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# Di-George Syndrome

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Network Study Day 25.1.21

NHS
Liverpool Heart and Chest Hospital
NHS Foundation Trust

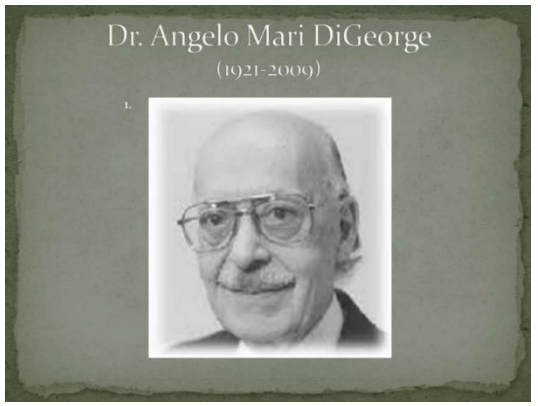
# Synonyms

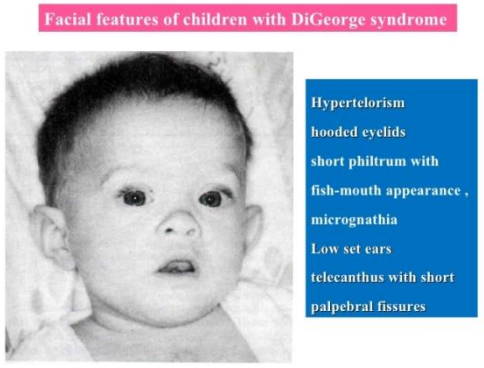
- Chromosome 22q11 deletion
- VCFS
- CATCH 22
  - **C**ardiac Anomalies
  - **A**bnormal facies
  - **T**hymic Hypoplasia
  - **C**left Palate
  - **H**ypocalcaemia

  *All the same genetic basis > differing phenotype*

# History

- Angelo DiGeorge 1965 described
  - Thymic Hypoplasia
  - Congenital cardiac anomalies
- Kinouchi et al 1975 described
  - Conotruncal anomalies
  - Facial features
- Sprintzen et al 1977 described
  - Velocardiofacial syndrome (VCFS)



# What is DiGeorge Syndrome?

- Caused by a genetic mutation on 22nd chromosome that results in the deletion of a portion of it
- Autosomal dominant immunodeficiency
- Results in poor development of several body systems
- The underlying cause is a shrunken or missing thymus gland

# Incidence

- Around 1:4,000
- 8% of Cleft palates > most commonly associated genetic defect
- Constitutes 25% of all congenital cardiac defects
- Race: No predispositions identified
- Sex: Equal
- Age: Congenital

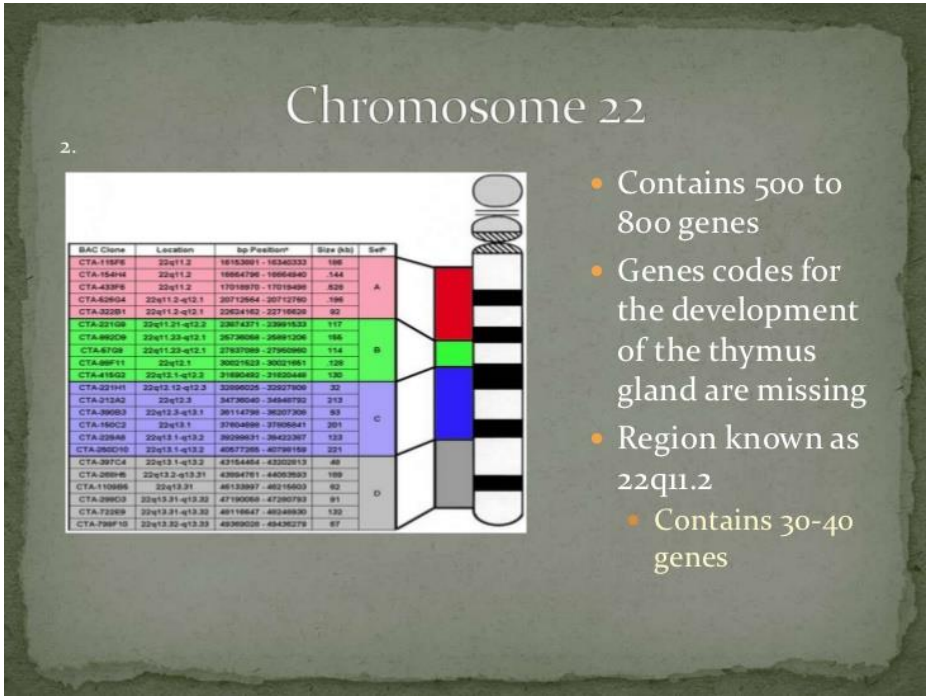
# Causes

**94% De-Novo deletions**
(25% of parents of de-novo case found to carry same deletion)

- Unbalanced translocation from a balanced parent
- Del/Interstitial del of 10p13 – rare cause of DGS (type II)
- **Phenotypic variability** > disease severity + age of presentation.
- Environmental factors:
  - Maternal C2H5OH
  - Retinoid exposure
  - Uncontrolled DM in pregnancy

# Genetics

- Deletion on long arm of Ch 22
- Deletion is long (2-3 Mb) in 95% of patients



# Pathogenesis

- Deletion results in
  - **Defective migration** of the neural crest cells during 4th week of embryogenesis
  - **Developmental field defect** (involving the 3rd and 4th pharnygeal pouches)of:
    - The heart > CHD
    - Head and neck > Cleft + other ENT presentations
    - Thymus > Immunodeficiency
    - Parathyroid > Hypocalcaemia

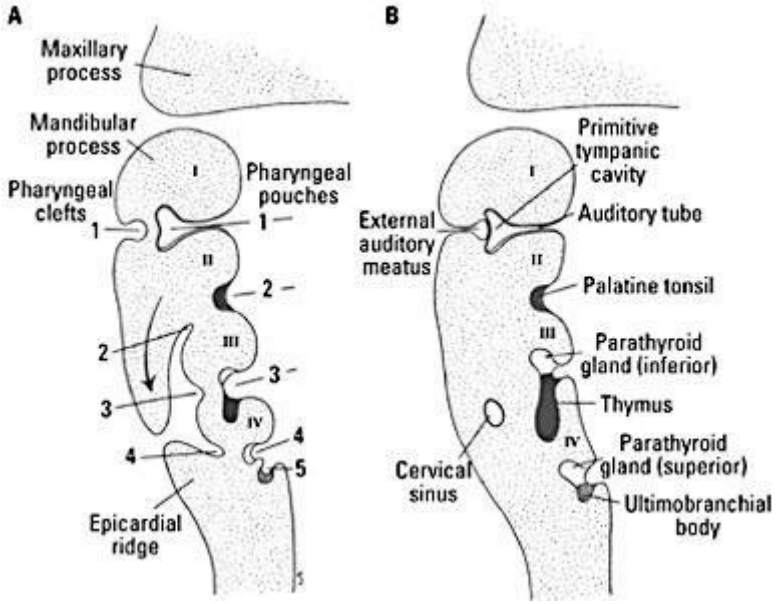
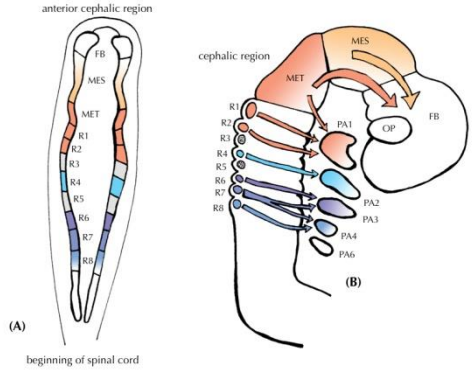
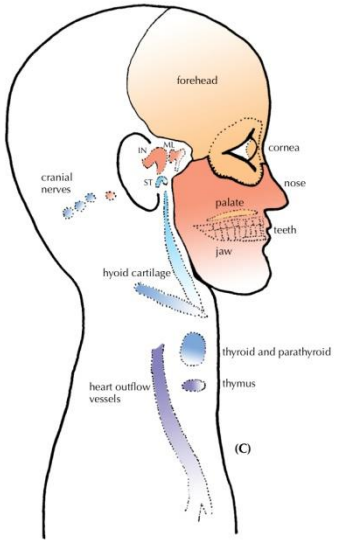



**Figure 1.** The sites of origin, migration, and arrival of cranial neural crest cells. (A) Embryonic neural tube showing the mesencephalon, metencephalon, and rhombomeres, with the dorsal face of tube coloured to show the location of neural crest before migration. (B) Sagittal view of embryo, showing paths of migration of cranial crest cells. (C) Sagittal view of adult human, showing the origins of various cranial crest derivatives.




**MES** mesencephalon
**MET** metencephalon
**FB** forebrain
**OP** optic vesicle
**R1** rhombomere 1
**R2** rhombomere 2
**R3** rhombomere 3
**R4** rhombomere 4
**R5** rhombomere 5
**R6** rhombomere 6
**R7** rhombomere 7
**R8** rhombomere 8
**PA1** first pharyngeal arch
**PA2** second pharyngeal arch
**PA3** third pharyngeal arch
**PA4** fourth pharyngeal arch
**PA6** sixth pharyngeal arch
**IN** incus
**ML** malleus
**ST** stapes

**Origin of structures in adult organism**
- Frontonasal process
- First pharyngeal arch
- Second pharyngeal arch
- Third pharyngeal arch
- Fourth pharyngeal arch

# The Phenotype of Chromosome 22q11.2 Deletion Syndrome

- Cardiac anomaly 75%
  - TOF 20%
  - IAA 15%
  - Truncus arteriosus 8%
- Palatal anomaly 69-100%
- Hypocalcemia 17-60%
- Speech delay 75%
- Renal anomaly 36-37%
- Skeletal anomaly 17-19%
- Immunodeficiency 60-77%

# Clinical Immunodeficiency

**7% of all ages have significant, serious infections**

**9% have autoimmune disease**

**Older children and adults continue to get infections**

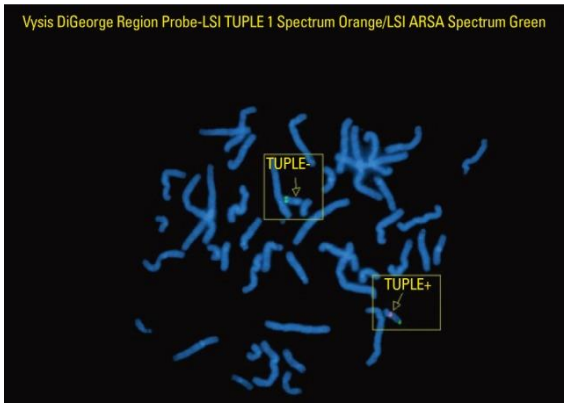
- **27% recurrent sinusitis**
- **25% recurrent otitis media**
- **7% recurrent bronchitis**
- **4% recurrent pneumonia**

# Tests, Limitations

- Cytogenetic analysis may detect del22q11 (a)
- FISH - suspected submicroscopic deletion (b)
- Molecular analysis using DNA probes from DiGeorge chromosomal region (DGCR) (c)

(a)


(b)




(c)

# Tests, Limitations

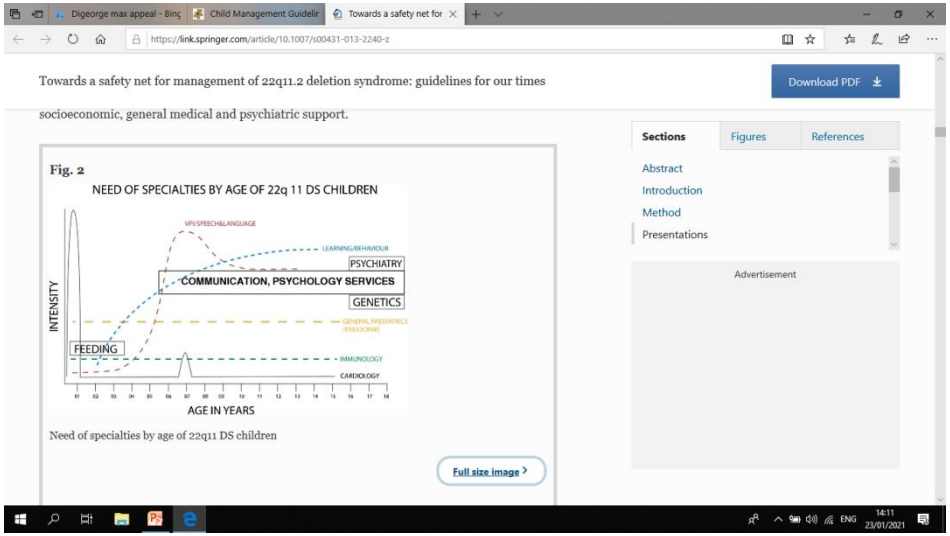
- 5% of patients with clinical symptoms of del22q11 have normal cytogenetic studies and FISH
- May be a variant of deletions of DGCR which may be detectable on a research basis only

# Genetic Counselling

- Parents
  - 94% have de novo del. of 22q11
  - 6% have inherited the 22q11del from a parent, thus both parents of an individual should have FISH testing
- Offspring
  - Of an individual with 22q11del have a 50% chance
  - If the parents of an individual have normal FISH, the recurrence risk is small, assuming a very low, and yet undefined risk of germ line mutation

# Consultations and FU

- Multidisciplinary Team:
- Primary > Secondary> Tertiary
  - Geneticists
  - Psychiatrists
  - Immunologist
  - Otolaryngologist
  - Cardiologist > ACHD
  - Craniofacial specialist
  - Endocrinologist
  - Surgeons
  - Therapists and AHP
  - Health and Social care agencies



# Advocacy, Education,Research Guidelines

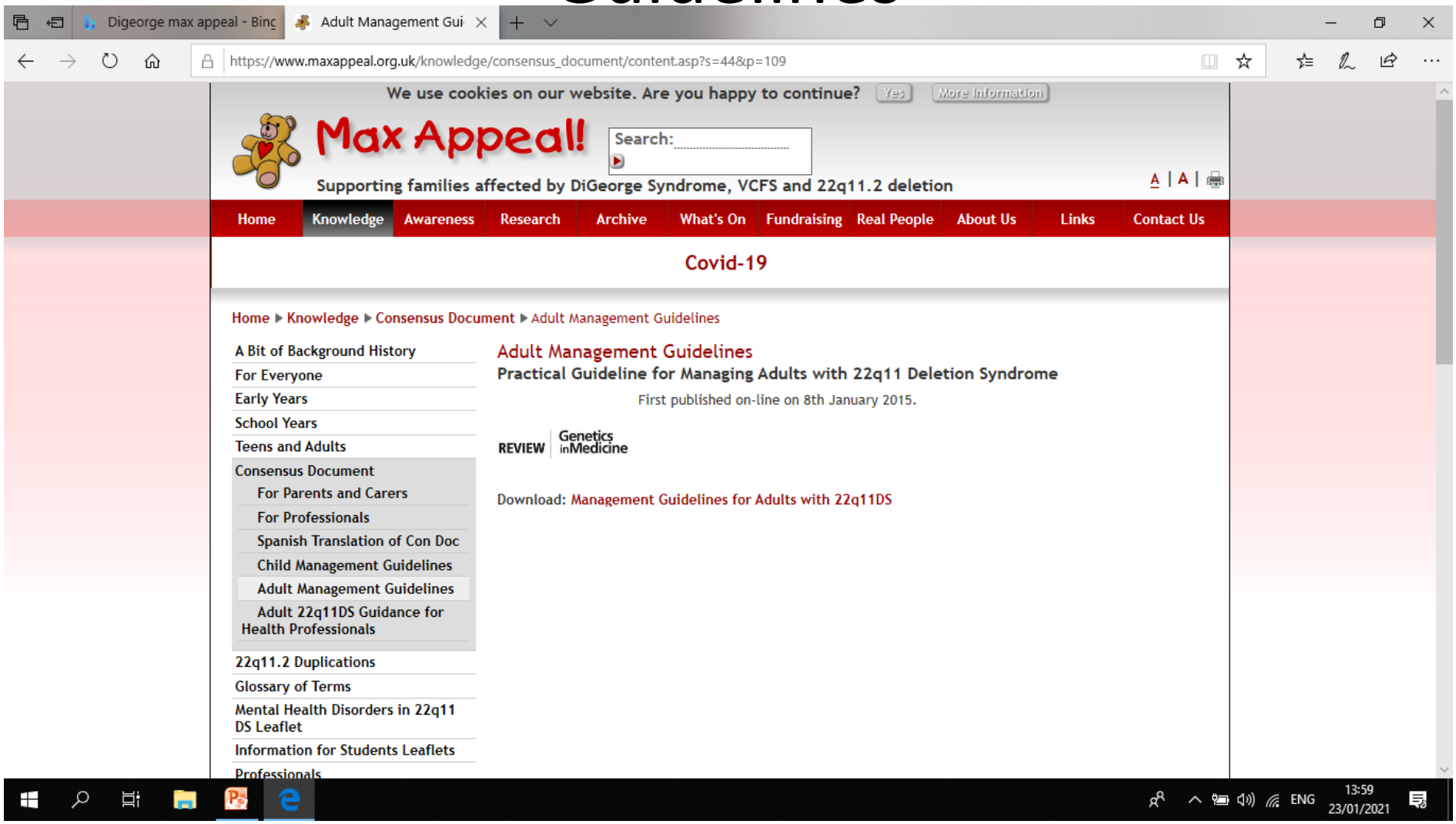


**Table 1** Recommendations for periodic assessments and health monitoring for adults with 22q11.2DS

| | Baseline workup at adult diagnosis or initial assessment at transition from pediatric care | | Annual or biennial f as an adult |
|---|---|---|---|
| **Recommendations** | **Complete** | **As needed** | **Complete** |
| Genetic/general assessments and management | | | |
| Consultation with medical geneticist and/or clinicians experienced with 22q11.2DS | ✓ | | ✓ |
| Genetic counseling[a] | ✓ | | ✓ |
| Clinical genetic testing | ✓[b] | | |
| Family planning and prenatal counseling | | ✓ | |
| Other clinical assessments | | | |
| Comprehensive medical history | ✓ | | |
| Systems review | ✓ | | ✓ |
| Psychiatric assessment[c] | ✓ | | |
| Cognitive and capacity assessments | ✓ | | |
| Neurological assessment | | ✓ | |
| Ophthalmological assessment | | ✓ | |
| Orthopedic assessment | | ✓ | |
| Family history | ✓ | | ✓ |
| Physical examination (including for hygiene and care) | ✓ | | ✓ |
| BMI/growth/nutritional assessment | ✓ | | ✓ |
| Other investigations | | | |
| 22q11.2DS-relevant laboratory tests[d] | ✓ | | ✓ |
| Electrocardiography | | ✓ | |
| Transthoracic echocardiography | | ✓ (If not previously performed) | |
| Abdominal ultrasound[f] | | ✓ | |
| Electroencephalography | | ✓ | |
| Other management | | | |
| Contraception and safe sex counseling | ✓ | | ✓ |
| Counseling on Internet safety | ✓ | | ✓ |
| Dental assessment | ✓ | | |
| Audiology assessment | ✓ | | |
| Other[g] | ✓ | | |

22q11.2DS, 22q11.2 deletion syndrome; BMI, body mass index.

[a]Described in the text. [b]Proband, offspring, and parents (siblings if parents unavailable). [c]In addition to monitoring for changes (Table 2), includes assessment


## ADULT 22q11DS GUIDELINES FOR HEALTH PROFESSIONALS

**Foreword**

When diagnosed in childhood, 22q11 is sometimes managed by a multidisciplinary approach. Once the transition into adult hood is made however, or if the patient is diagnosed in adulthood then these safety nets are not available to them and this is where GP and other health professional services become vital for their life long care to be the link to all areas of support that are needed to help them live a long and productive life.

To help assist your patient with their care plan we would be grateful if you could spare a few minutes to familiarise yourself with the care recommendations contained within this document which has been written by Dr Alex Habel, a leading expert on the condition and founder of the 22q11 clinic at Great Ormond Street and Dr Dinakantha Kumararatne, Max Appeal trustee and immunologist at Addenbrooke's hospital.

**by Mark Tripp, Trustee of Max Appeal**

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# Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times

Alex Habel, Richard Herriot, Dinakantha Kumararatne, Jeremy Allgrove, Kate Baker, Helen Baxendale, Frances Bu'Lock, Helen Firth, Andrew Gennery, Anthony Holland, Claire Illingworth, Nigel Mercer, Merel Pannebakker, Andrew Parry, Anne Roberts & Beverly Tsai-Goodman

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## Abstract

The commonest autosomal deletion, 22q11.2 deletion syndrome (22q11DS) is a multisystem disorder varying greatly in severity and age of identification between affected individuals.