DIGEORGE SYNDROME: BED TO BENCH TO BED

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DISCLOSURE INFORMATION

I have no financial relationships to disclose

OBJECTIVES

- 1. To introduce the audience to previous phenotypes of DiGeorge Syndrome
- 2. To introduce the audience to the translational genotype of DiGeorge Syndrome chromosome 22Q11.
- 3. To introduce the audience to the expanded phenotype using the genotype of DiGeorge Syndrome.
- 4. To introduce the audience to the concept of "Bed to Bench to Bed"

"WHAT'S IN A NAME": AT THE BED

- DiGeorge syndrome (DGS)
- DiGeorge anomaly
- Velo-cardio-facial syndrome
- Shprintzen syndrome
- Conotruncal anomaly face syndrome
- Strong syndrome
- Congenital thymic aplasia
- Thymic hypoplasia

HISTORICAL SIGNIFICANCE

- Dr. Angelo M. DiGeorge in the mid-1960's presented his ground breaking discovery of a disorder characterized by
  - Congenital absence of the thymus, resulting in immunodeficiencies
  - Hypoparathyroidism, which results in hypocalcemia
  - Conotruncal heart defects (i.e., tetralogy of Fallot, interrupted aortic arch, ventricular septal defects, vascular rings)
  - Cleft lip and/or palate

HISTORICAL SIGNIFICANCE

- In the 1970s, Robert Shprintzen, PhD, a speech pathologist, described a group of patients with similar clinical features including :
  - cleft lip and/or palate,
  - conotruncal heart defects,
  - absent or hypoplastic thymus,
  - and some with hypocalcemia.
- Dr. Shprintzen named this group of features velo-cardio-facial syndrome, but the syndrome was also referred to as Shprintzen syndrome.

ORIGINAL PHENOTYPE

- Dr. Angelo DiGeorge identified multiple children with a congenital absence of a thymus, concurrent absence of parathyroid glands, and anomalies of the aortic arch which gave rise to his namesake: DiGeorge Syndrome.
- DiGeorge syndrome includes a pattern of more than 200 different defects,
- Velocardiofacial syndrome is marked by the association of congenital conotruncal heart defects, cleft palate or velar insufficiency, facial anomalies and learning difficulties.
- It is now accepted that these two syndromes represent the different expression of a unique disorder manifesting at different stages of life. DiGeorge Syndrome is one of the most common genetic disorders known, occurring in about one every 4,000 livebirths

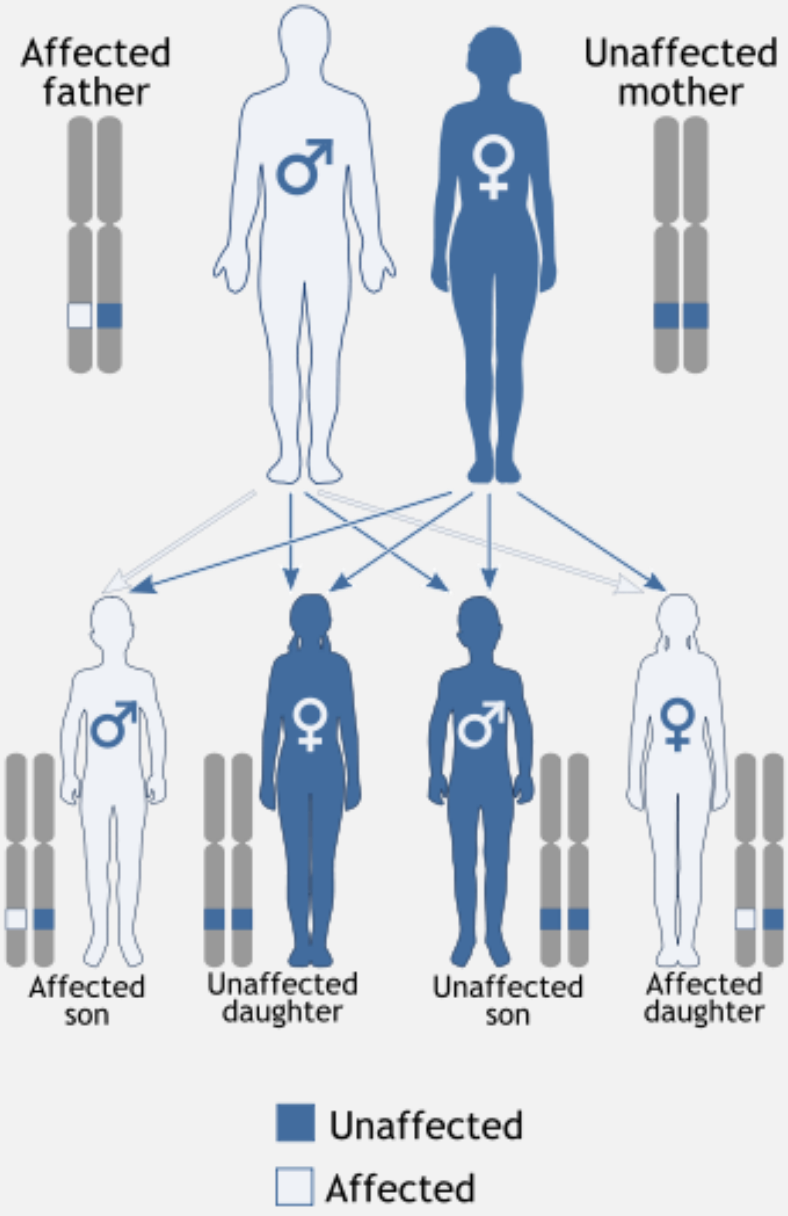
ORIGINAL PHENOTYPE

- Throughout the years however, multiple variations of this syndrome began to arise. In 1979, clinical and autopsy data struck researchers due to the variability and relatively high frequency of this syndrome.
- What began as a strict diagnosis of absent thymus, hypoparathyroidism, and congenital heart disease, increasing reports indicated that the syndrome was more variable than initially thought.
- Was it advanced maternal age? Peripartum toxins? Environment? Sporadic mutations? The term partial DiGeorge syndrome began to arise.
- While the original triad remained true, in 1979, Conley et al recommended clinicians to consider DiGeorge Syndrome when caring for patients with an interrupted aortic arch, truncus arteriosis, hypocalcemia, failure to thrive, chronic purulent rhinitis or mild cognitive delay.
  - This laundry list alone lends a hand to a greater question. what else is going on?
  - This is the art of translational medicine

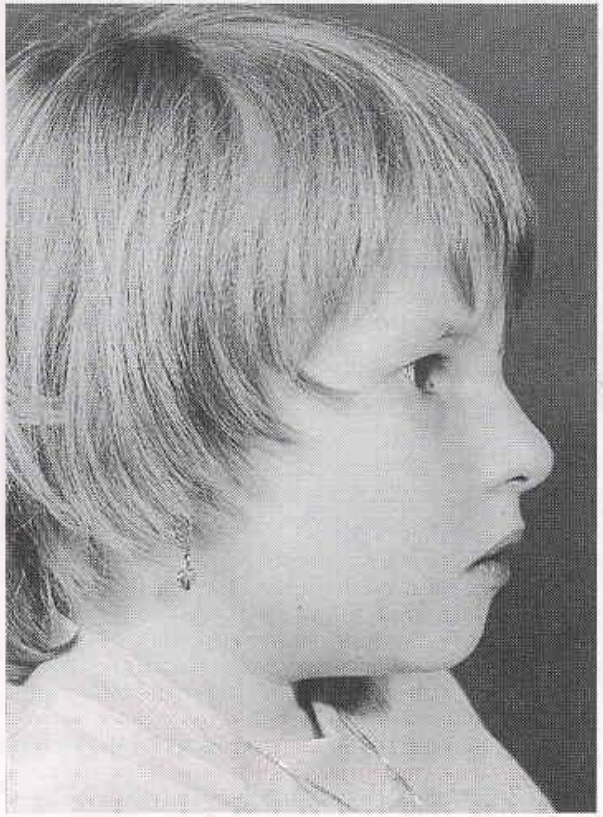
DIGEORGE SYNDROME

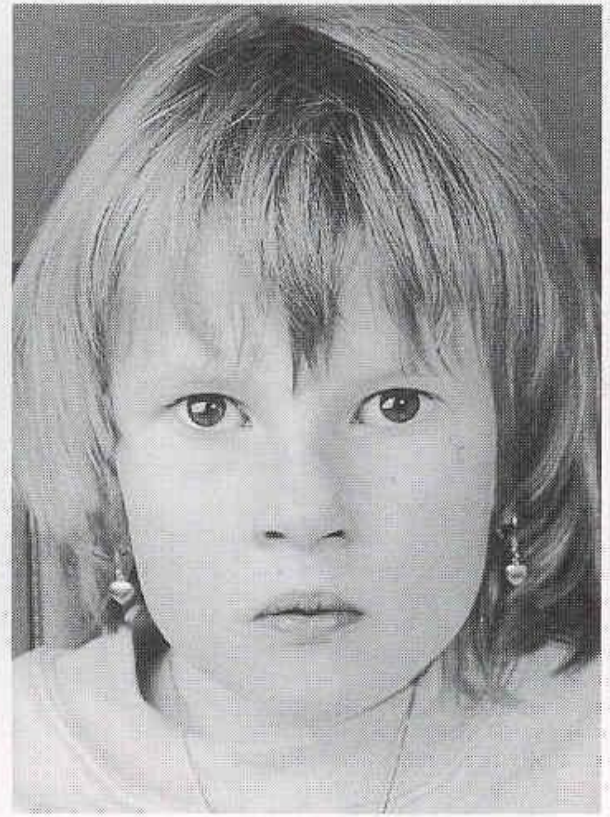
- 1/4000 live births
- Clinical features are highly variable
  - Variable expressivity and incomplete penetrance
- Affects pharyngeal and neurobehavioral development
- Which genes are critically involved ?
  - Mouse models: candidate TBX1, T-box family of genes
  - Highly expressed in pharyngeal arches, TBX1 KO

Autosomal dominant



VCFS: CLEFT PALATE, VELOPHARYNGEAL INSUFFICIENCY, SMALL MOUTH, RETROGNATHIA, BULBOUS NASAL TIP, MICROCEPHALY, CONCOTRUNCAL HEART DEFECTS, MR, LEARNING DISABILITIES, SHORT STATURE





CATCH-22

- **C**ardiac Abnormality (especially tetralogy of Fallot)
  Abnormal facies
  Thymic aplasia
  Cleft palate
  Hypocalcemia/**H**ypoparathyroidism.

HEART DISEASE

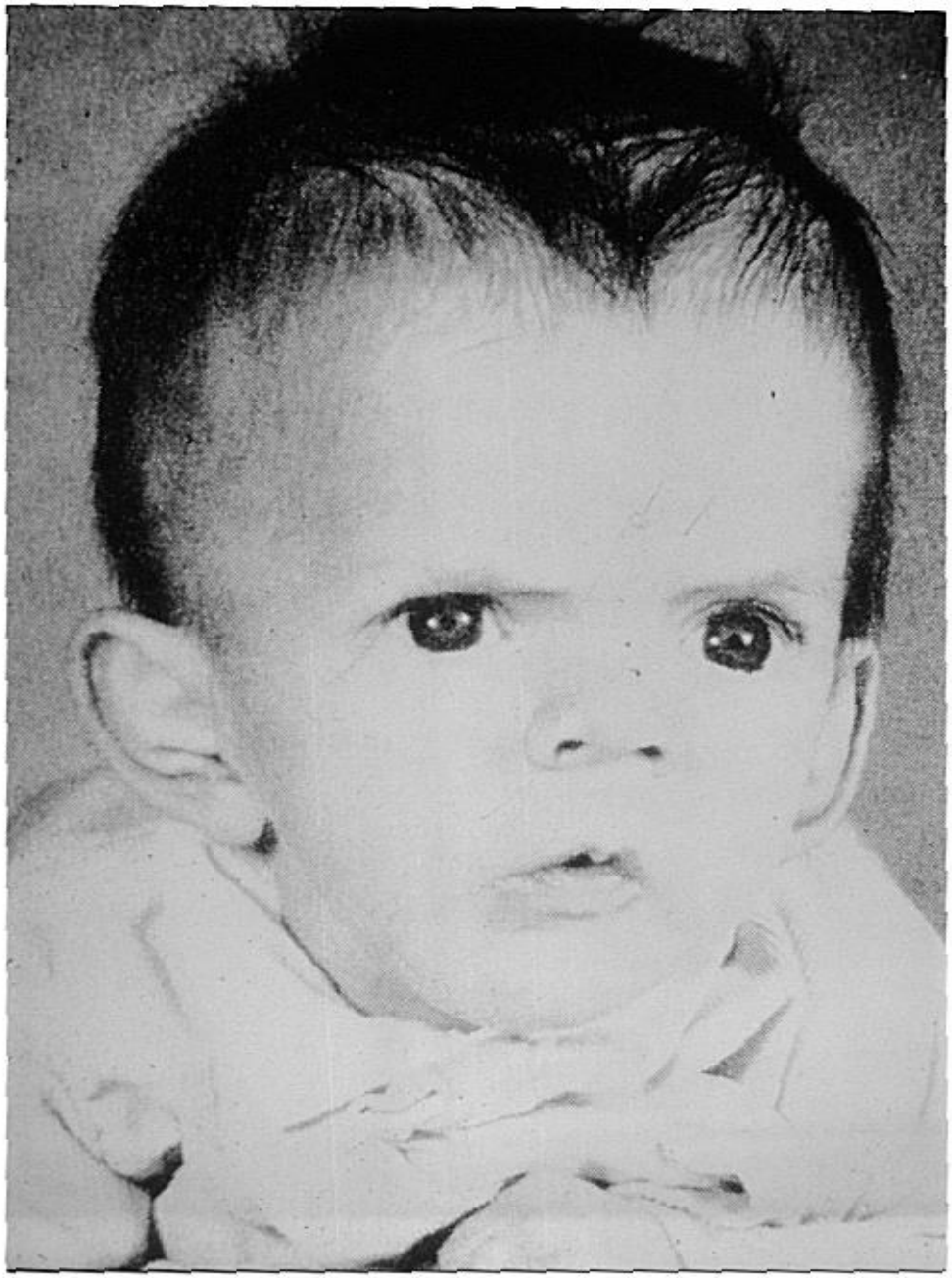
- Congenital heart disease (74-80% of individuals), particularly conotruncal malformations
  - Tetralogy of Fallot,
  - Interrupted aortic arch
  - Isolated arch anomalies
  - Ventricular septal defect
  - Persistent truncus arteriosus
  - Atrial septal defects
  - Hypoplastic left heart

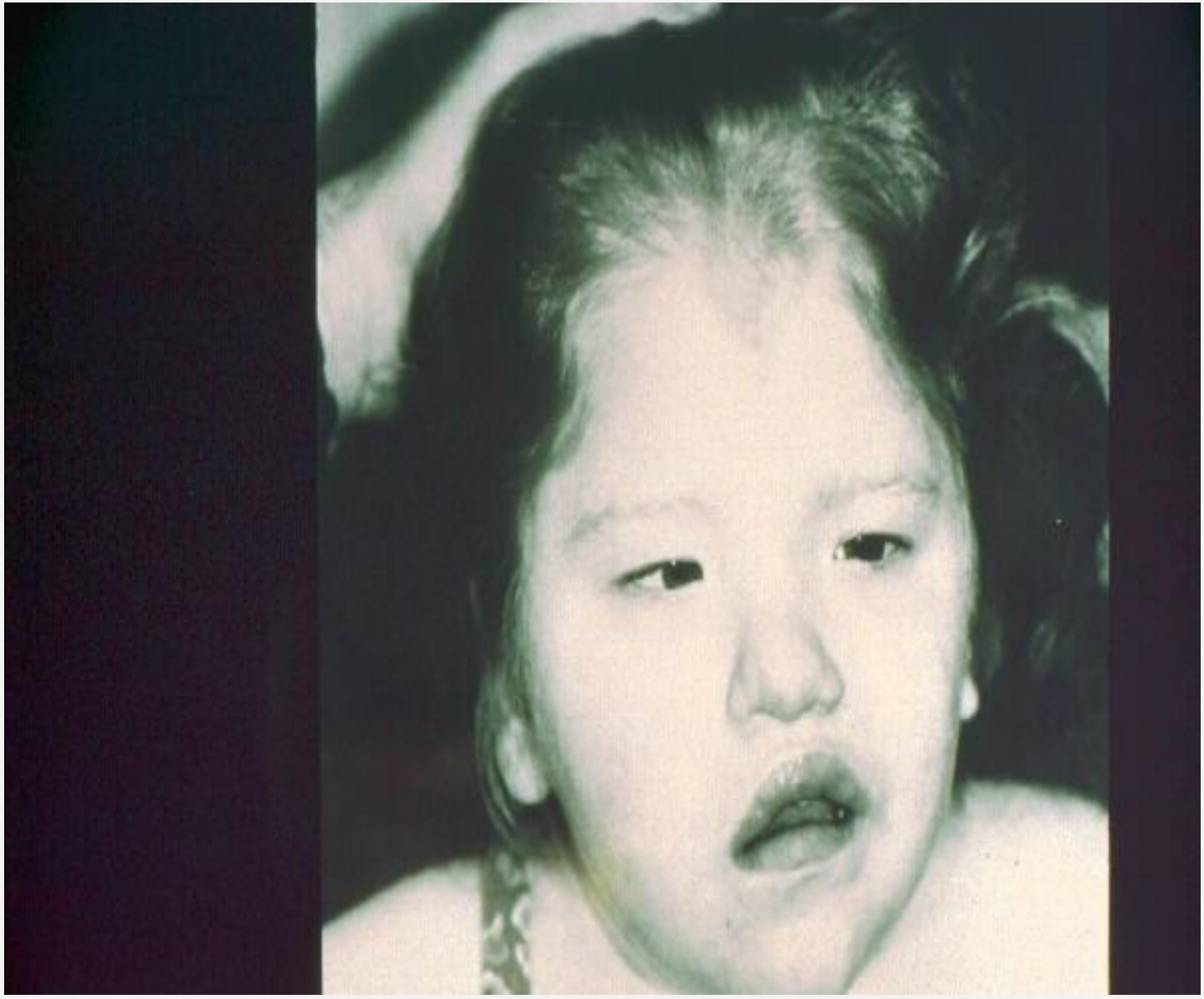
PALATE

- Palatal abnormalities (49-69%),
  - Cleft palate
  - Bilateral cleft lip and palate
  - Submucosal cleft palate
  - Velopharyngeal incompetence (VPI),
    - Manifested as hypernasal speech
    - Nasal air emission
    - Compensatory articulation disorders

FACIAL CHARACTERISTICS

- Small carp shaped mouth
- Hypognathism
- Long philtrum
- Low set ears
- Anti-mongolian slant of eyes
- Wide set eyes





SOME HAVE MILDER FACIAL FEATURES

ABSENT THYMIC SHADOW

IMMUNODEFICIENCIES

- Nearly 80% who carry the deletion have demonstrable abnormalities in their immune system
- Mild to moderate decrements in T cell numbers secondary to thymic hypoplasia
- Humoral defects including IgA deficiency.

LEARNING

- Learning difficulties (90%), but broad range
- Pattern of non verbal learning disability with verbal IQ exceeding performance IQ is a well documented finding in the literature.

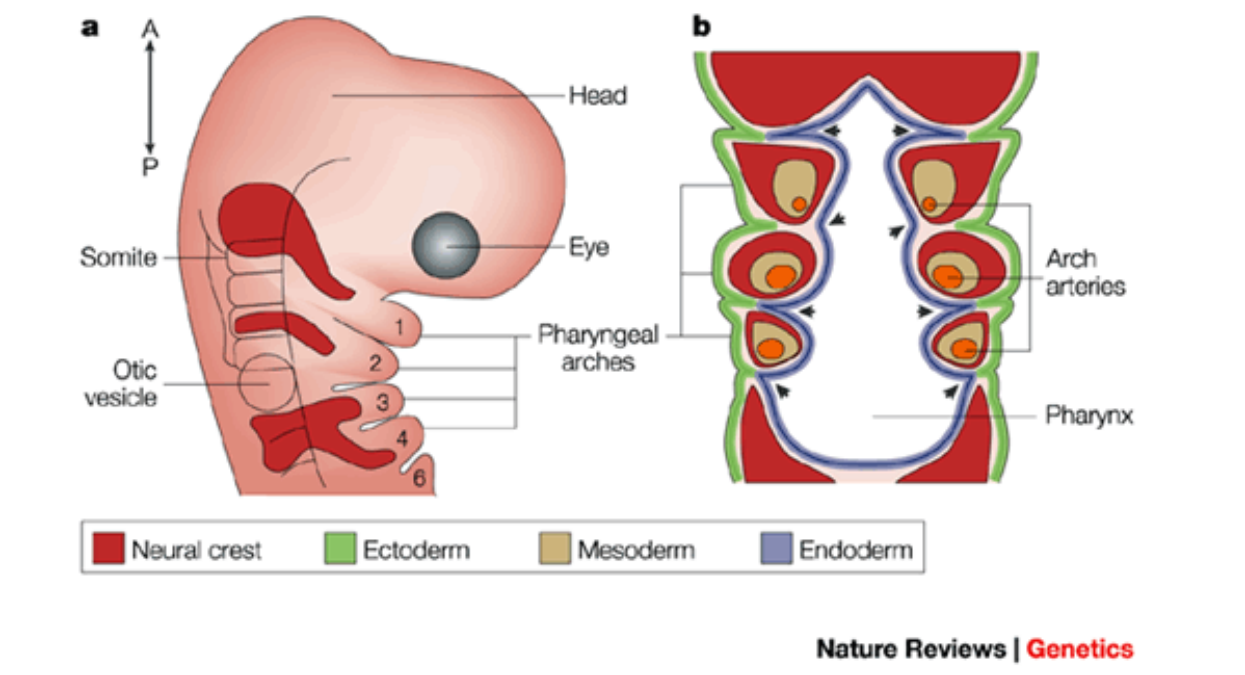
ENDOCRINE

- Hypocalcemia (50%)(due to hypoparathyroidism)
  - Usually outside the neonatal period

OTHERS

- Renal anomalies (37%)
- Hearing loss (both conductive and sensorineural) (hearing loss with craniofacial syndromes)
- Laryngotracheoesophageal anomalies
- Growth hormone deficiency
- Autoimmune disorders
- Immune disorders due to reduced T cell numbers
- Seizures (with or without hypocalcemia)
- Skeletal abnormalities
- Psychiatric disorders

MOLECULAR MECHANISMS FOR CONSTITUTIONAL CHROMOSOMAL REARRANGEMENTS IN HUMANS



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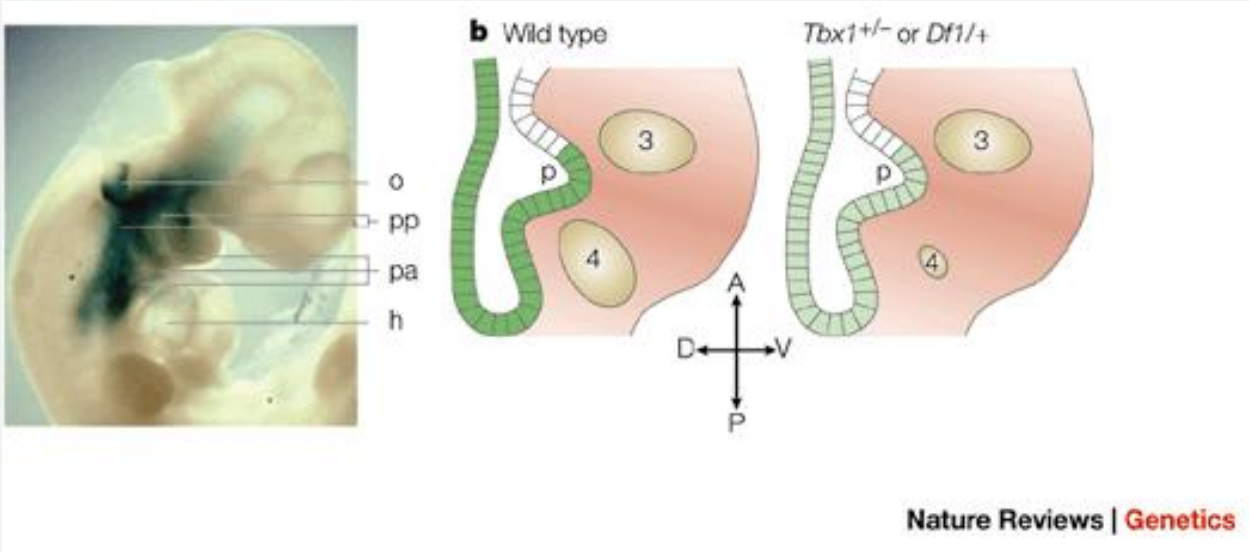


PROGRESS IN HUMAN CYTOGENETICS IS FUELED BY TECHNICAL INNOVATIONS

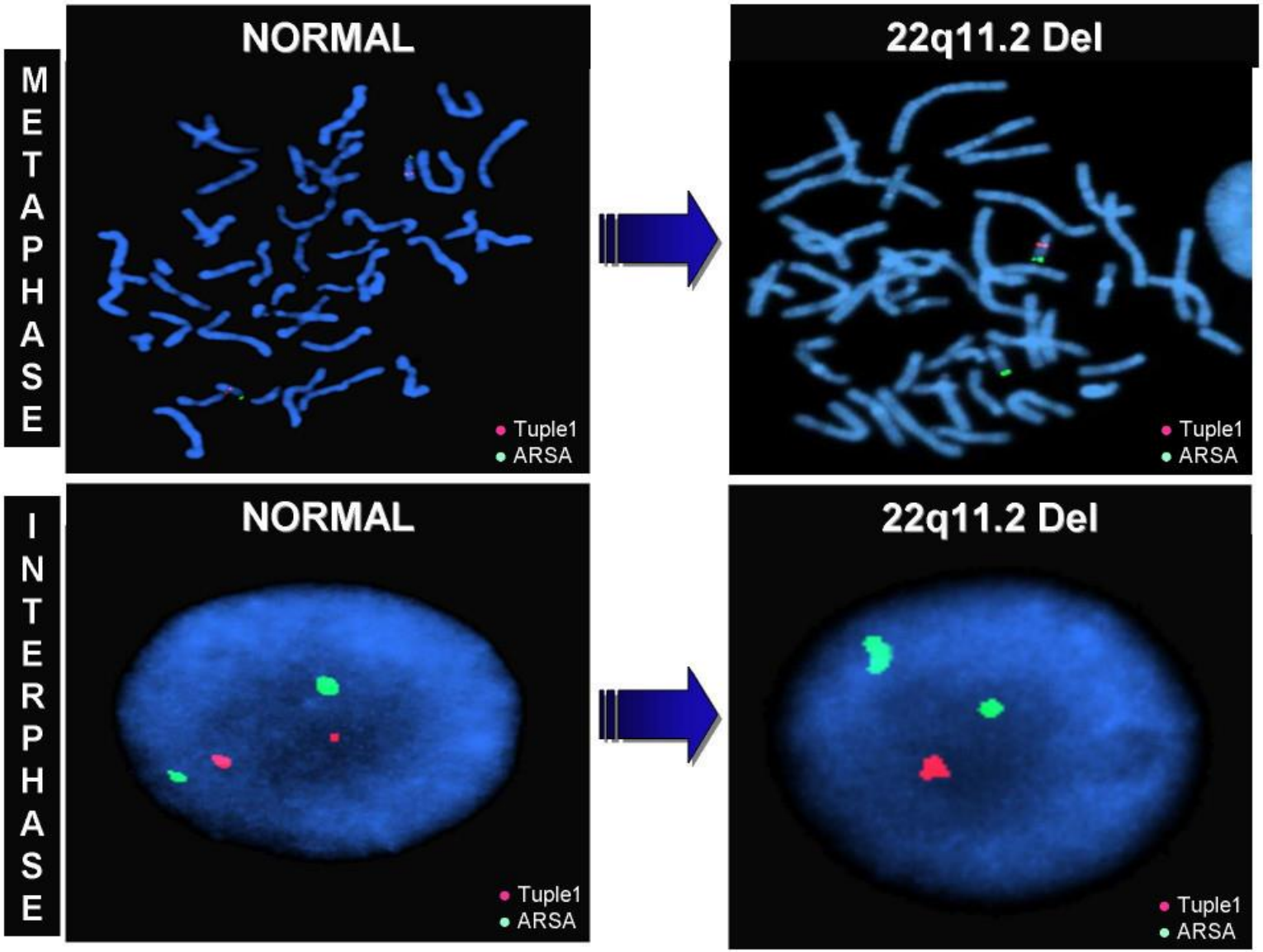
- Late 1980's introduction of FISH
- Significant increase of sensitivity (10.000x), various applications eg gene mapping, genetic diagnosis, research

DISCOVERY OF THE GENOTYPE: THE BENCH

- In 1993 molecular studies identified chromosome 22 Q11.2 deletions in ~94% of patients with clinical features of DiGeorge and ~ 83% of velocardiofacial cases.
- Negative FISH however, does not exclude a diagnosis of this spectrum of disease as smaller/atypical/point mutations make occur.

MONOSOMIC MICRODELETION OF CHROMOSOME 22Q11.2

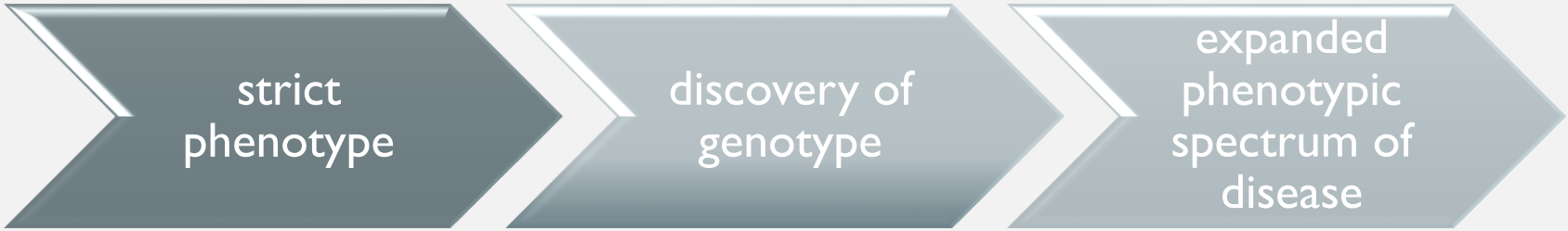
- Result of FISH analysis using LSI probe :TUPLE 1 is from DiGeorge/velocardiofacial syndrome critical region.
- Absence of the orange signal indicates deletion of the TUPLE 1 locus at 22q11.2.


METAPHASE
NORMAL
Tuple1
ARSA
22q11.2 Del
Tuple1
ARSA
INTERPHASE
NORMAL
Tuple1
ARSA
22q11.2 Del
Tuple1
ARSA

CHROMOSOME 22 Q 11.2

- 22q11.2 is an umbrella term used to describe all deletion associated phenotype
- In a review of recent literature, it is believed that the deletion itself is a single syndrome rather than several distinct syndrome.
- Gene haploinsufficiency syndrome 90% de novo, 10% inherited
- Chromosome 22 itself is the second smallest chromosome
  - The most recurrent rearrangements occur within 22Q11, suggesting genomic instability in this region
  - Deletion encompasses ~30 genes

THE EXPANDED SPECTRUM BACK TO BED



22Q11.2

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TREATMENT

- Early identification!
  - Testing for 22q11 deletions routinely available in most cytogenetic labs (FISH)
    - Current method of choice in identifying microdeletions
- Endocrine- hypoparathyroidism and hypocalcemia are managed with calcium supplements and vitamin D administration.
- Cardiac- surgical repair
- Palate- ENT/OMFS evaluation
- Immunology-
  - B cell: Prophylactic antibiotics, Immunoglobulin replacement
  - T cells: Prophylactic Bactrim, irradiated RBC if transfusion if needed, thymic transplantation
- Developmental support
- Speech evaluation
- Genetic testing

CONCLUSION

- Molecular analysis of a presumably rare developmental disorder with a strict phenotypic diagnosis led to the genotypic discovery of the most common deletion syndrome known to date, 22q11 deletion syndrome.
- This multisystem syndrome is characterized by remarkable variability among individuals.
- Management is individualized according to the underlying pathology and relying on age and phenotype
- Early diagnosis is key for optimal anticipatory medical care and family planning.

CONCLUSION

- Important concepts of understanding the evolution of the diagnosis of diseases such as DiGeorge:
  - 1. Phenotypical identification of disease, initially a strict/tight diagnosis
  - 2. Genotypic discovery
  - 3. A newfound spectrum of the most common chromosomal deletion leading to diagnosis of milder phenotypes, even in the adult population, and providing medical help back to the bedside by this process of translational medicine.
- Bed to bench to bed

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