22q – An Overview

Donna M. McDonald-McGinn MS, LCGC

Clinical Professor of Pediatrics, Perelman School of Medicine of the University of Pennsylvania
Director, 22q and You Center
Associate Director, Clinical Genetics Center
Chief, Section of Genetic Counseling
Children's Hospital of Philadelphia, Philadelphia, PA, USA
Founding Board Member, International 22q11.2 Foundation, Inc., Matawan, NJ, USA
Founding Trustee and Secretary, 22q11.2 Society, London, UK

Philadelphia – Birthplace of America – City of Brotherly Love

- 1 hour from NYC
- 2 1/2 hours from Washington, DC
- 1 hour from pristine beaches
- 2 hours from the mountains

Disclosure:

I have presented lectures on 22q11.2DS for Natera

Boat House Row - Philadelphia

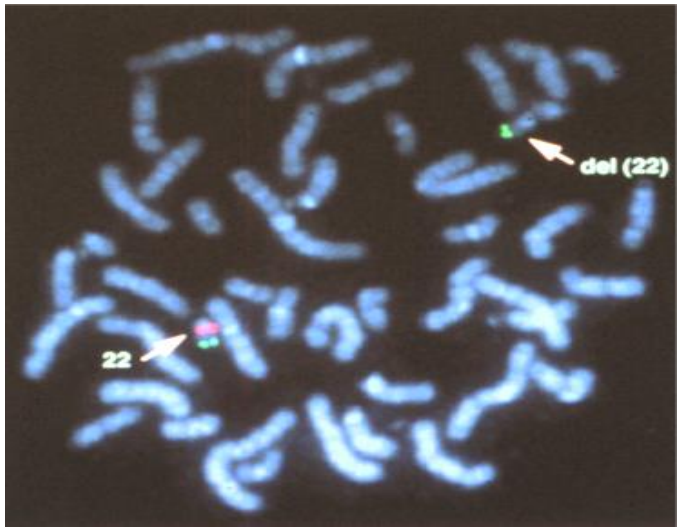
Disclosure: I am a fan of Adele

Who reminds us that:

Time flies - only yesterday was the time of our lives

- >25 years since the development of FISH studies
- Turning point for our group at the Children's Hospital of Philadelphia (CHOP)

Adele with Hannah who has 22q11.2DS in 2016



Elaine Zackai, MD

Beverly Emanuel, PhD

Donna McDonald-McGinn, MS, LCGC

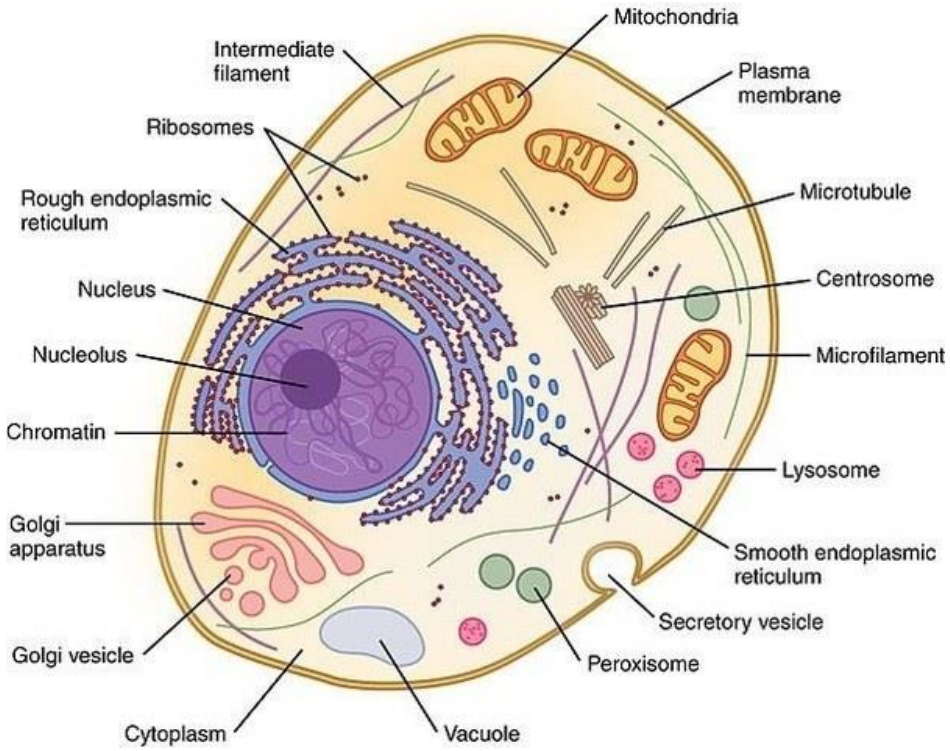
Deborah Driscoll, MD

Before Discussing the 22q11.2 Deletion syndrome we need to talk about chromosomes

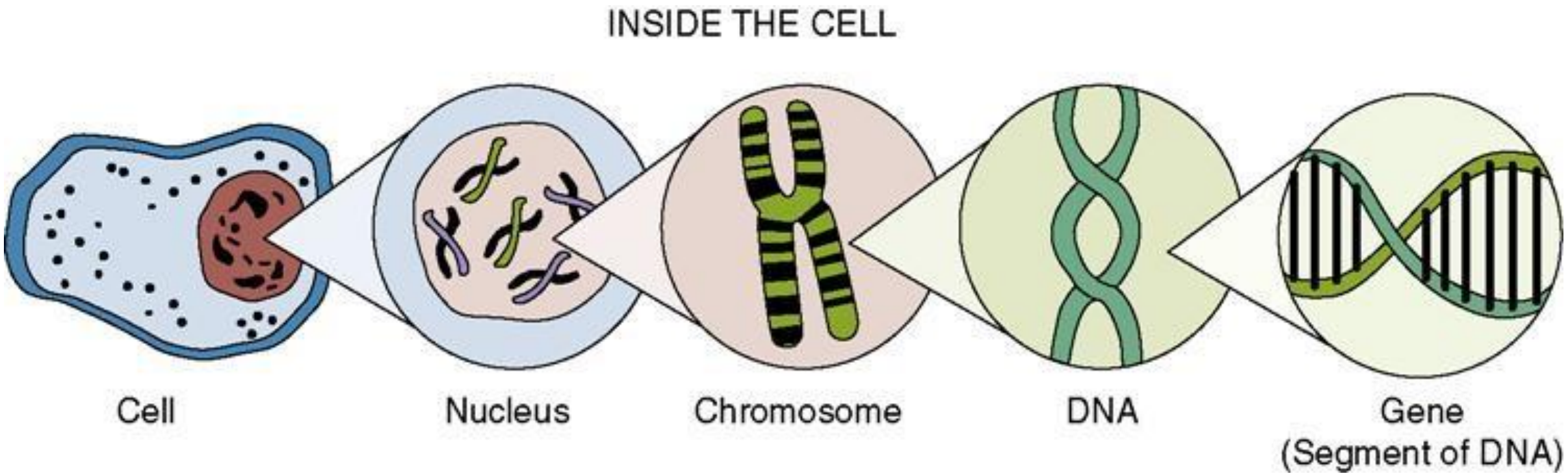
Before discussing chromosomes and genes we need to back up and talk about cells…

All living things are made up of cells including this leaf where the cells are visible as boxes

All humans are made up of cells



Chromosomes are located within the nucleus of the cells

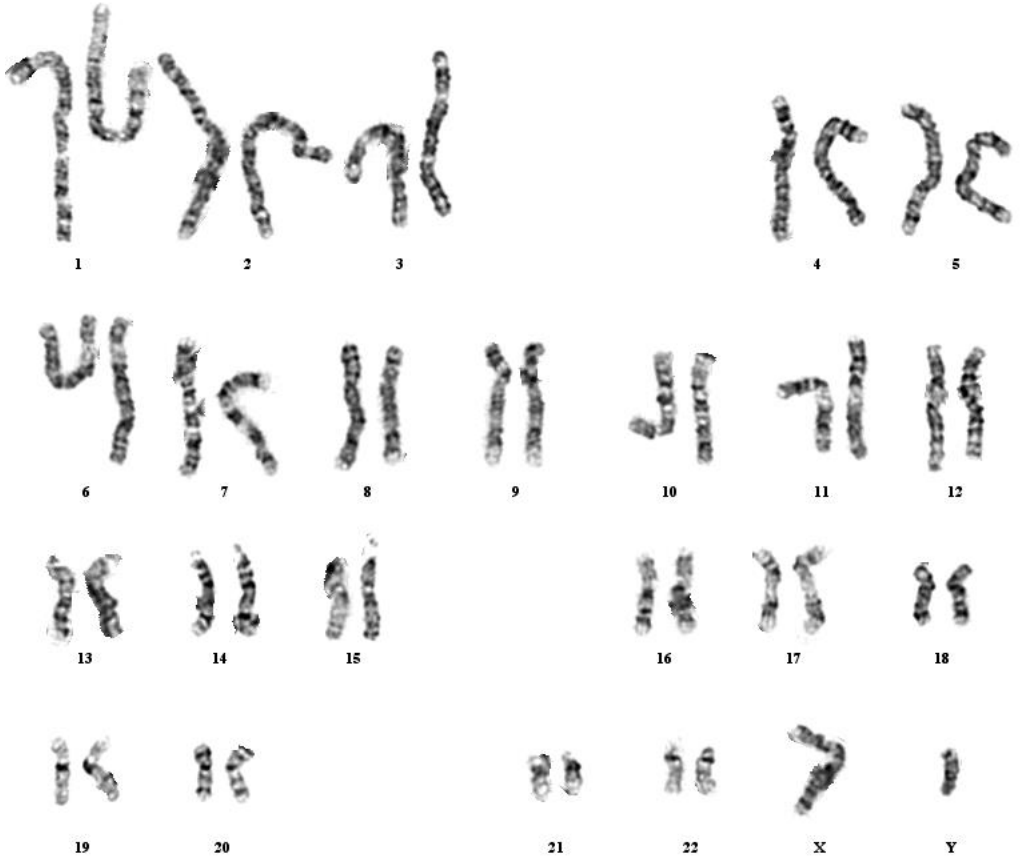


Chromosomes Are Visible Under A Microscope

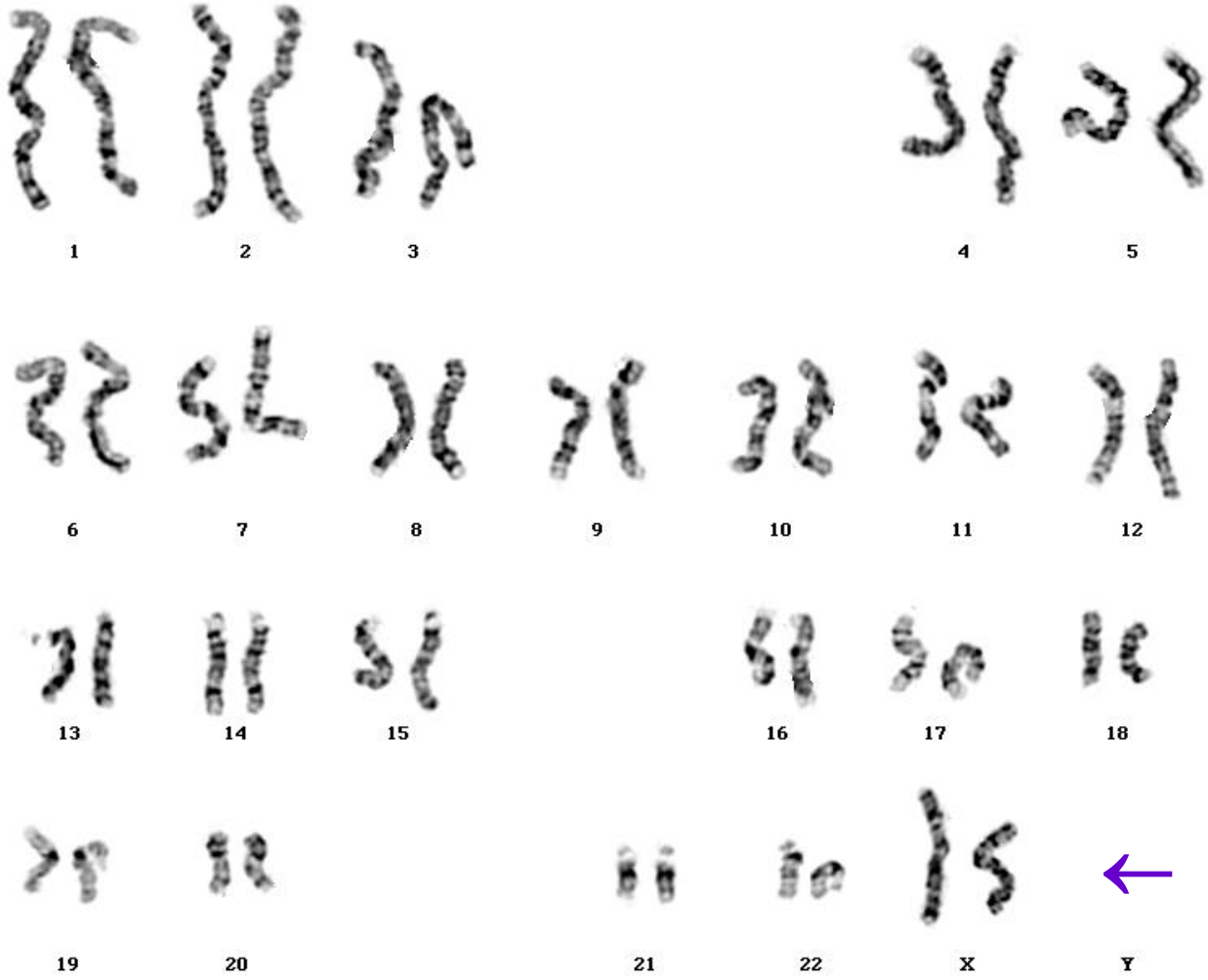
- We expect to find 46 chromosomes in each cell
- We take a photo of them
- Match them up – call it a karyotype

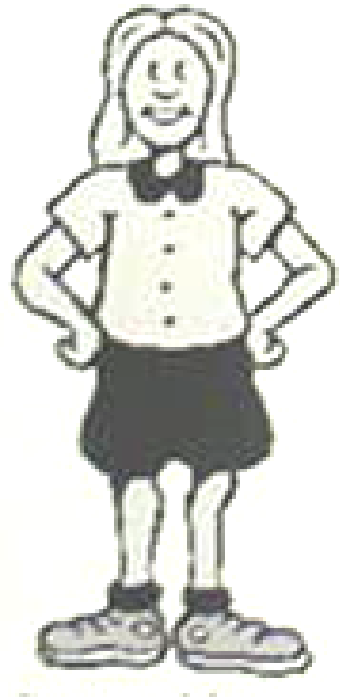
Within a karyotype the chromosomes are:

- Arranged in pairs – totaling 23
- Numbered from the largest to smallest
- Include the sex chromosomes – X and Y



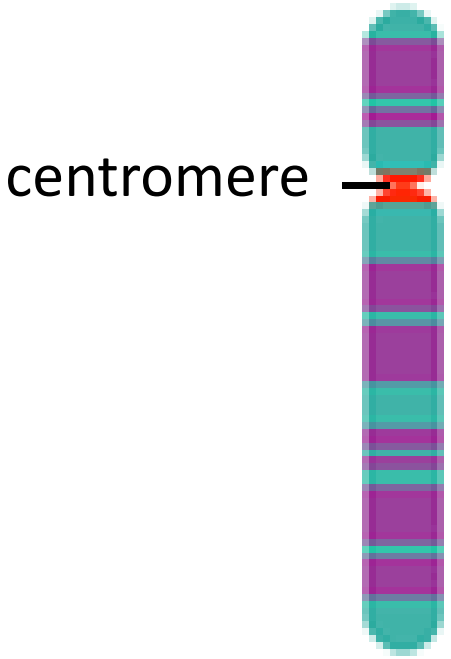
← **Male Karyotype**



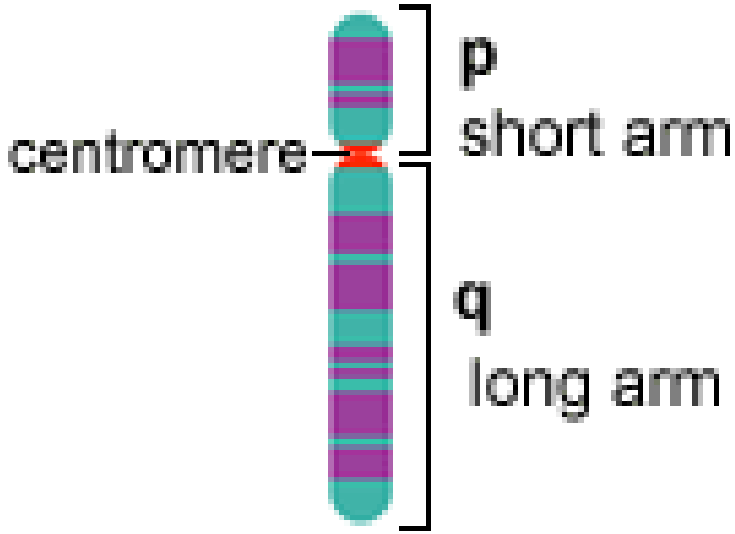


← **Female Karyotype**

All chromosomes have a top and bottom half separated by a waist (the centromere)



Chromosomes were first described by the French



a b c d e f g h i j k l m n o **p q** r s t u v w x y z

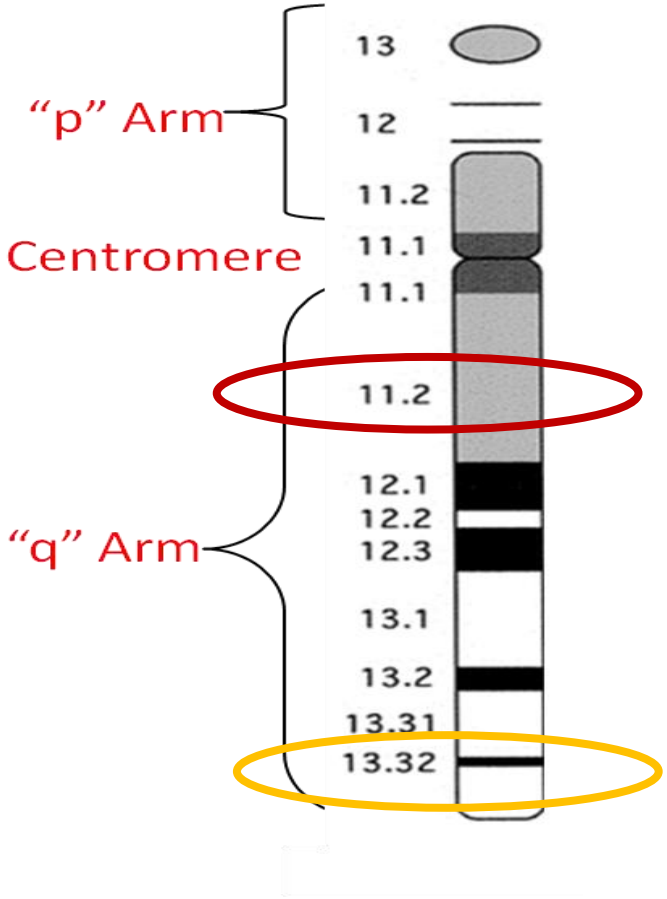
“p” stands for petite (or short) **“q” follows “p” in the alphabet**

Chromosomes are further defined by a numbering system

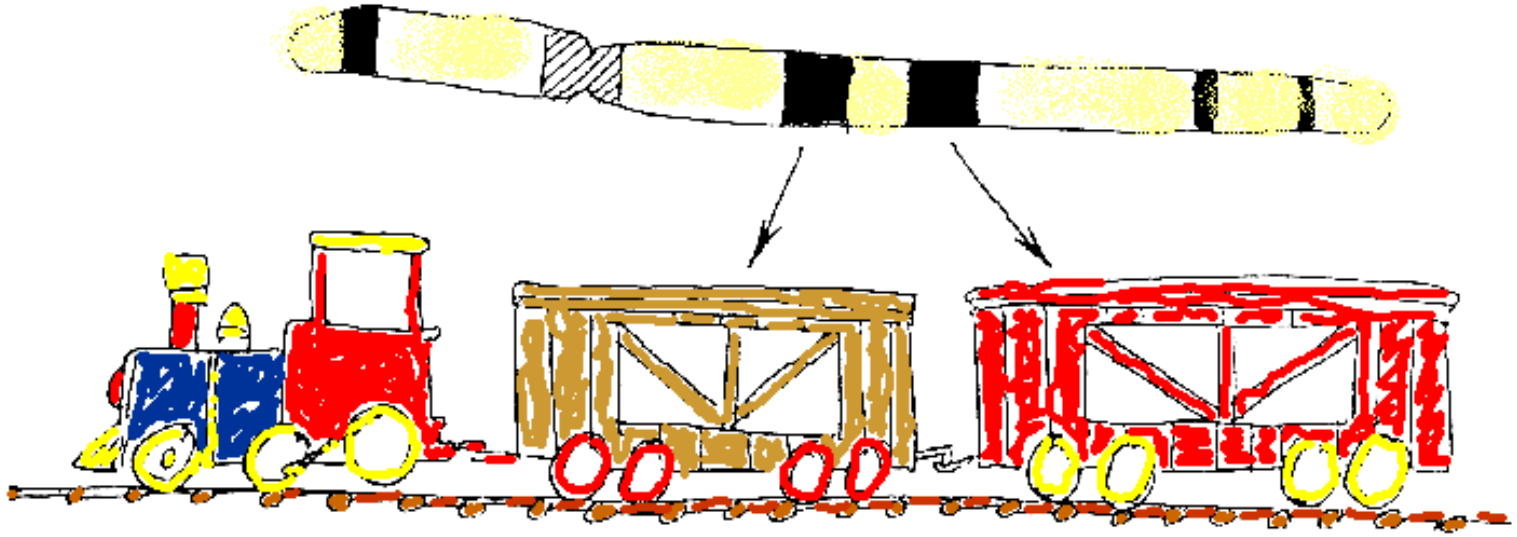
- Names the individual bands (stripes) when stretched out like an accordion
- Creates a universal language
- 22q11.2 is completely different than 22q13.3

22q11.2

22q13.32

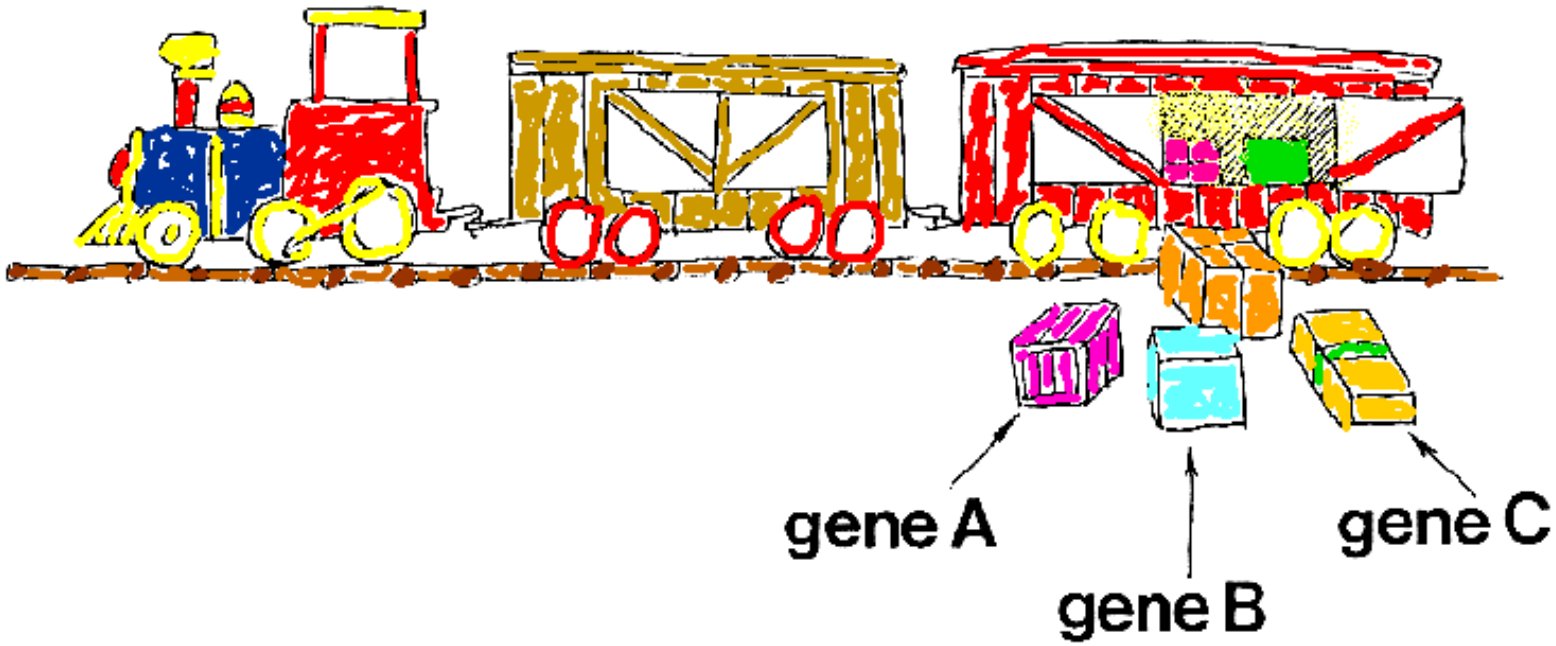


Chromosomes bands are like the box cars on a train:



- If a boxcar is missing we see it with our eyes
- If a band is missing or extra we generally see it under the microscope

The Genes are the Packages Inside



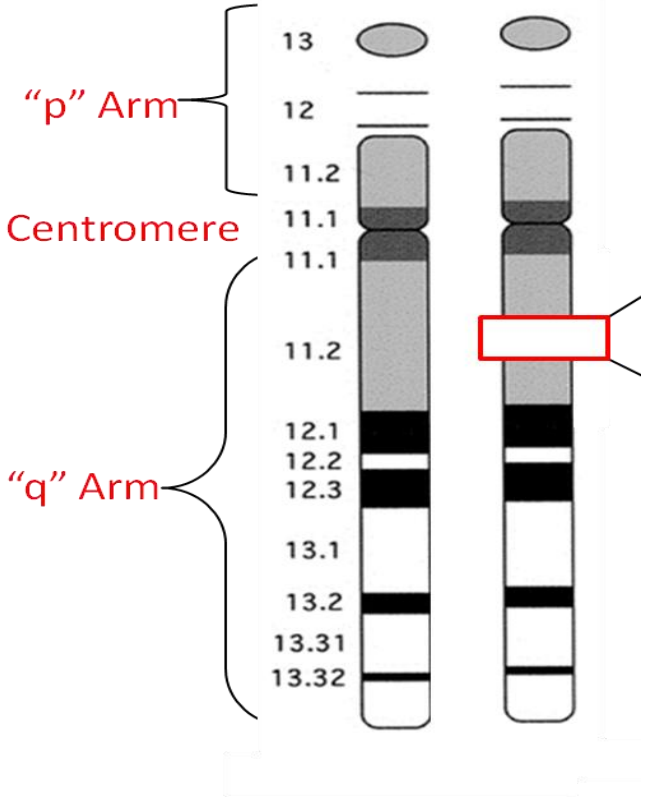
If a chromosomal band is missing or extra - genes are missing or extra!

Genes set up a blueprint for the body

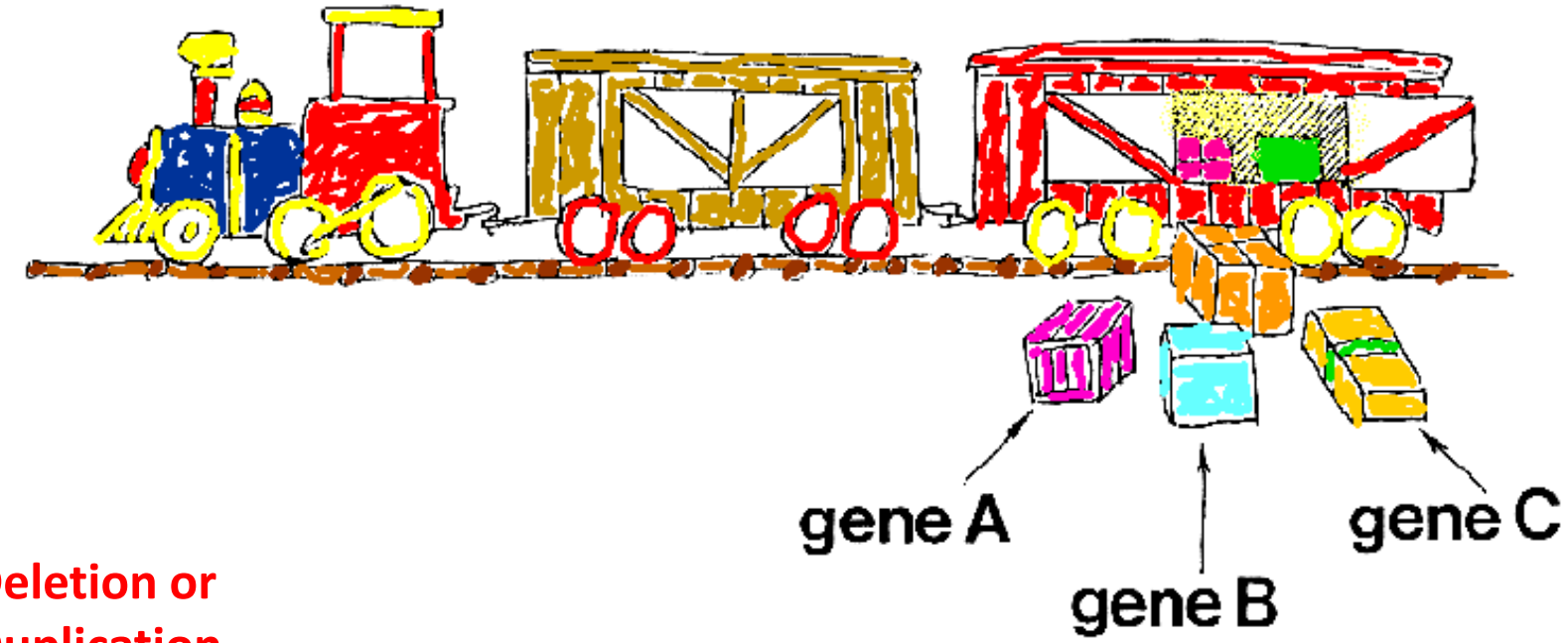
Determine:

- Hair color
- Eye color
- Height
- Etc.

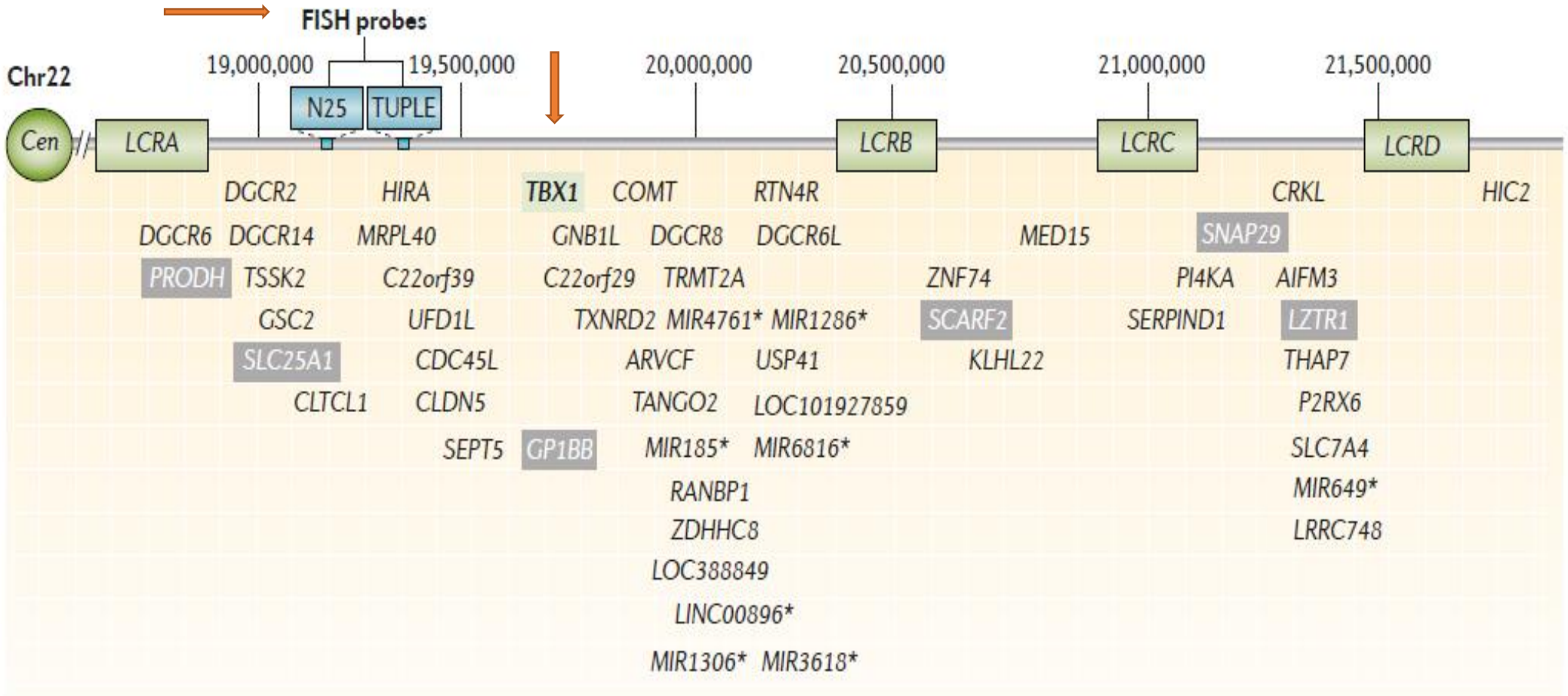
The 22q11.2 deletion and duplication syndromes involve missing or extra genes



Deletion or Duplication



About 50 genes in total are missing or extra



McDonald-McGinn 2015

In 1965, Dr. Angelo DiGeorge first described a triad of features now known to be caused by a chromosome 22q11.2 deletion*

- Low calcium
- Poor immune system
- Congenital heart disease (added later)

- The diagnosis later came to bear his name - DiGeorge syndrome
- *Syndrome just means a collection of findings*

DiGeorge 1965

* There are other less common causes of DiGeorge syndrome, e.g. maternal diabetes or a mutation in a gene on chromosome 8 (*CHD7*)

16 years later this child was seen by Dr. Elaine Zackai at CHOP with features of DiGeorge syndrome:

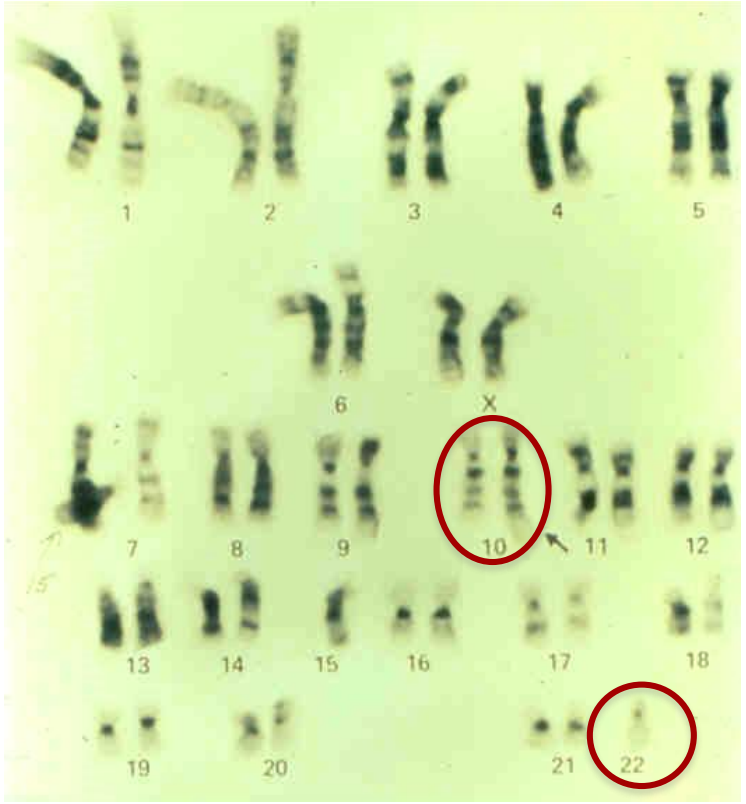
- Hypocalcemia
- Immunodeficiency
- Congenital heart disease (truncus arteriosus)
- Cleft palate
- A gastrointestinal abnormality (jejunal web)

Typical triad

Kelley 1982

Laboratory studies revealed:

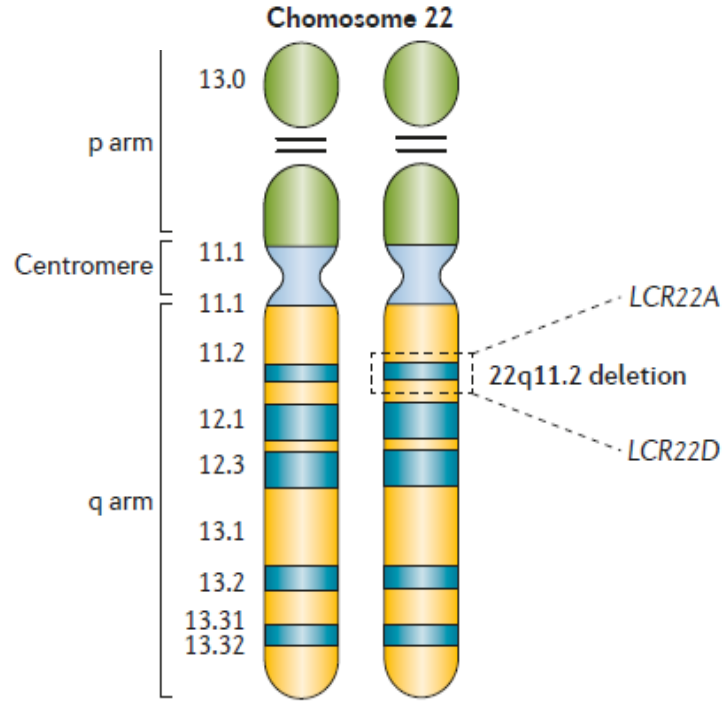
- Only 45 chromosomes
- Including a 10;22 rearrangement
- Resulting in deletions on both chromosomes 10 and 22



Kelley 1982

Thereafter additional patients came to attention with rearrangements involving chromosome 22q11.2

- The conclusion was drawn that a 22q11.2 deletion was a cause of DiGeorge syndrome
- From 1982 -1992 visible deletions were observed in 25% of patients
- But the puzzle remained – what about the other 75%?

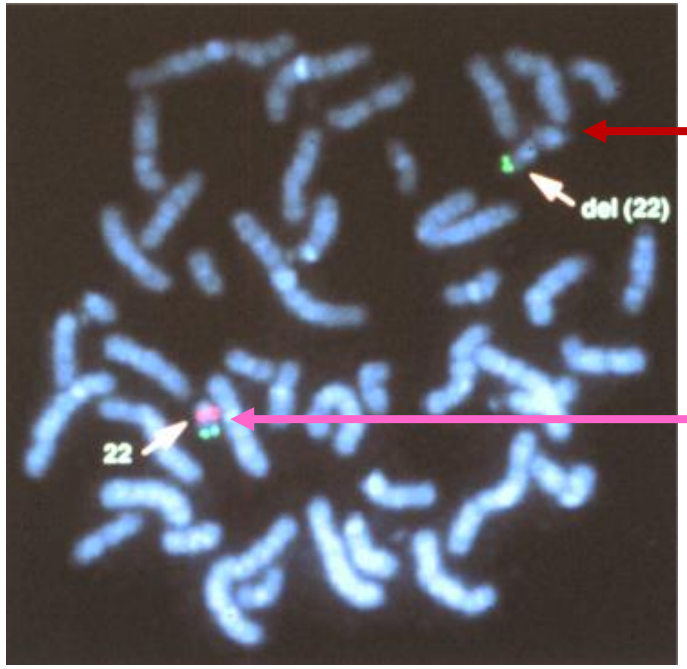


de la Chapelle 1981; Kelley 1982

McDonald-McGinn 2015

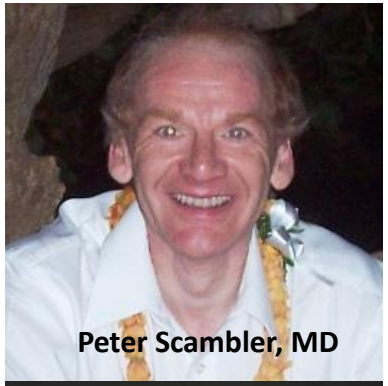
This led to the development of FISH probes in the early 1990's

- By Peter Scambler in the UK and Debbie Driscoll at CHOP
- Using "fluorescent probes" that lit up when the piece of chromosome was present
- Identified deletions too small to be detected by just looking under the microscope
- Found 22q11.2 deletions in the majority of patients with DiGeorge syndrome

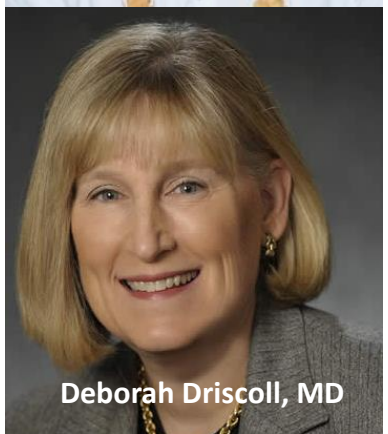


Chromosome 22 with Deletion

Non-deleted Chromosome 22



Peter Scambler, MD



Deborah Driscoll, MD

Scambler 1991; Driscoll 1992

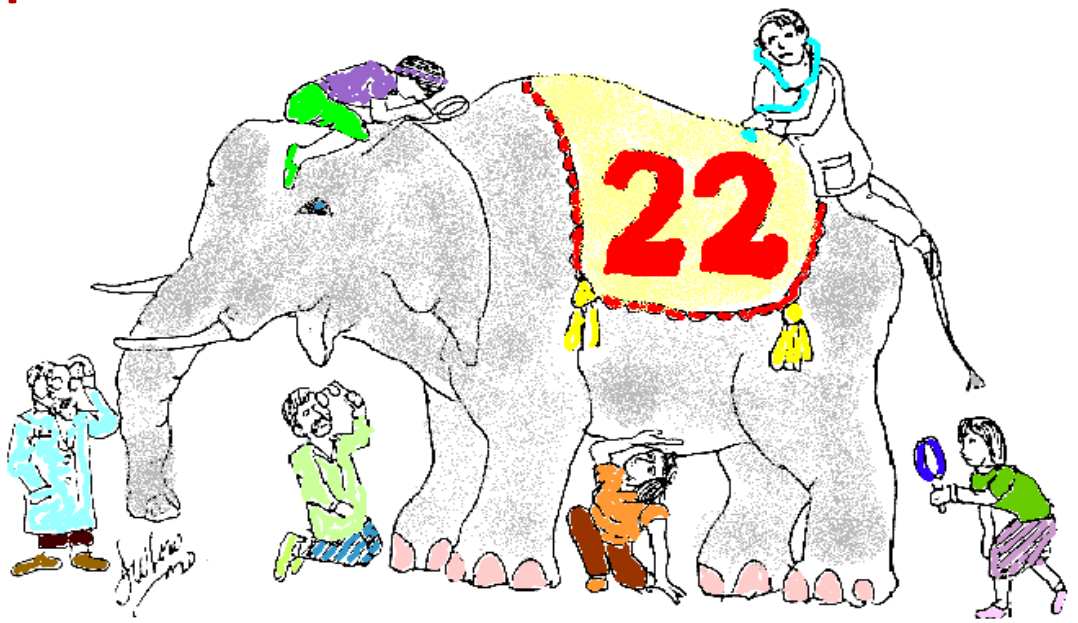
The 22q11.2DS is now known to be the cause of multiple other clinical diagnoses

DiGeorge syndrome	• Immunodeficiency • Hypocalcemia • Congenital heart disease
Velocardiofacial syndrome (VCFS)	• Palatal defects • Congenital heart disease • Dysmorphic facial features
Conotruncal anomaly face syndrome (CTAF)	• Conotruncal cardiac anomalies • Dysmorphic facial features
OPITZ/GBBB syndrome	• Hypertelorism • Cleft lip/palate • Hypospadias • Laryngotracheoesophageal anomalies
Cayler Cardiofacial syndrome	• Congenital heart disease • Asymmetric crying facies

McDonald-McGinn 2015

All described prior to the association with 22q11.2DS

- By clinicians concentrating on specific areas of expertise
  - *Endocrinology (DGS) – Dr. DiGeorge*
  - *Cardiology (CTAF) – Dr. Takao*
  - *Speech Pathology (VCFS) – Dr. Shprintzen*
- **22q11.2DS is now the preferred term – as the 22q11.2 deletion is the one thing that all patients have in common**

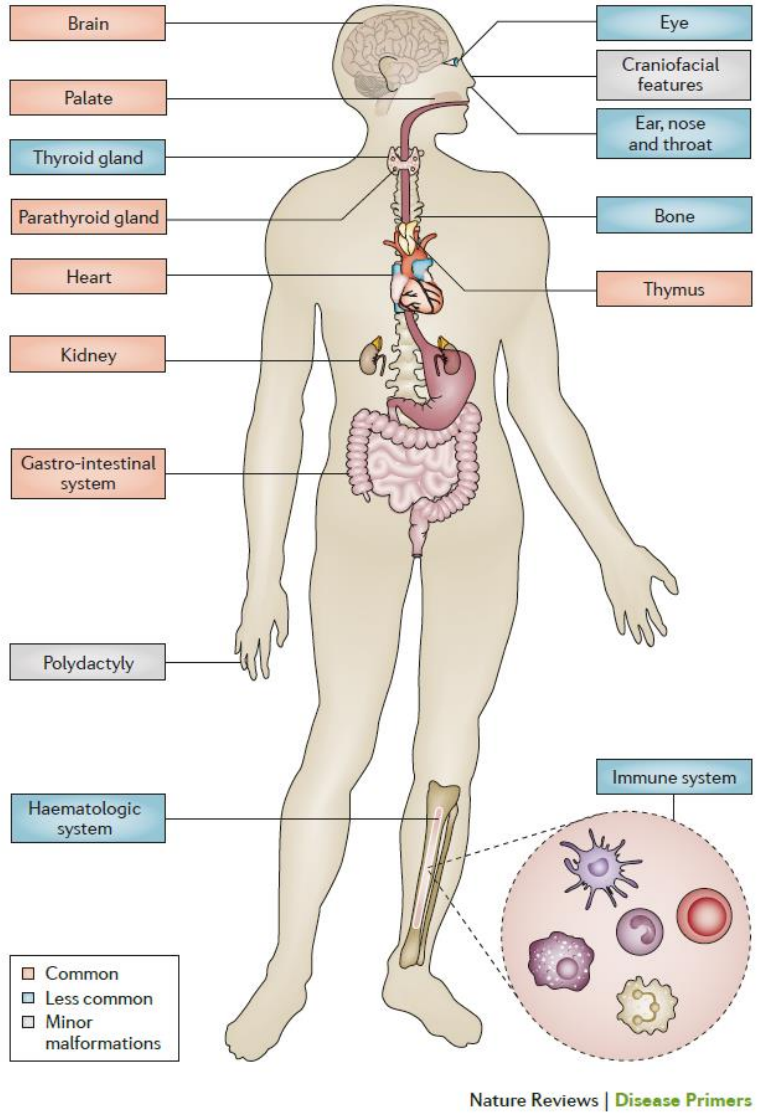


McDonald-McGinn 1997, 2015

22q11.2 deletion syndrome is now known to cause:

- Additional birth defects
- Later-onset conditions
- Cognitive delays
- Behavioral differences
- Psychiatric illness

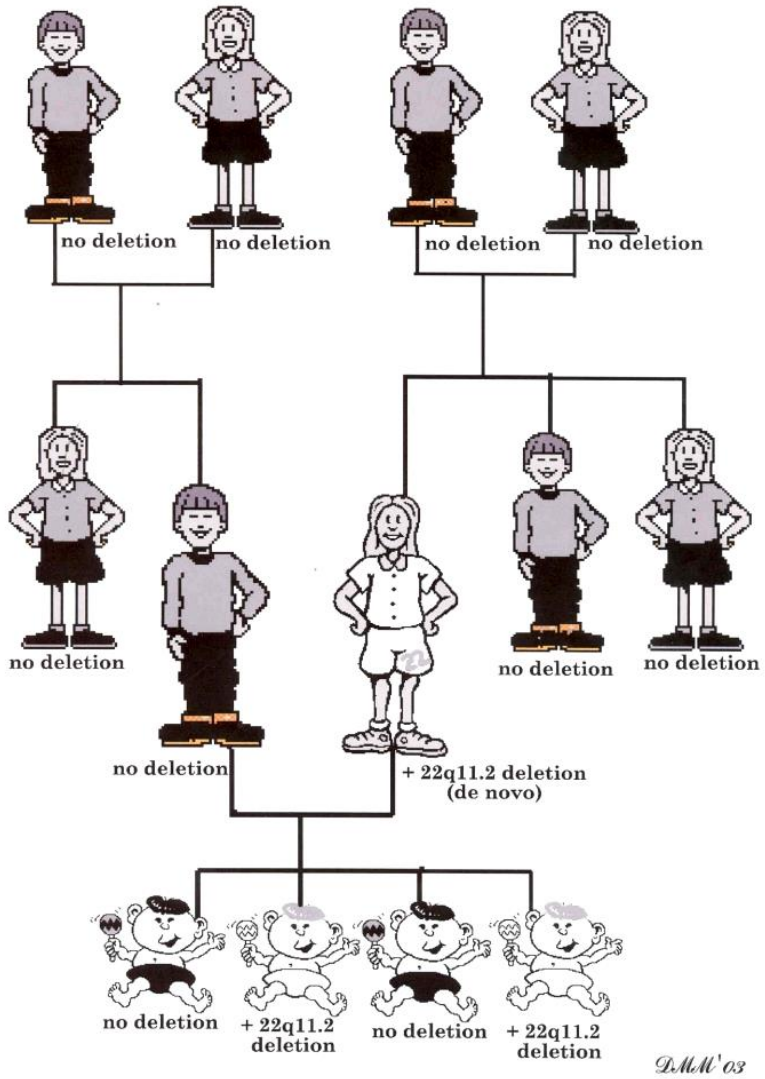
All far extending the original description of DiGeorge syndrome



McDonald-McGinn 2015

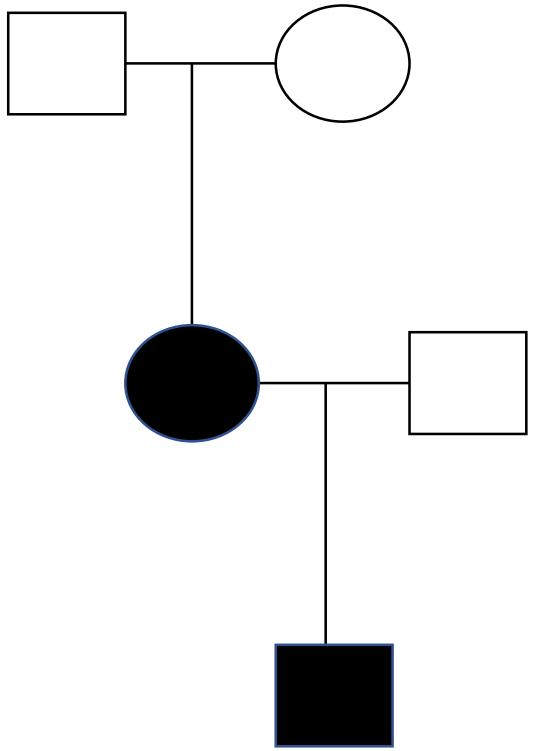
Although common - lack of recognition of the condition and/or lack of familiarity with genetic testing methods together with wide variability delays diagnosis which could improve outcomes

Many parents with the 22q11.2 deletion are identified only through a child born with congenital heart disease



Most deletions are not running in the family (>90%)

- But a person with the deletion has a 50:50 chance of passing it on to his/her child
- Child could be more significantly affected than the parent – unable to predict
- Egg and sperm cells have no memory – so every pregnancy has the same 50% chance of the child having the deletion or not



90 – 95% first occurrence in the family

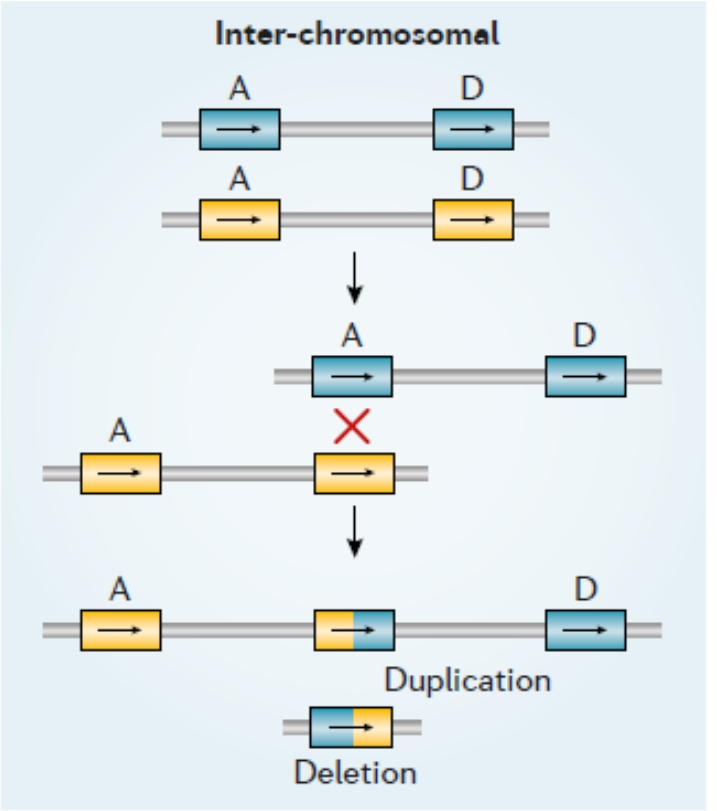
50% recurrence risk

50% recurrence risk

McDonald-McGinn, 2001; Bassett, 2005; McDonald-McGinn 2015

De novo (new) deletions occur as a result of the structure of the chromosome

- The way the chromosomes align and cross over in the early egg and sperm cells
- This is termed meiotic non-allelic homologous recombination
- Due to the presence of low copy repeats
- Flank the 22q11.2 region ➡ abnormal crossing over
- Resulting in either a duplication or a deletion

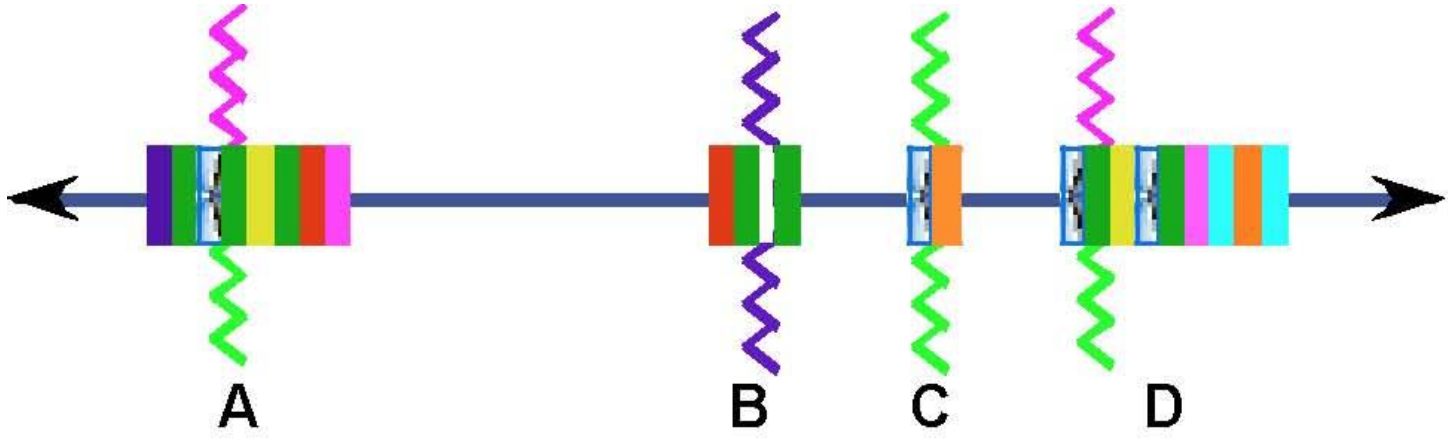


There is nothing that the parent did or didn't do to make it happen!

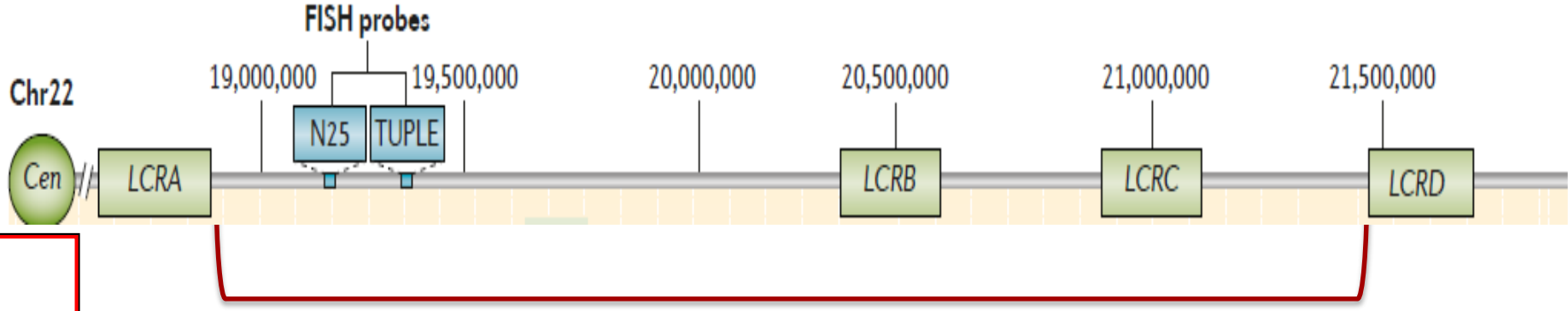
McDonald-McGinn 2015

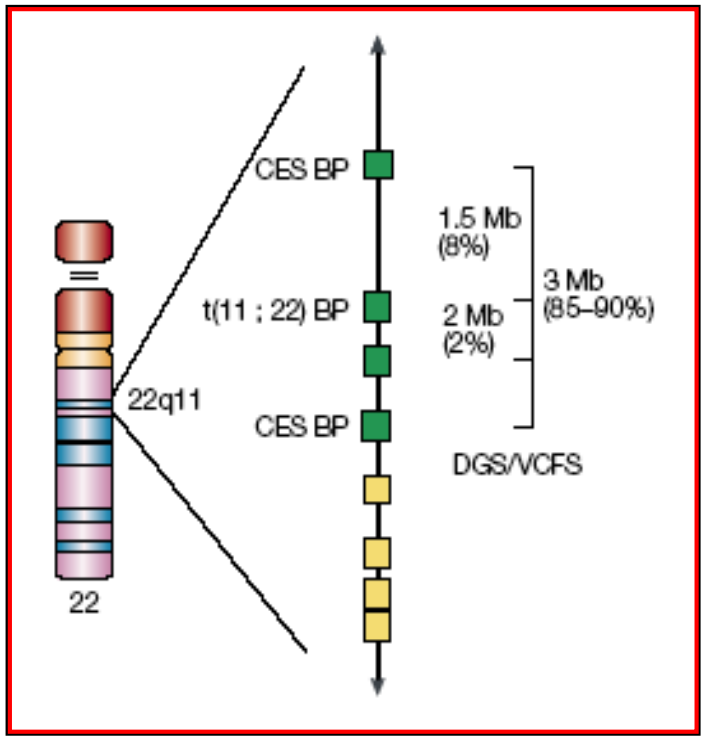
Low Copy Repeats (LCRs):

- Define the break points of the deletion or duplication
- Are used to describe the size of the resultant deletion or duplication
- *A typical deletion or duplication extends from A to D*
- *A nested deletion or duplication is smaller (A-B, A-C, B-D, C-D) and involves fewer genes*

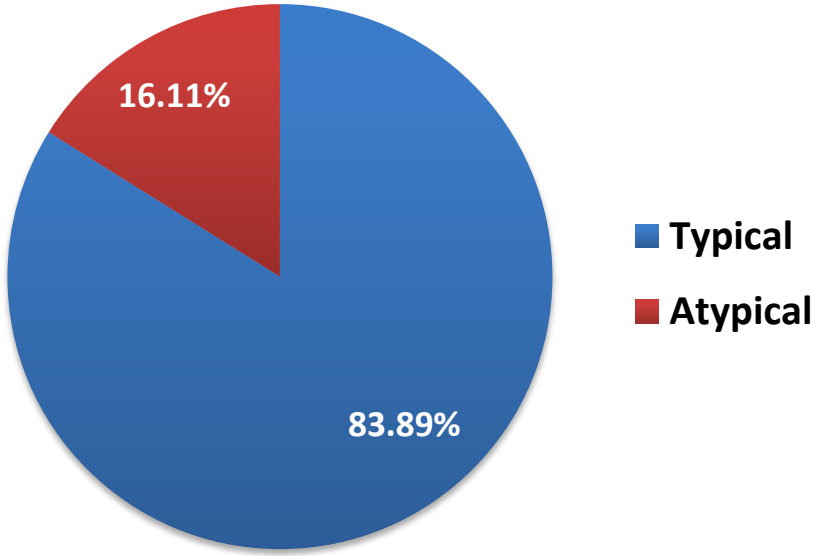


Most patients (84%) have a standard A-D deletion





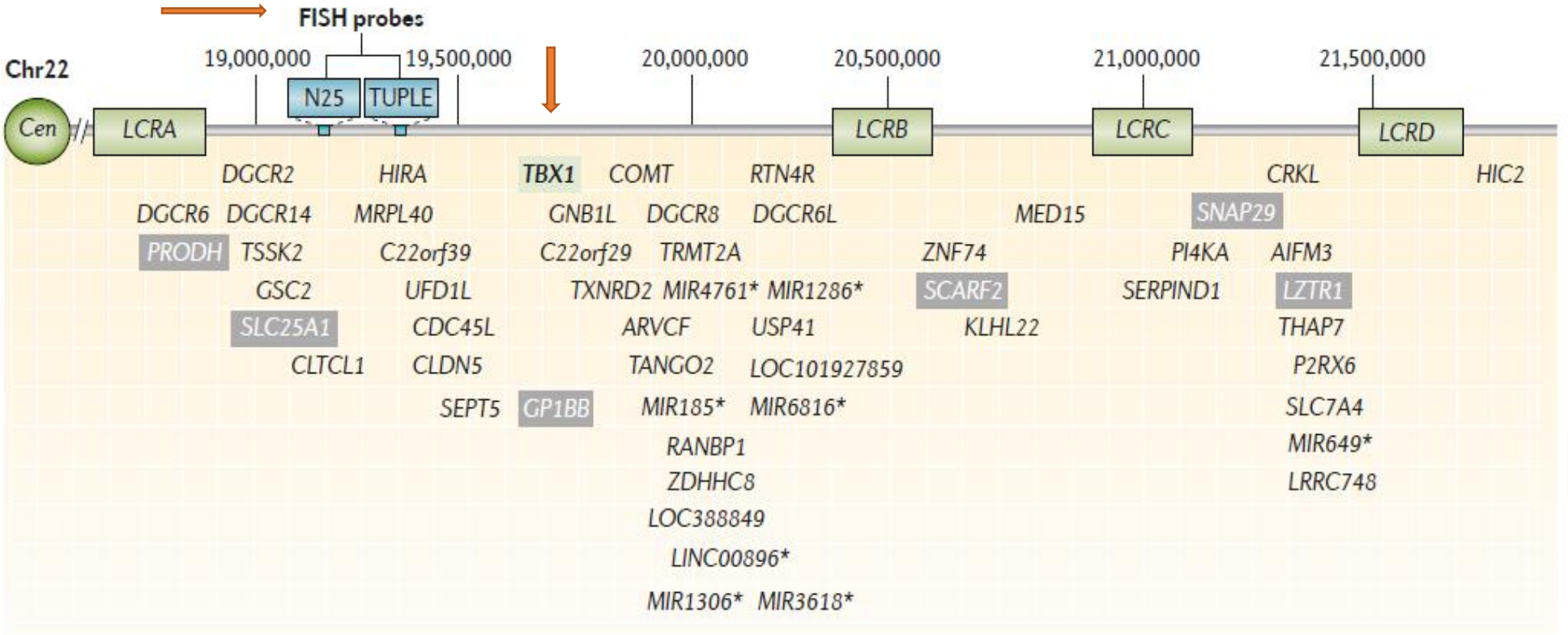
84% - LCR22A-LCR22D deletion



McDonald-McGinn 2015

FISH probes are located between A and B

- As is an important developmental gene - *TBX1*
- *Thought to be a major cause of congenital heart disease in patients with a chromosome 22q11.2 deletion*



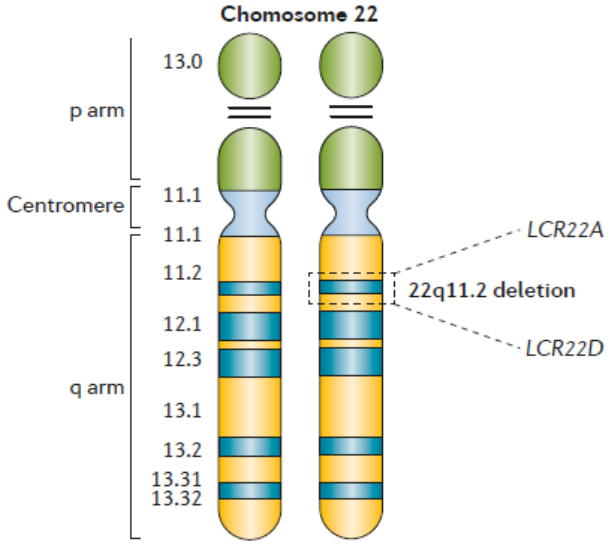
McDonald-McGinn 2015

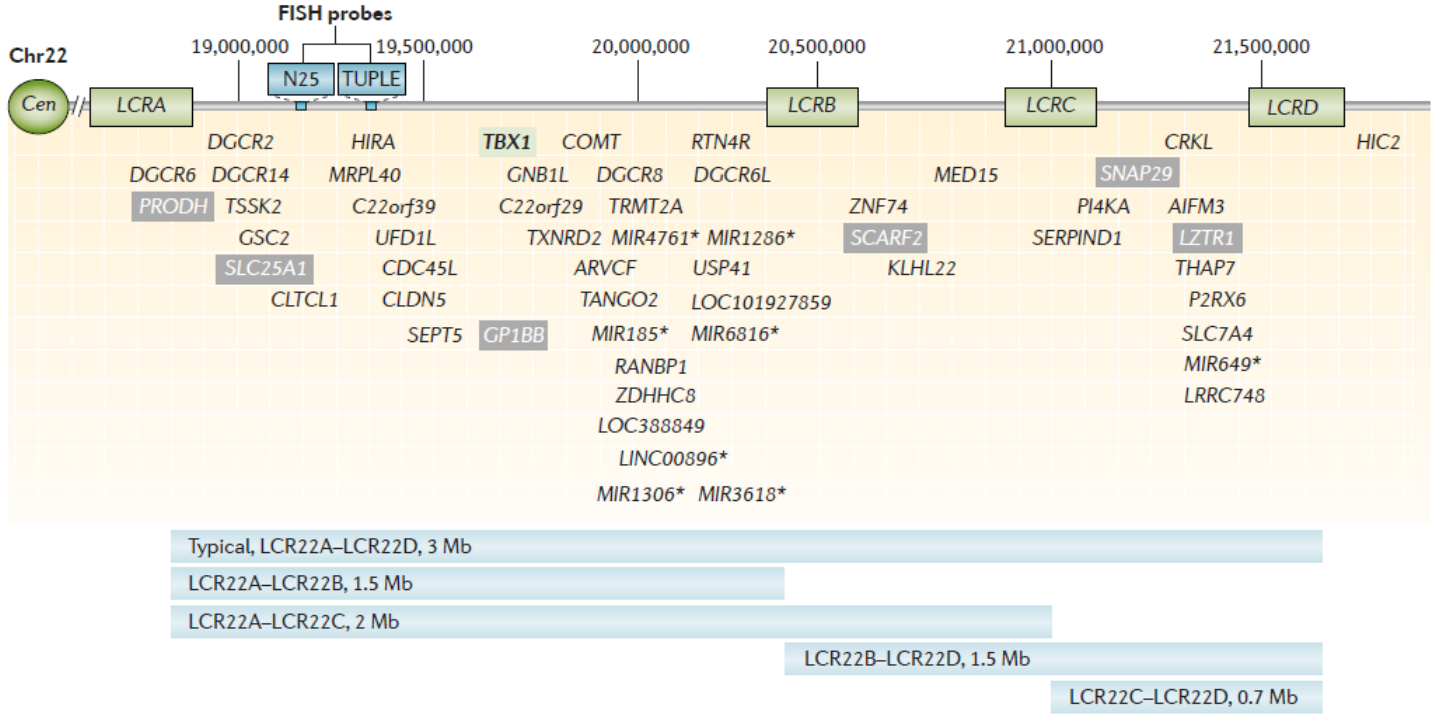
Patients with nested deletions have similar but less frequent associated features, e.g. congenital heart defects

- A-B - 5%
- A-C - 2%
- *B-D - 4% - missed by FISH*
- *C-D - 1% - missed by FISH*

} **missed by FISH alone**

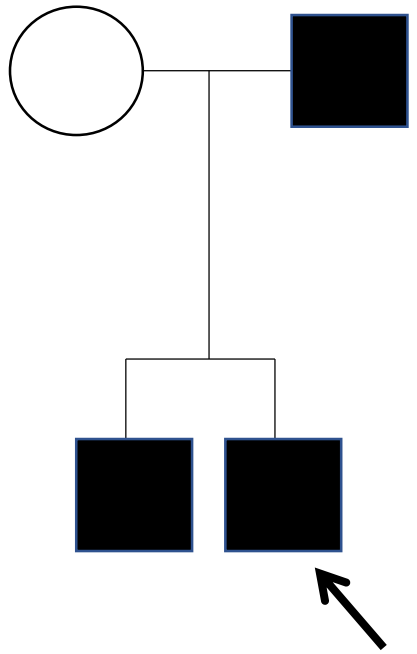
- Other (not LCR mediated) - 4%



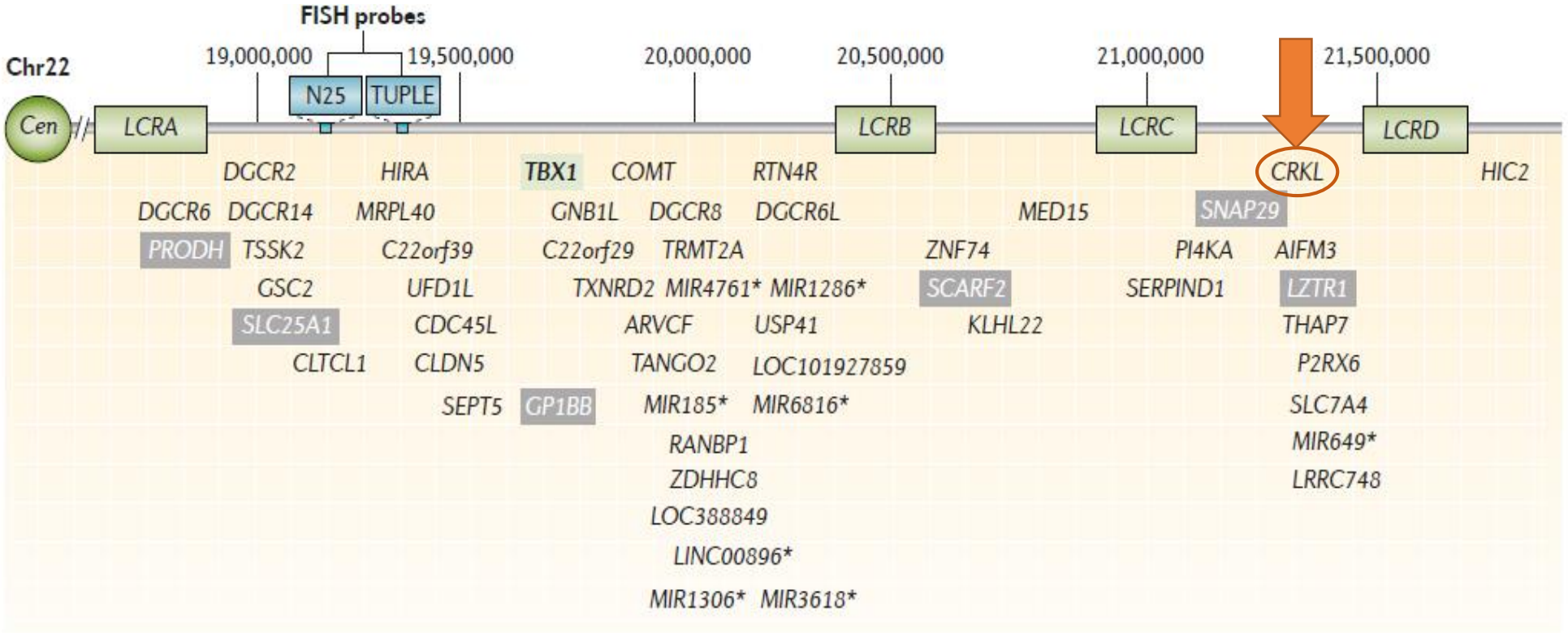


Unlike A-D deletions, where <10% are familial, nested B-D and C-D deletions are often familial and there is broad variability

- As in this family where the younger child came to attention in infancy with congenital heart disease
- Then the father was diagnosed
  - *He has a Master's Degree and no medical issues*
- Then we diagnosed the 2 year old sibling
  - *Single kidney*
  - *Speech delay*
  - *Frequent infection*



This family was key in discovering that a gene within the C-D region is important for heart and kidney development



The NEW ENGLAND JOURNAL of MEDICINE

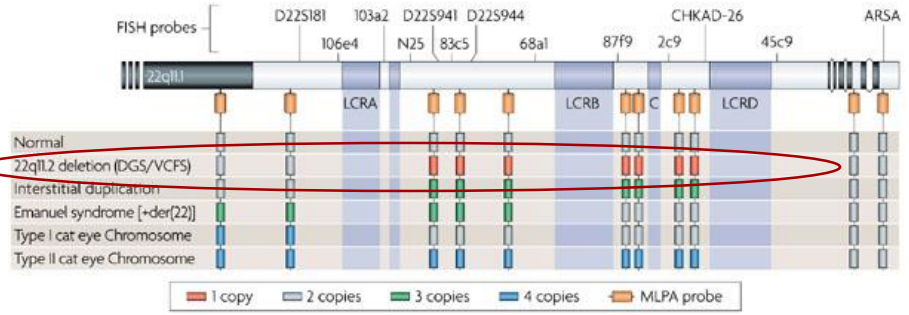
ORIGINAL ARTICLE

Genetic Drivers of Kidney Defects Esther Lopez-Rivera…Donna M. McDonald-McGinn….and Simone Sanna-Cherchi N Engl J Med 2017; 376:742-754February 23, 2017

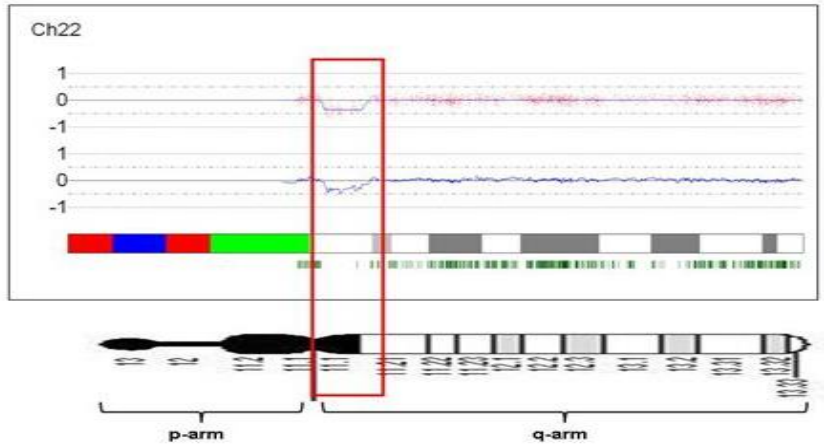
Current detection methods still include FISH

- But MLPA and microarrays are preferred
- As they both size the deletion
- *But microarrays detect other chromosomal differences so they do not require the ordering clinician to suspect a 22q11.2 deletion in advance of sending the test*

MLPA (multiplex ligation probe amplification)



Microarray



Verhoeven 2011

22q11.2 Deletion Syndrome

- The most common microdeletion syndrome
- ~1 in 3000 - 6000 live births
- ~1 in 1000 unselected fetuses
- Based on a prevalence of 1/2000 there should be ~150,000 affected Americans*
- Including 35,000 children and adolescents - so where are they?
- *Waiting to be diagnosed?*

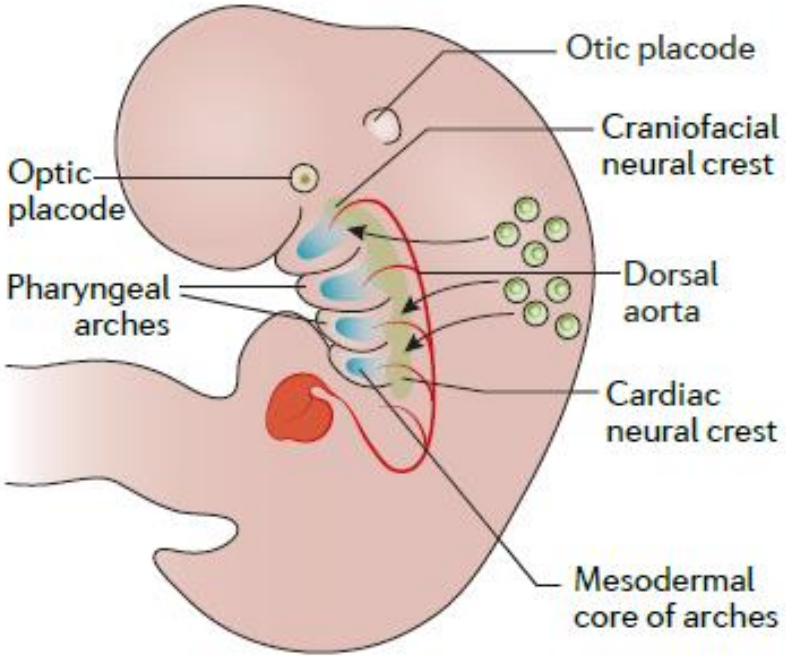
Goodship 1998; Tezenas 1996; Oskarsdottir 2004; Wapner 2012; Costain 2014; Grati 2015; McDonald-McGinn 2015

*2010 US Census

22q11.2DS affects cells in the developing embryo

Causing structural abnormalities:

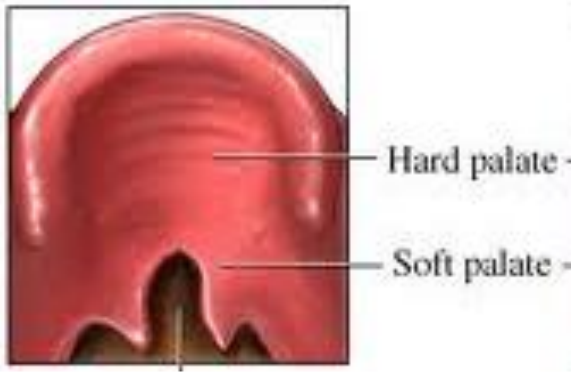
1. Outflow tract of the heart ➡ conotruncal heart defects
2. Absence or underdevelopment of the thymus ➡ immunodeficiency
3. Underdevelopment of the parathyroid glands ➡ hypocalcemia

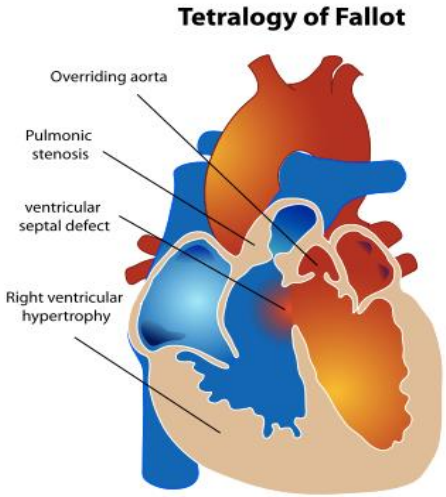


McDonald-McGinn 2015

22q11.2DS

- The most common cause of syndromic palatal anomalies
- 2nd most common cause of major congenital heart disease and developmental delay after Down syndrome

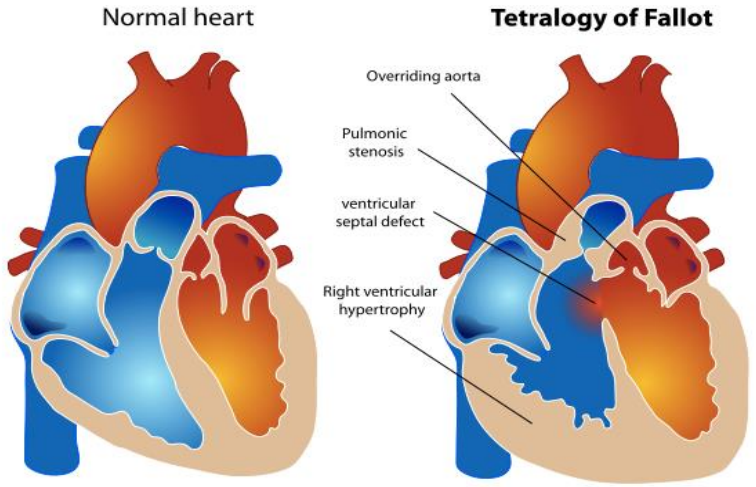




22q11.2DS has been identified in:

- 52% of patients with IAA type B
- 34% with Truncus arteriosus
- 16% with tetralogy of Fallot (TOF)

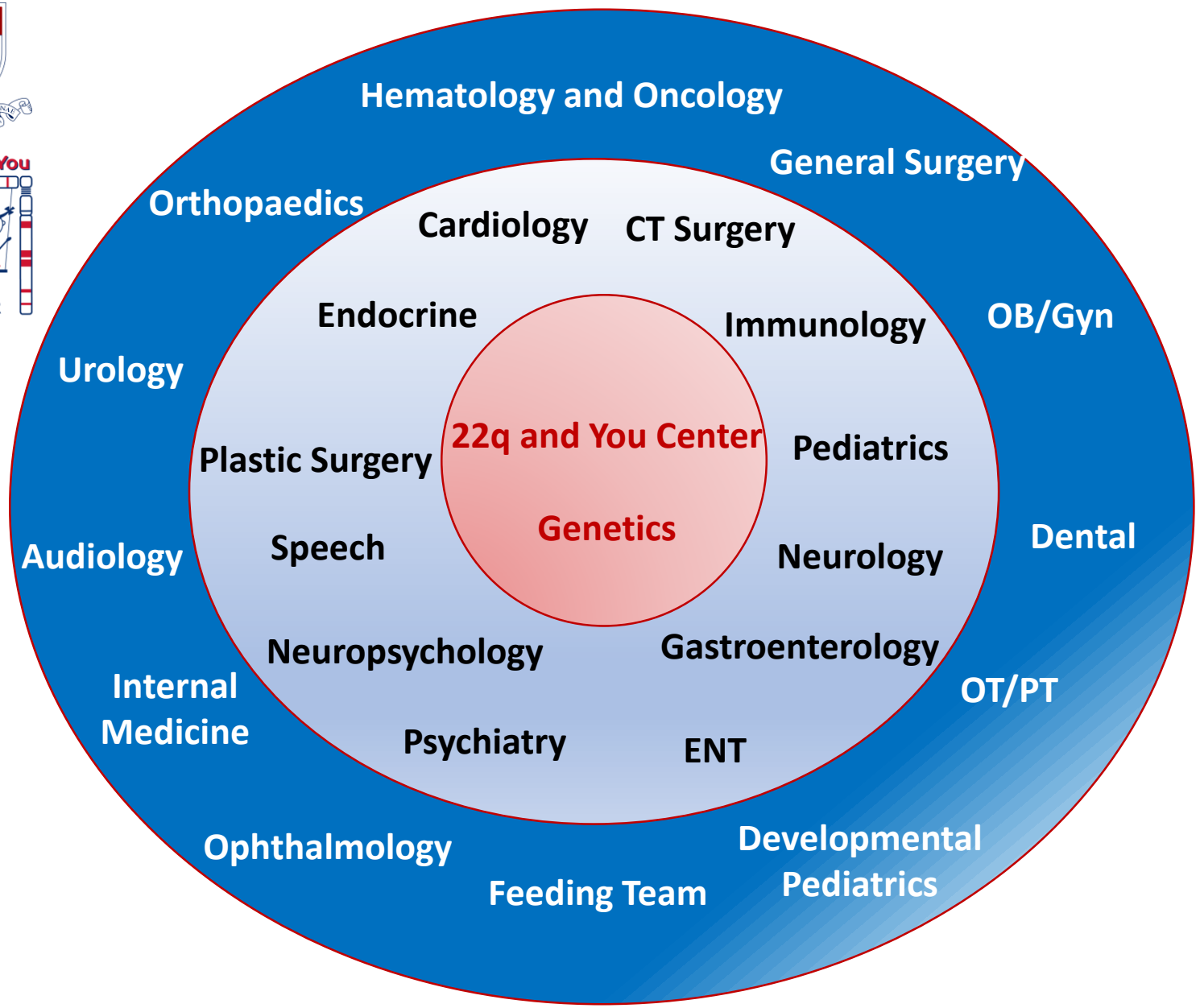
More common cause of TOF than Down syndrome



Goldmuntz 1993

To date, we have evaluated >1400 patients at CHOP

In the 22q and You Center

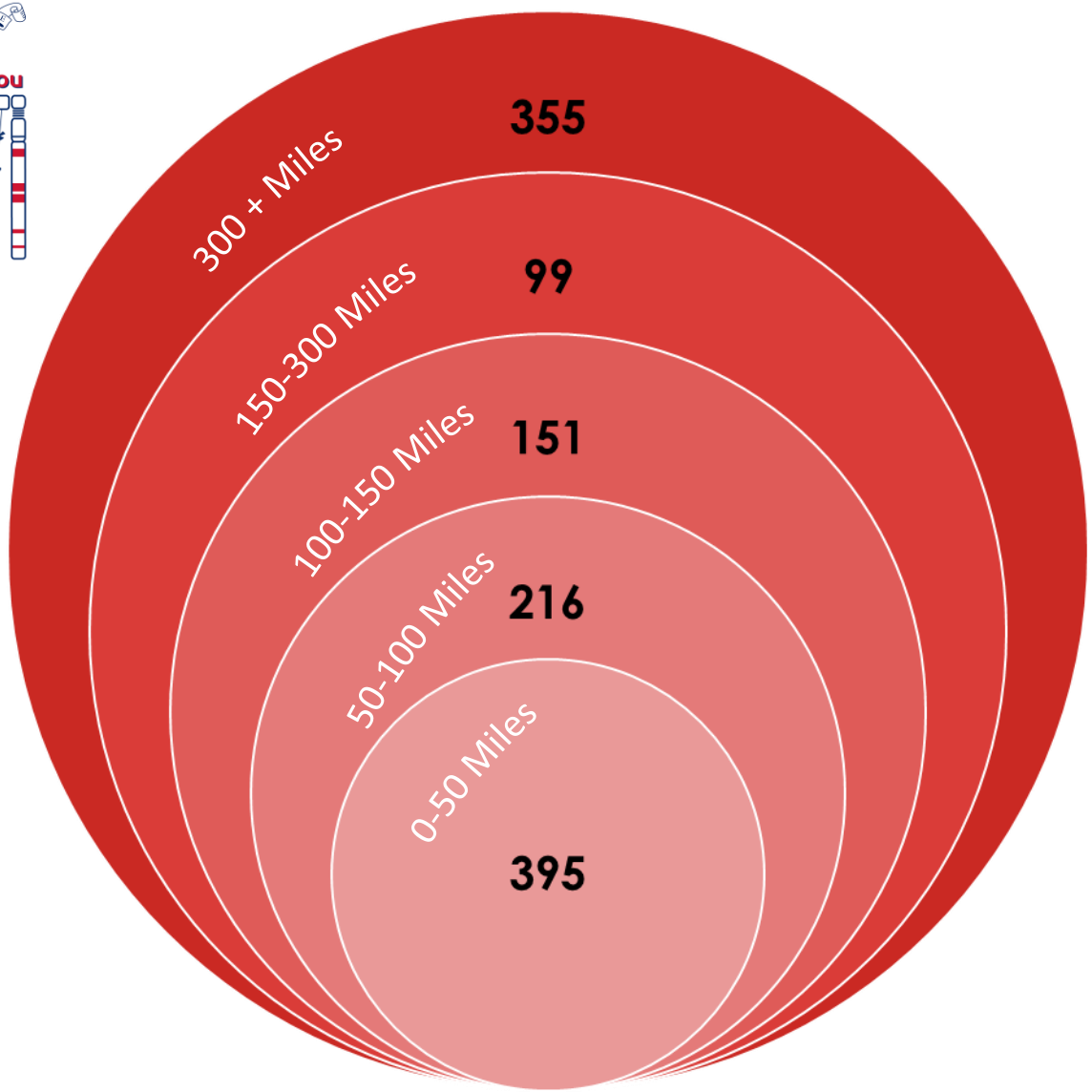


- Coordinating hub
- Primary circle of caregivers
- Extended circle includes providers across the entire institution
- *Enormous "Give and Take" between the coordinators and subspecialists*

Predicated on identifying experts or developing expertise in juniors who go on to become leaders at CHOP or elsewhere

Longevity has an enormous impact on programmatic success…likewise the loss of a member can be quite difficult to overcome*

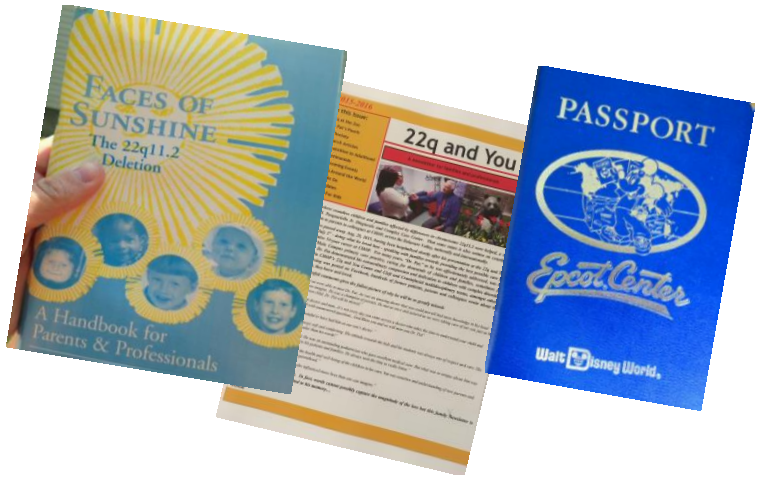
Center supports patients locally and beyond (N = 1249 Geocodes)



- ~50% (N=611) within 100 miles of CHOP
- 48% (N = 605) >100 miles from CHOP within the US
- *2% (N= 33) – International*

Logistics – “Locals”

- Thorough history – *no reason to reinvent the wheel by repeating evaluations that are complete, e.g. a normal renal ultrasound*
- 22q specific intake forms, lab order sets, letters of medical necessity, summary letters - *including recommended follow-up with names and contacts of subspecialists with expertise in this area*
- Coordinated evaluations *– grouping appointments where possible*
- Timing of appointments *– e.g. no sedated MRI prior to a speech evaluation*
- Social Functions *- e.g. 22q and Boo*
- Newsletters and handbook – *Faces of Sunshine*
- “Passport” (stamp book) program



Logistics – “Out of Towners”

- Same as locals
- Obtain and upload all records into EMR
- Coordinate low cost housing - *e.g. Ronald McDonald House*
- Where possible obtain free airline tickets – *American Airlines “Miles for Kids”*
- Meet and greet upon arrival to Philadelphia and plan for follow-up
- Recommending activities for down time, e.g. Please Touch Museum

Evaluations follow the international pediatric and adult healthcare guidelines

- Supports early diagnosis and comprehensive care thereafter
- Provides transition to adult care

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**

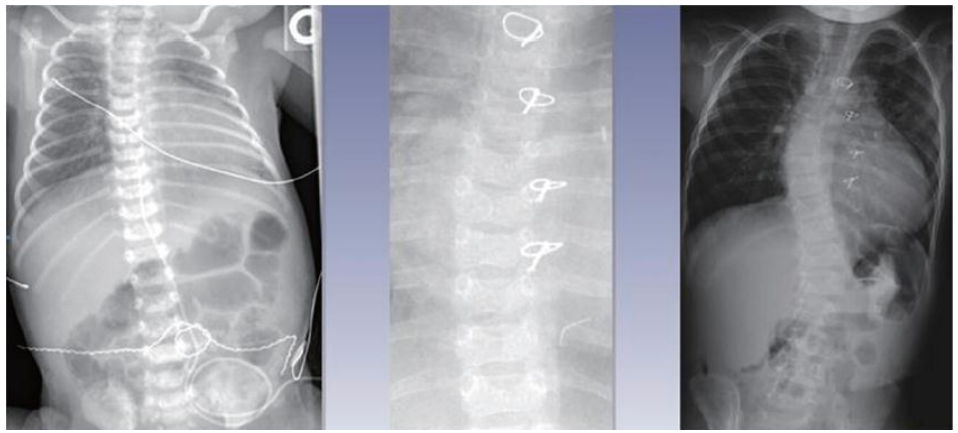
REVIEW | Genetics inMedicine

Practical guidelines for managing adults with 22q11.2 deletion syndrome

Wai Lun Alan Fung, MD, ScD[1–4], Nancy J. Butcher, MSc[2,5], Gregory Costain, PhD[2,5], Danielle M. Andrade, MD, MSc[1,6], Erik Boot, MD, PhD[1–4,7], Eva W.C. Chow, MD, FRCPC[2,4], Brian Chung, MRCPCH, MBBS[8], Cheryl Cytrynbaum, MS, CGC[9], Hanna Faghfoury, MD[10], Leona Fishman, MD, FRCPC[9], Sixto García-Miñaúr, MD[11], Susan George, MD, FRCPC[1,12,13], Anthony E. Lang, MD, FRCPC[6,14], Gabriela Repetto, MD[15], Andrea Shugar, MS, CGC[9], Candice Silversides, MD, FRCPC[1,16,17], Ann Swillen, PhD[18,19], Therese van Amelsvoort, MD, PhD[20], Donna M. McDonald-McGinn, MS, CGC[21–23] and Anne S. Bassett, MD, FRCPC[1–5,12,17]

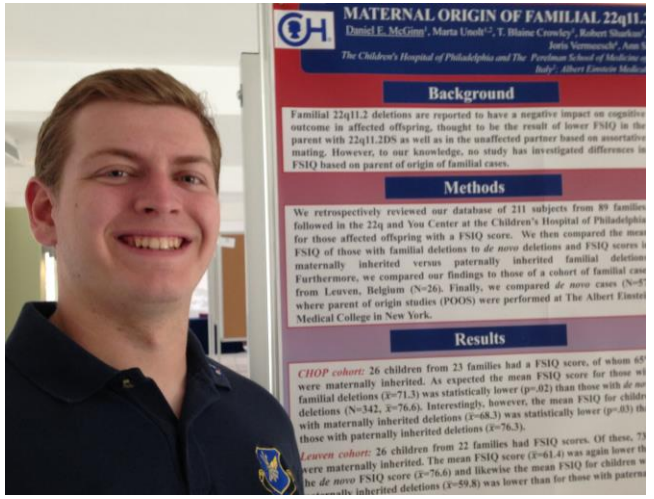
At diagnosis:

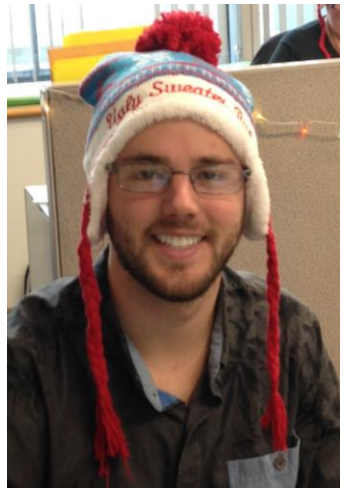
- Cardiac evaluation including an echocardiogram, ECG, and chest x-ray
- Immune labs including antibodies to determine if the vaccines were effective
- Kidney ultrasound
- Calcium and thyroid studies (annually thereafter)
- X-rays of the neck (4 years or older)
- Spine x-rays (initial evaluation at 6-8 years; periodically thereafter)



Hire and train young people to help support the program

- No dedicated funding for our Center
- Concurrently educating future clinicians and scientists





Partner globally with families – sharing this type of information

- Raising awareness
- Providing support
- *22q and Boo, 22k for 22q, 2.2 for 22q, 22q at the Zoo*

Working closely with the broader international community

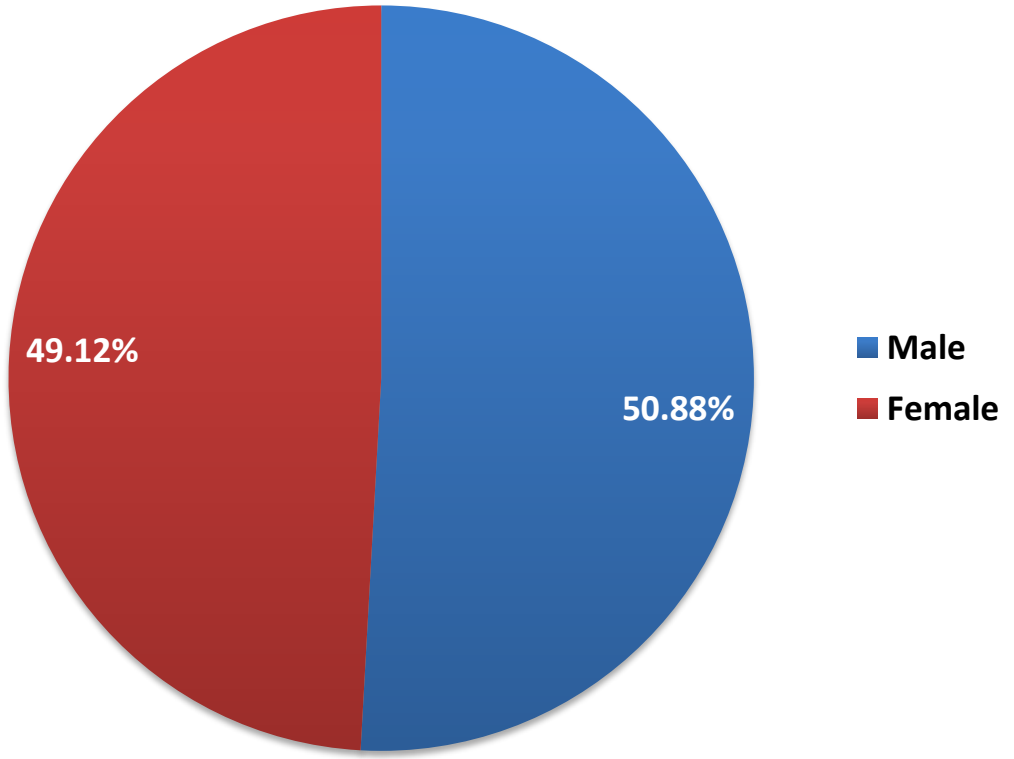
- 22q11.2 Society
- Biennial International 22q11.2 Conference

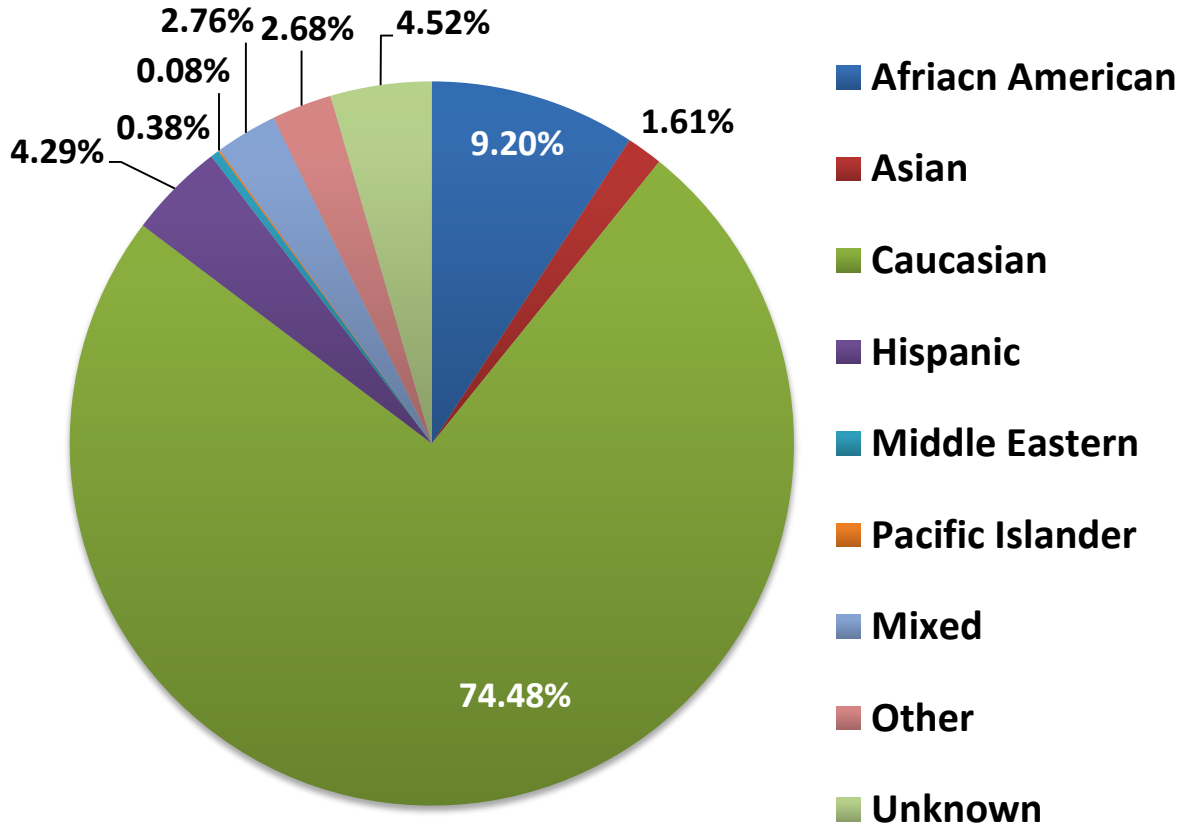
Leading to close collaborations and friendships

Concurrently helping individual patients and families through research initiatives and guidance regarding best care practices

What have we observed?

- Males and females are equally affected
- Most (75%) patients are Caucasian
- In contrast to the CHOP general population where ~40% are AA





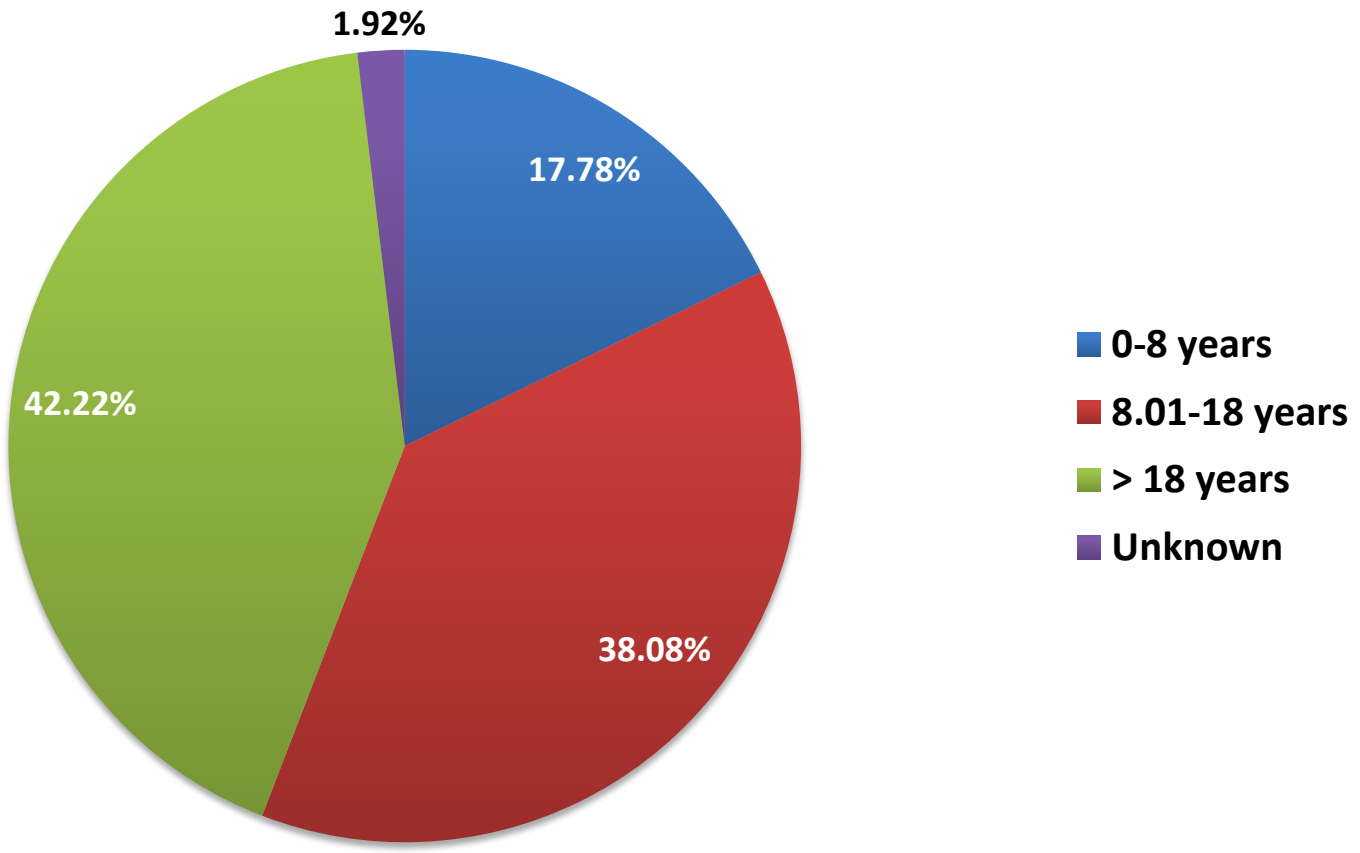
Perhaps related to a lack of typically associated features in non-Caucasians?

- But could be a result of variability in the structure of the chromosome
- Currently being studied as a collaboration led by Joris Vermeesch, PhD in Leuven, Belgium, with Bernice Morrow, PhD in NYC, Tamim Shaikh, PhD in Denver and Beverly Emanuel, PhD at CHOP

McDonald-McGinn 2005

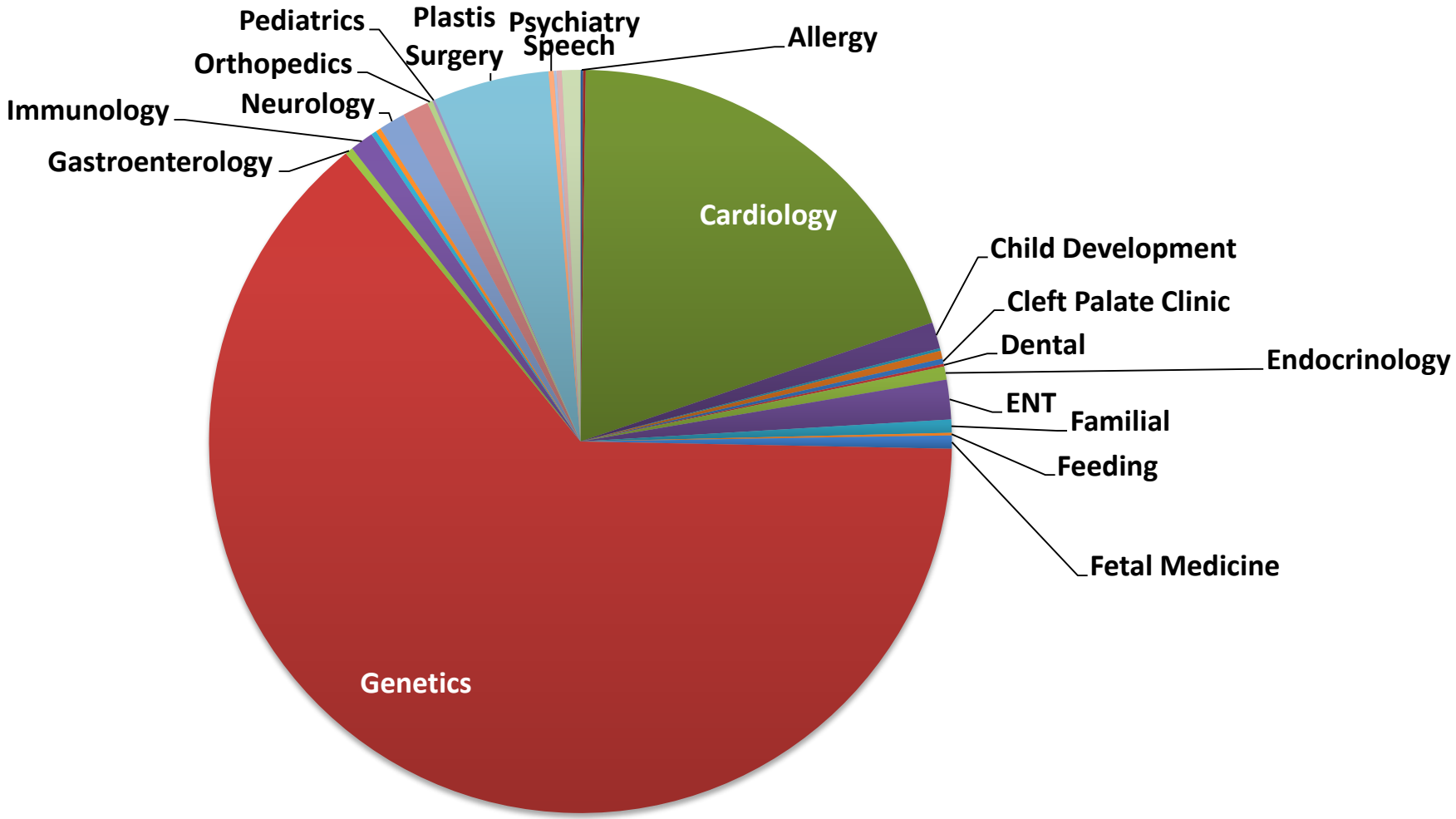
Mean age at diagnosis – 3.8 years +/- 7.5 years

- Our patients remains primarily pediatric (58%) but they are aging
  - *20% are <8 years*
  - *38% are 8-18 years*
  - *42% are >18 years*



Most patients are diagnosed by Genetics (67%)

- Other subspecialists are contributing to the diagnosis
- *Cardiology (20%), Cleft Team (8%), etc.*



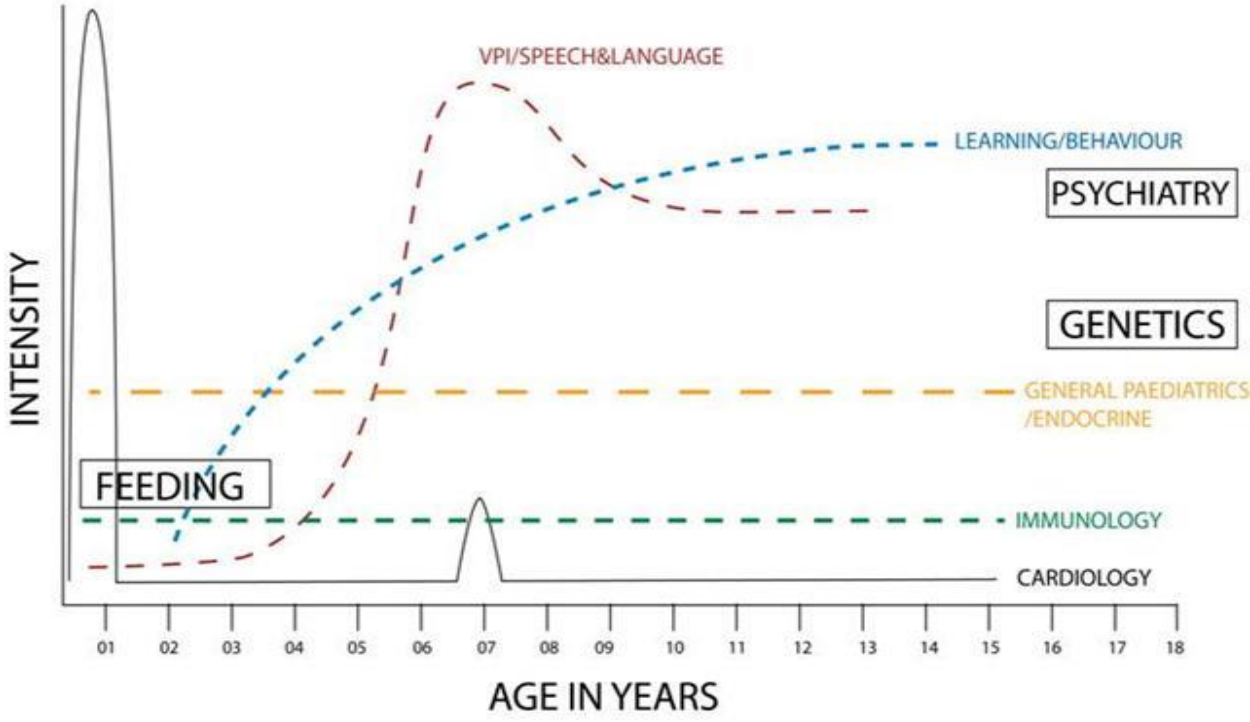
Overall prevalence of significant medical features varies by age at ascertainment

	Children	Adults
▪ Immunodeficiency	77%	?
▪ Congenital heart disease	69%	40% (serious)
▪ Palatal anomalies	68%	?
▪ Gastrointestinal problems	66%	?
▪ Hypocalcemia	55%	65%
▪ Genitourinary abnormalities	36%	?
▪ Hypothyroidism	?	20%
▪ Behavioral/psychiatric differences	25%	60%

McDonald-McGinn 2001; Bassett 2005; Sullivan 2008; Bassett 2011; McDonald-McGinn 2015

Presence and severity of features varies by age – focus changes

- Infancy and early childhood:
  - *Attention to birth defects, associated medical issues, motor milestones, speech and language*
- School age:
  - *Academics and peer relations*
- Adolescents and adulthood:
  - *Independence*
  - *Behavioral differences*
  - *Recurrence risk*



Habel 2012

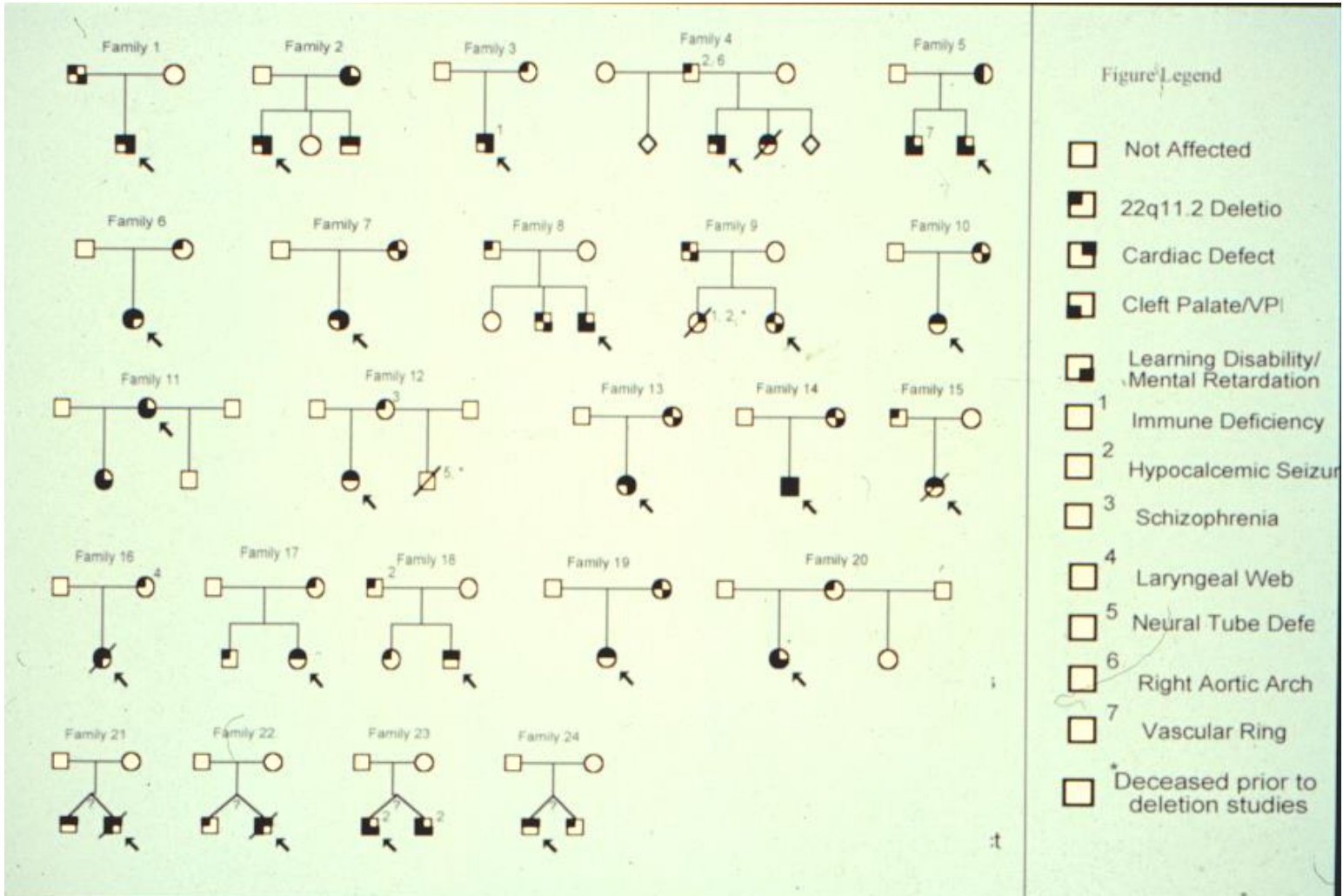
In the absence of typical features - the diagnosis may be missed

- This is especially true in adolescents, adults and non-Caucasians
- Even in university based medical centers

McDonald-McGinn 2001, 2005, 2015

Complicated by wide variability within and between families

- Even between identical twins who share the same genes but can be differ from one another, e.g. one with and one without a congenital heart defect



McDonald-McGinn 2001

Complicated by dual diagnoses unrelated to 22q

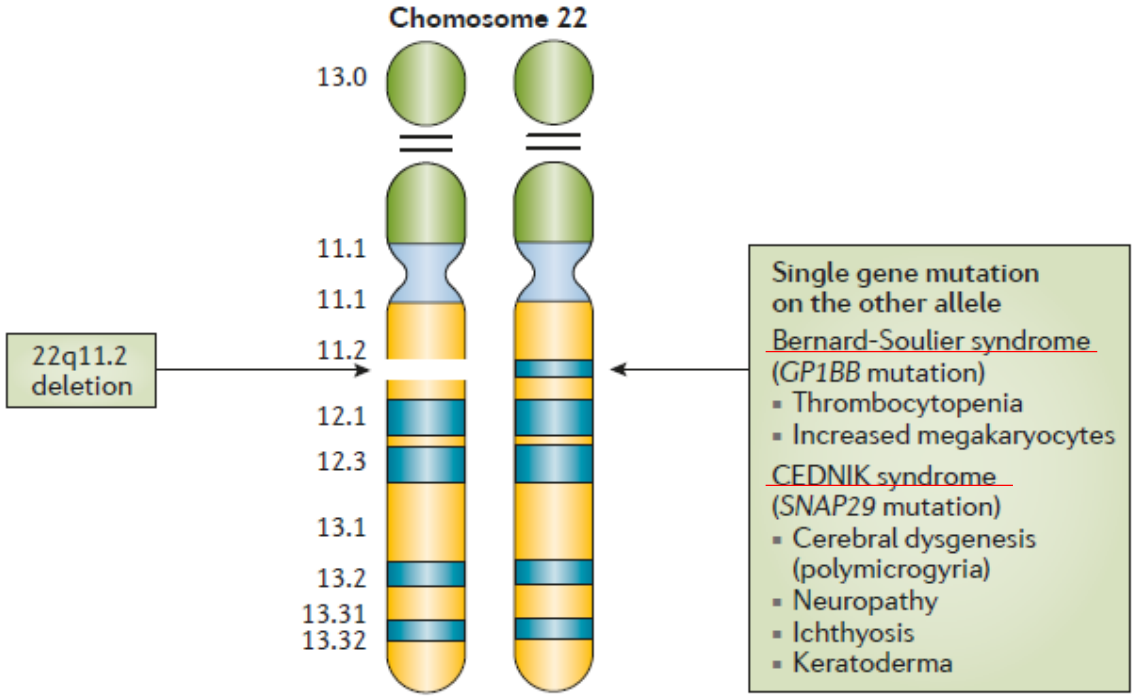
Patients with the 22q11.2 deletion and:

- *Severe Combined Immunodeficiency (SCID)*
- *Down syndrome (trisomy 21)*
- *Marfan syndrome*
- *CHARGE (due to a CHD7 mutation)*
- *Neurofibromatosis*
- *Achondroplasia*
- *FGFR3 mutation (familial)*
- *Ehlers-Danlos syndrome (familial)*
- *Trisomy 8 mosaicism*

McDonald-McGinn 2001

Complicated by dual diagnoses related to 22q11.2DS

- A 22q11.2 deletion on one chromosome
- A change in a gene on the other chromosome 22
  - *Bernard-Soulier syndrome – low platelets and giant platelets*
  - *CEDNIK syndrome – smooth brain and skin changes*

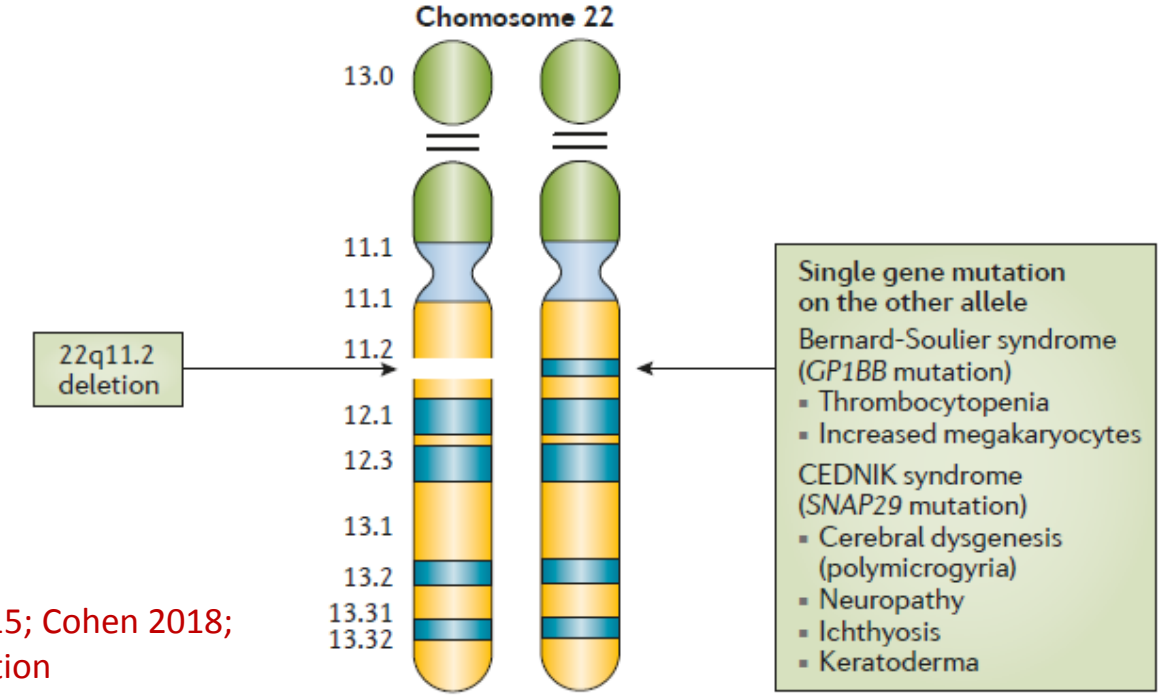


Budarf 1995; McDonald-McGinn 2013, 2015

22q11.2DS is common

We have identified 24 patients with dual diagnoses related or unrelated to the chromosome 22q11.2DS

- Representing 1.7% of our overall clinic population (N=1422)
- Including 16 patients with a 22q11.2 deletion on one chromosome and a deletion or single gene mutation on the other chromosome 22 allele
- Important to consider when rare features are present



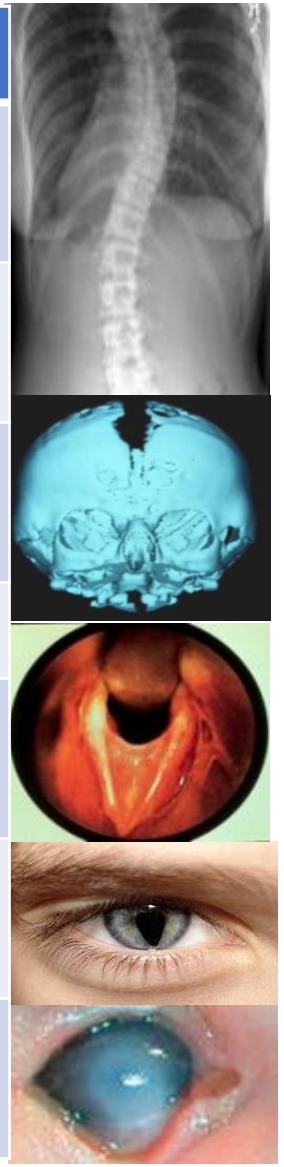
Budarf 1995; McDonald-McGinn 2013, 2015; Cohen 2018; Unolt, submitted; Nowakowska in preparation

Common significant associated features

Findings	Prevalence
Immune related problems *Low T cells and immunoglobulins, problems mounting antibodies to vaccines, allergies*	**77%**
Heart defects (excluding self closing VSD, PDA, PFO) *Half with severe defects – mostly TOF +/- PA and IAAB*	**69%**
Abnormalities of the palate (roof of the mouth) *Mostly SMCP/VPI; Only 10% with overt cleft and 1-2% cleft lip*	**68%**
Gastrointestinal problems *Mostly GERD, dysphagia, constipation, imperforate anus, Hirschsprung's disease, intestinal malrotation*	**66%**
Endocrine abnormalities *Hypocalcemia, thyroid disease, growth hormone deficiency*	**55%**
Differences in the bones of the neck	**50%**
Absent kidney	**16%**

Less common significant features

Findings	Specifics
Bones	*Scoliosis, Hemi or butterfly vertebrae, craniosynostosis, limb differences*
Brain and spine	*Seizures, polymicrogyria (underdeveloped brain), spina bifida, small head size, low muscle tone, dystonia*
Autoimmune – bleeding & thyroid	*Idiopathic thrombocytopenia, hypo or hyperthyroidism, hemolytic anemia, neutropenia, juvenile arthritis, vitiligo*
Genitourinary	*Hypospadias, cryptorchidism, absent uterus, hernias*
ENT	*Laryngeal web, choanal atresia, TEF, tracheal atresia, microtia, sensorineural and conductive hearing loss*
Eye	*Coloboma, scleracornea, ptosis, strabismus, tortuous retinal vessels, posterior embryotoxon*
Malignancies	*Hepatoblastoma, Wilms tumor, renal cell carcinoma, thyroid carcinoma, melanoma, leukemia*



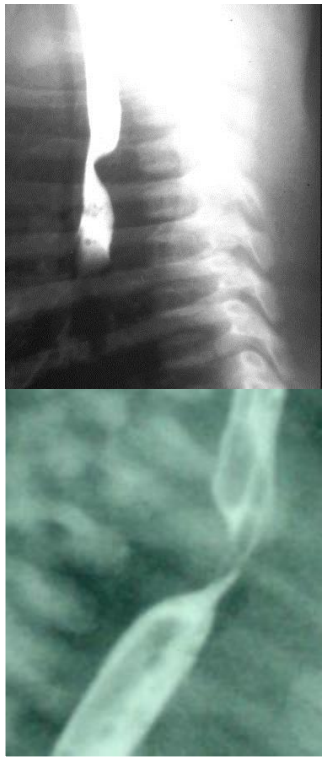
Features leading to prenatal diagnosis (besides CHD and cleft palate):

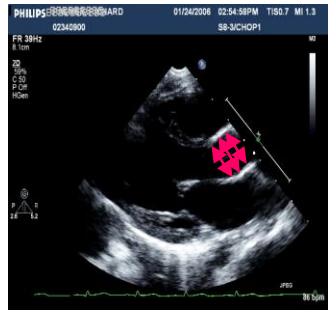
- Diaphragmatic hernia (bowel protruding through the diaphragm into the chest)
- Polyhydramnios – too much amniotic fluid (due to palatal/swallowing problems)
- Absent/small thymus
- Extra fingers or toes
- Club Foot
- Spina bifida
- Abnormal vertebrae
- Umbilical hernia

Ming 1997; McDonald-McGinn 2001, 2005, 2006, 2011, 2015; Richetti 2004; Bassett 2009, 2011; Besseau-Ayasse 2014; Unolt 2016

Important cardiac considerations:

- VSD is the 2nd most common lesion associated with 22q11.2DS
  - *~1/100 newborns are found to have a VSD in the general populations*
  - *Should we be screening all children with a VSD? Will NBS solve this for us?*
- Aortic arch anomalies can present with respiratory symptomatology, e.g. vascular ring
- Aortic root dilation is common
  - *Clinical significance is unclear*
  - *Periodic surveillance is recommended even if no congenital heart defect*





McElhinney 2001; John 2009

Cardiac outcomes in patients with 22q11.2DS:

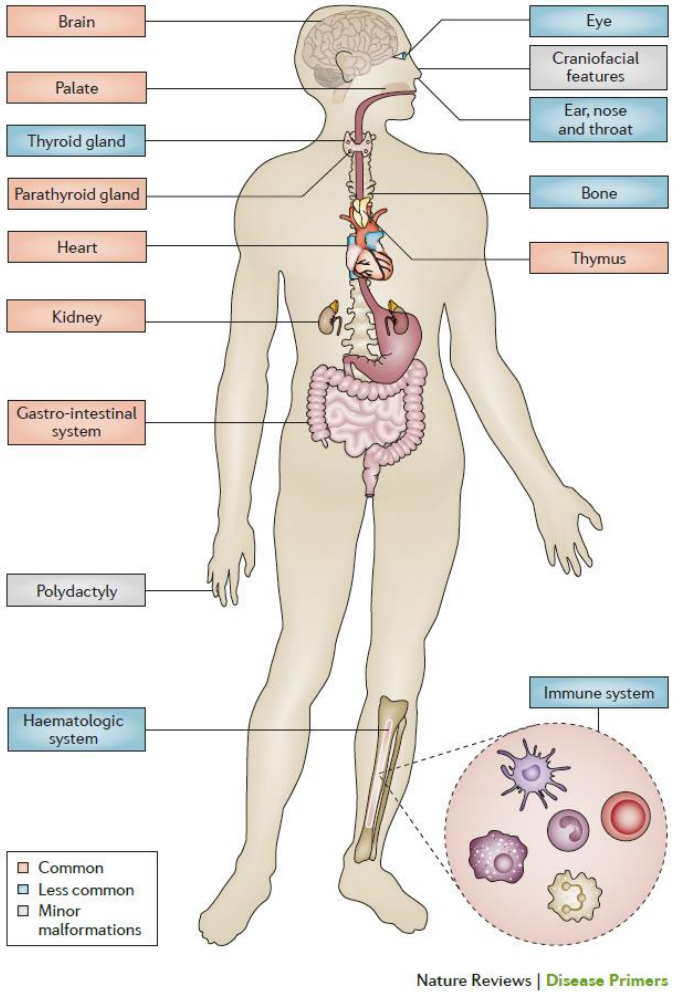
- Infants have a longer hospital course during cardiac surgery than their non-deleted counterparts
  - *Not related to rate of infection*
- Children and adolescents with repaired heart defects have worse exercise performance than their non-deleted counterparts
- Cardiac patients with 22q11.2DS have more hospitalizations and lower reported Quality of Life ratings than their non-deleted counterparts
- *Understanding why is an important next step in providing better treatment*

Mahle 2003; Mercer-Rosa 2013, 2015; O'Byrne 2014

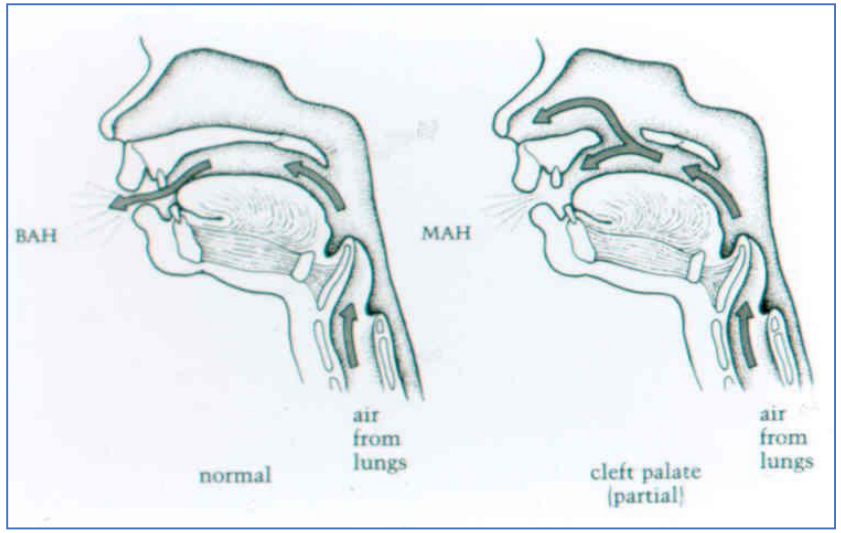
Despite these findings - unlike the early reports on DiGeorge syndrome only 4% of our patients have died

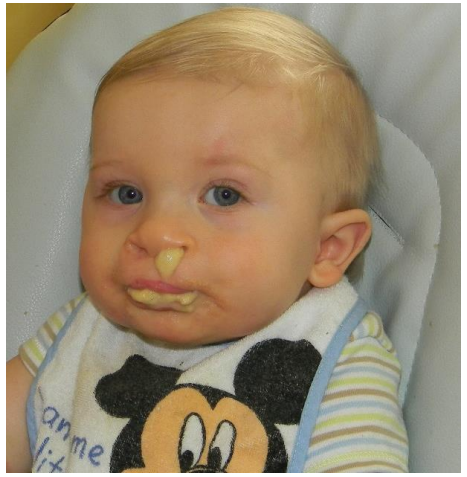
- Most related to complex congenital heart disease
- Some secondary to airway issues
- *Median age at death - 5 months*

For surviving patients it is important to carefully consider other associated systems across the lifespan



Palatal anomalies affect feeding and speech





Patients with isolated cleft palate are unlikely to have 22q11.2DS

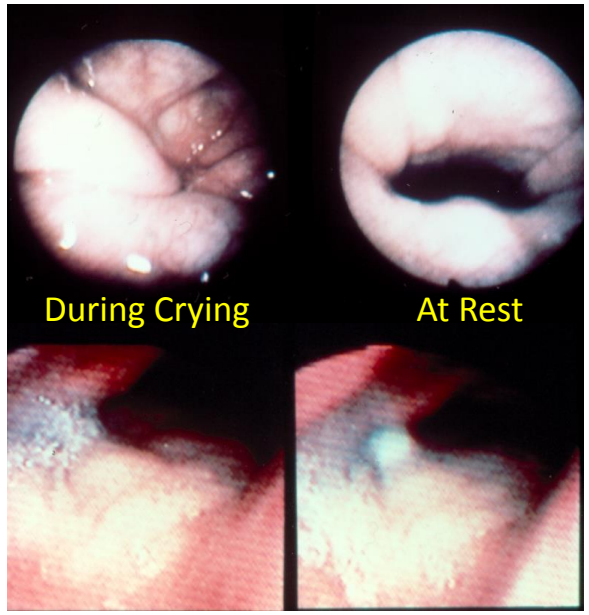
- In contrast, all patients with VPI (VPD) should be screened for 22q11.2DS
- Polyhydramnios may be a prenatal clue to the diagnosis (palate/swallowing issues)
- Milk coming through the nose in infancy may be a clue to VPI but may not always necessitate palatal repair
- Sleep apnea/displaced carotids can alter the surgical approach to palatal repair
- *At CHOP we perform pre and post-operative sleep studies and pre-op MRAs in all patients*

Submucosal cleft

Bifid uvula

Overt cleft palate

Lip cleft/palate



Control

Patient with 22q11.2 DS

Velopharyngeal Dysfunction

McDonald-McGinn 2001

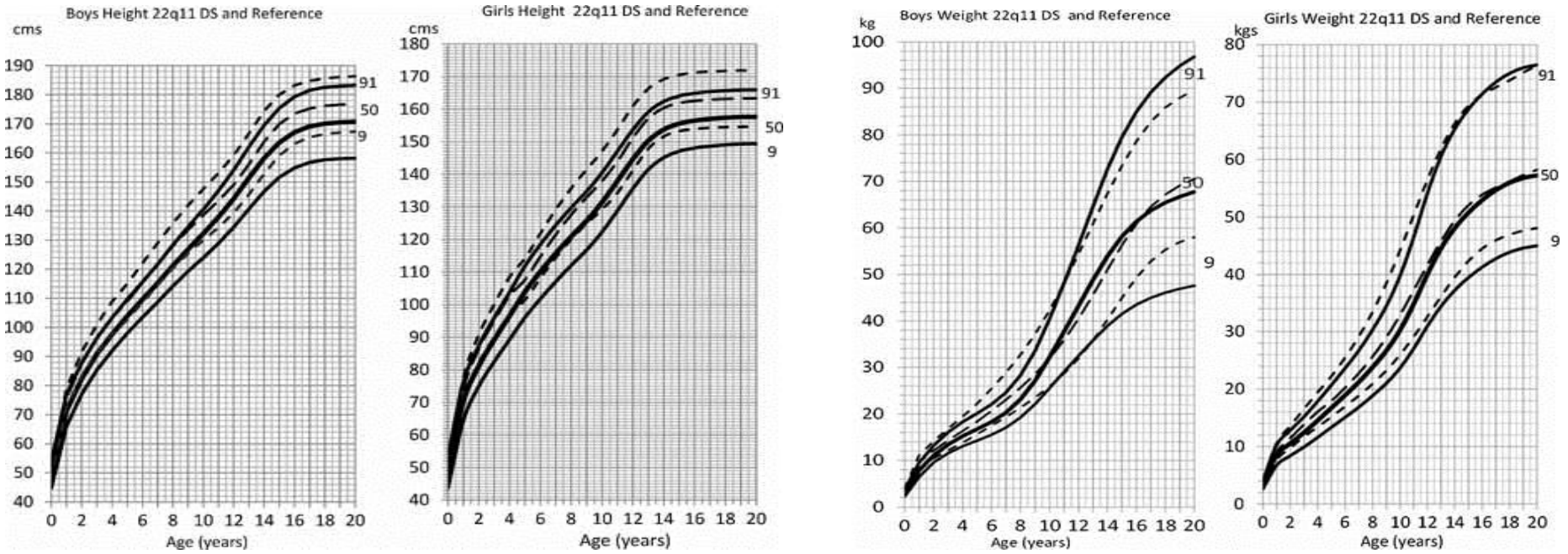
Endocrine problems require lifetime surveillance

- Hypocalcemia is seen in 55-65% of patients generally presenting neonatally with:
  - *Muscle spasms/twitching (tetany)*
  - *Seizures*
  - *Significant feeding difficulty*
  - *Noisy breathing (Laryngeal stridor)*
- Frequently transient but can require lifetime treatment
- Recurrent hypocalcemia may occur during times of stress:
  - *With illness*
  - *Perioperatively*
  - *During pregnancy*
  - *During adolescence*

Cuneo 1997; McDonald-McGinn 1997, 1999, 2001; Greig 1996; Weinzimmer 2001; Digilio 2001; Choi 2006; Hieronimus 2006; Bassett 2005, 2009, 2011; McDonald-McGinn 2015

Additional endocrine manifestations include

- Short stature with height <2% (15%) – *diagnosis specific growth curves*
- Growth hormone deficiency (4%) – *that responds well to therapy*
- Intrauterine growth retardation – *may be a prenatal clue to the diagnosis*
- Autoimmune thyroid disease – *both hypo and hyperthyroidism*

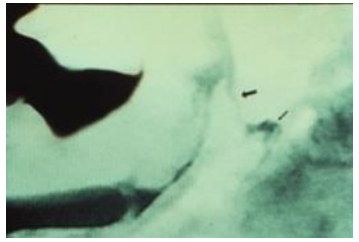


Kawame 2001; Weinzimmer 2001; Digilio 2001; Elder 2001; Gennery 2002; Brown 2004; Choi 2006; Gelfand 2007; Lima 2010; Bassett 2005, 2009, 2011; Nakada 2013; Habel 2012

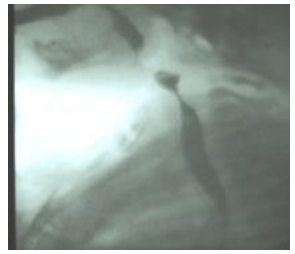
Feeding, swallowing, and constipation issues are common (~66%) and often complicated

- Severe feeding problems leading to prolonged tube feeds
- Nasopharyngeal reflux
- Esophageal dysmotility
- GERD
- Lifetime constipation

- *Esophageal atresia/TEF*
- *Intestinal malrotation*
- *Hirschsprung's disease*
- *Imperforate anus*

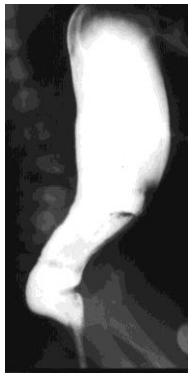


Nasopharyngeal reflux



Esophageal dysmotility

Intestinal malrotation



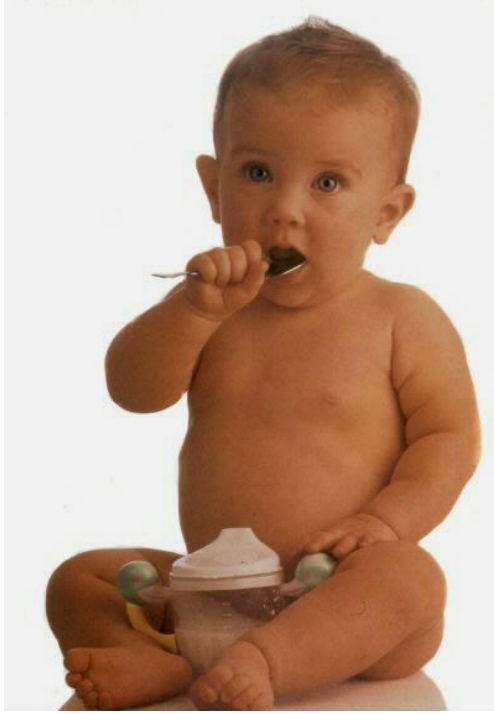
Hirschsprung’s disease

Eicher 1997

Feeding difficulty may erroneously be attributed to heart disease

- All symptoms are treatable
- Complications of GERD include:
  - *Esophageal inflammation*
  - *Aspiration into the lungs*
  - *Poor weight gain*
  - *Feeding refusal*

- Treatment includes life style changes and medication
  - *Formula changes/thickened formula*
  - *Positioning during and following feeds*
  - *Acid blockades and pro-motility agents*
  - *Less frequently – surgical intervention (Nissen fundoplication)*



Mascarenhas in preparation

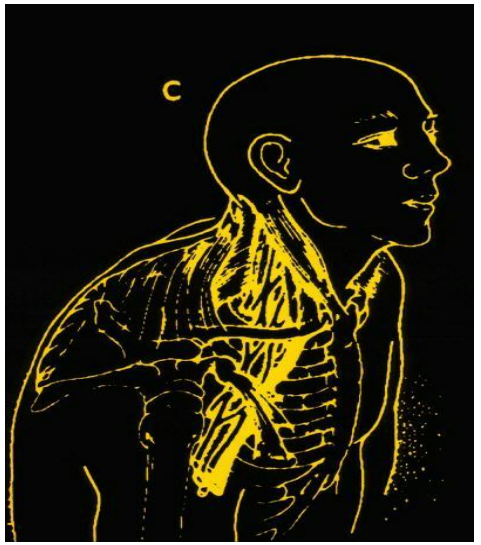
Additional factors affecting feeding should be considered

Medical

- Endocrine:
  - *low calcium*
  - *Thyroid disease*
- Neurologic:
  - *Poor muscle tone*
  - *Abnormalities of the brain (polymicrogyria – smooth brain)*
- Respiratory
  - *Increased work of breathing*
  - *Congestion*
  - *Cardiac*

Gross motor

- *Posture and alignment*
- *Oral motor pattern and tongue retraction*



Mascarenhas in preparation

Genitourinary abnormalities are common (36%)

- Absent kidney (16%)
- Cystic or underdeveloped kidneys
- Duplicated kidney
- Kidney reflux
- Undescended testes
- Hypospadias
- Absent uterus
- Inguinal hernia
  - *Renal ultrasound is recommended for all*

Wu 2001; Kapadia 2008; Bassett 2011

Mild facial features can be a clue to the diagnosis

- Hooded eyelids
- Nasal differences – with and without cleft lip
- Asymmetric crying facies (14%)

Gripp 1997; Passick 2014

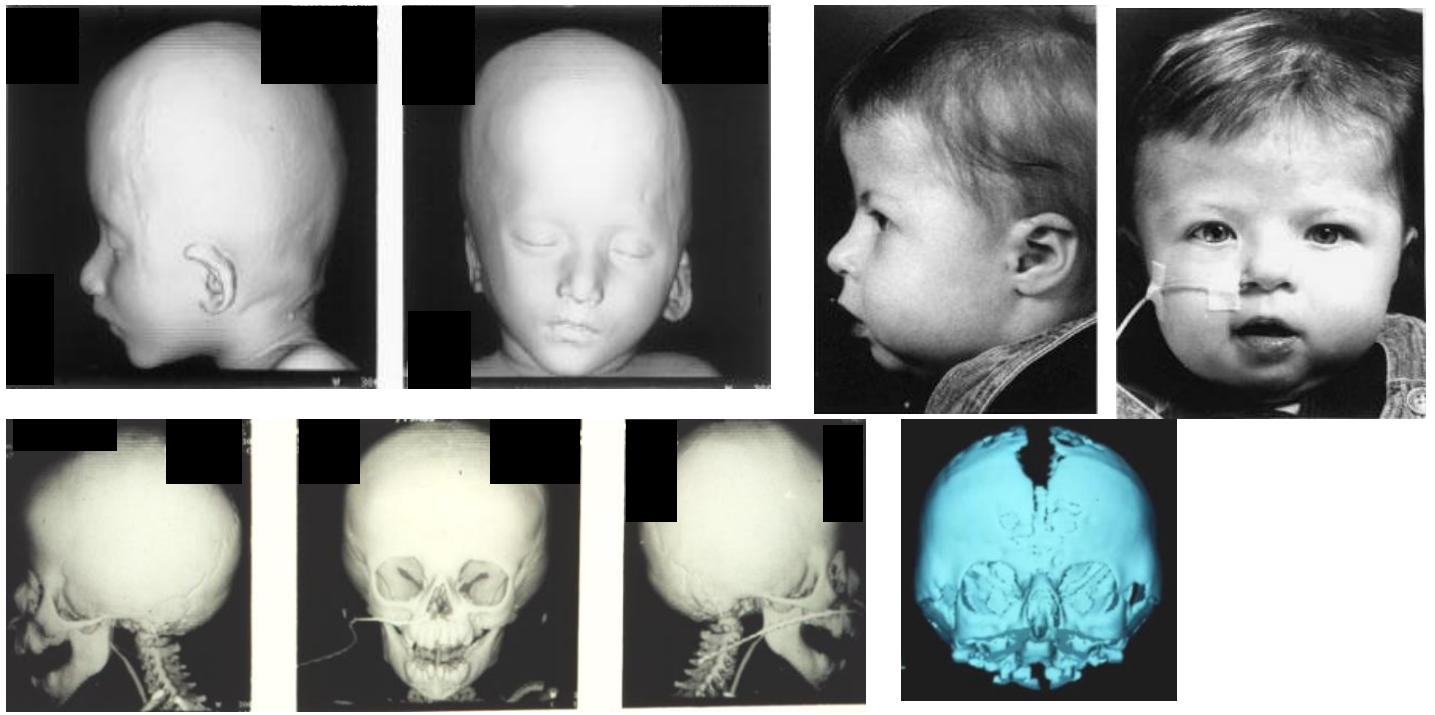
Ear differences

- Small/absent ears
- Tags
- Pits
- Cupped
- Helical differences

Digilio 2009; Derbent 2013

Craniosynostosis (premature fusion of the skull bones)

- Results in an abnormal skull shape
- Likely due to a change in a gene on the other chromosome



McDonald-McGinn 2005; Al-Hertain 2013; Unolt submitted

Pierre Robin (small chin and tongue obstructing the airway)

- With or without cleft palate
- Often requiring mandibular distraction/tracheostomy

Developmental delay and cognitive deficits are common:

- >95% of both children and adults

Moss 1991; Woodin 2001; Bassett 2005; Chow 2006; Antshel 2008; Green 2009; Fung 2010; Swillen and McDonald-McGinn 2015; McDonald-McGinn 2015

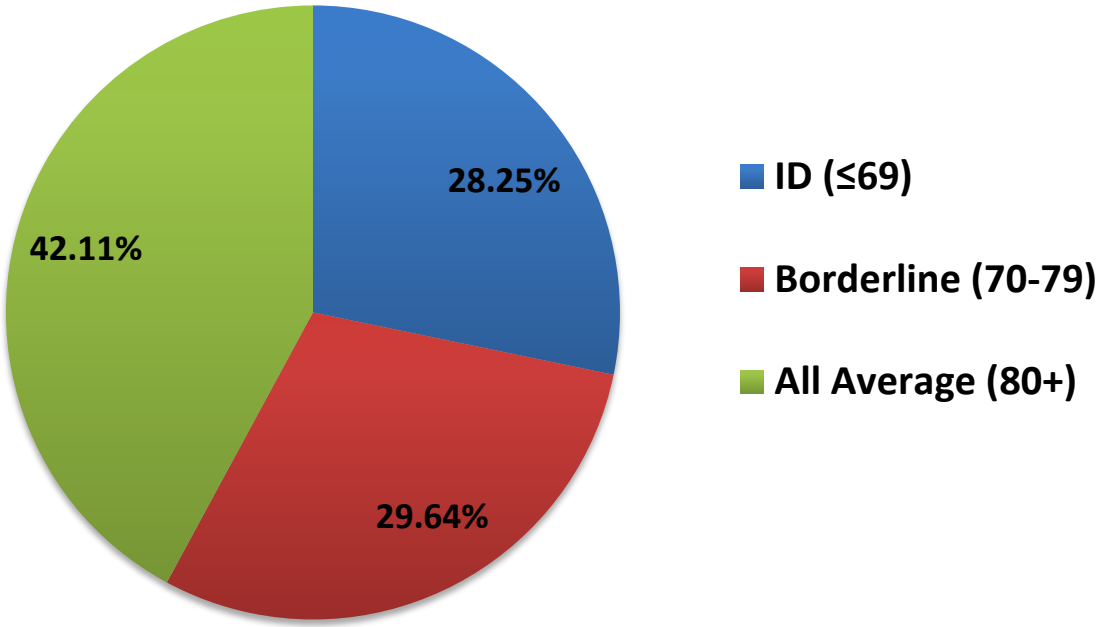
Young children:

- Have delays in achieving motor milestones
  - Mean age of walking – 18 months
- Delays in emergence of language
  - Mean age of speaking – 30 months
  - With some non-speakers as old as 5-7 years
- Autism or autistic spectrum disorder
  - >10%
- All benefit from Early Intervention
  - Especially speech therapy
  - Sign language – does not prevent the emergence of verbal speech and often decreases frustration

Gerdes 2001; Solot 2001; Fine 2004; Vorstman 2006; DeSmedt 2007; Swillen and McDonald-McGinn 2015; McDonald-McGinn 2015

School aged children

- Generally attend mainstream schools with academic/behavioral support
- Many children have a >10 split between the verbal and performance IQ which may render the full scale IQ inaccurate and affects the approach to learning support
- Mean Full Scale IQ in a subset of CHOP patients (361/1305 - WISC)
  - *76 +/- 13.5*
- Majority of patients (72%) fall within the average to borderline range
  - *80+ (42%) - Average*
  - *70 – 79 (30%) - Borderline*
  - *<69 (28%) – ID*

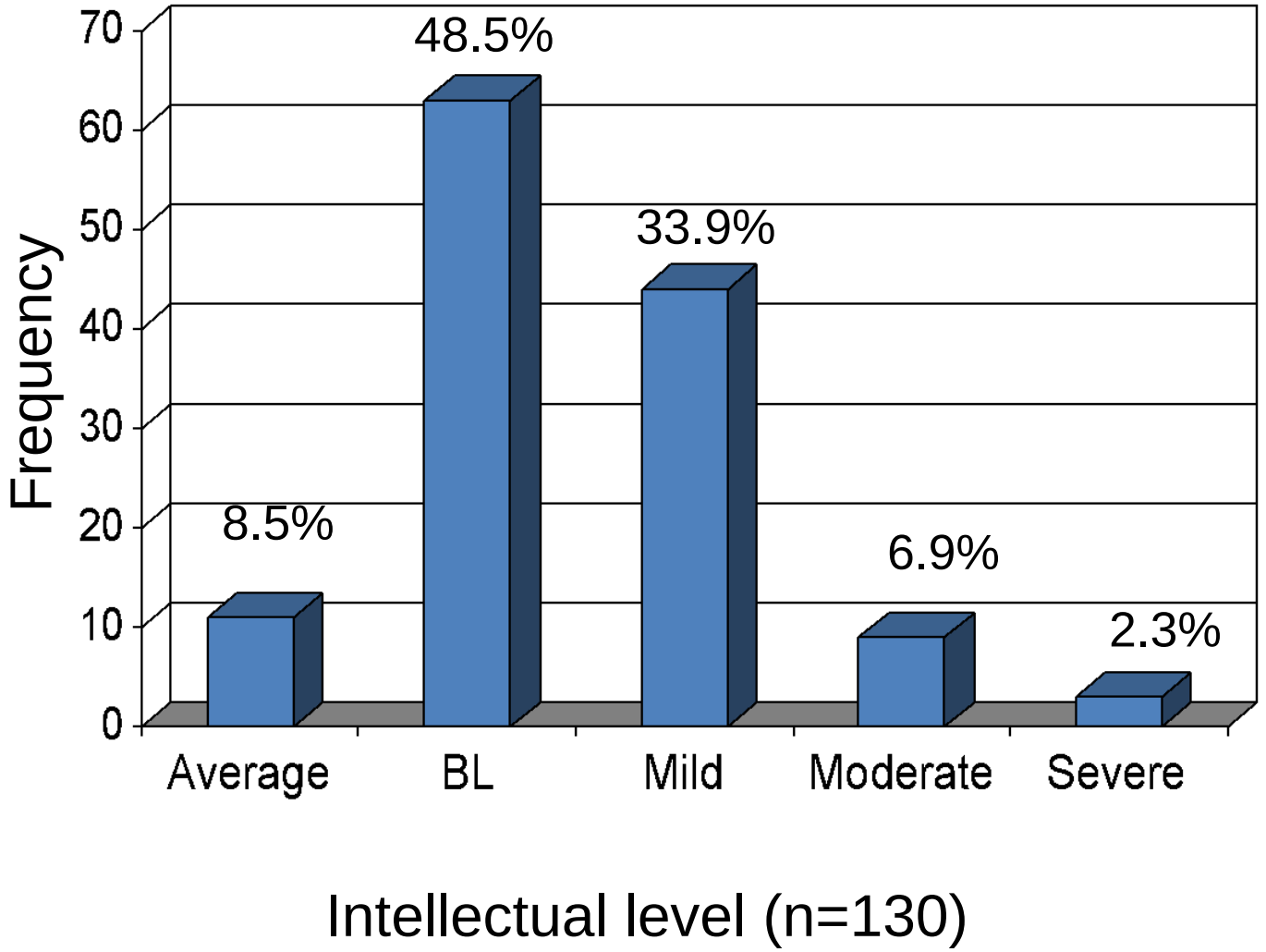


Moss 1999; Woodin 2001; Swillen and McDonald-McGinn 2015

Intellectual levels in adults are generally lower

Could be the result of ascertainment bias:

- *Psychiatric illness*
- *CHD repair prior to innovative surgical procedures*
- *Paucity of Early Intervention*



Bassett 2009

Behavioral differences are common:

	Children	Adults
	~25%	~60%

Pediatrics:

- *Attention Deficit Hyperactivity Disorder*
- *Autism Spectrum Disorder*
- *Anxiety*
- *Obsessive Compulsive Disorder*
- *Oppositional Defiant Disorder*

Adults:

- *Depression*
- *Anxiety*
- *Obsessive Compulsive Disorder*
- *Schizophrenia (25%)*

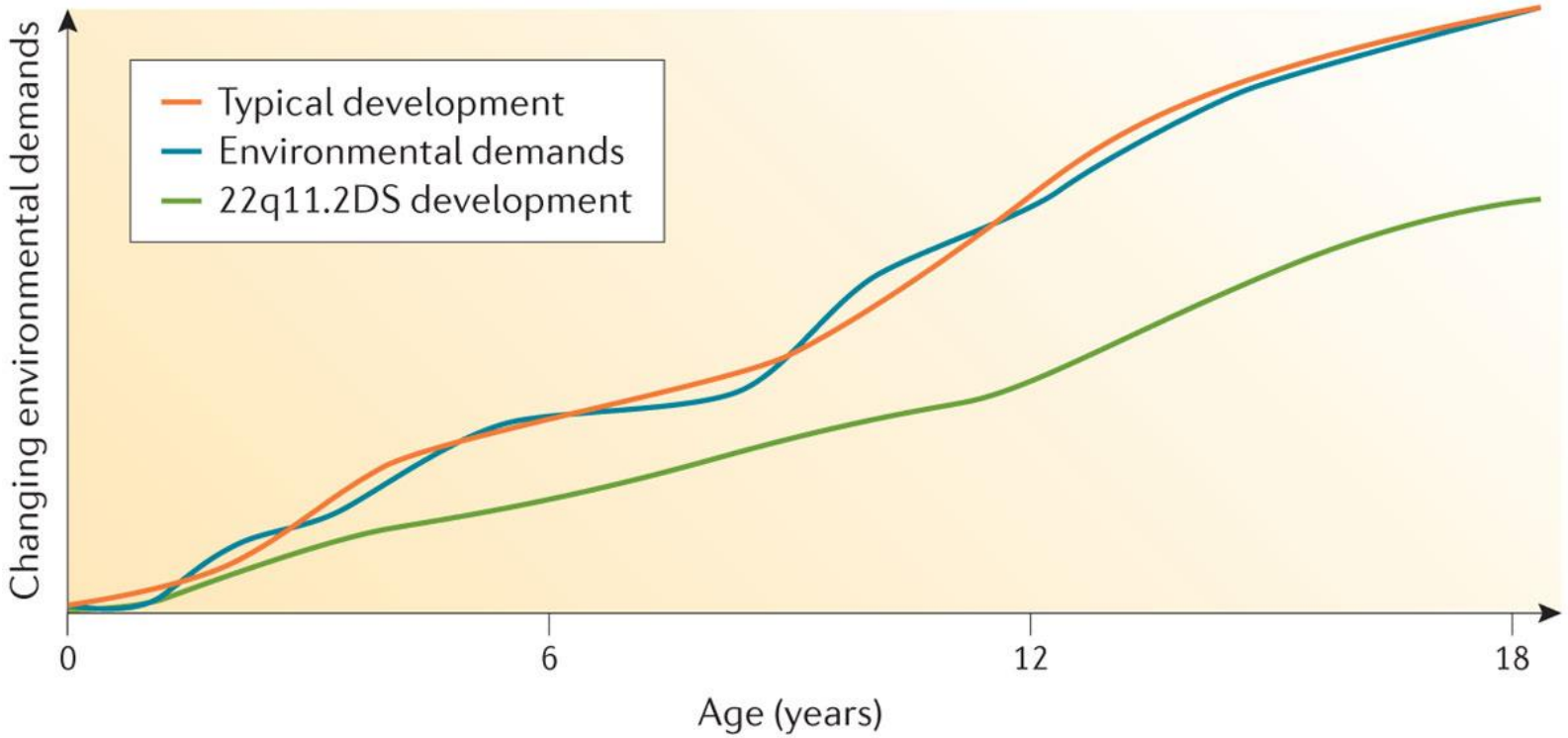
Bassett 2005; Chow 2006; Antshel 2008; Green 2009; Fung 2010; Swillen and McDonald-McGinn 2015; McDonald-McGinn 2015

The full neuropsychiatric symptoms are broad

- Neonatal seizures *(usually hypocalcemic)*
- Developmental delay and intellectual disabilities
- Autism spectrum features and disorder
- Attention deficit disorder
- Idiopathic recurrent seizures/epilepsy
- Mood and anxiety disorders
- Schizophrenia and other psychotic disorders
- Neurodegenerative disorders *(Parkinson disease)*

Children “grow into deficit”

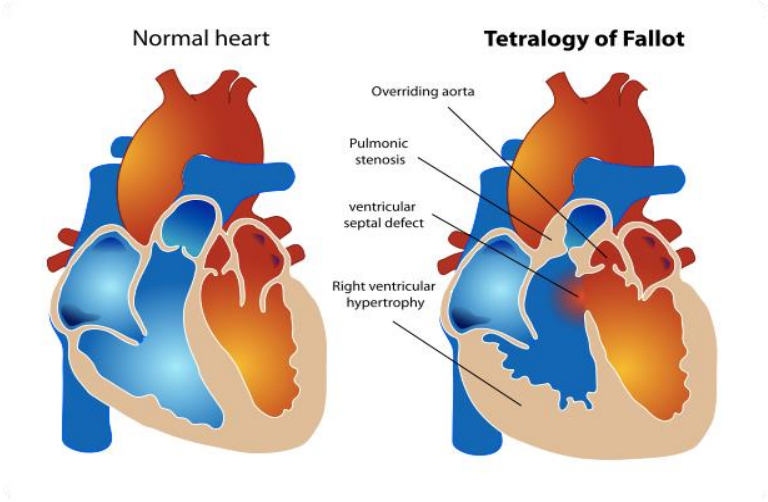
- Difficulty keeping up with peers developmentally
- Difficulty keeping up with environmental demands (school)
- With a decline in FSIQ (mostly the Verbal IQ falling to meet the Performance IQ)
- *May be a sign of emerging psychiatric illness*



Vorstman, 2015; Swillen and McDonald-McGinn 2015; Swillen and McDonald-McGinn 2015

Attempting to identify confounding factors for variability in IQ

- Cross referenced patients with cardiac disease and IQ data (WISC)



V.

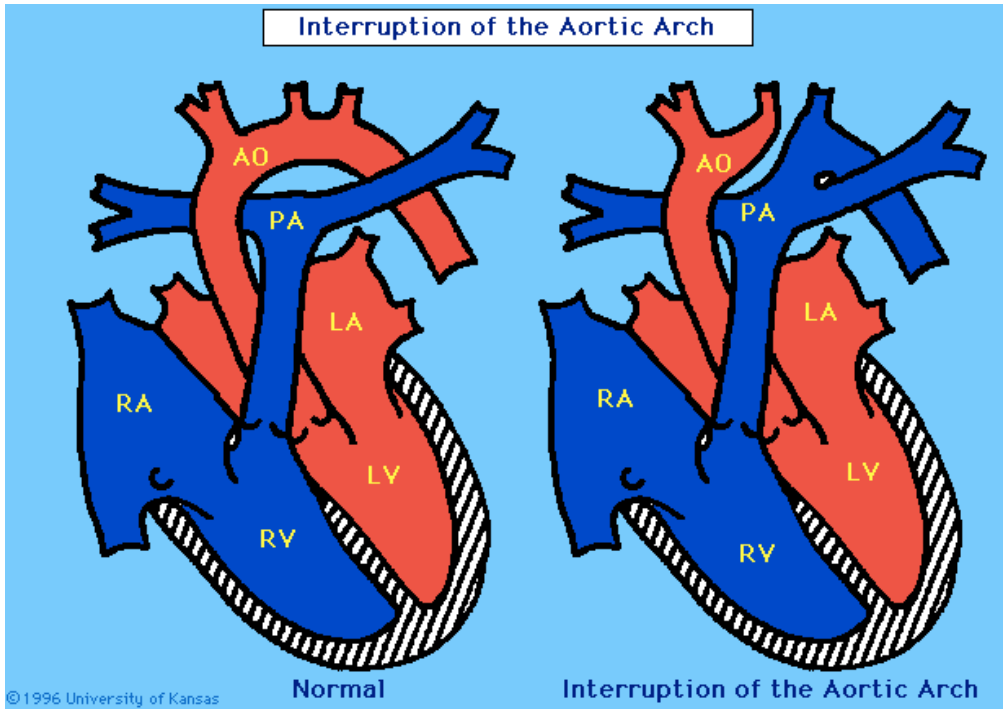
WISC results revealed (N = 366):

Classification	N	Mean FSIQ*	Standard Deviation
Total cohort	366	76.22	13.48
No consequential CHD	159	76.86	12.70
Simple CHD	97	78.74	11.95
Moderate CHD	82	73.06	15.91
Complex CHD	28	74.09	13.65

- No statistically significant difference in FSIQ in those with or without CHD
- *Perhaps the neurologic effect of 22q11.2DS supersedes the impact of cardiac surgical intervention on FSIQ*

Unolt 2018

If this is true than what are the benefits of early diagnosis?



Patient 1

- Diagnosed prenatally by fetal echocardiogram
- Started on prostaglandins
- Early surgery - complete repair
- Discharged to home
- Currently doing well

Courtesy of Michael Mitchell, MD - CHW

Patient 2

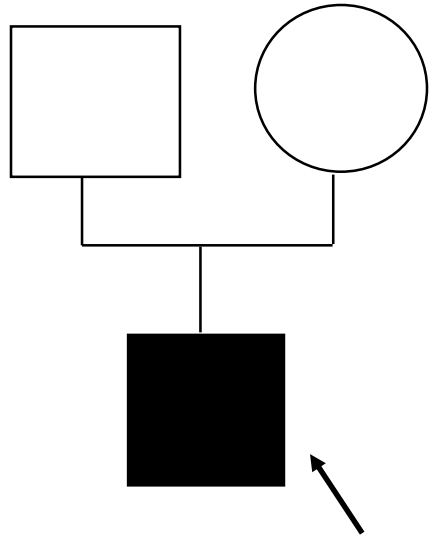
- No prenatal diagnosis
- Discharged on DOL 2
- Presented on DOL 9 extremely ill
  - Complicated resuscitation
  - Suffered a stroke
- Diagnosed with IAA and 22q11.2DS
- Multiple additional surgeries
- $750,000 in increased hospital charges over the first year of life

…and living with a **stroke**

Courtesy of Michael Mitchell, MD - CHW

Newborn in the CICU:

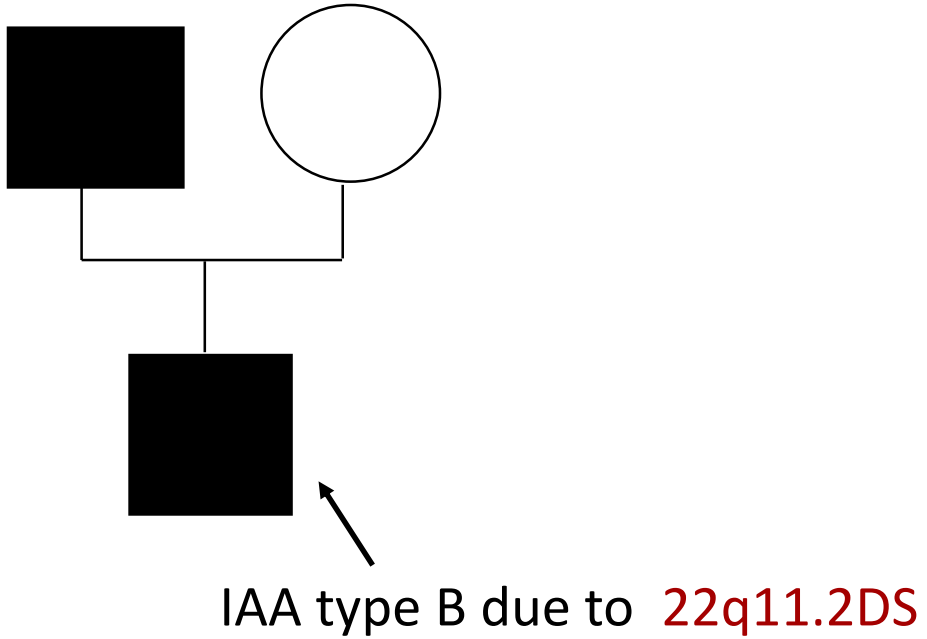
- Prenatal diagnosis of club foot and polyhydramnios
- Discharged to home
- Cyanosis on DOL 12
- Emergent transport
- Complicated resuscitation and diagnosis with CHD
- *Transferred to CHOP* → *IAA-B* → *22q11.2DS*
- Subsequent complex cardiac management and hypocalcemia



At the bedside - we met the family

Dad:

- Repaired heart defect
- Repaired cleft palate
- Learning disability



- *Parental studies confirmed paternal 22q11.2 deletion*
- *No previous concern based on his history*

Early diagnosis may improve the medical course

- May decrease morbidity and perhaps even mortality
- Concurrently reducing overall healthcare costs
- *Making 22q11.2DS a reasonable candidate for newborn screening*

Abnormal T-cells are bringing infants to attention via newborn screening for Severe Combined Immunodeficiency (SCID)

- Such as in a recent patient who presented with low T-cells but without SCID
- Immunology sent a microarray ⟶ 22q11.2DS (age 6 weeks)
- At diagnosis additional findings included:
  - Inguinal and umbilical hernia
  - Significant feeding difficulties with nasal regurgitation and GERD
  - *Calcium of 7.0 without frank seizures*
  - *Raising concerns for long term impact on the brain*

Jessica Barry, MS, LCGC

Kathleen Sullivan, MD, PhD

Barry 2017

Does hypocalcemia affect developmental outcome?

- U Toronto (N = 149)
  - Neonatal seizures +/- hypocalcemia predicted greater intellectual deficits regardless of CHD or brain malformations in adults with 22q11.2DS

- CHOP cohort with FSIQ and laboratory calcium levels (N = 265)
  - No difference in FSIQ with or without a history of hypocalcemia
    - *Hx of hypocalcemia (N=146) - Mean FSIQ 77.08*
    - *No hx of hypocalcemia (N=119) - Mean FSIQ 77.27*

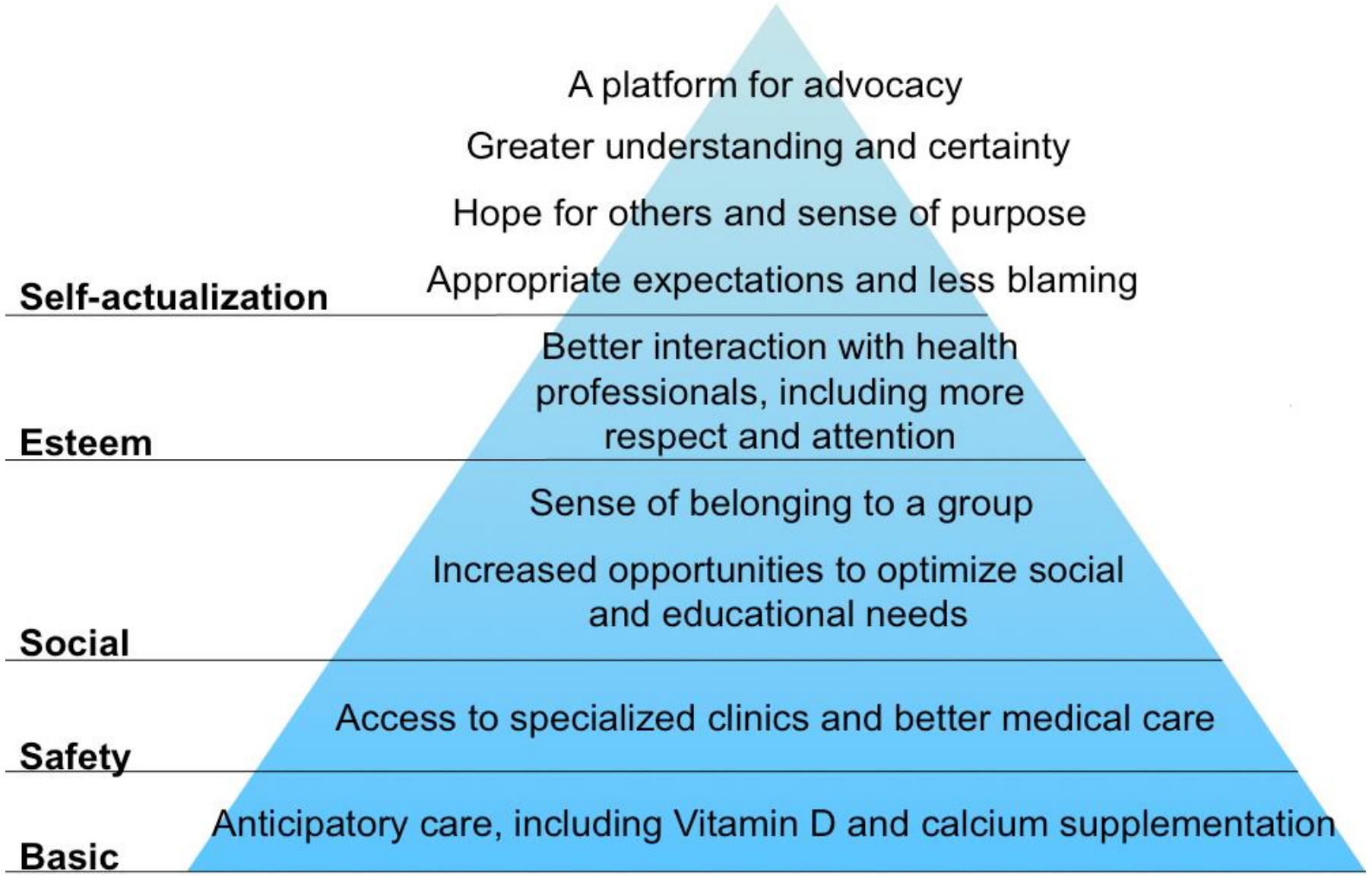
Katheryn Grand, MS, LCGC

Lorraine Katz, MD

- *Early treatment for hypocalcemia may protect the brain*
- *As seen in our patients followed at CHOP compared with the adult patients followed in Toronto*

Cheung, 2013; Grand 2018

Additional benefits of 22q11.2DS diagnosis



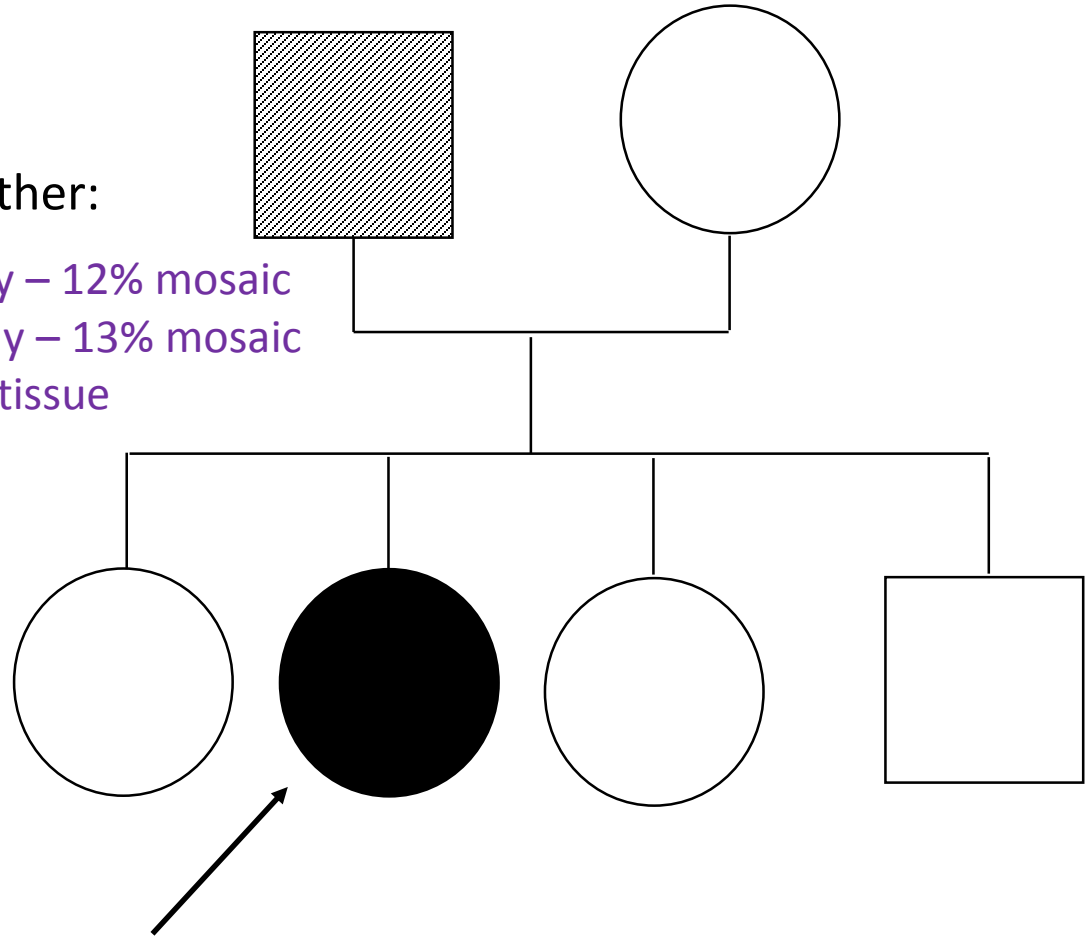
Costain et al., 2011

Important Genetic Counseling Considerations

Somatic mosaicism (some blood/other tissue cells with the deletion and some without) may be seen with 22q11.2DS

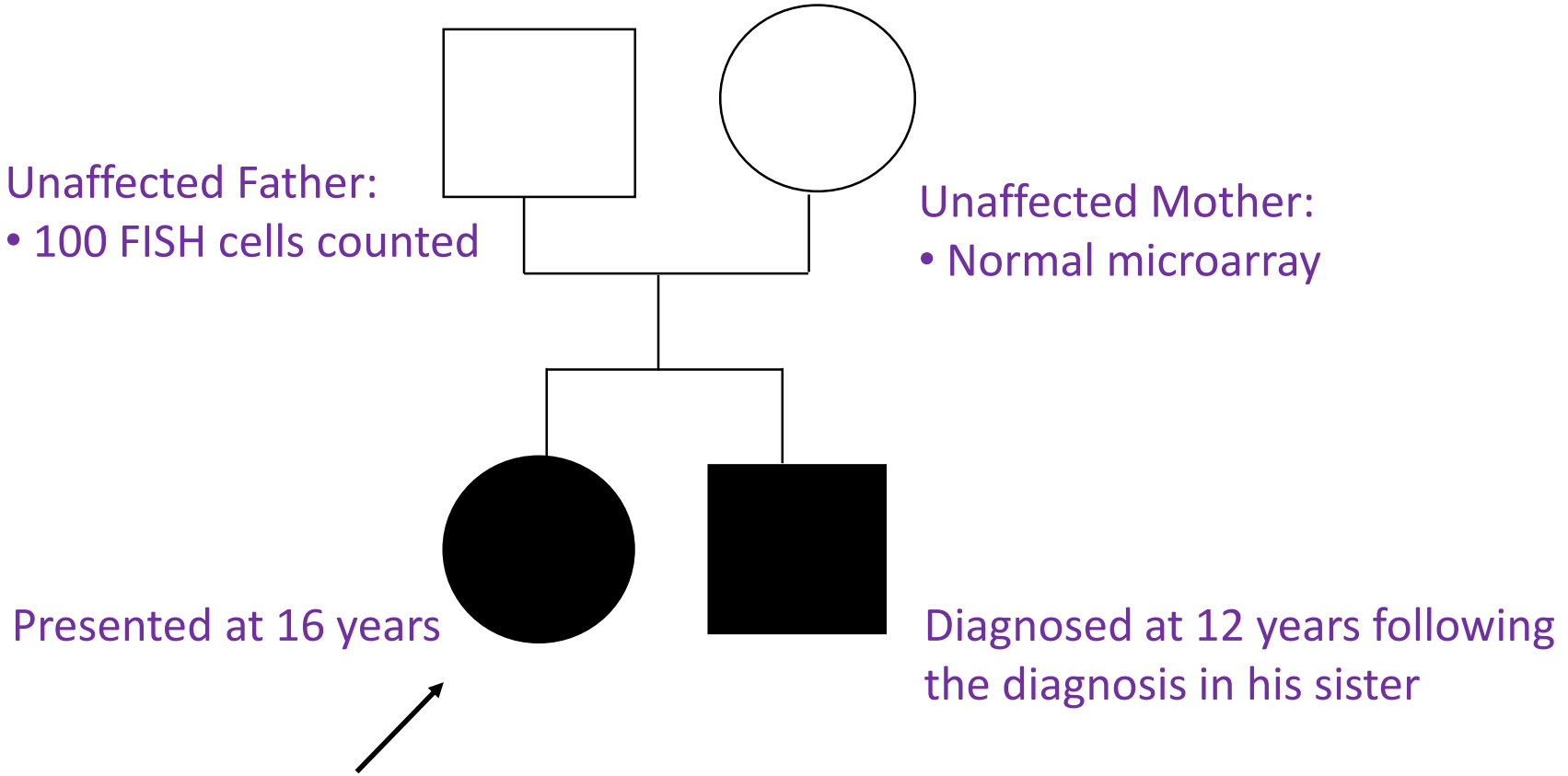
Unaffected Father:

- 1st Blood Study – 12% mosaic
- 2nd Blood Study – 13% mosaic
- No additional tissue



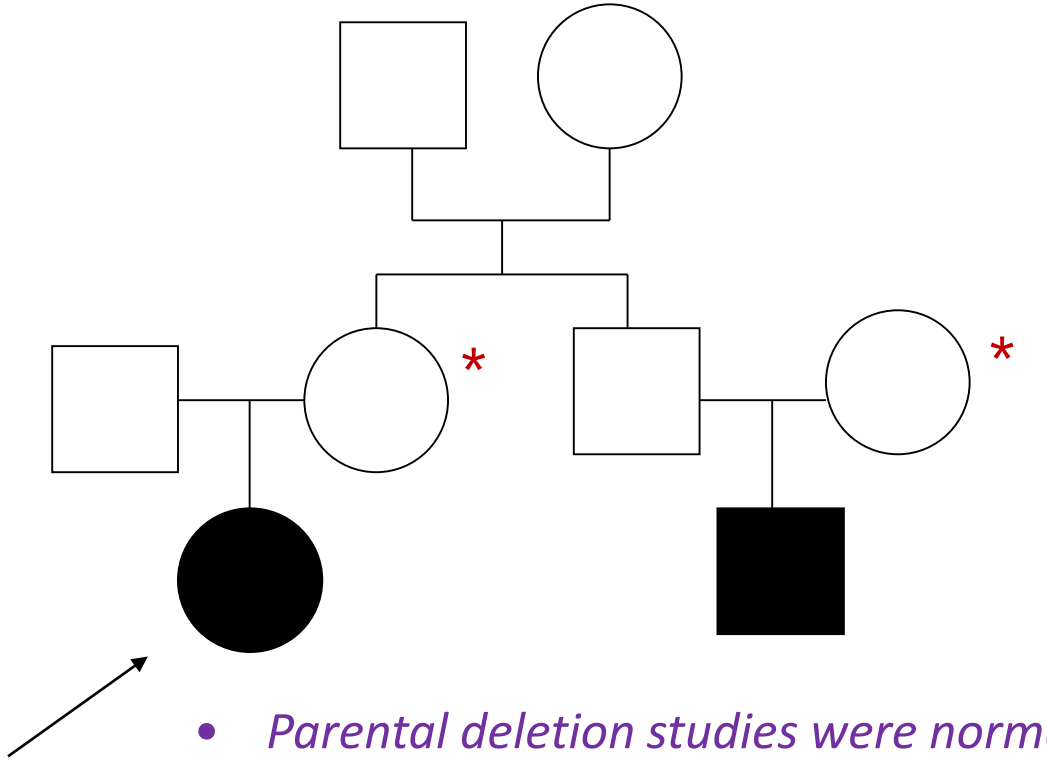
Supporting 22q11.2DS studies in all parents

Presumed germline mosaicism (22q11.2 deletion in some egg or sperm cells) has been reported to explain some families where two children have the deletion but parental studies are normal



Recurrence risk is close to zero but not zero

Familial occurrence by chance alone



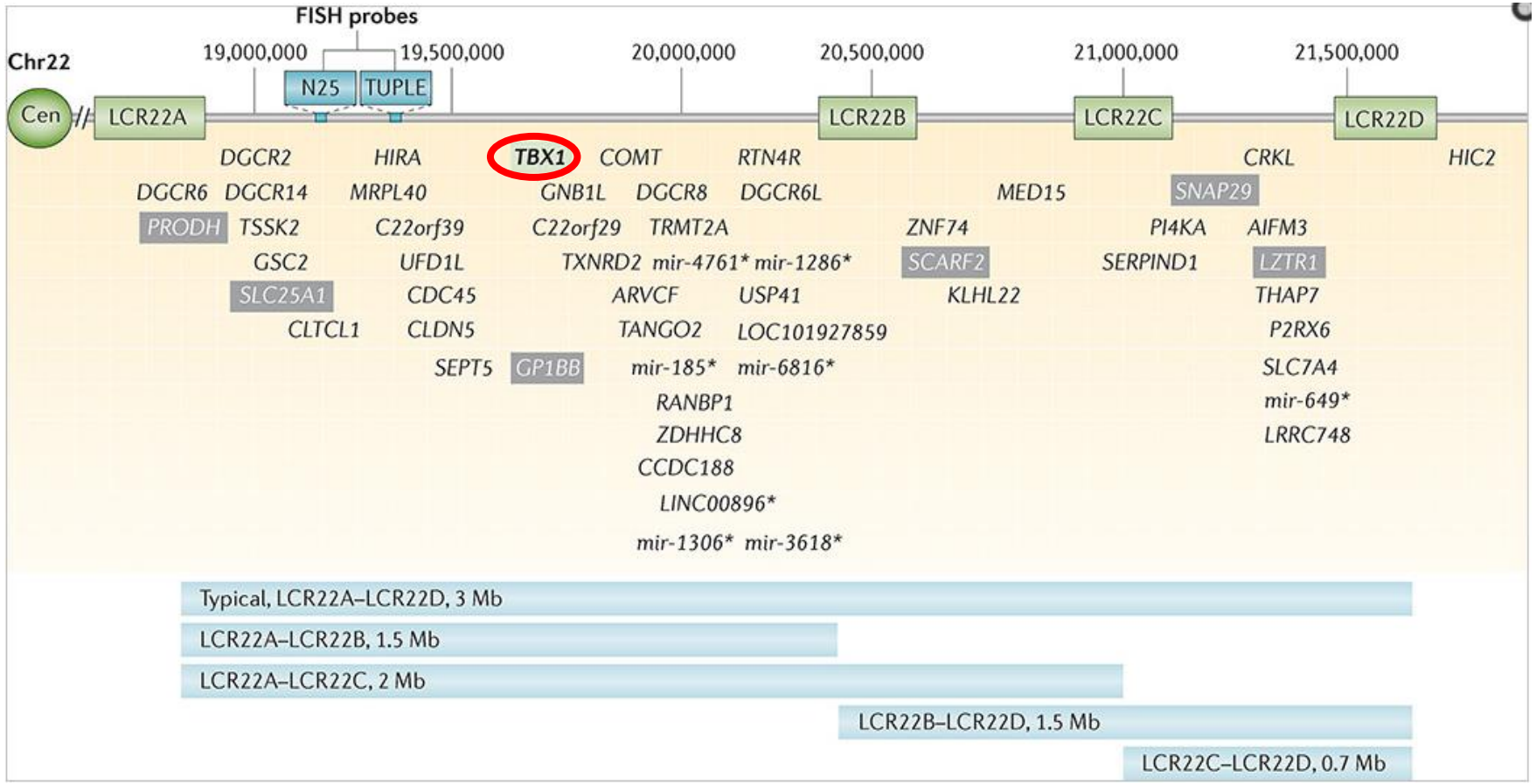
- *Parental deletion studies were normal*
- *Research parent of origin studies revealed that both deletions occurred in the egg cells of the unrelated mothers*
- *So it occurred in the two cousins by chance alone*

22q11.2DS is common

Saitta 2004

Features suggestive of 22q11.2DS due to a mutation in *TBX1*

- Consider in patients without a deletion but with typical features
- Negative MLPA/microarray



4 year old child – heart defect and hypocalcemia

- Birth history:
  - *Congenital heart defect (IAA-B)*
  - *22q11.2 deletion – normal by MLPA and microarray*
- Follow up in Plastic Surgery - hypernasal speech and developmental delay
- Genetics suggested *TBX1* and *CHD7* mutational analysis
- Positive *TBX1* mutation identified to explain findings

Illustrative Patients

Patient 1 - Diagnosed at 3 days of age - Tetralogy of Fallot

- At home twitching and jerking
- Hospitalized with seizures and a ? of a stroke
- Calcium of 4.7
- Diagnosis of 22q11.2DS
- Subsequently:
  - *Recurrent sinusitis and otitis – myringotomy tube placement*
  - *Significant T cell dysfunction - live viral vaccines held until 7 years*
  - *Speech/language delay, VPI – repaired*
  - *Enamel hypoplasia - dental procedures under GA x 3*
  - *Cervical, thoracic vertebral anomalies, Scoliosis – repaired*
  - *Recurrent hypocalcemia, Short stature, ITP, constipation*
  - *Intellectual deficits, dyslexia, significant anxiety, ADHD*
  - *Graduated High School – will remain until 21*
  - *Gold medal winner in Special Olympics*

Patient 2 - Diagnosed in infancy - complex heart defect

- Hypocalcemic seizures → 22q11.2DS
- Low platelets
- Overwhelming infection
- *Expired at 4 months of age*

Patient 3 - diagnosed in infancy - respiratory distress

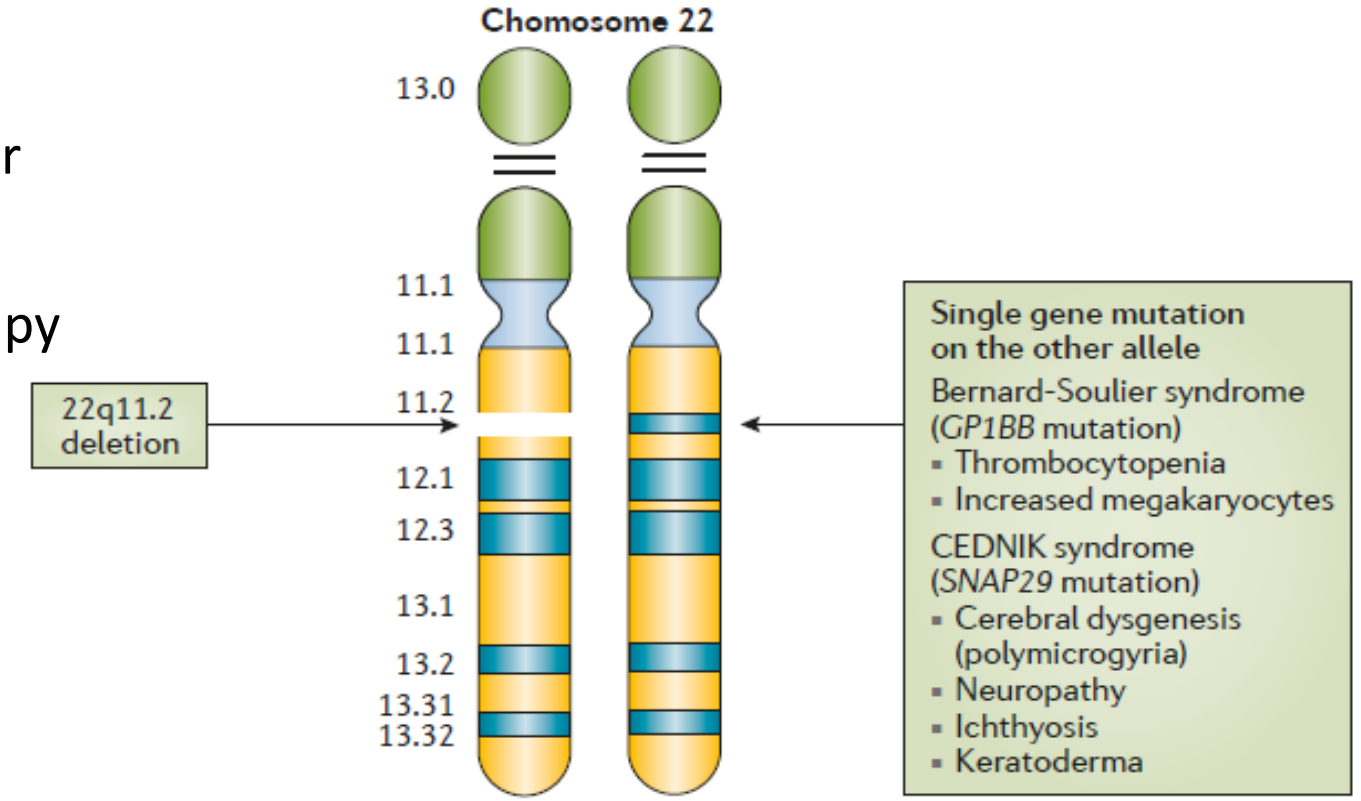
- Significant swallowing issues - tracheostomy and G-tube
- Hypocalcemia → 22q11.2DS
- Severe gastroesophageal reflux and chronic otitis media requiring IV antibiotics
- Short stature and Grave's disease
- *Mild motor and speech delay*

Patient 4 - Diagnosed in infancy with “failure to thrive”

- Severe reflux resulting in G-tube placement
- At 5 years - an atypical intestinal malrotation was identified and repaired
- Mild learning differences with an IQ in the average range
- ADHD and anxiety
- Graduated high school
- *College with accommodations*

Patient 5 - Diagnosed in infancy – cleft palate and reflux

- Sensorineural hearing loss
- Problems with his voice box and breathing tube
- Sleep apnea
  - *s/p tonsillectomy and adenoidectomy*
- Significant feeding problems
  - *G-tube placement*
- Bilateral inguinal hernia repair
- Cryptorchidism repair
- Chronic infection – IVIG therapy
- Structural brain difference
- *Age 11 years*
  - *Non-verbal*
  - *Non-ambulatory*



McDonald-McGinn 2013

Patient 6 - Diagnosed at 5 years

- Was “pokey” in the newborn period
- FTT, GERD, nasal regurgitation and chronic infection
- Delayed developmental milestones, particularly speech
- Evaluated by 27 specialists without a unifying diagnosis
- His two physician parents were relentless
- Growth hormone replacement therapy
- VPI repair
- *Difference in learning style and ADHD*

Patient 7 - Diagnosed at 32 years of age

- Following the birth of her child with complex CHD
- History of scoliosis and learning differences requiring a tutor
- *Master's Degree in Family Therapy*

Patient 8 - Diagnosed at 14 years of age due to a history of a congenital heart disease and a breathing tube problem

- Had a palate repair for hypernasal speech
- Attended private school without therapies and was admitted to college without entrance exam accommodations
- Statistics II - waived to allow graduation with a degree in Education
- Working continuously since graduation
- Recently married
- *Pursued Preimplantation Genetic Diagnosis due to concerns surrounding the chance of having a more severely affected child*
- *Recently had a healthy baby*

Patient 9, 10, 11 … coming to attention during pregnancy

- Often following Non-invasive prenatal screening
- Most with heart defects
- Some with additional abnormalities
- Difficult to prognosticate in utero with such broad variability
- Most parents feel that medical management is feasible
- Major concerns regarding
  - *Long term developmental outcome*
  - *Psychiatric illness*

How do we address such broad variability?

- Familiarity with the condition is the first step
- International 22q11.2 Consortium has developed pediatric and adult healthcare guidelines for management

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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**

REVIEW | Genetics inMedicine

Practical guidelines for managing adults with 22q11.2 deletion syndrome

Wai Lun Alan Fung, MD, ScD[1–4], Nancy J. Butcher, MSc[2,5], Gregory Costain, PhD[2,5], Danielle M. Andrade, MD, MSc[1,6], Erik Boot, MD, PhD[1–4,7], Eva W.C. Chow, MD, FRCPC[2,4], Brian Chung, MRCPCH, MBBS[8], Cheryl Cytrynbaum, MS, CGC[9], Hanna Faghfoury, MD[10], Leona Fishman, MD, FRCPC[9], Sixto García-Miñaúr, MD[11], Susan George, MD, FRCPC[1,12,13], Anthony E. Lang, MD, FRCPC[6,14], Gabriela Repetto, MD[15], Andrea Shugar, MS, CGC[9], Candice Silversides, MD, FRCPC[1,16,17], Ann Swillen, PhD[18,19], Therese van Amelsvoort, MD, PhD[20], Donna M. McDonald-McGinn, MS, CGC[21–23] and Anne S. Bassett, MD, FRCPC[1–5,12,17]

Highlights include:

- Treating what's treatable – including psychiatric illness
- Monitoring and treating endocrine manifestations
- Early Intervention, especially speech therapy
- Emphasizing that early diagnosis and effective treatment improve outcome
- *Both from a physical and a cognitive perspective*

(Practical Guidelines for Managing 22q11.2 Deletion Syndrome Journal of Pediatrics, 2011)

Several tables emphasize the multi-system nature of the disorder:

- Includes recommendations for assessment by age and at diagnosis
- Includes important cautions such as:
  - *"Removing the adenoids may worsen the hypernasal speech"*
  - *"Treatment for low calcium may cause kidney stones"*

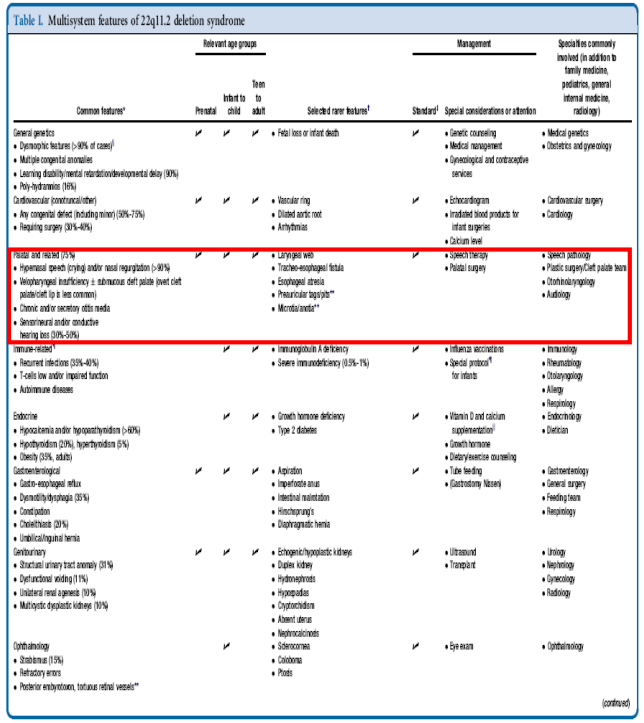


Table I. Multisystem features of 22q11.2 deletion syndrome

Common features*	Relevant age groups: Prenatal	Infant to child	Teen to adult	Selected rarer features†	Management: Standard‡	Special considerations or attention	Specialties commonly involved (in addition to family medicine, pediatrics, general internal medicine, radiology)
General genetics • Dysmorphic features (>90% of cases)§ • Multiple congenital anomalies • Learning disability/mental retardation/developmental delay (90%) • Poly-hydramnios (16%)	✓	✓	✓	• Fetal loss or infant death	✓	• Genetic counseling • Medical management • Gynecological and contraceptive services	• Medical genetics • Obstetrics and gynecology
Cardiovascular (conotruncal/other) • Any congenital defect (including minor) (50%–75%) • Requiring surgery (30%–40%)	✓	✓	✓	• Vascular ring • Dilated aortic root • Arrhythmias	✓	• Echocardiogram • Irradiated blood products for infant surgeries • Calcium level	• Cardiovascular surgery • Cardiology
Palate and related (75%) • Hypernasal speech (crying) and/or nasal regurgitation (>90%) • Velopharyngeal insufficiency ± submucous cleft palate (overt cleft palate/cleft lip is less common) • Chronic and/or secretory otitis media • Sensorineural and/or conductive hearing loss (10%–50%)	✓	✓	✓	• Laryngeal web • Trachea-esophageal fistula • Esophageal atresia • Preauricular tags/pits** • Microtia/anotia**	✓	• Speech therapy • Palatal surgery	• Speech pathology • Plastic surgery/Cleft palate team • Otorhinolaryngology • Audiology
Immune-related¶ • Recurrent infections (33%–40%) • T-cells low and/or impaired function • Autoimmune diseases		✓	✓	• Immunoglobulin A deficiency • Severe immunodeficiency (0.5%–1%)	✓	• Influenza vaccinations • Special protocol¶ for infants	• Immunology • Rheumatology • Otolaryngology • Allergy • Respiratory
Endocrine • Hypocalcemia and/or hypoparathyroidism (>60%) • Hypothyroidism (10%), hyperthyroidism (5%) • Obesity (33%, adults)		✓	✓	• Growth hormone deficiency • Type 2 diabetes	✓	• Vitamin D and calcium supplementation‖ • Growth hormone • Dietary/exercise counseling	• Endocrinology • Dietician
Gastroenterological • Gastro-esophageal reflux • Dysmotility/dysphagia (35%) • Constipation • Cholelithiasis (20%) • Umbilical/inguinal hernia	✓	✓	✓	• Agnosia • Imperforate anus • Intestinal malrotation • Hirschsprung's • Diaphragmatic hernia	✓	• Tube feeding • (Gastrostomy, Nasal)	• Gastroenterology • General surgery • Feeding team • Respiratory
Genitourinary • Structural urinary tract anomaly (31%) • Dysfunctional voiding (11%) • Unilateral renal agenesis (10%) • Multicystic dysplastic kidneys (10%)	✓	✓	✓	• Echogenic/hypoplastic kidneys • Duplex kidney • Hydronephrosis • Hypospadias • Cryptorchidism • Absent uterus • Nephrocalcinosis	✓	• Ultrasound • Transplant	• Urology • Nephrology • Gynecology • Radiology
Ophthalmology • Strabismus (15%) • Refractory errors • Posterior endyotoxon, tortuous retinal vessels**		✓		• Sclerocornea • Coloboma • Ptosis	✓	• Eye exam	• Ophthalmology

(continued)

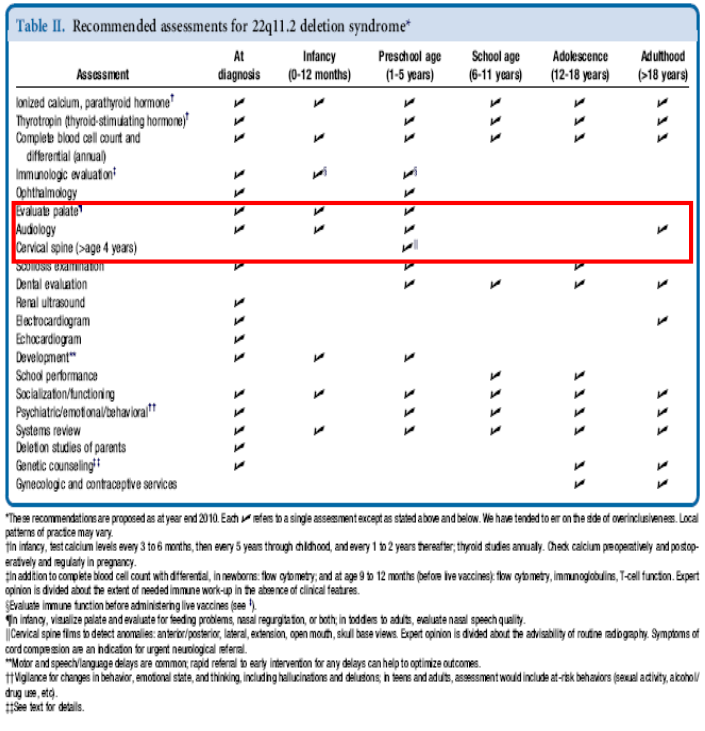


Table II. Recommended assessments for 22q11.2 deletion syndrome*

Assessment	At diagnosis	Infancy (0–12 months)	Preschool age (1–5 years)	School age (6–11 years)	Adolescence (12–18 years)	Adulthood (>18 years)
Ionized calcium, parathyroid hormone†	✓	✓	✓	✓	✓	✓
Thyrotropin (thyroid-stimulating hormone)†	✓		✓	✓	✓	✓
Complete blood cell count and differential (annual)	✓	✓	✓	✓	✓	✓
Immunologic evaluation‡	✓	✓§	✓§			
Ophthalmology	✓		✓			
Evaluate palate¶	✓	✓	✓			
Audiology	✓	✓	✓			✓
Cervical spine (>age 4 years)			✓‖			
Scoliosis examination	✓		✓		✓	
Dental evaluation			✓	✓	✓	✓
Renal ultrasound	✓					
Electrocardiogram	✓					✓
Echocardiogram	✓					
Development**	✓	✓	✓			
School performance				✓	✓	
Socialization/functioning	✓	✓	✓	✓	✓	✓
Psychiatric/emotional/behavioral††	✓		✓	✓	✓	✓
Systems review	✓	✓	✓	✓	✓	✓
Deletion studies of parents	✓					
Genetic counseling‡‡	✓				✓	✓
Gynecologic and contraceptive services					✓	✓

*These recommendations are proposed as at year end 2010. Each ✓ refers to a single assessment except as stated above and below. We have tended to err on the side of overinclusiveness. Local patterns of practice may vary.
†In infancy, test calcium levels every 3 to 6 months, then every 5 years through childhood, and every 1 to 2 years thereafter; thyroid studies annually. Check calcium pre-operatively and postoperatively and regularly in pregnancy.
‡In addition to complete blood cell count with differential, in newborns: flow cytometry; and at age 9 to 12 months (before live vaccines): flow cytometry, immunoglobulins, T-cell function. Expert opinion is divided about the extent of needed immune work-up in the absence of clinical features.
§Evaluate immune function before administering live vaccines (see ¶).
¶In infancy, visualize palate and evaluate for feeding problems, nasal regurgitation, or both; in toddlers to adults, evaluate nasal speech quality.
‖Cervical spine films to detect anomalies: anterior/posterior, lateral, extension, open mouth, skull base views. Expert opinion is divided about the advisability of routine radiography. Symptoms of cord compression are an indication for urgent neurological referral.
**Motor and speech/language delays are common; rapid referral to early intervention for any delays can help to optimize outcomes.
††Vigilance for changes in behavior, emotional state, and thinking, including hallucinations and delusions; in teens and adults, assessment would include at-risk behaviors (sexual activity, alcohol/drug use, etc).
‡‡See text for details.

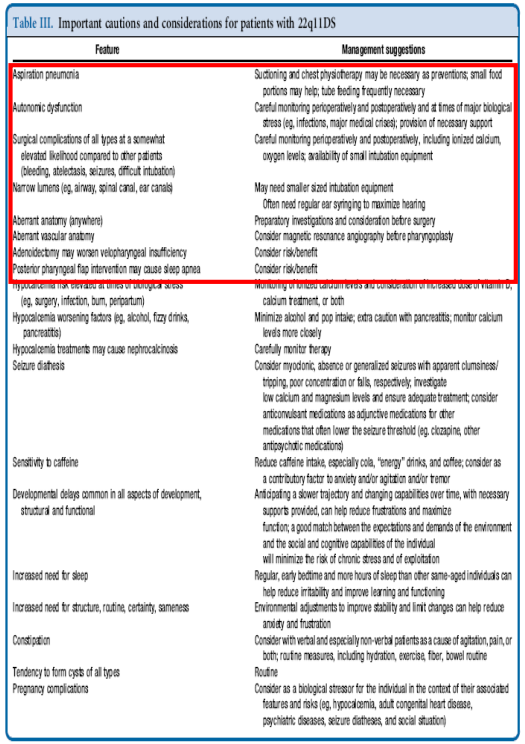


Table III. Important cautions and considerations for patients with 22q11DS

Feature	Management suggestions
Aspiration pneumonia	Suctioning and chest physiotherapy may be necessary as preventions; small food portions may help; tube feeding frequently necessary
Autonomic dysfunction	Careful monitoring perioperatively and postoperatively and at times of major biological stress (eg, infections, major medical crises); provision of necessary support
Surgical complications of all types at a somewhat elevated likelihood compared to other patients (bleeding, atelectasis, seizures, difficult intubation)	Careful monitoring perioperatively and postoperatively, including ionized calcium, oxygen levels, availability of small intubation equipment
Narrow lumens (eg, airway, spinal canal, ear canals)	May need smaller sized intubation equipment Often need regular ear syringing to maximize hearing
Aberrant anatomy (anywhere)	Preparatory investigations and consideration before surgery
Aberrant vascular anatomy	Consider magnetic resonance angiography before pharyngoplasty
Adenoidectomy may worsen velopharyngeal insufficiency	Consider risk/benefit
Posterior pharyngeal flap intervention may cause sleep apnea	Consider risk/benefit
Hypocalcemia risk elevated at times of biological stress (eg, surgery, infection, burn, peripartum)	Monitoring of ionized calcium levels and consideration of increased dose of vitamin D, calcium treatment, or both
Hypocalcemia worsening factors (eg, alcohol, fizzy drinks, pancreatitis)	Minimize alcohol and pop intake; extra caution with pancreatitis; monitor calcium levels more closely
Hypocalcemia treatments may cause nephrocalcinosis	Carefully monitor therapy
Seizure diathesis	Consider myoclonic, absence or generalized seizures with apparent clumsiness/tripping, poor concentration or falls, respectively; investigate low calcium and magnesium levels and ensure adequate treatment; consider anticonvulsant medications as adjunctive medications for other medications that often lower the seizure threshold (eg, clozapine, other antipsychotic medications)
Sensitivity to caffeine	Reduce caffeine intake, especially cola, "energy" drinks, and coffee; consider as a contributory factor to anxiety and/or agitation and/or tremor
Developmental delays common in all aspects of development, structural and functional	Anticipating a slower trajectory and changing capabilities over time, with necessary supports provided, can help reduce frustrations and maximize function; a good match between the expectations and demands of the environment and the social and cognitive capabilities of the individual will minimize the risk of chronic stress and of exploitation
Increased need for sleep	Regular, early bedtime and more hours of sleep than other same-aged individuals can help reduce irritability and improve learning and functioning
Increased need for structure, routine, certainty, sameness	Environmental adjustments to improve stability and limit changes can help reduce anxiety and frustration
Constipation	Consider with verbal and especially non-verbal patients as a cause of agitation, pain, or both; routine measures, including hydration, exercise, fiber, bowel routine
Tendency to form cysts of all types	Routine
Pregnancy complications	Consider as a biological stressor for the individual in the context of their associated features and risks (eg, hypocalcemia, adult congenital heart disease, psychiatric diseases, seizure diathesis, and social situation)

(Practical Guidelines for Managing 22q11.2 Deletion Syndrome Journal of Pediatrics, 2011)

Pregnancy is listed as a biologic stressor in women with 22q11.2DS

- Risk for new onset hypocalcemia
- Adult congenital heart disease related risks
- Risks related to treatment for underlying seizure disorders
- Associated autoimmune disease, e.g. platelet and thyroid disorders
- Problems associated with underlying psychiatric disease
- Social considerations such as the need for:
  - *Genetic counseling*
  - *Prenatal monitoring*
  - *Future preconception counseling*

Emphasizes that transition to adulthood requires a dedicated approach

- Individualized, multidisciplinary, coordinated care
- Recognizing that issues are chronic - requiring longitudinal management
- Multi-system nature and potential side effects of treatment demand attention by all clinicians – primary care providers and specialists
- *Requires an overall manager – Adult Medical Geneticist*

We recently launched our transition program

- Data on 13 patients
- Does not include patients already followed in the adult CHD clinic
- 6 adults are living independently with their own partners/children
  - *5/6 came to attention only following the birth of a child with CHD*
  - *Age 20 – 52 years*
- Remaining 7 patients reside within their childhood home
  - *Age 20 – 28 years*

Past Medical History (N=13)

- Only 7 patients came to attention independent of an affected relative although 9/13 had congenital heart disease
- 9 had a history of hypocalcemia - *Often post-operatively/post-partum*
- 6 continue to have chronic infection - *Primarily ear, sinus, skin*
- 6 had scoliosis - *4 requiring growing rod placement*

Past Medical History (N=13)

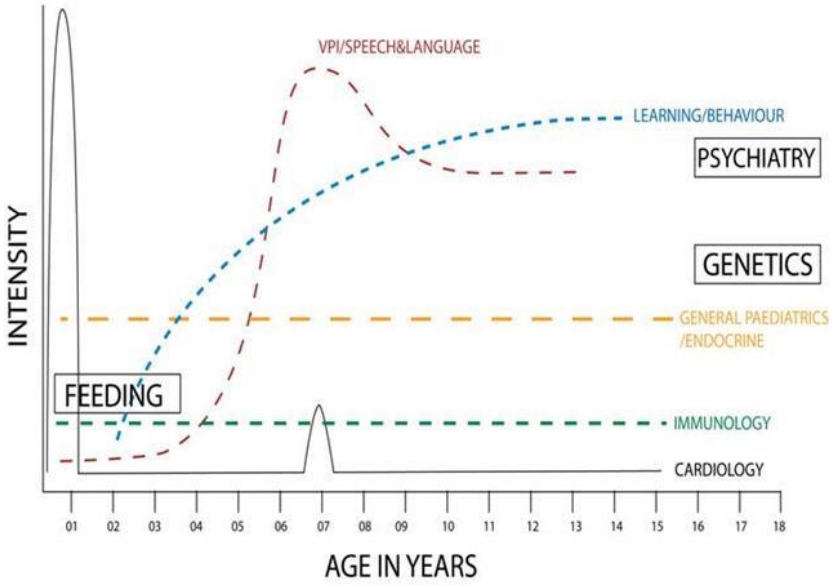
- 5 - anemic
- 4 - hypothyroid
- 4 - chronic constipation
  - *1 irritable bowel syndrome*
  - *1 gastric bypass*
- 3 - short stature (height <2%)
- 2 - adult onset seizure disorder
- 2 - renal abnormalities
  - *1 single kidney*
  - *1 horseshoe kidney*
- 2 - Type 2 diabetes mellitus
  - *Likely unrelated to 22q11.2DS*

Brain and behavior (N=13)

- History of a learning disability – 10 (77%)
- Graduated high school – 8 (62%)
- Graduated college/enrolled in college - 2
- Employed - 6 (46%)
- Stay at home moms – 2
- Anxiety – 5 (38%)
- ADHD – 4 (31%)
- Psychosis - 1

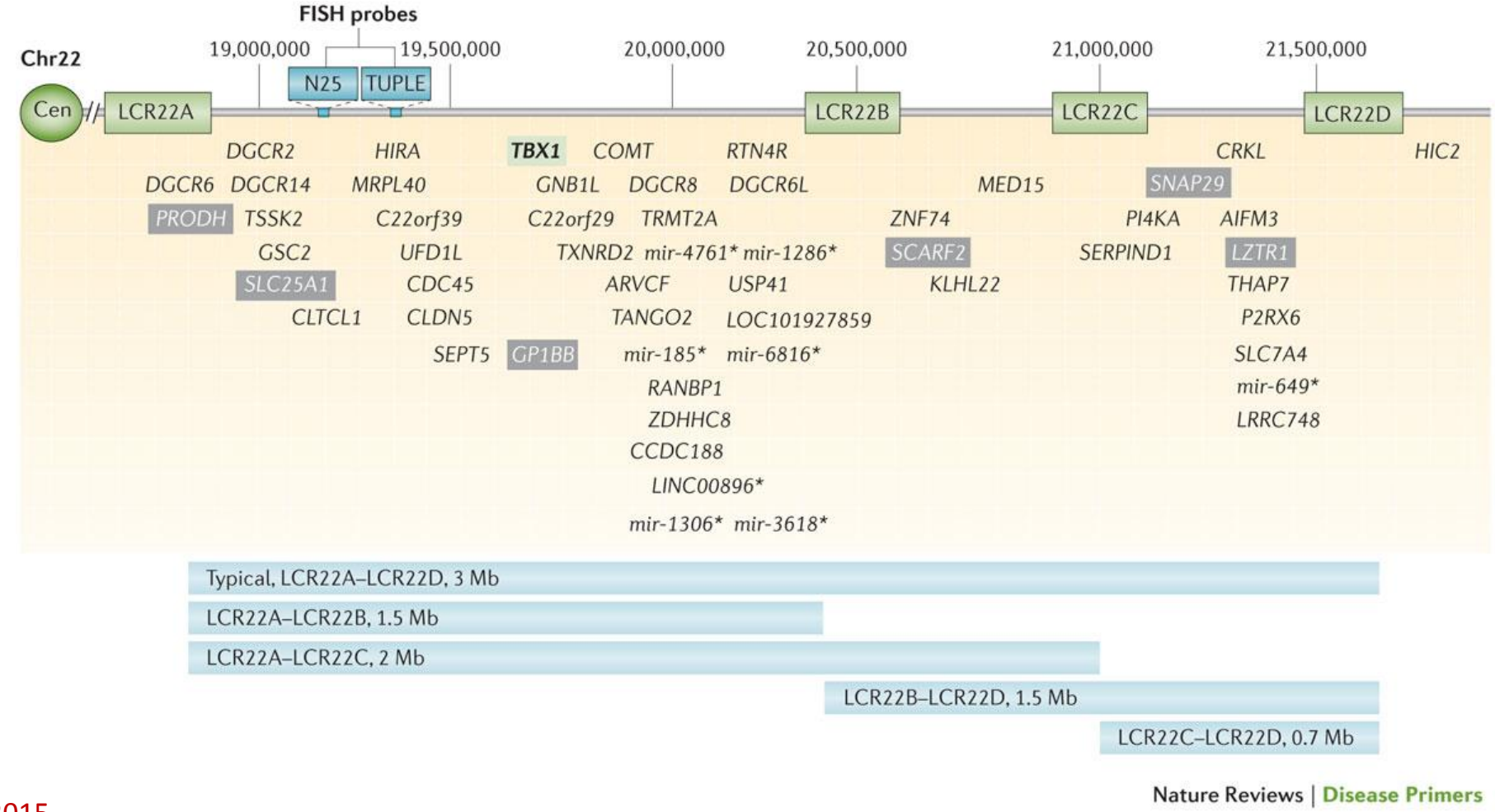
Anything to ameliorate the results of the 22q blueprint?

- Surgical procedures for structural differences, e.g. CHD
- Medical treatments, e.g. calcium, Vitamin D, antiepileptic's
- Early Intervention, cognitive and behavioral therapies across the lifespan



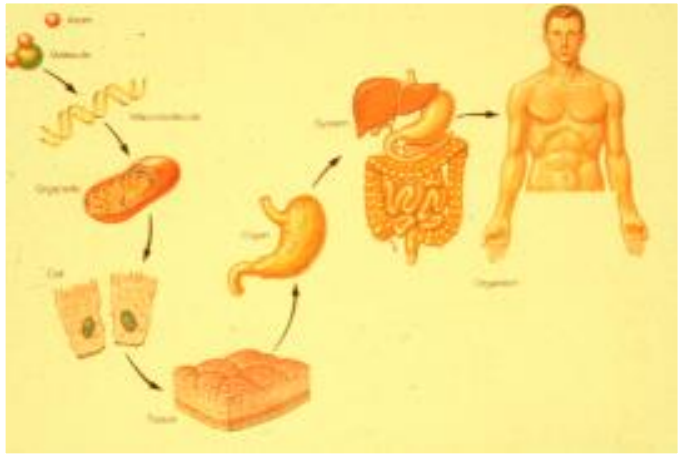
Can we target the brain?

Identify a gene/genes that affect an important brain pathway and a drug that will modify the pathway?



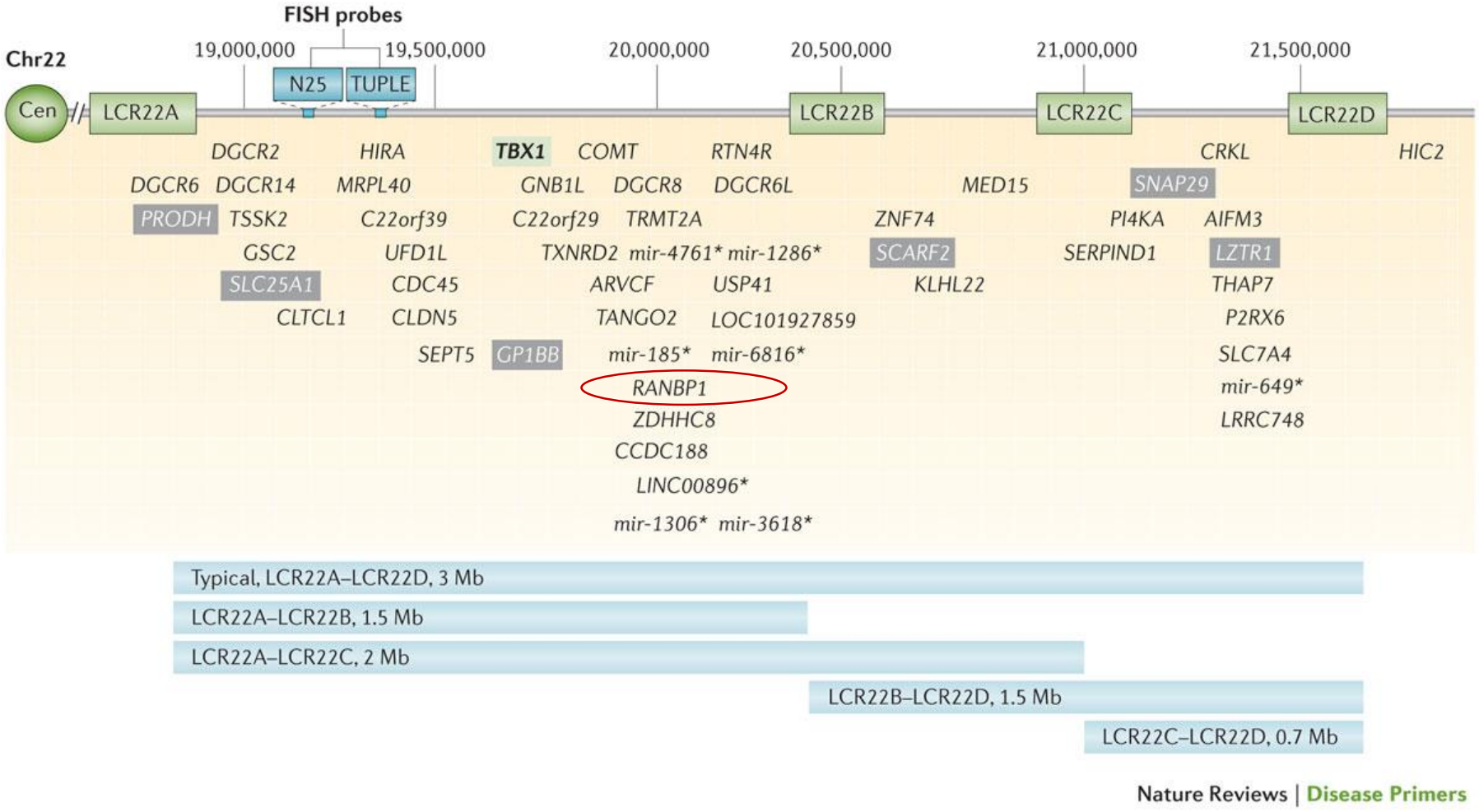
McDonald-McGinn 2015

Personalized or precision medicine for 22q11.2DS



Ongoing endeavors:

Partnering with Dr. Hakon Hakonarson in targeting the mGluR pathway (deletion of *RANBP1*) using a repurposed drug that impacts this pathway *(NFC1)* for treatment of associated behavioral differences



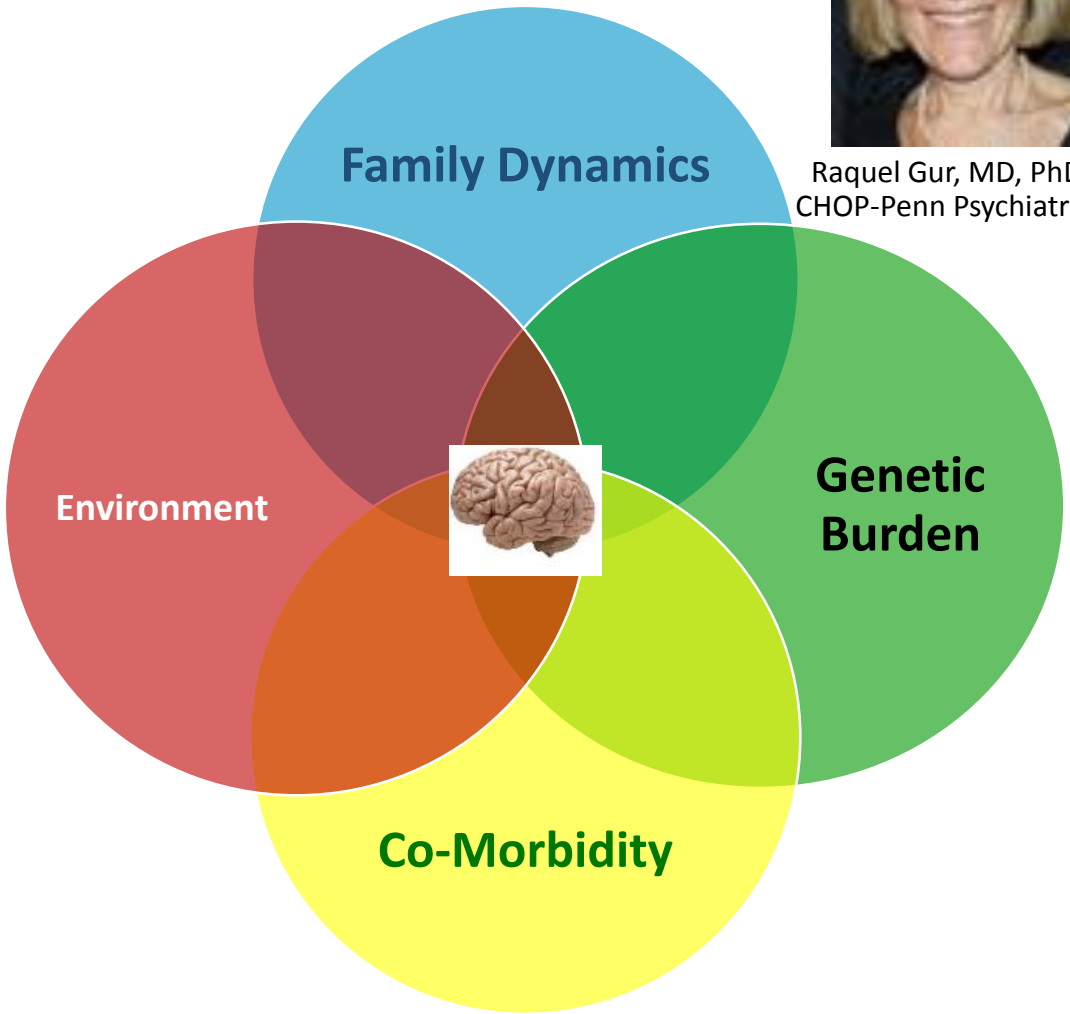
Hakon Hakonarson, MD, PhD
CHOP – Genetics and Pulmonary

Partnering with the International 22q11.2DS Brain and Behavior Consortium to examine genes outside of the 22q11.2 region

- Using data from 22 clinical sites and 5 genomic sites across 4 continents
- Led by Dr. Raquel Gur and myself

Raquel Gur, MD, PhD
CHOP-Penn Psychiatry

22q IBBC
International 22q11.2 Brain Behavior Consortium

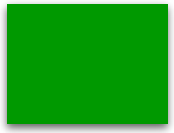


We have already examined possible associations towards predicting the onset of psychiatric illness

• Autism *(Vorstman 2013)*	No
• Intellectual level	?No
• Congenital heart defect	No
• Hypocalcemia *(Cheung under review)*	No
• Mood and anxiety disorders	No
• COMT gene on the other allele *(Murphy 1999; Bassett 2007, Franconi 2017)*	No
• Intellectual decline *(Vorstman 2015)*	Yes

But there is more work to be done…

Can we examine the collective influences on behavior?



Genetic Burden:

Deletion size, # of deletions/duplications outside of 22q, polygenic risk score, gender, modifier genes, other allele, parental genomic architecture, etc.

Co-Morbidities:

*CHD, **immune/autoimmune**, hypocalcemia, seizures, ID, etc.*

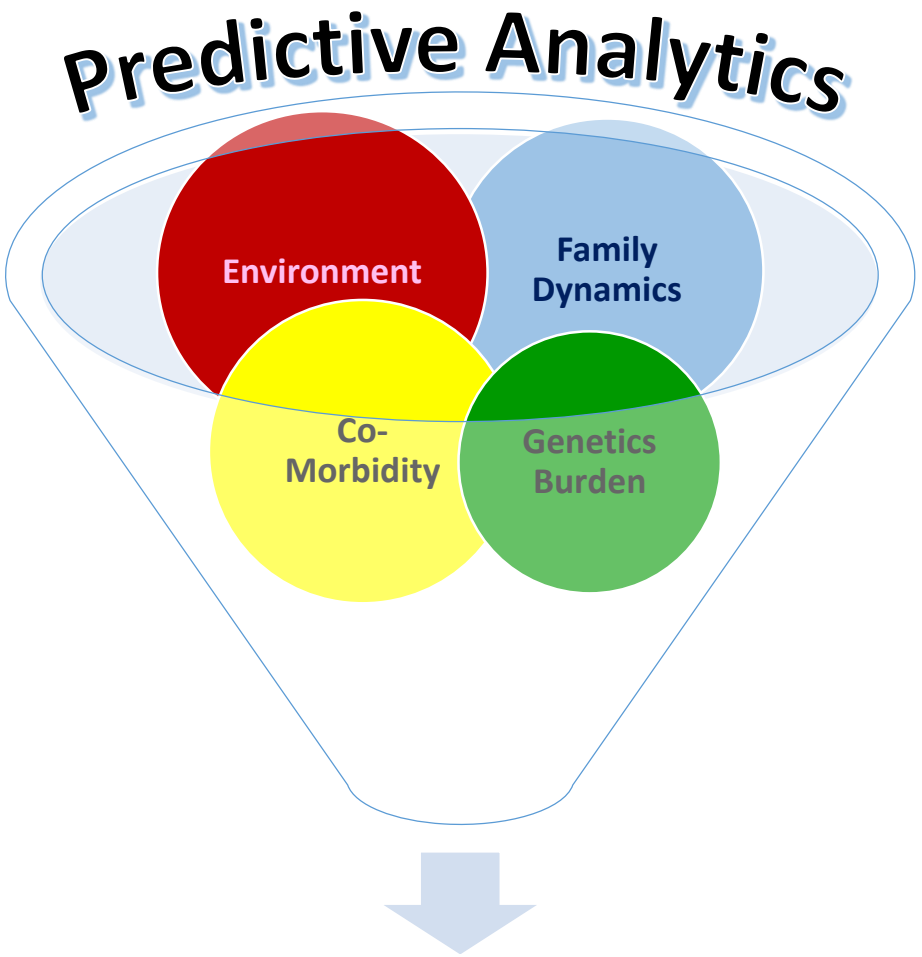
Environmental exposures:

# of anesthetics, geocode, medications, stress, etc.

Family Dynamics (Life Stressors):

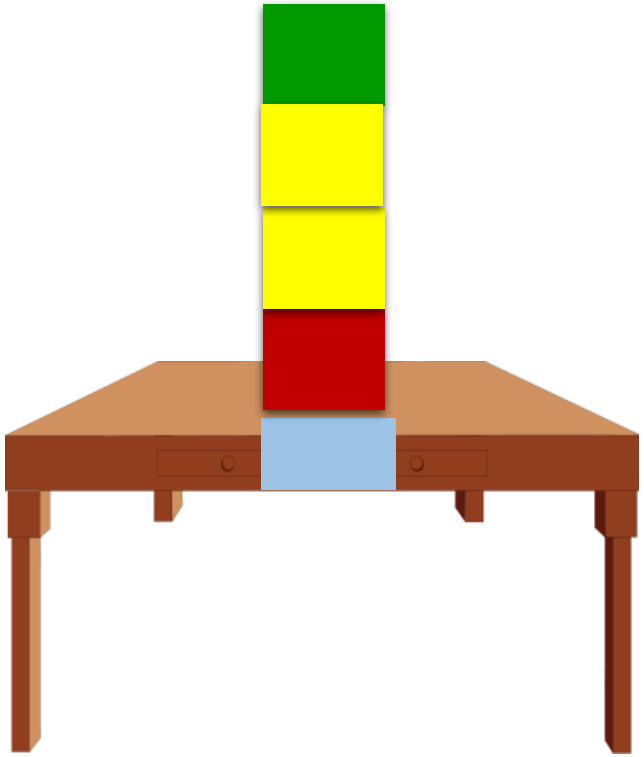
Familial deletion, adoption, parental LOE, socioeconomics, etc.

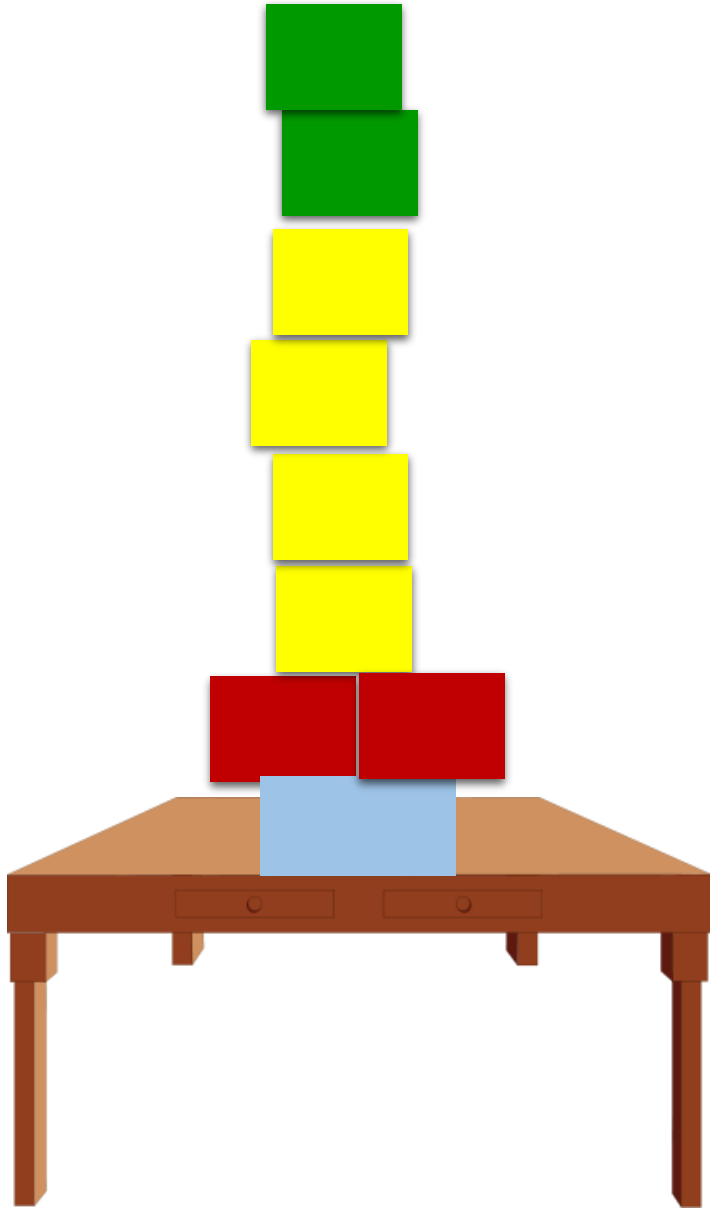
Allowing us to develop a risk assessment score?

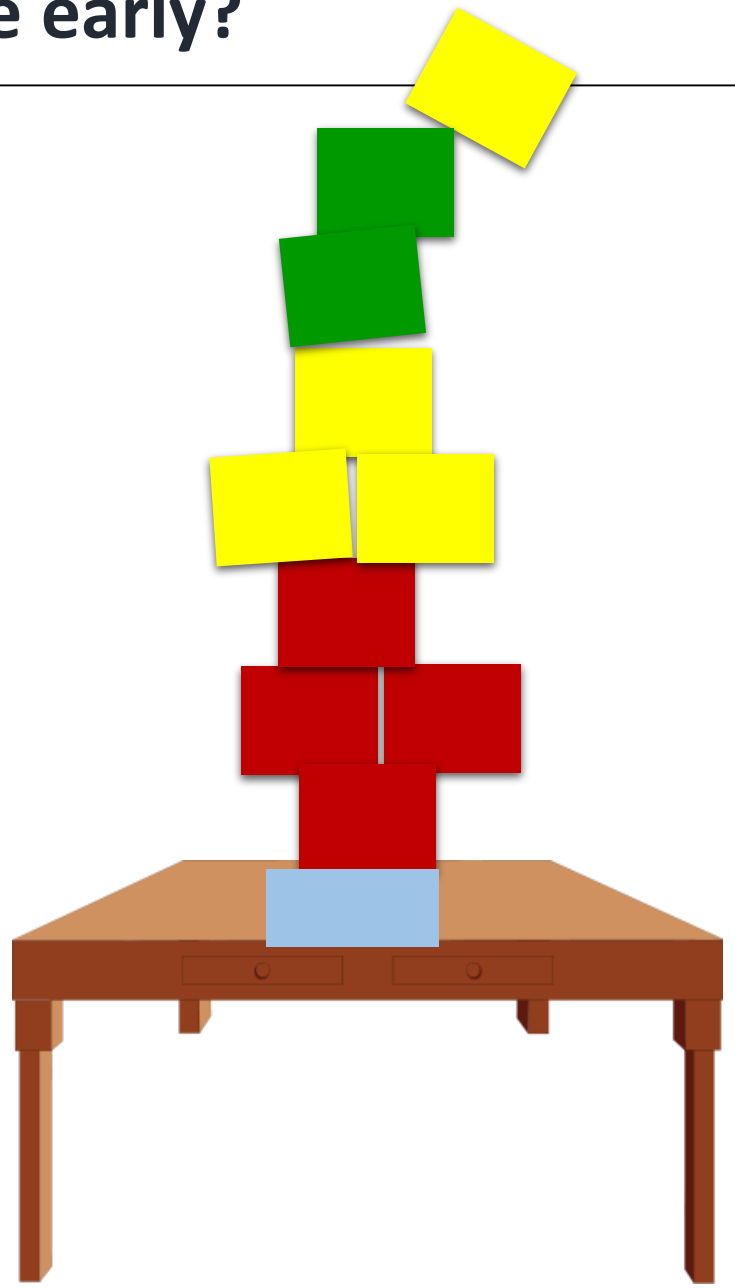


A Novel Predictive Brain Risk Score (BRISKS)

To identify individuals at risk and intervene early?





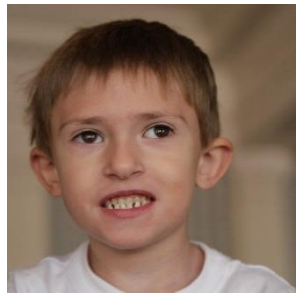


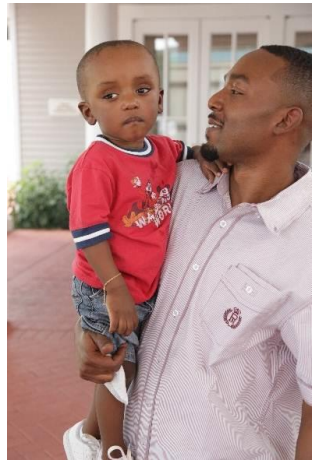
Possibly employ novel treatment approaches – including new medications

- And combining standard therapies with complimentary/integrative medicine
- Mindfulness, meditation, aromatherapy, yoga, anti-inflammatory diet, massage, and narrative medicine

Maria Mascarenhas, MD
CHOP- GI and Integrative Medicine

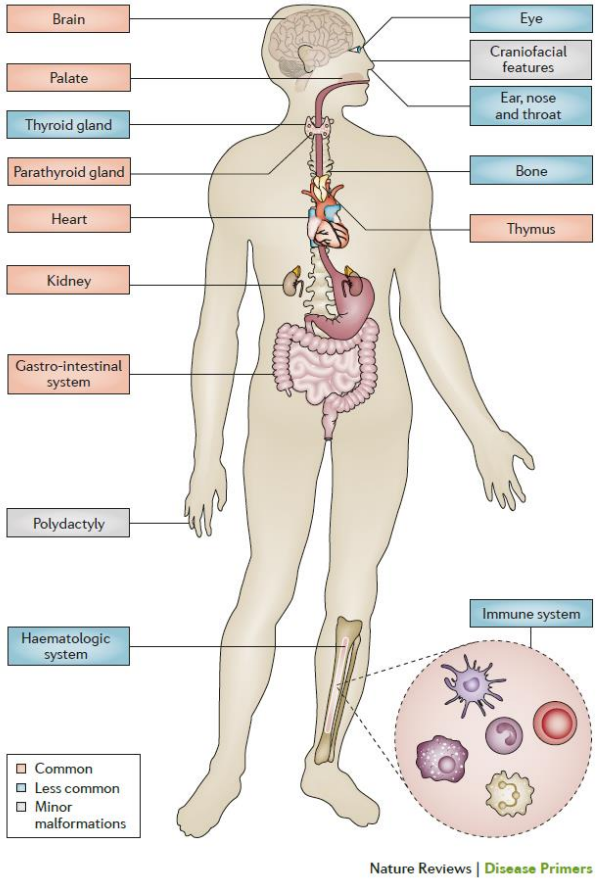
We are collectively hopeful that these and other new approaches will be successful in the near future





In summary:

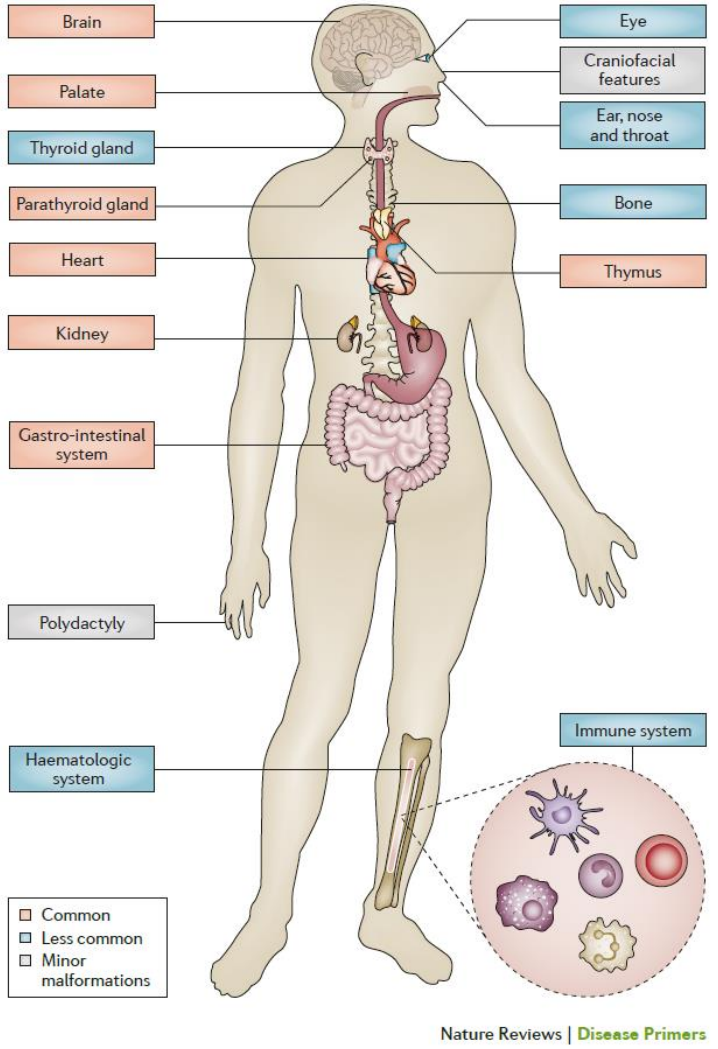
- 22q11.2DS leads to significant medical issues
- With multi-organ system involvement:
  - Congenital anomalies such as CHD
  - Immune, Endocrine and Gastrointestinal problems
  - *Variable cognitive deficits and psychiatric illness*



McDonald-McGinn 2015

Requiring input from healthcare providers in multiple settings

- Pediatrics
- Adult Medicine
- Oncology
- Prenatal Diagnosis
- Newborn Screening



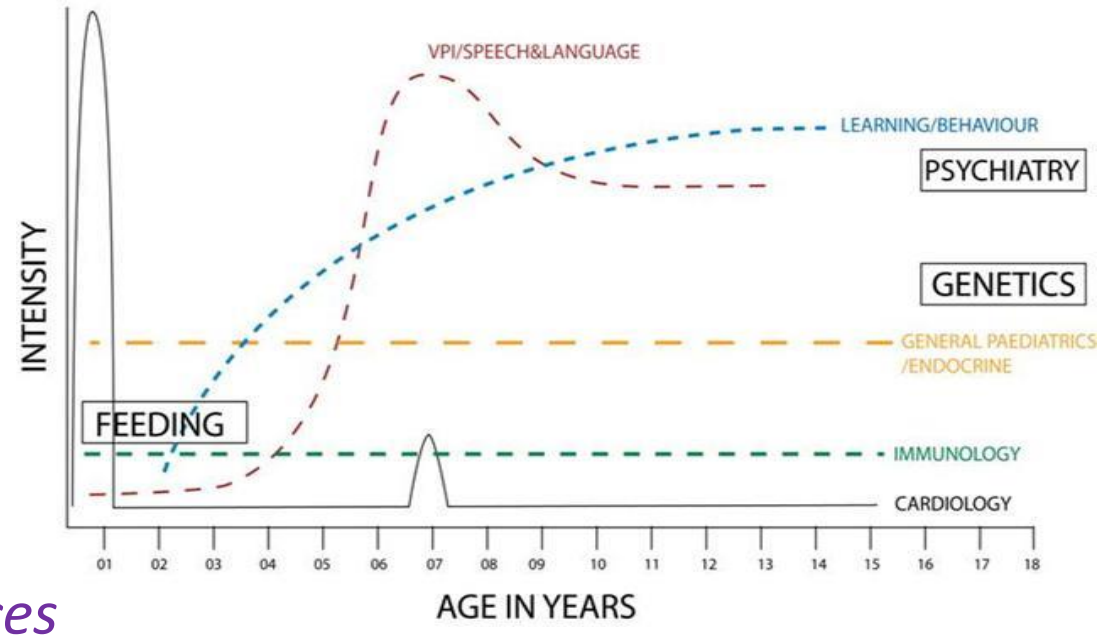
McDonald-McGinn 2013, 2015

22q11.2 deletion syndrome is common

- Most common cause of syndromic palatal anomalies
- 2nd most common cause of CHD and developmental differences after Down syndrome
- More common cause of tetralogy of Fallot than Down syndrome

Presence and severity of features varies by age – focus changes

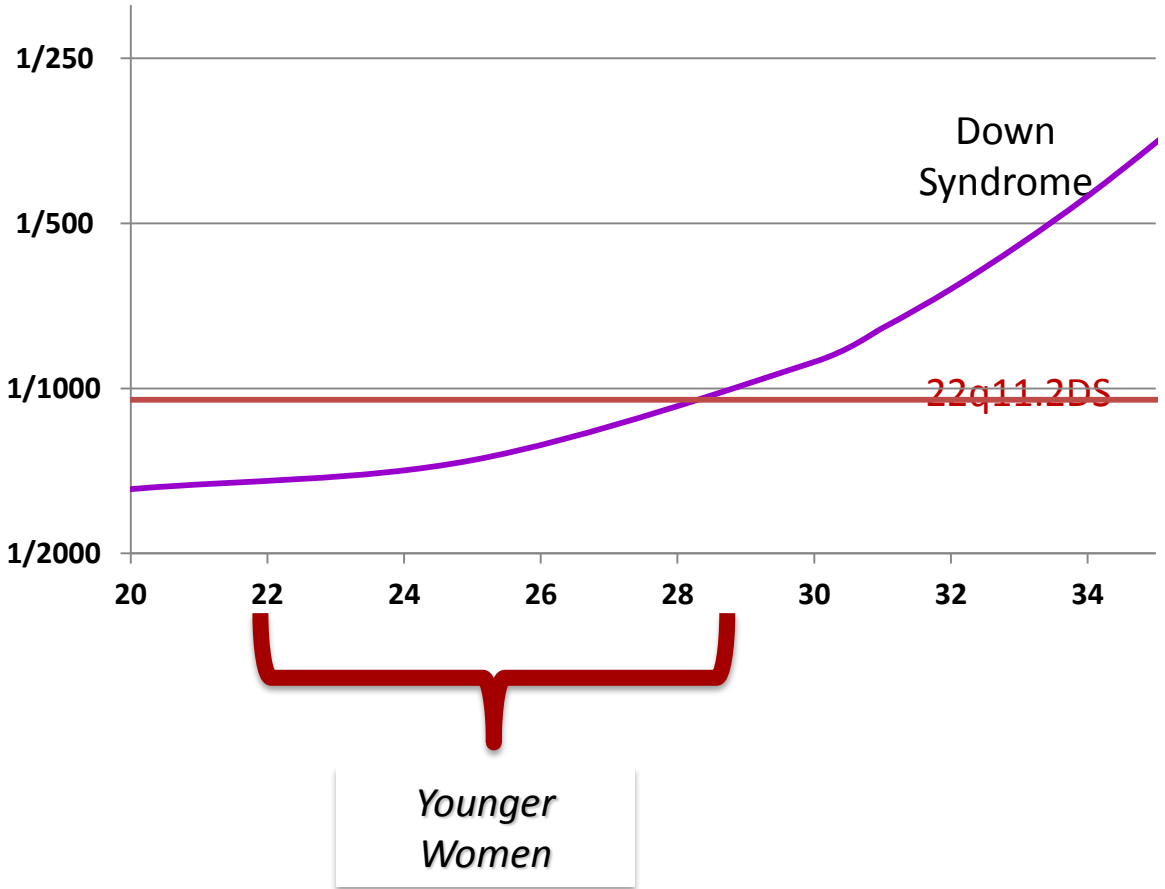
- Infancy and early childhood:
  - *Attention to birth defects, associated medical issues, motor milestones, speech and language*
- School age:
  - *Academics and peer relations*
- Adolescents and adulthood:
  - *Independence, behavioral differences and recurrence risk*



Habel 2012

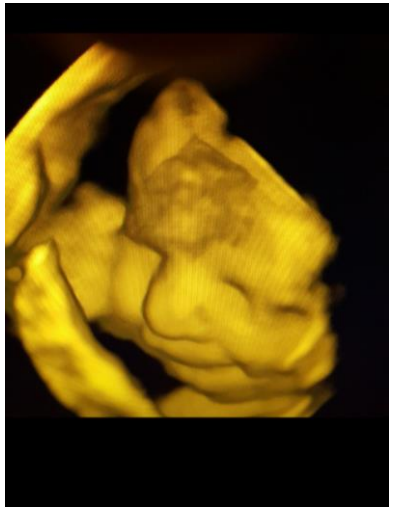
22q11.2DS is not related to advanced maternal age:

- Affected offspring are equally likely to be born to young mothers as to those with Advanced Maternal Age



Wide variability hampers early diagnosis – pre and postnatally

- Delaying interventions and leading to poorer prognoses
- Sending families and healthcare providers on a diagnostic odyssey
- *Conversely - early diagnosis including in the prenatal or neonatal setting offers medical and emotional preparedness*
- *Concurrently reducing costs medically, emotionally and fiscally related to late or missed diagnoses*



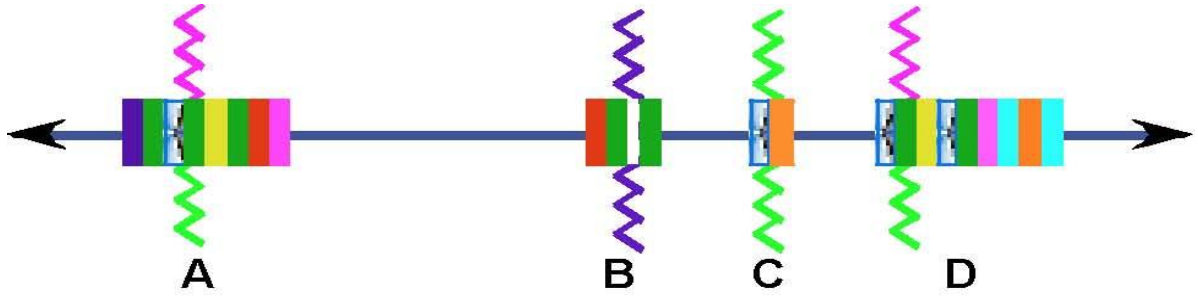
22q11.2 Duplication Syndrome

We have evaluated 150 patients with a 22q11.2 Duplication

- Age range – 20 weeks in the pregnancy to 63 years
- Mean age – 8.1 years
- 63% males

Majority of duplications are A-D but there are more nested duplications than deletions

Duplication Size (N=121)	Prevalence
A-D	67%*
A-B	5%
A-C	2%
B-D	7%
C-D	12%
Dups extending beyond LCR D (A-F [2], A-H, C-E [2]**)	6%
Dups within LCR A	2%



Clinical indications for testing most frequently include developmental differences

Reasons for referral (N=121)	Percentile
Developmental delay	56%
Heart defects (TOF, HLHS, VSD)	16%
Autism	13%
Growth differences (LGA, FTT, short stature)	9%*
Neurologic issues (seizures, microcephaly, macrocephaly)	6%
Palate abnormalities (VPI, cleft palate, cleft lip and palate)	5%
Mild differences in facial features	5%
Hearing loss	2%
ADHD	1%
Family history of 22q11.2 duplication	28%

Associated features overlap with 22q11.2 deletion syndrome but with less frequency

Feature	Prevalence
Neurologic (seizures, hypo/hypertonia, macrocephaly, microcephaly, balance and coordination difficulties, structural brain differences)	62%
GI (GERD, dysphagia, chronic constipation, FTT, hepatomegaly, splenomegaly, colitis, eosinophilic esophagitis, mega colon, hiatal and umbilical hernia)	62%
ENT (chronic otitis, sensorineural/conductive hearing loss, laryngomalacia, chronic epistaxis, complete tracheal ring, tracheal stenosis, pyriform aperture stenosis)	58%
Endocrine (short stature, overgrowth, obesity, hypocalcemia, hypothyroid)	48%
Heart (TOF, truncus arteriosus, ASD, VSD, HLHS, subvalvular aortic stenosis)	41%
Bones (Hemihypertrophy, joint laxity, C-spine anomalies, scoliosis, patellar dislocations, radioulnar dysostosis, pectus excavatum, clinodactyly, 2-3 syndactyly, broad digits)	32%
Immune (chronic infection, low immunoglobulins) and **GU** (cryptorchid, hypospadias, inguinal hernia, reflux, duplicated collecting system, hypoplastic kidneys)	32%
Palate (overt cleft palate, CLP, SMCP, VPI, bifid uvula, high narrow palate)	28%
Blood (easy bruising, thrombocytopenia (low platelets), leukocytopenia, lymphocytopenia)	20%

Growth appears to be an important feature

Measure	Percentile
Height >90th	22%
Height <10th	22%
Weight >90%	24%
Weight <10%	19%

~50% of patients were above or below the average curve for height and weight

Most patients who were diagnosed first in their families had developmental differences (86%)

Finding	Percentage
Overall Developmental Issues	86%
Speech/Language	76%
Motor	70%
Overall Behavioral	76%
Autism	24%
ADHD	26%
PDD	16%
Anxiety	10%
Sleep Disturbance	7%
Other (depression, psychosis, ODD, OCD)	Single patients

Males were more likely to have developmental delay and autism

Gender	Overall developmental differences	Overall behavioral differences	PDD	Autism
Males	94%	77%	25%	38%
Females	78%	82%	18%	8%

A subset of patients had formal IQ testing (N = 22)

- Mean FSIQ – 92.8 +/- 16.3
- Falling primarily in the average range (a FSIQ of 100)

Most 22q11.2 duplications are familial

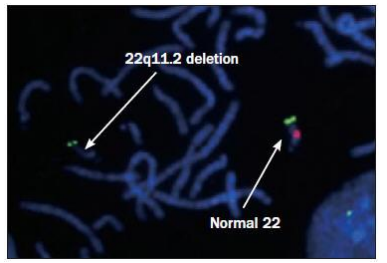
- 76/121 (where we had both parents available to test) **(63%)**
- 51% - paternally inherited
- Most parents had no associated features
- *Making it difficult to prognosticate for the child or make a consistent plan for follow-up*

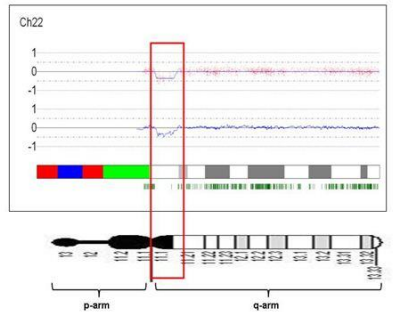
In summary

- Patients with 22q11.2 duplications are being referred to 22q centers for care
- Often with features of 22q11.2 deletion syndrome
- Often with growth differences
- But without any published guidelines as to how the patients should be followed
- We are currently following patients like those with the deletion until more data becomes available

So while time has marched on - from FISH to microarrays to WGS

- We have made great strides in understanding 22q11.2 deletion and duplication syndromes and in helping patients and families
- *But there is always more work to be done*



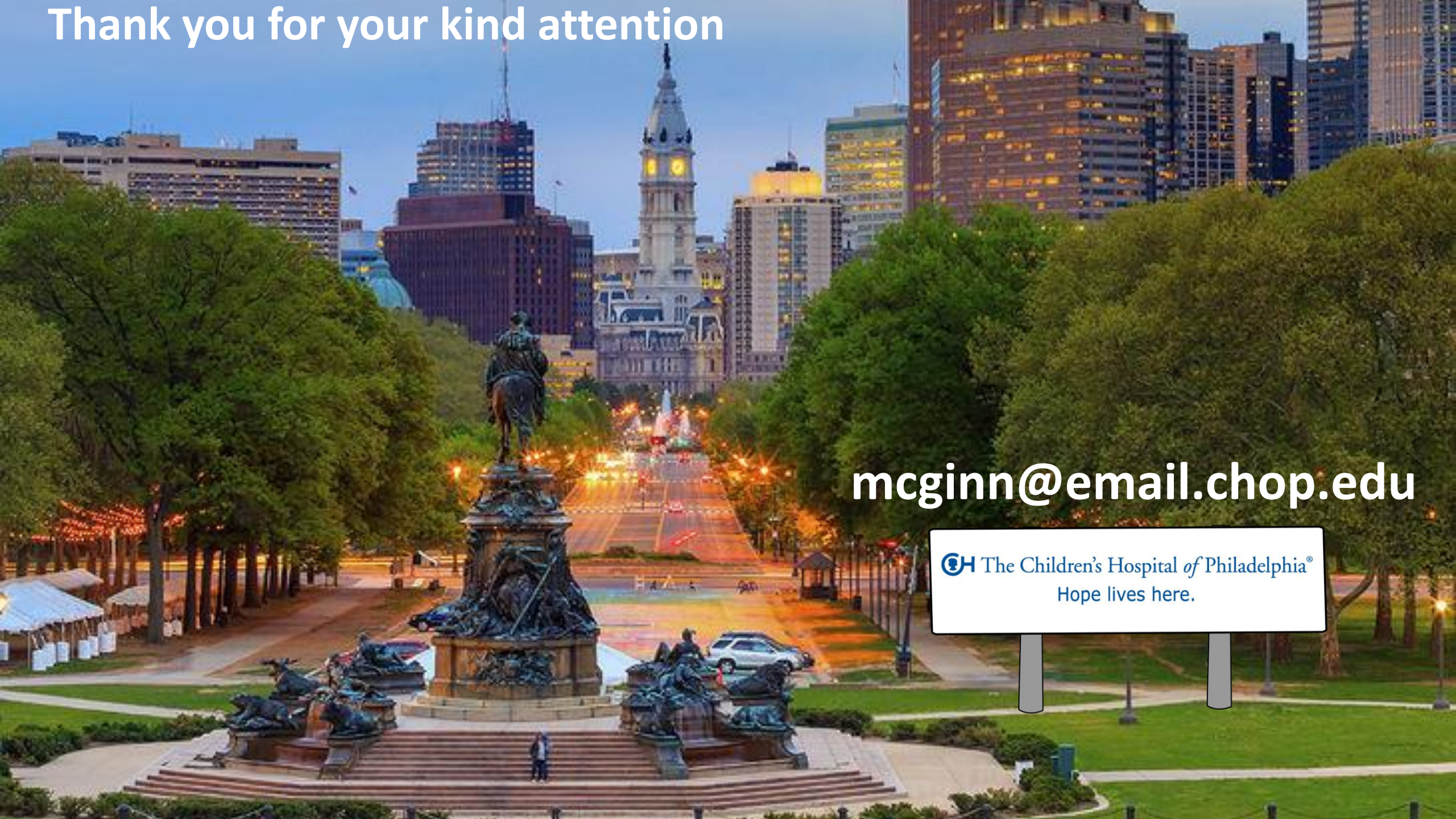


Thank my collaborators at CHOP and around the globe because it takes a village to care for a patient with 22q11.2DS

Thank the patients and families for everything they've taught us…

…because it always begins with a patient

Join families for
22q at the Zoo – Worldwide Awareness Day

May 19, 2019
Coming to a zoo near you
www.22q.org

Thank you for your kind attention