sport, photography, animals (pets/horses/dogs,….)
- Contact with other teenagers/young adults with 22q11 DS
- Find an **appropriate educational/vocational track**
  - (normal) school/workcircuit + support
  - special school/sheltered work
  - written information about the needs/ necessary adaptations,……

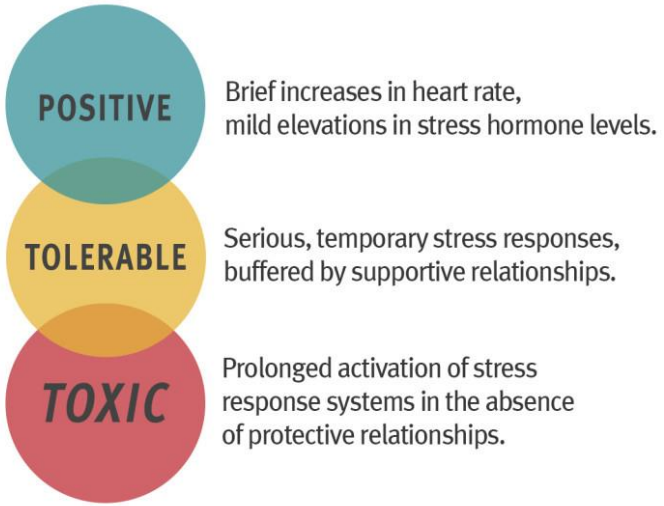
…..

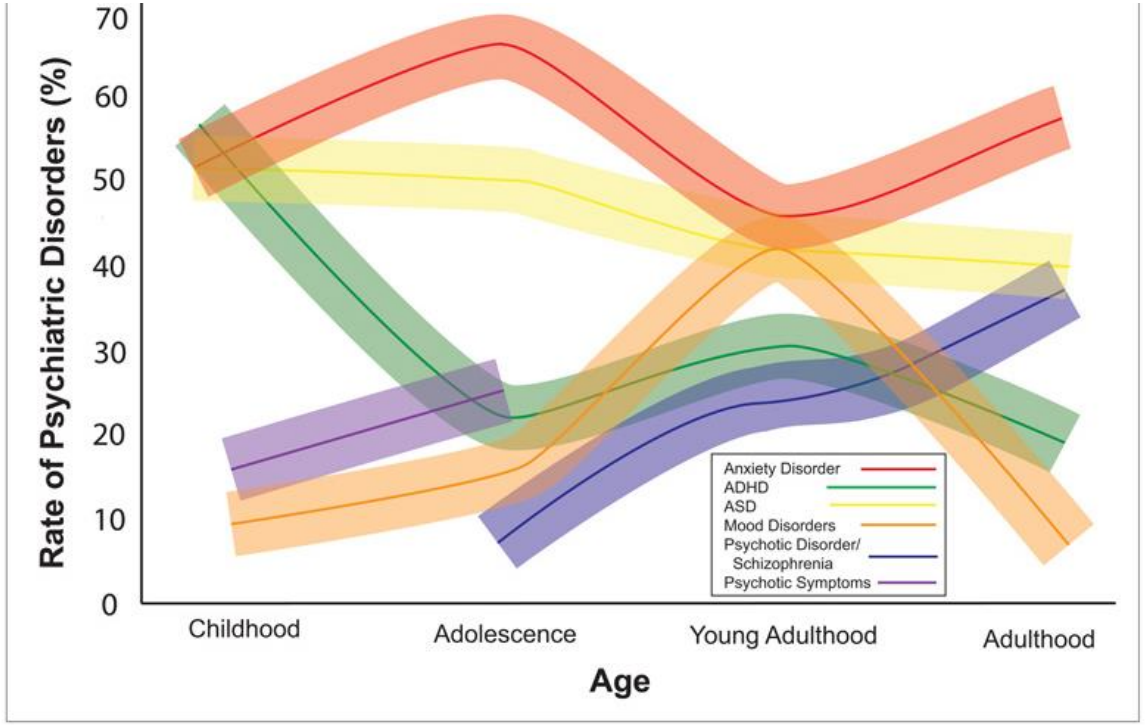
Support for parents

- Support in working through attitudes, feelings and uncertainties about their child's abilities/disabilities
- Support parents in acceptance of the disability and limitations of their child ("develop a realistic and adequate image")
- **provide parents knowledge on "puberty/adolescence" and "p/a in del22q11DS"**
- encourage parents to foster more skills of independence according to their children/adolescent's developmental level
- Importance of sexual education for their children (sexuality in a healthy and protective way)
- Information on resources, legal issues (guardianships, ….)

4. Risk for psychiatric disorders in 22q11 DS

Individuals with 22q11 DS, have a high stress sensitivity





Jonas R, Montojo C, Bearden C. The 22q11.2 Deletion Syndrome as a Window into Complex Neuropsychiatric Disorders Over the Lifespan. Biological Psychiatry. 2014;75(5):351-360.

22q11.2 deletion syndrome

Anxiety disorders

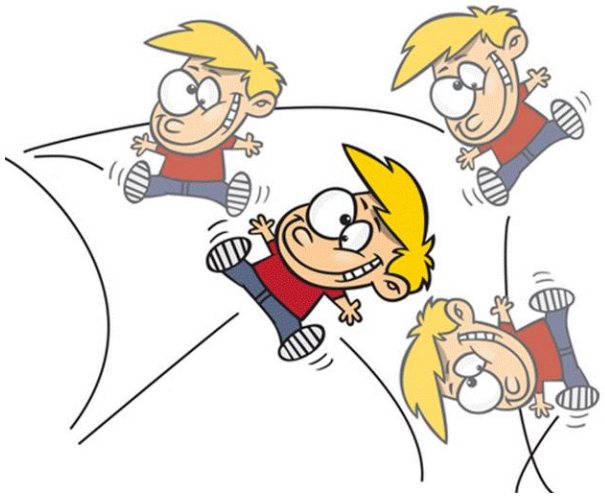
- Small decrease in frequency with age: 35% ->25%
- At child age:
  - Specific and social phobia
  - Separation anxiety disorder
- Adult age:
  - Panic disorder

Bron: **Psychiatric Disorders From Childhood to Adulthood in 22q11.2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome**. Schneider, M., Debbané, M., Bassett, A. S et al. 2014 The American Journal of Psychiatry, 171(6), 627–639

22q11.2 deletion syndrome

ADHD

- Decrease in frequency with age: 37% -> 16%
- ♂ > ♀



ASD

- Adolescents: ± 25%

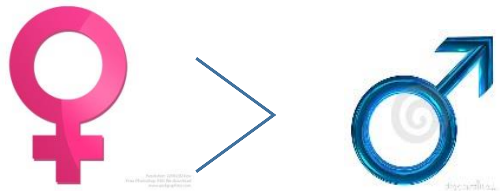
: **Psychiatric Disorders From Childhood to Adulthood in 22q11.2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome**. Schneider, M., Debbané, M., Bassett, A. S et al. 2014 The American Journal of Psychiatry, 171(6), 627–639

22q11.2 deletion syndrome

Major Depressive Disorder:

Increase in frequency with age:

- 10-15% adults
- 9% adolescents



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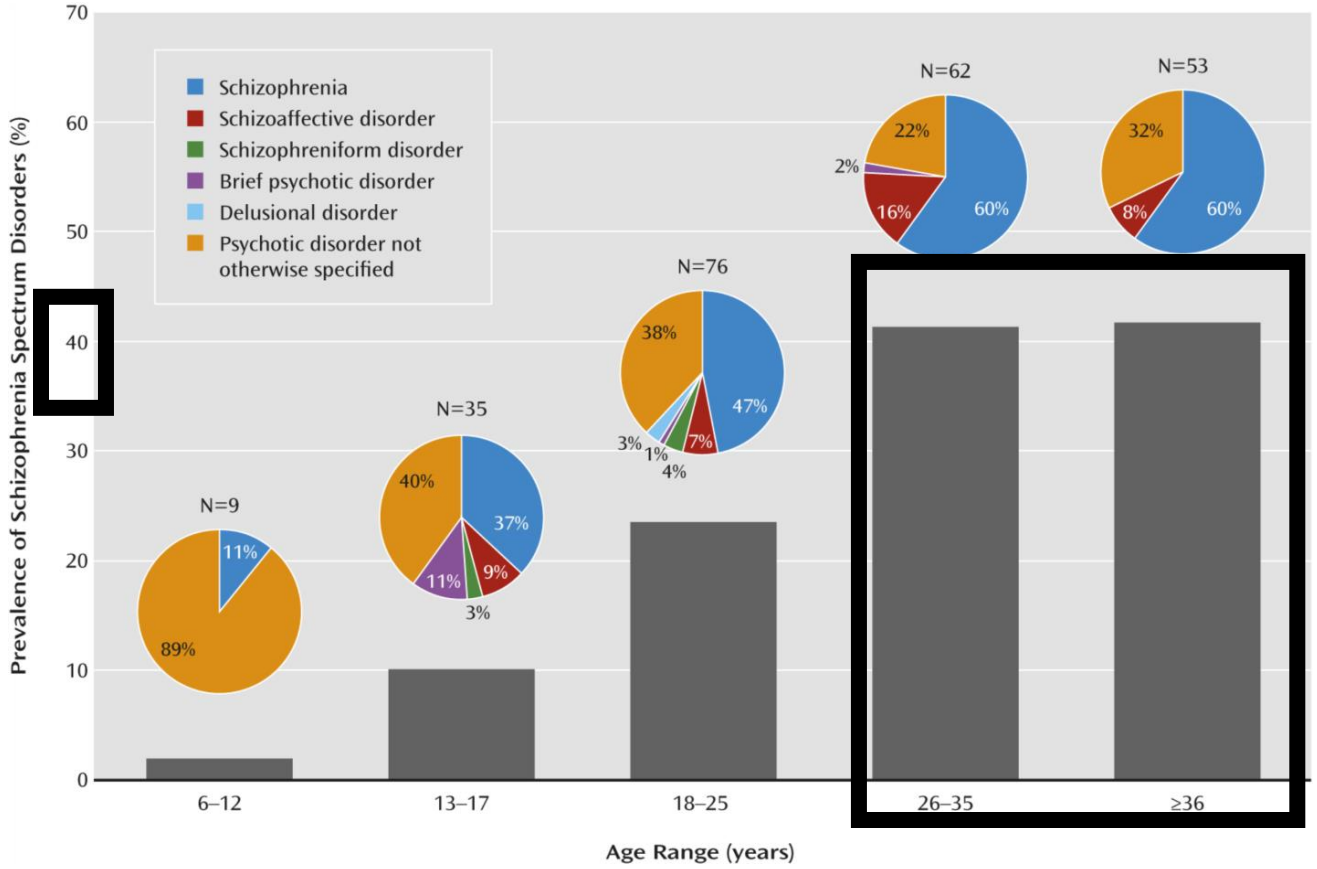
THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

From: Psychiatric Disorders From Childhood to Adulthood in 22q11.2 Deletion Syndrome: Results From the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome

Am J Psychiatry. 2014;171(6):627-639. doi:10.1176/appi.ajp.2013.13070864



41%

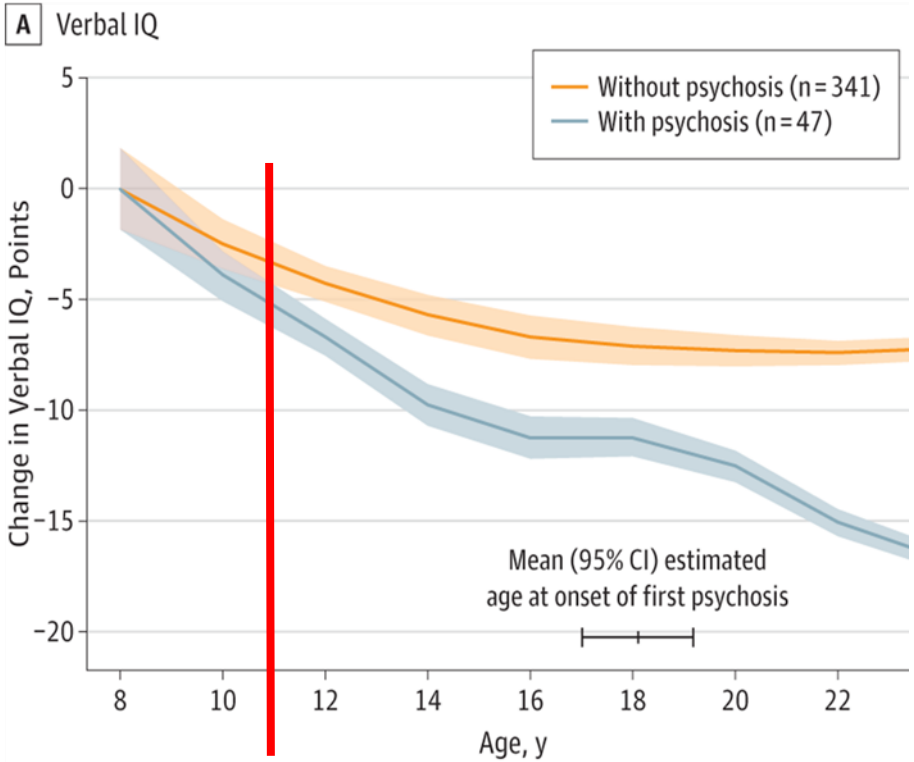
Figure Legend:

Prevalence of Schizophrenia Spectrum Disorders and Distribution of Specific Disorders by Age in Participants With 22q11.2 Deletion Syndrome[aa] Among the 235 subjects with schizophrenia spectrum disorders, the prevalence of a schizophrenia diagnosis increased significantly over the age groups (χ^2=12.54, df=4, p=0.01), whereas the diagnosis of psychotic disorder not otherwise specified decreased (χ^2=17.17, df=4, p=0.002).

Findings from the International Brain and Behaviour Consortium

Vorstman et al., 2015

- 829 subjects with a confirmed 22q11.2 deletion
- recruited through 12 international clinical research sites
- Both psychiatric assessment and longitudinal IQ measurements were available for a subset of 411 subjects



Vorstman et al, A cognitive decline precedes the onset of psychosis in patients with the 22q11.2 deletion syndrome, JAMA Psychiatry, 2015

22q IBBC
International 22q11.2 Brain Behavior Consortium

Guidance/treatment psychiatric problems

⦿Multidisciplinary & holistic approach:

- Guidance of individual AND family by (Child) psychiatrist & team)

  - **Reduction of pressure/stimuli: build in regular rest breaks**
  - **Restore sleep/improve sleep !**
  - Safety and structure
  - Predictability
  - Medication

  - Always be alert for additional medical problems (fatigue, thyroid problems, neurological problems,….)

A

Brain, Behavior, and Immunity 70 (2018) 88–95

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

A pilot study on immuno-psychiatry in the 22q11.2 deletion syndrome: A role for Th17 cells in psychosis?

Elfi Vergaelen [a,b,*,1], Carmen Schiweck [a,1], Kristof Van Steeland [a], Jacqueline Counotte [d], Wim Veling [e], Ann Swillen [b,f], Hemmo Drexhage [c], Stephan Claes [a]

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Th17 cells
T-cell immune deficiency
Psychosis
Neuro-inflammation

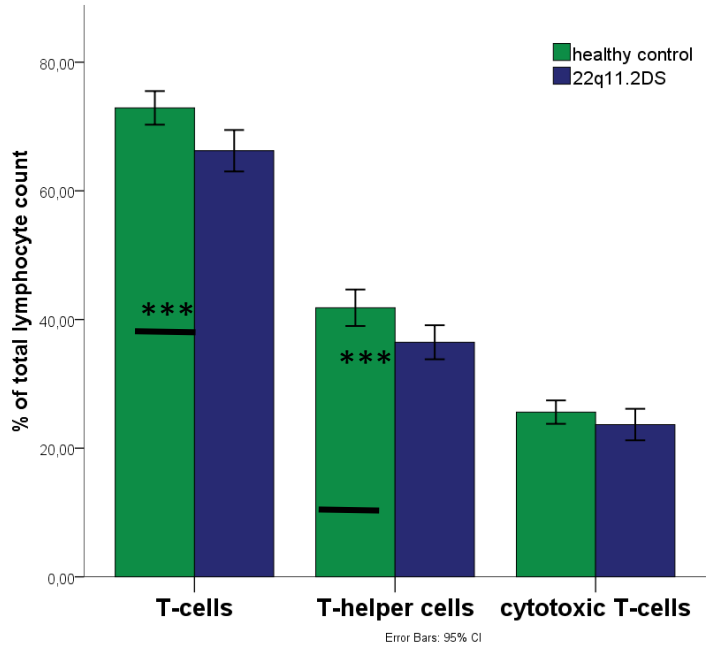
ABSTRACT

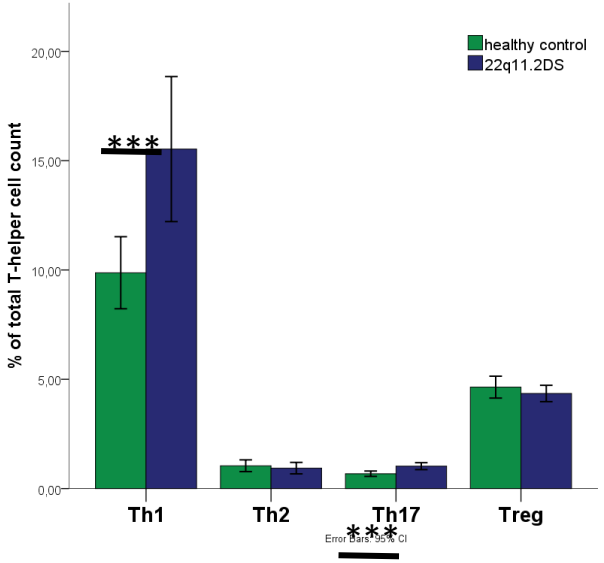
Background: A growing body of evidence supports a role for immune alterations in Schizophrenia Spectrum Disorders (SSD). A high prevalence (25–40%) of SSD has been found in patients with 22q11.2 deletion syndrome (22q11.2DS), which is known for T-cell deficits due to thymus hypoplasia. This study is the first to explore the association between the T-cell subsets and psychotic symptoms in adults with 22q11.2DS.

Methods: 34 individuals (aged 19–38 yrs.) with 22q11.2DS and 34 healthy age- and gender matched control individuals were included. FACS analysis of the blood samples was performed to define T-cell subsets. Ultra-high risk for psychosis or diagnosis of SSD was determined based on CAARMS interviews and DSM-5 criteria for SSD. Positive psychotic symptom severity was measured based on the PANSS positive symptoms subscale.

Results: A partial T-cell immune deficiency in 22q11.2DS patients was confirmed by significantly reduced percentages of circulating T and T-helper cells. Significantly higher percentages of inflammatory Th1, Th17, and memory T-helper cells were found in adults with 22q11.2DS. Most importantly an increased Th17 percentage was found in adults with psychotic symptoms as compared to non-psychotic adults with 22q11.2DS, and Th17 percentage were related to the presence of positive psychotic symptoms.

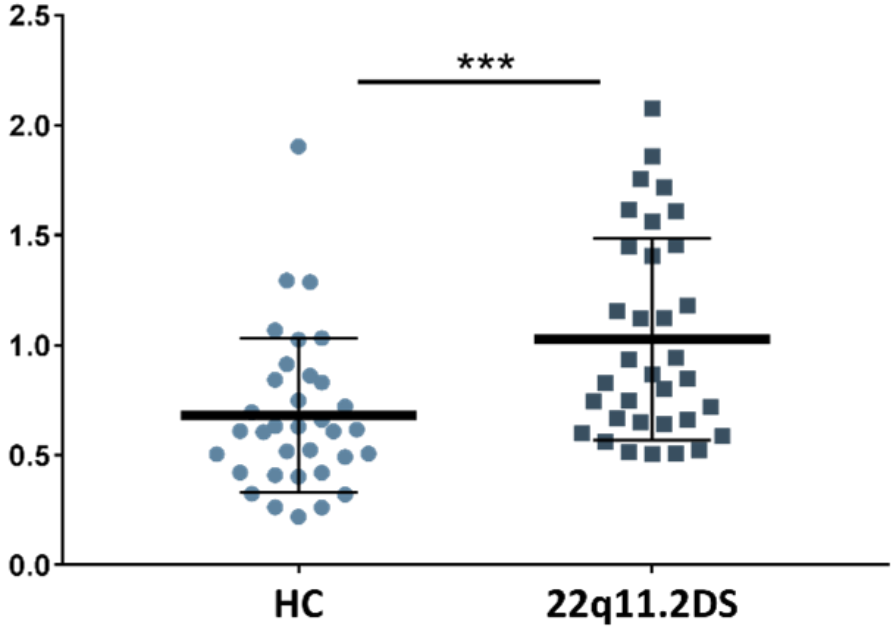
Conclusions: Given the literature on the role of T cells and in particular of Th17 cells and IL-17 in hippocampus development, cognition and behavior, these results support the hypothesis for a role of Th17 cells in the development and/or regulation of psychotic symptoms in 22q11.2DS. This pilot study underlines the importance to further study the role of T-cell defects and of Th17 cells in the development of psychiatric symptoms. It also supports the possibility to use 22q11.2DS as a model to study T-cell involvement in the development of SSD.



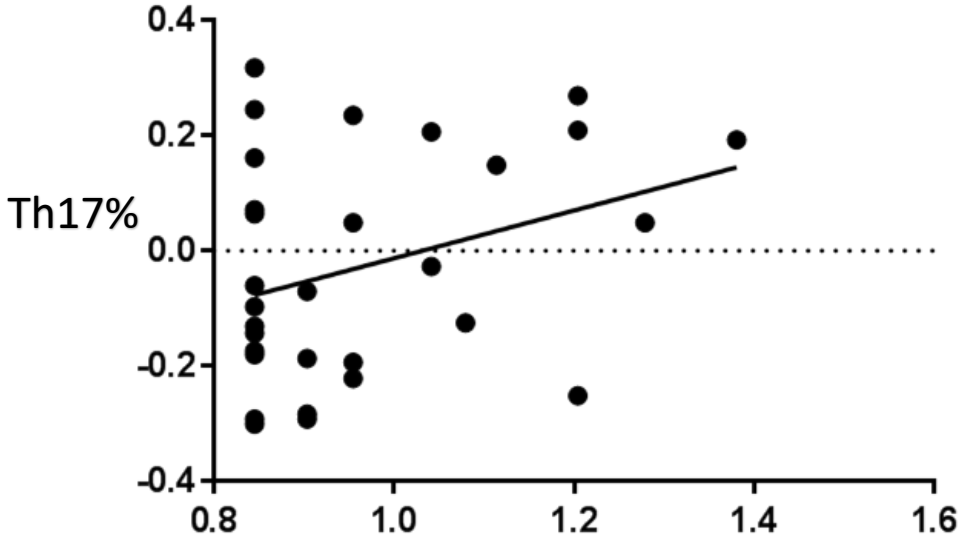


The immune system and psychotic symptoms

Th17 = T cell that increases



Th17 % is increased in 22q11



Psychotic symptoms

Fatigue from adolescence on !

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

High Prevalence of Fatigue in Adults with a 22q11.2 Deletion Syndrome

Elfi Vergaelen,[1,2]* Stephan Claes,[2] Stefan Kempke,[3] and Ann Swillen[1,4]

I feel tired!

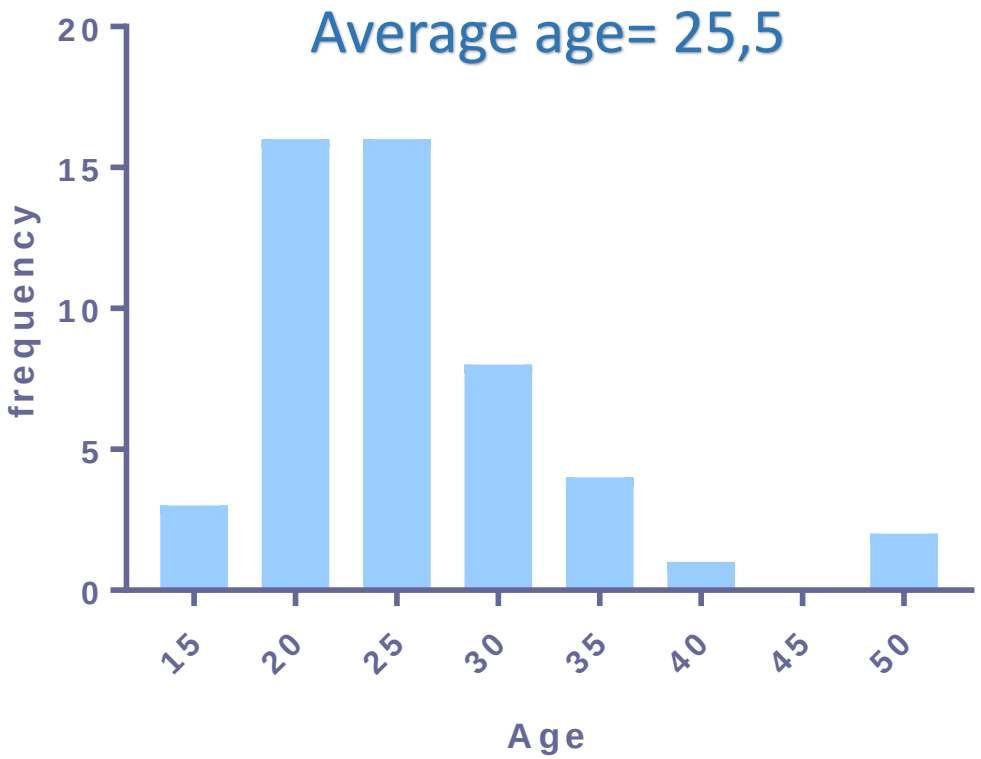
My mind wanders…

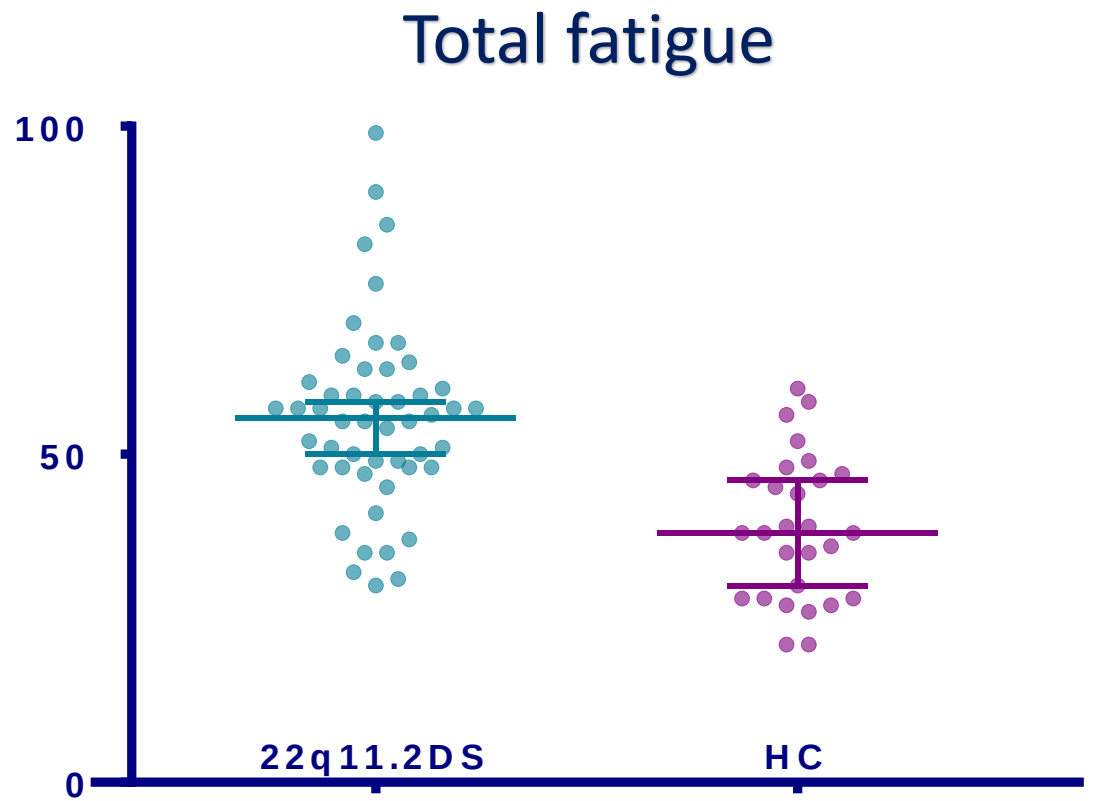
I don’t want to do anything.

Physically I don’t feel strong…

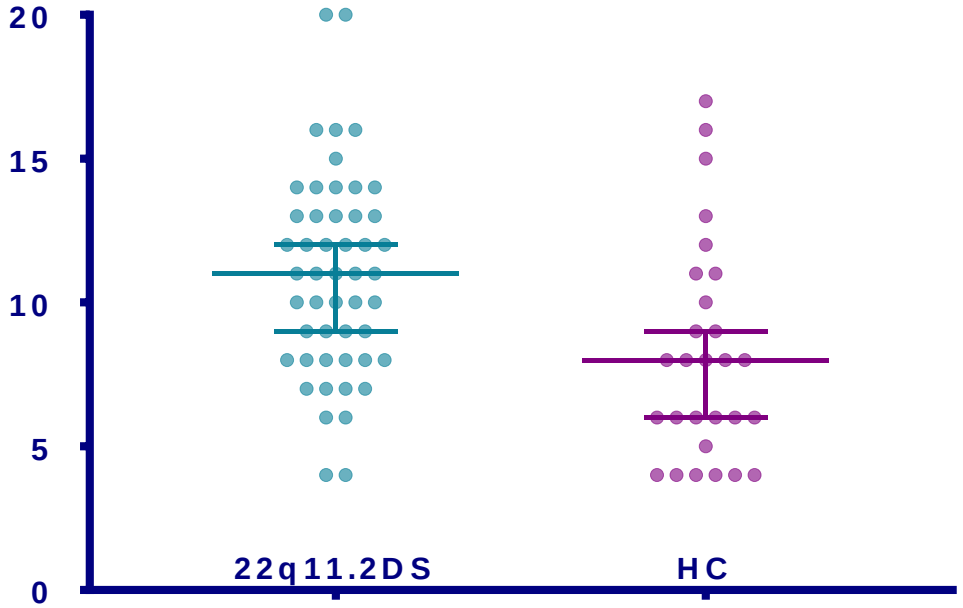
I think I do almost nothing during the day…

Fatigue in (young) adults

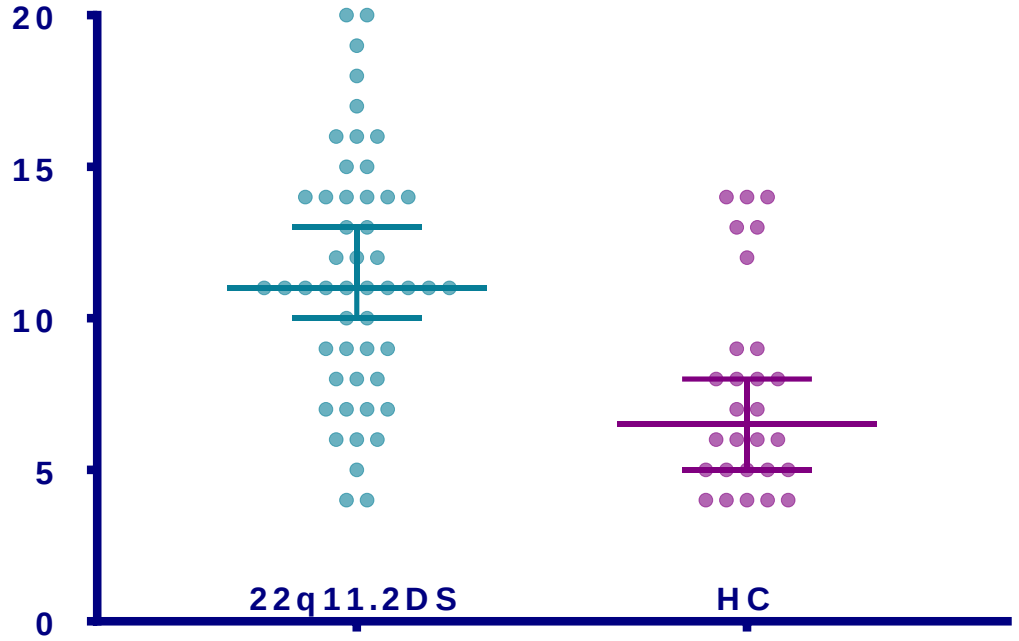




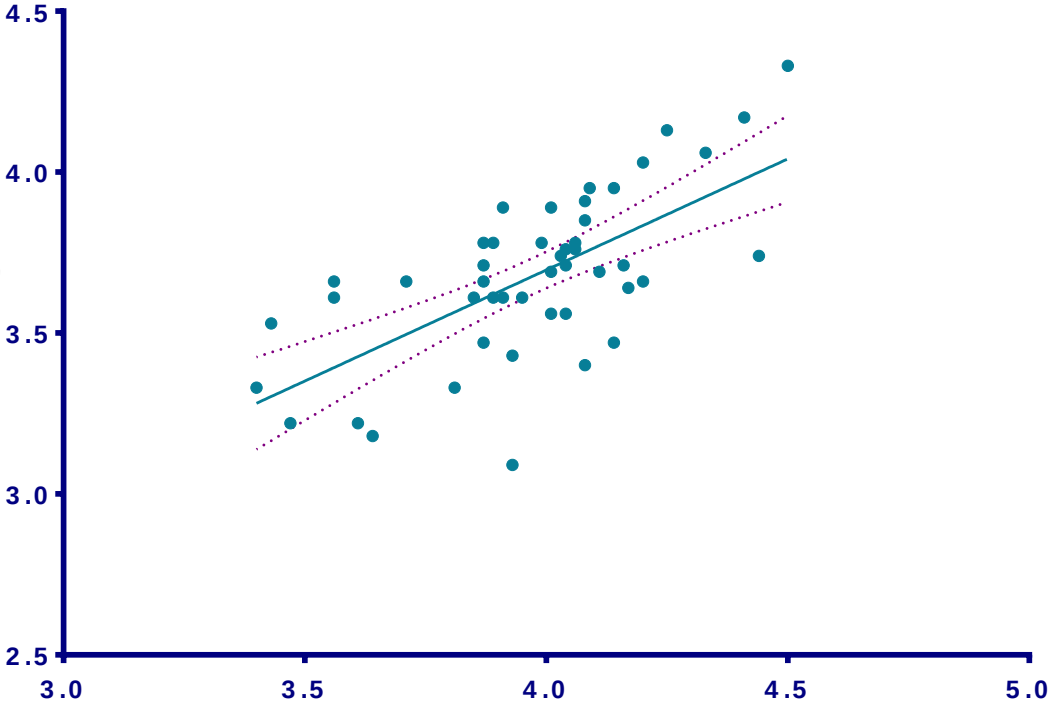
Mental fatigue



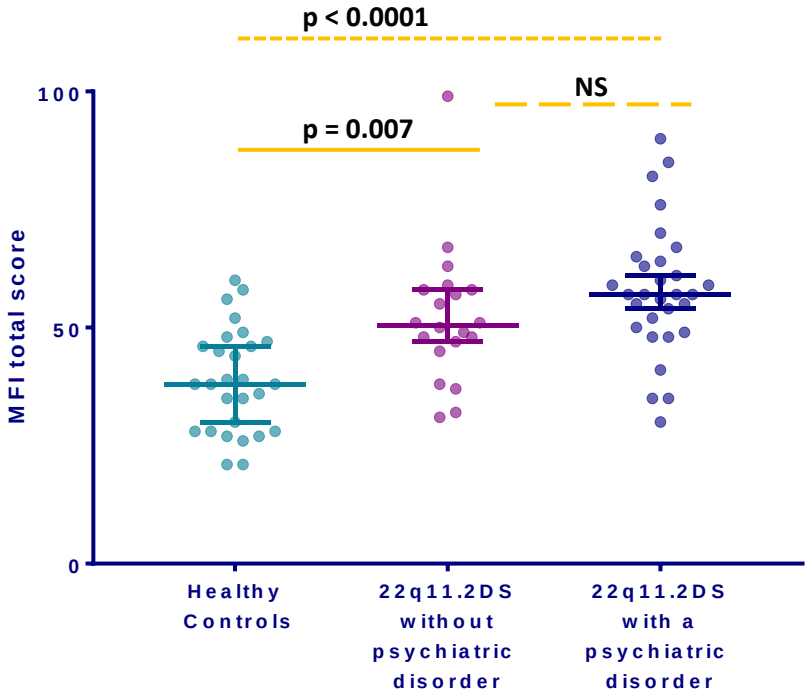
Physical fatigue



Anxiety



Total fatigue



Conclusion:

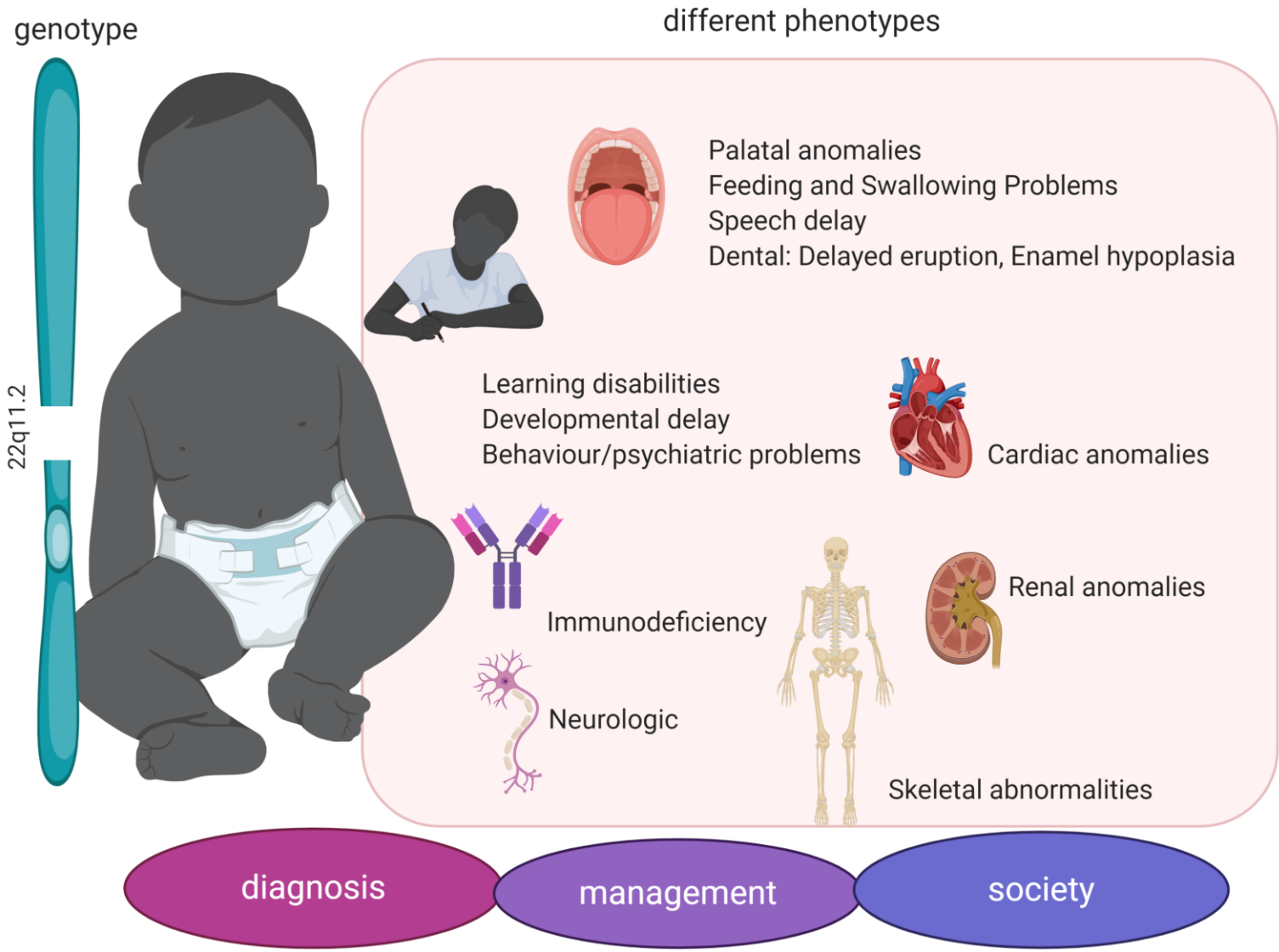
From infant to adult with 22q11 deletion (22q11 DS):

→ **wide variability**

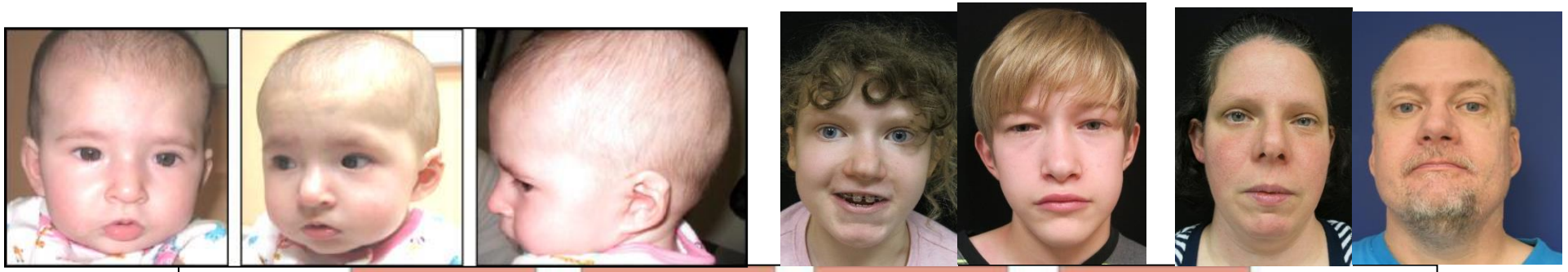
* medical features (clinical phenotype)

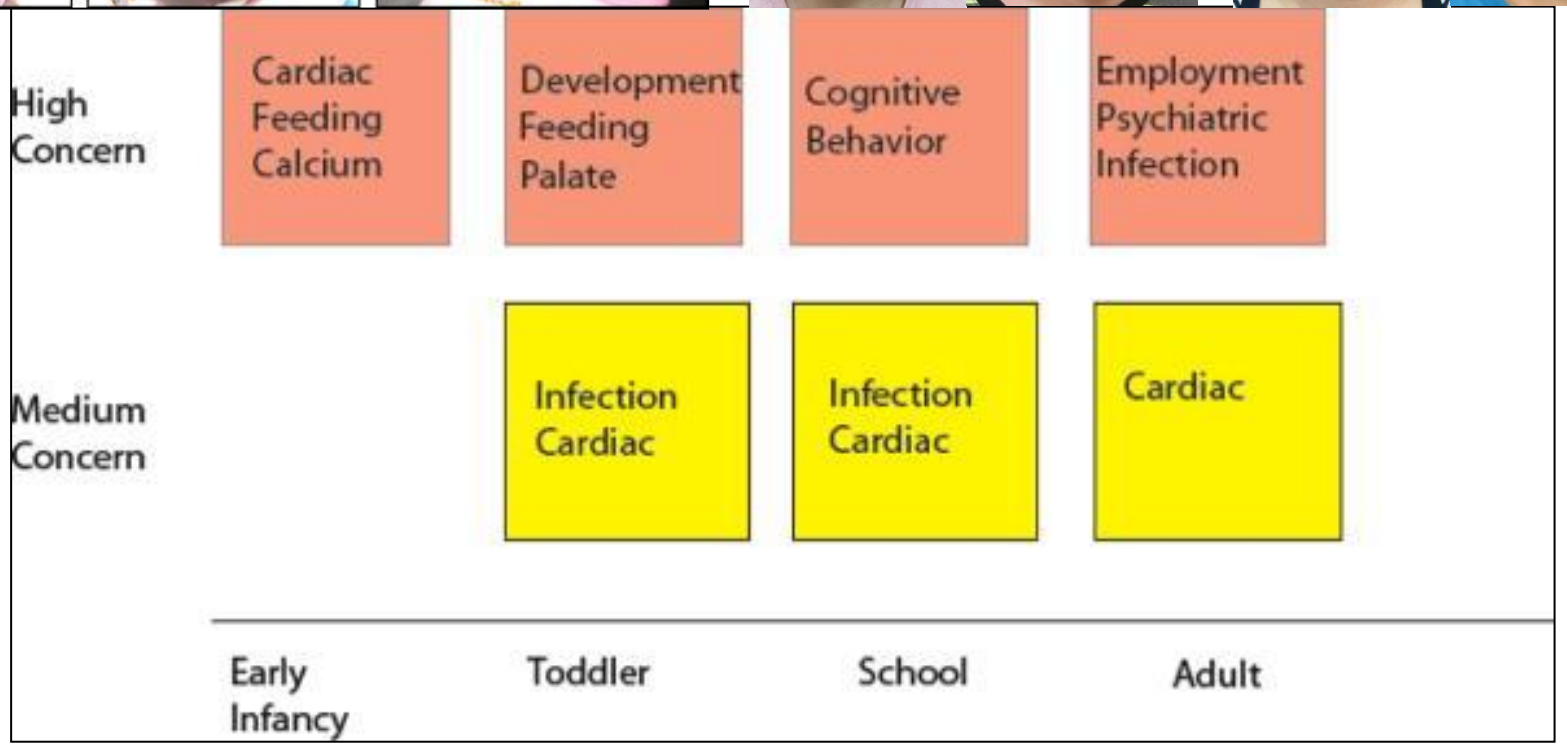
* cognitive, behavioural/social-emotional features (behavioural phenotype)

22q11.2 microdeletion syndrome



The dynamic nature of health & developmental/behavioural/ psychiatric concerns in patients with 22q11.2 DS





Multidisciplinary care (the Leuven model)

- **Holistic focus (interaction body and mind + person and context)**
- **Early assessment of patient needs & psycho-education**
- **Multidisciplinary** consultations & meetings
- **Coordination and continuation of perzonalized care**
- **Anticipatory guidance and longitudinal follow-up**

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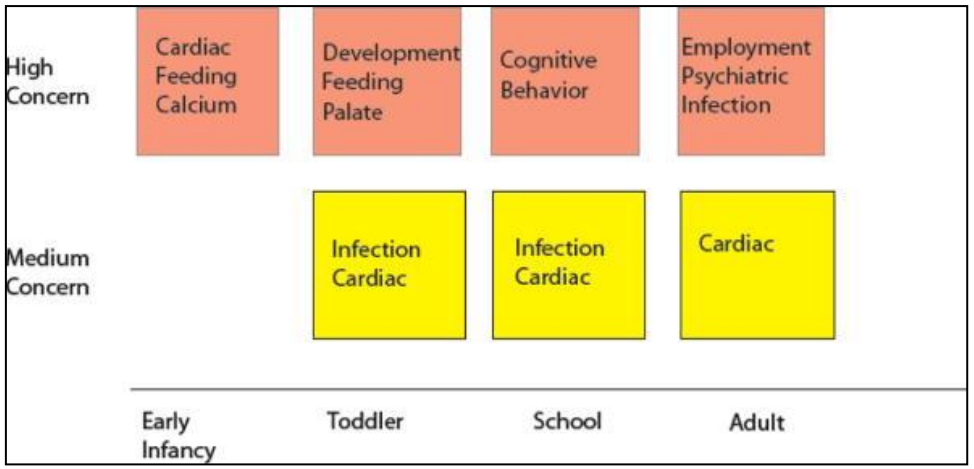
"Combined consultations" & "Partnership" between many disciplines

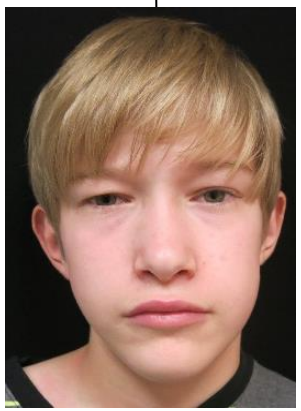
DEVELOPMENTAL/ BEHAVIORAL CONCERNS

MEDICAL CONCERNS



MEDICAL CONCERNS

DEVELOPMENTAL/ BEHAVIORAL CONCERNS



American Journal of Medical Genetics Part C (Seminars in Medical Genetics)

ARTICLE

Developmental Trajectories in 22q11.2 Deletion

ANN SWILLEN AND DONNA McDONALD-McGINN

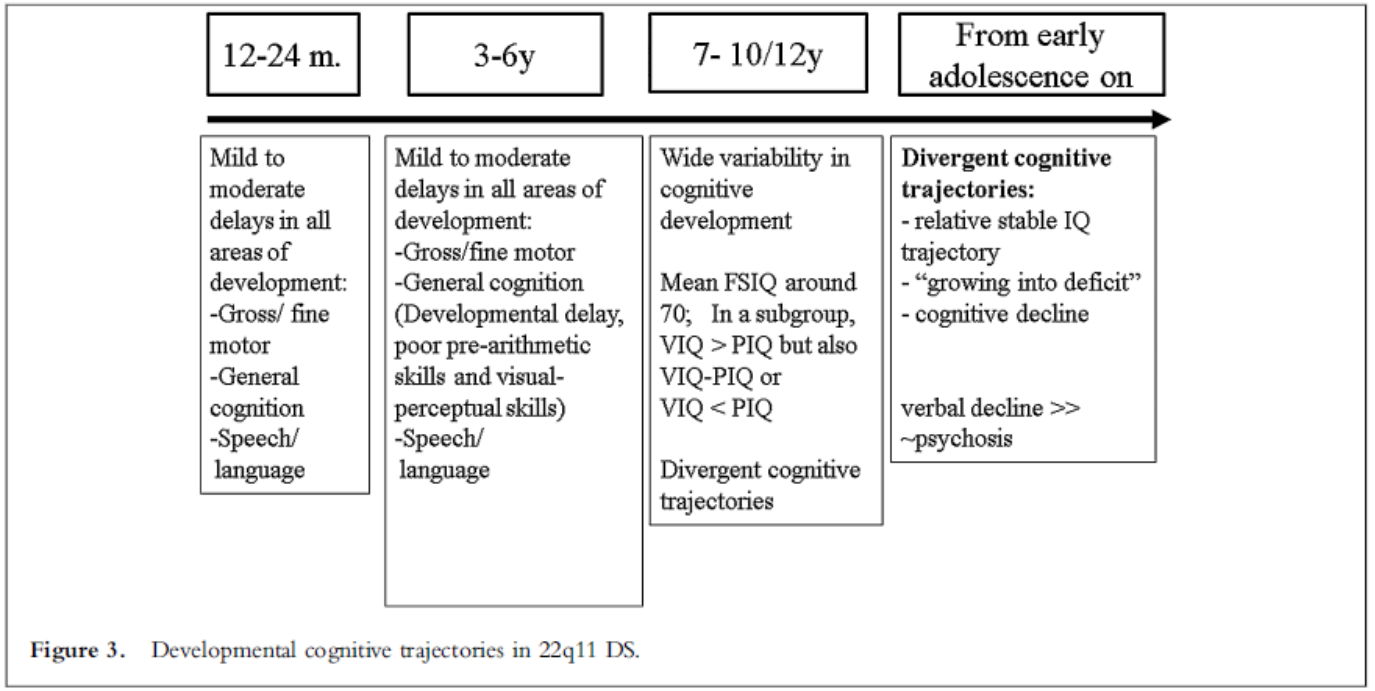


Figure 3. Developmental cognitive trajectories in 22q11 DS.

Multidisciplinary care (the Leuven model)

- **Holistic focus (interaction body and mind + person and context)**
- **Early assessment of patient needs & psycho-education**
- **Multidisciplinary** consultations & meetings
- **Coordination and continuation of perzonalized care**
- **Anticipatory guidance and longitudinal follow-up**

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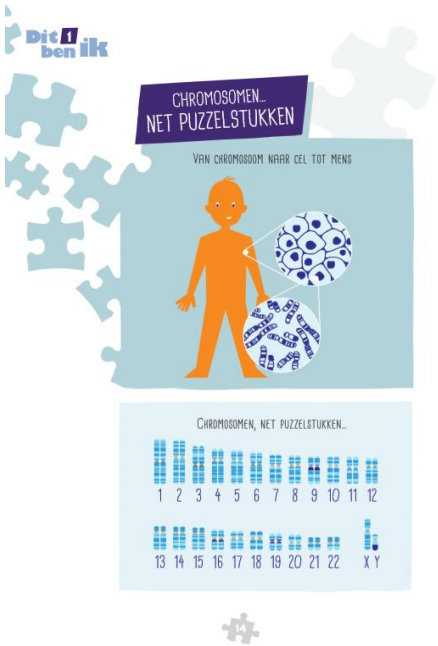
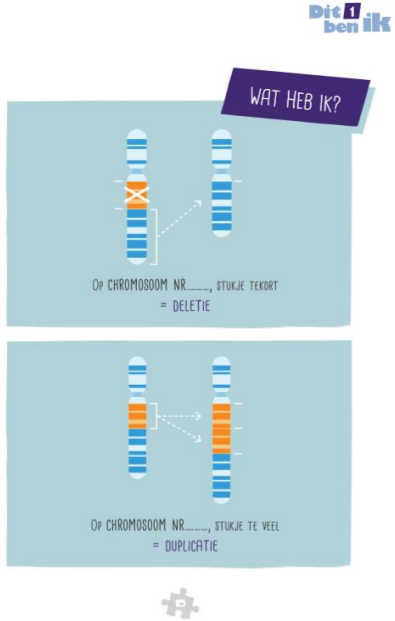
Early diagnosis and assessment of needs is an opportunity

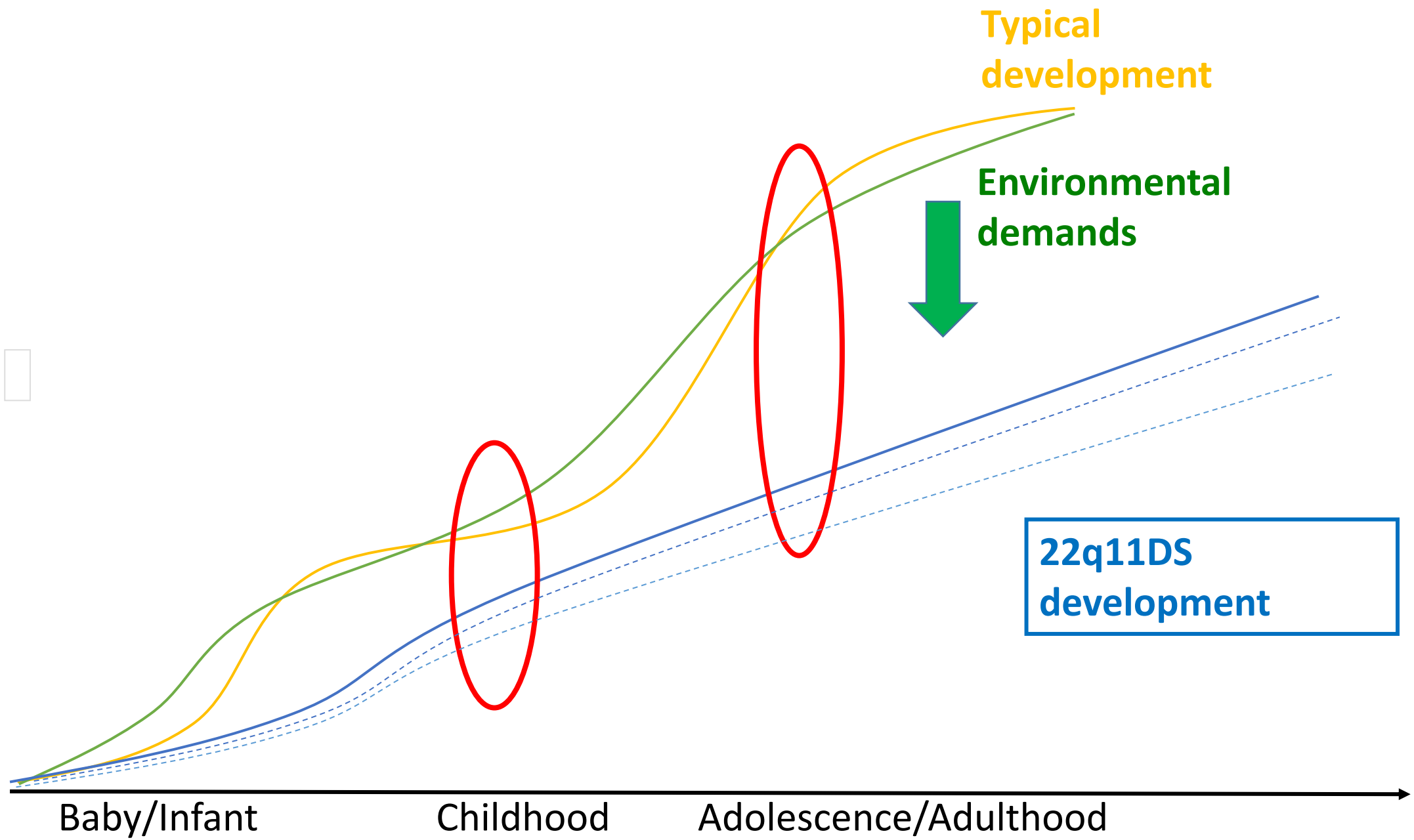
- to start, organize and coordinate the personalized & multidisciplinary care for child and parents
- for (psycho)-education: inform and explain



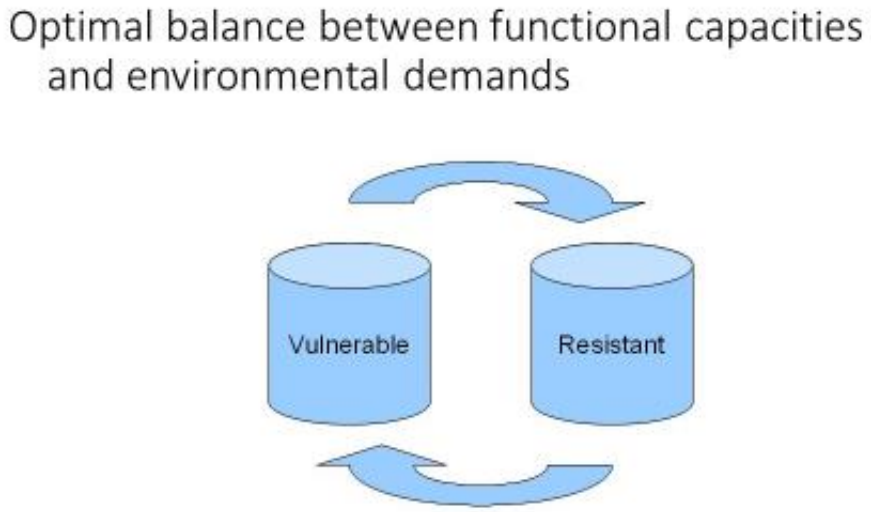


https://www.thegeneticpuzzle.eu

- to anticipate and manage the medical, psychosocial and educational needs


Typical development
Environmental demands
22q11DS development
Baby/Infant
Childhood
Adolescence/Adulthood

- The care = personalized care



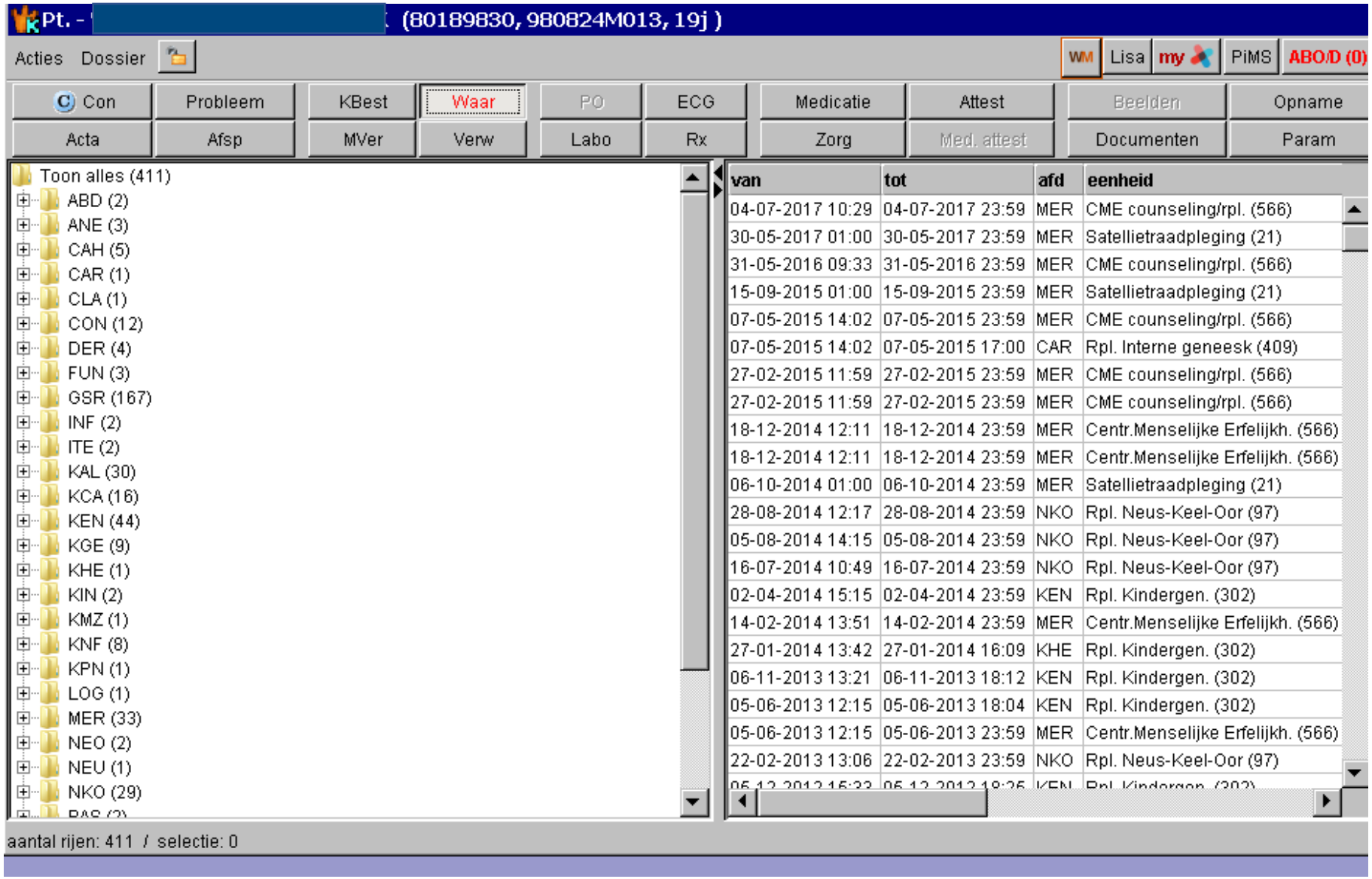
- Information & psycho-education, follow-up, support and a coordinated care by a multidisciplinary expert network/team are indispensable.

Steps towards a holistic, integrated care (& research)

- Install **multidisciplinary teams** (MDT) with a clear **vision** and division of responsibilities (resource centre & excellency)
- **Personalized, coordinated and continued care** AND good **communication between professionals of different disciplines and between MDT and patients** → 1 digital patient record ("KWS") with all relevant reports AND appointments for patient + my health-nexus

- **Integrated health sciences campus**

Since 2000,
1 central digital patient record
(“KWS”) with all relevant reports AND appointments for patient
+ my health-nexus



Integrated health & research campus

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“Under the same roof”

Steps towards a holistic, integrated care (& research)

- Guidelines

THE JOURNAL OF PEDIATRICS • www.jpeds.com GRAND ROUNDS

Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome

Anne S. Bassett, MD,* Donna M. McDonald-McGinn, MS, CGC,* Koen Devriendt, MD, Maria Cristina Digilio, MD, Paula Goldenberg, MD, MSW, Alex Habel, MD, Bruno Marino, MD, Solveig Oskarsdottir, MD, PhD, Nicole Philip, MD, Kathleen Sullivan, MD, PhD, Ann Swillen, PhD, Jacob Vorstman, MD, PhD, and The International 22q11.2 Deletion Syndrome Consortium**

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RESEARCH REVIEW

WILEY AMERICAN JOURNAL OF medical genetics PART A

Neurodevelopmental outcome in 22q11.2 deletion syndrome and management

Ann Swillen[1] | Edward Moss[2] | Sasja Duijff[3]

TABLE 1 Treatment recommendations for improving neurodevelopmental outcome in 22q11 DS during infancy and early childhood (0–6y)

Developmental area	Developmental features	Treatment recommendations
Motor development	Hypotonia and neuromotor deficits	Physiotherapy, occupational therapy, and sensory integration therapy from early age on
Feeding	Poor sucking, nasal reflux, and oral motor coordination problems	Medical guidance/monitoring of feeding problems Feeding advice (feeding specialist with expertise in 22q11 DS)
Speech and language	Impaired speech and language development, hypernasality, high-pitched voice, and compensatory speech	Speech and language therapy, total communication approach (verbal, non-verbal, and sign language in combination with oral speech) (Solot et al., 2001) In the case of severe hypernasality, a pharyngoplasty is sometimes required
Neurodevelopment/ Cognitive development	Varying degree of impairment (from borderline development to mild–moderate ID)	Educational monitoring Early childhood specialist Anticipatory guidance
Social–emotional development and social skills	Emotionally reactive Problems with regulation of emotion and behavior Socially withdrawn, poor peer relations, self-directed behavior Social anxiety and general anxieties	Provide a secure and highly structured environment Infant mental health intervention Play therapy (structured play to promote social play) Structured (social) group experience
Attention	Easily distracted, impulsiveness	Structured (learning) environment Environment free from stimuli Use visual aids to improve sustained attention (sand timer; time-timer, etc.)

- Annual meeting and partnership between clinicians/researchers & parent/patient organization

22q11 Vecarfa

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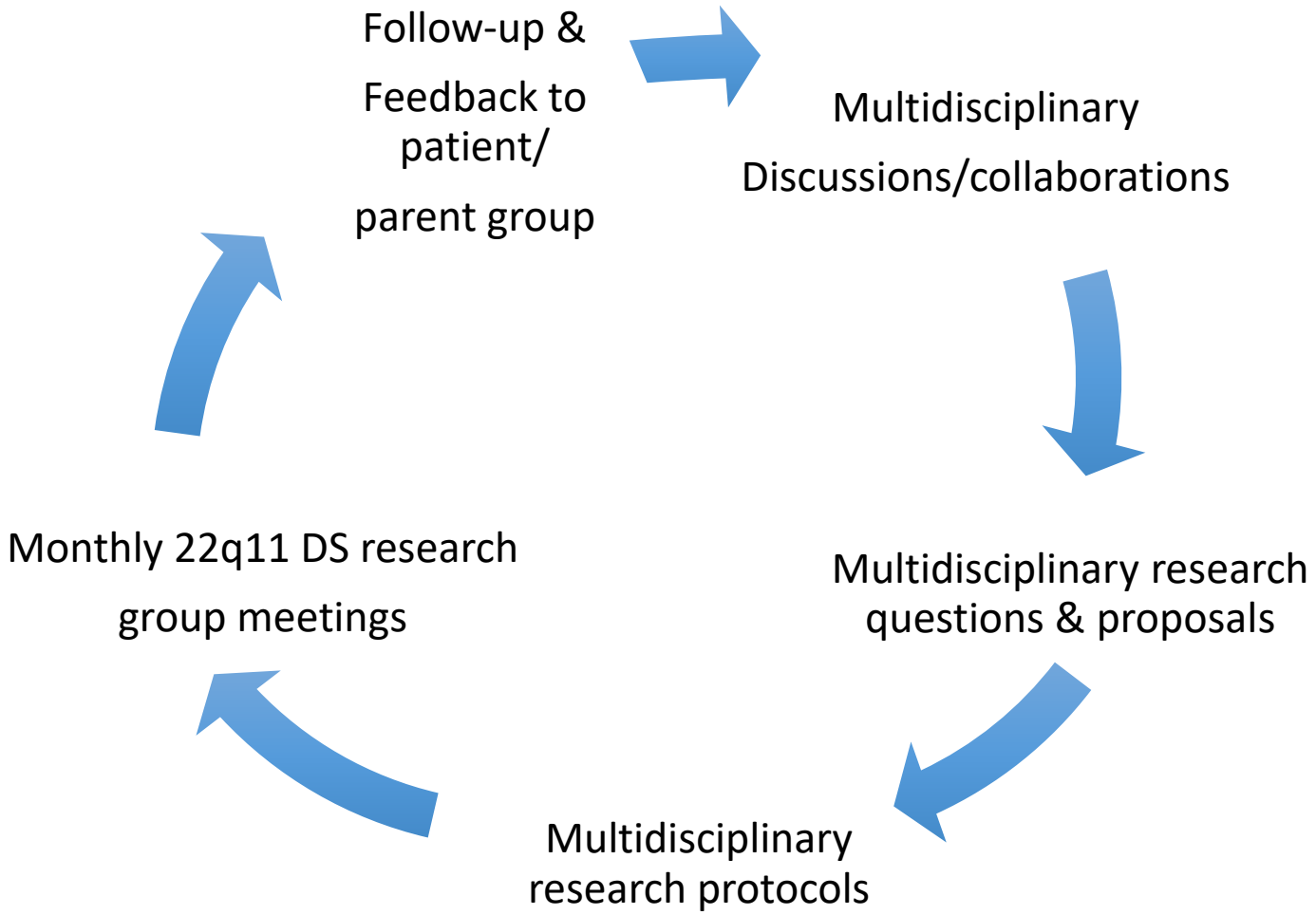
Multidisciplinary research (the Leuven model)



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A pilot study on immuno-psychiatry in the 22q11.2 deletion syndrome: A role for Th17 cells in psychosis?

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ABSTRACT

Background: A growing body of evidence supports a role for immune alterations in Schizophrenia Spectrum Disorders (SSD). A high prevalence (25–40%) of SSD has been found in patients with 22q11.2 deletion syndrome (22q11.2DS), which is known for T-cell deficits due to thymus hypoplasia. This study is the first to explore the association between the T-cell subsets and psychotic symptoms in adults with 22q11.2DS.

Methods: 34 individuals (aged 19–38 yrs.) with 22q11.2DS and 34 healthy age- and gender matched control individuals were included. FACS analysis of the blood samples was performed to define T-cell subsets. Ultra-high risk for psychosis or diagnosis of SSD was determined based on CAARMS interviews and DSM-5 criteria for SSD. Positive psychotic symptom severity was measured based on the PANSS positive symptoms subscale.

Results: A partial T-cell immune deficiency in 22q11.2DS patients was confirmed by significantly reduced percentages of circulating T and T-helper cells. Significantly higher percentages of inflammatory Th1, Th17, and memory T-helper cells were found in adults with 22q11.2DS. Most importantly an increased Th17 percentage was found in adults with psychotic symptoms as compared to non-psychotic adults with 22q11.2DS, and Th17 percentage were related to the presence of positive psychotic symptoms.

Conclusions: Given the literature on the role of T cells and in particular of Th17 cells and IL-17 in hippocampus development, cognition and behavior, these results support the hypothesis for a role of Th17 cells in the development and/or regulation of psychotic symptoms in 22q11.2DS. This pilot study underlines the importance to further study the role of T-cell defects and of Th17 cells in the development of psychiatric symptoms. It also supports the possibility to use 22q11.2DS as a model to study T-cell involvement in the development of SSD.

https://www.kuleuven.be/labbehaviourandneurodevelopment

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Understanding Neurodevelopment in 22Q and other CNV's

A major concern of families of patients with a rare disease is the risk of developing a developmental disorder including intellectual disability (ID) and psychopathology. Developmental disorders (DD) are broadly defined as cognitive and/or behavioral conditions that have early onset in childhood and include language disorders, intellectual disability, motor disorders or autism spectrum disorders. In a subgroup of patients, these rare diseases are caused by rare recurrent Copy Number variations (CNV's). Psychopathology in CNVs encompasses emotional, perceptual, motor, behavioral and social disruptions in domains that cut across traditional diagnostic categories Rare developmental disorders collectively mean an important physical, psychological and socio-economic burden to patients, families, and society. The multi-system nature of many rare recurrent CNVs requires a multidisciplinary clinical care and research approach.

Team leader

Ann Swillen is professor at the Department of Human Genetics, KU Leuven and at the Department of Rehabilitation Sciences, KU Leuven (University of Leuven, Belgium).

Trained as an educational psychologist, she is also affiliated to CME-UZ (the clinical unit of the Department of Human genetics), an international centre of excellence in the field of clinical and molecular genetics.

She has more than 25 years of experience and expertise in clinical follow-up and research of neurodevelopmental disorders such as intellectual disability (ID), developmental delay (DD) and autism spectrum disorders (ASD) in children, adolescents and adults with pathogenic Copy Number Variants (CNV's) such as microdeletions and - duplications (22q11.2 deletions and duplications, 16p deletions and duplications, 22q13 deletions, etc.) resulting in more than 100 scientific papers on neurodevelopmental disorders and behaviors in CNV's. She teaches courses on" Developmental Psychology" and on "Psychopathology in children and adolescents" . She has obtained funding(from FWO, NIH, Lejeune Foundation, Marguerite Delacroix Foundation, KBS,…, and supervised over 7 PhD students, of which 2 of them became independent professors.

KU Leuven 22q11 DS/Vecarfa Fund

Ann Swillen is holder of the 22q11 DS/Vecarfa fund at the KU Leuven, in order to raise awareness and multidisciplinary care and guidance for families with 22q11 DS.

Deletie syndroom 22q11.2

'Samen leggen we de puzzel'

Upcoming meetings

June 23 - 26: International 22q11 DS research meeting in Croatia

Questions ?

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Partnership & team spirit between clinicians and researchers

Thank you patients and families, clinicians and researchers of multidisciplinary 22q11 DS team/lab @

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