# Genetics (of) and Anorectal Malformations



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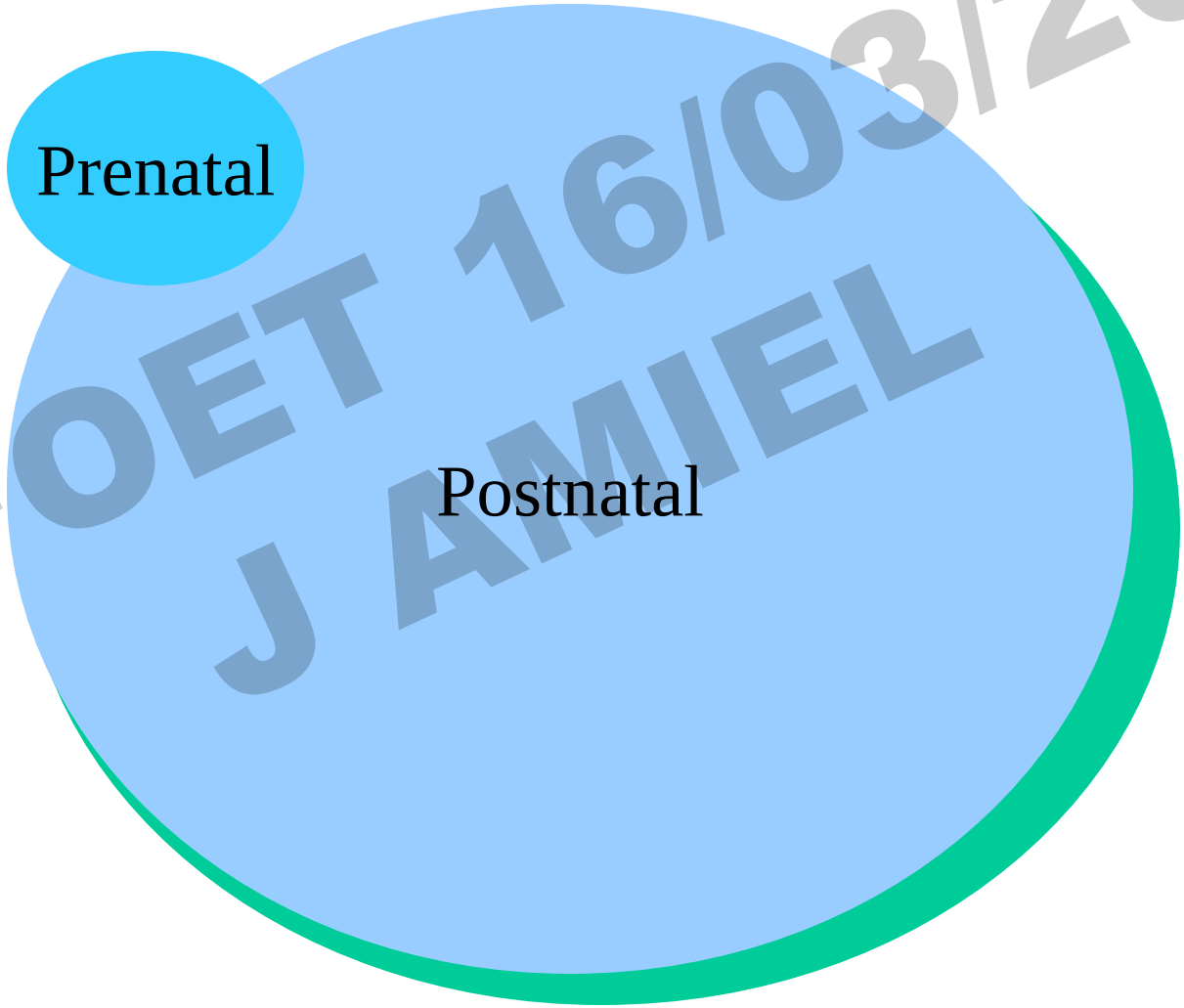
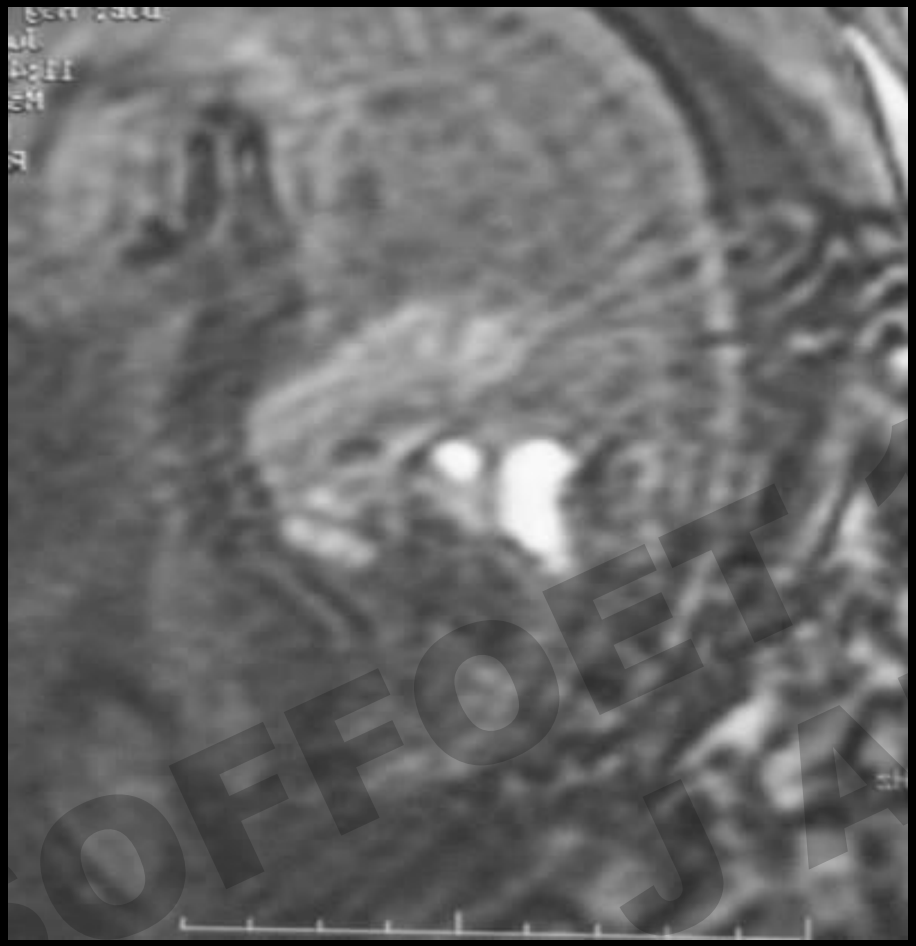
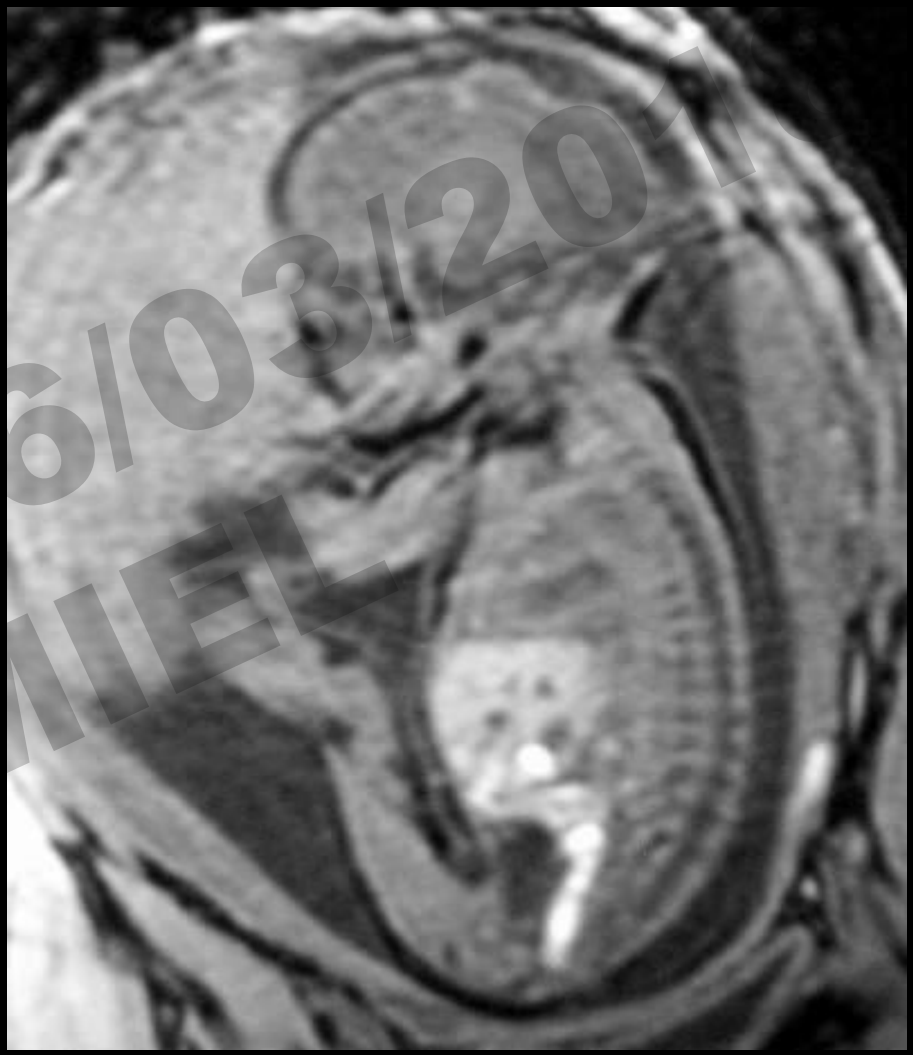
# Diagnostic of Anorectal Malformations





Anorectal Malformation



Control

Dr P. Sonigo, Service de Radiologie Pédiatrique, NEM

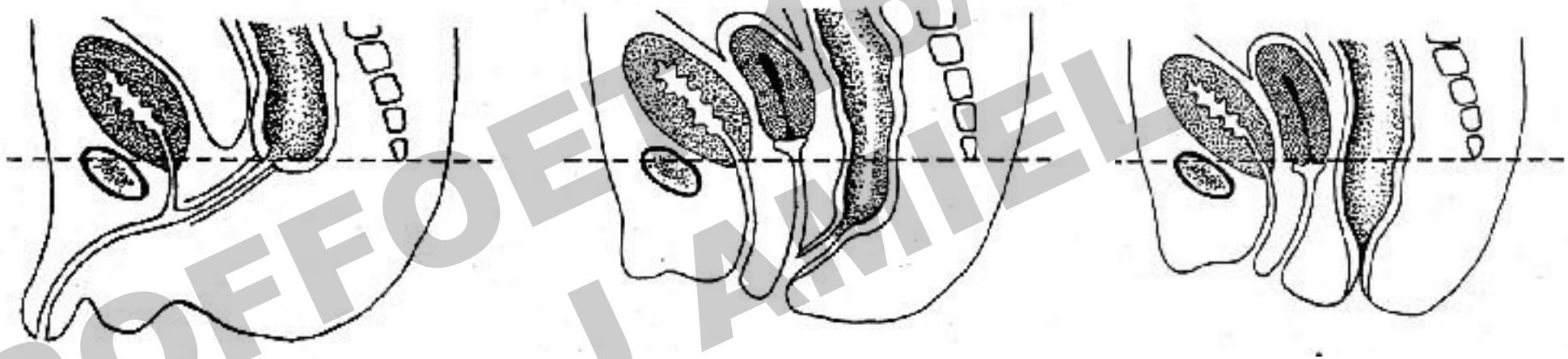
# Epidemiology

- Frequent malformation
  (1/2500 to 1/5000 life birth)
- Sex biais (M:F ~1.6:1)
- *No ethnic biais*

# Anatomical Classification and Epidemiology

Wing Spread Conference Classification (1984)

High | Intermediate | Low





Distribution varies according to gender

| | High | Intermediate | Low |
|---|---|---|---|
| ♂ | ~ 50% | 10% | ~ 40% |
| ♀ | ~ 20% | ~ 25% | ~ 55% |

# Genetic Counselling for Isolated Anorectal Malformation



- Concordant monozygotic twins
- Low recurrence risk (~ 1%)
- Recurrence in sibs and vertical transmission described
  - ♂>♀
  - low-int : high ~ 2:1
  - AD, AR, XLR

Kubiak and Upadhyay. ***J Ped Surg*** 2005; 40: E1-4

# Non Isolated Anorectal Malformation

Major publications (retropective studies)

- Hasse W. 1976
  1420 patients — 42%
- Boocock and Donnai. 1987
  169 patients — 53%
- Hassink et al. 1996
  264 patients — 67%
- Cho et al. 2001
  103 patients — 71%

# « Associated » Anorectal Malformation

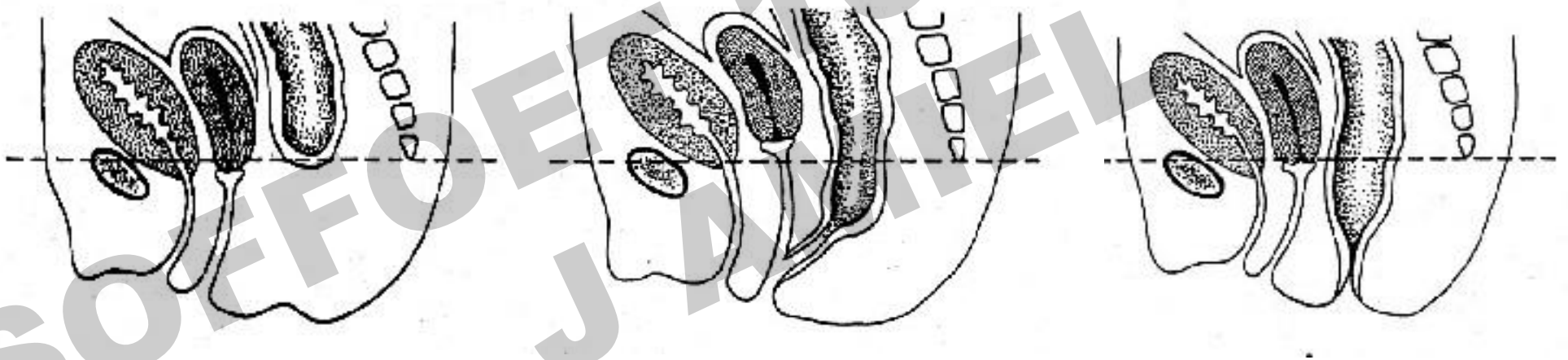
| | | |
|---|---|---|
| Urogenital | ~ *40%* | (hypospadias, renal agenesis) |
| Skeletal | ~ *30%* | (thoraco-lombo-sacral vertebrae) |
| Gastro-intestinal | ~ *20%* | (œsophagal atresia) |
| Cranio-facial | ~ *20%* | (abn. ear position) |
| Heart defects | ~ *20%* | (VSD) |
| CNS | < *10%* | |
| Other | ~ *5%* | |

# « Associated » Anorectal Malformation



*High* | *Intermediate* | *Low*

(~ 1/3 of cases) | (~ 2/3 of cases)



Associated malformations
In 80% of the cases

♂~ ♀

Associated malformations
In 36% of the cases

Boocock and Donnai. ***Arch Dis Childh*** 1987; 62: 576-579

# « Associated » Anorectal Malformations

- Teratogen exposure
- Chromosomal anomalies
- Syndromes (AR, AD, XLR, XLD)
- Association
- Sequence

# Multiple Congenital Anomalies

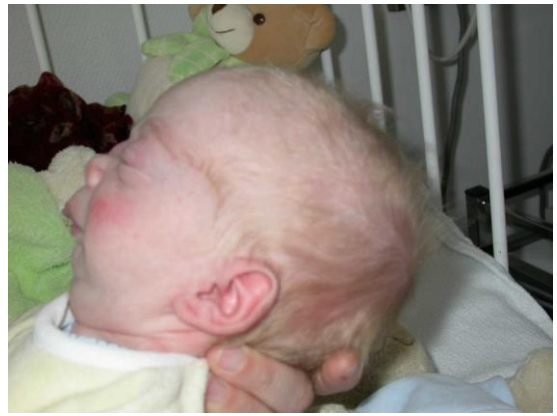
What is the embryologic scenario?

V vertebrae
A anus
T tracheo-oesophageal
E
R radial

- Association: combination is more frequently observed than expected by chance

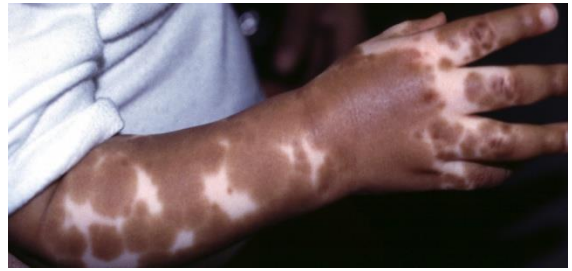
- Sequence: all other anomalies are the consequence of a single one

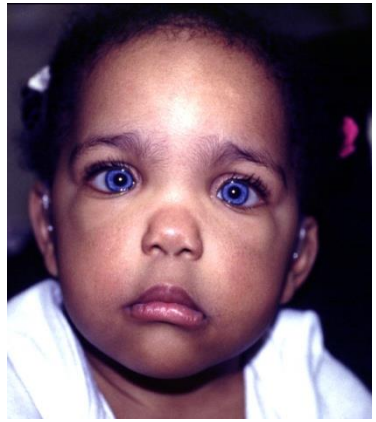
Pierre Robin



- Syndrome: Combination of anomalies resulting from a known (or suspected) genic cause

Waardenburg





# « Associated » Anorectal Malformation

- Teratogen exposure
- Chromosomal anomalies
- Syndromes (AR, AD, XLR)
- Association
- Sequence

# « Associated » Anorectal Malformation

- Chromosomal anomalies

  T21
  T13, del13q, r13
  Trisomie 18
  Cat-eye
  Pallister-Killian
  MIDAS (MLS)
  mat UPD16
  del22q11.2
  del6qter
  ….

*Human Molecular Genetics, 2013, Vol. 22, No. 3* **621–631**
*doi:10.1093/hmg/dds451*
*Advance Access published on October 29, 2012*

# Genome-wide copy number variation study in anorectal malformations

**Emily H.M. Wong[1,†], Long Cui[2,†], Chun-Laam Ng[2,†], Clara S.M. Tang[1,2], Xue-Lai Liu[2], Man-Ting So[2], Benjamin Hon-Kei Yip[1,2], Guo Cheng[2], Ruizhong Zhang[2], Wai-Kiu Tang[2], Wanling Yang[5], Yu-Lung Lau[5], Larry Baum[7], Patrick Kwan[7], Liang-Dan Sun[8,9], Xian-Bo Zuo[8,9], Yun-Qing Ren[8,9], Xian-Yong Yin[8,9], Xiao-Ping Miao[10], Jianjun Liu[11], Vincent Chi-Hang Lui[2,4], Elly Sau-Wai Ngan[2,4], Zhen-Wei Yuan[12], Shi-Wei Zhang[13], Jinglong Xia[13], Hualong Wang[14], Xiao-bing Sun[15], Ruoyi Wang[15], Tao Chang[16], Ivy Hau-Yee Chan[2], Patrick Ho-Yu Chung[2], Xue-Jun Zhang[8,9], Kenneth Kak-Yuen Wong[2], Stacey S. Cherny[1,6], Pak-Chung Sham[1,3,4,6], Paul Kwong-Hang Tam[1,2,4] and Maria-Mercè Garcia-Barcelo[24,*]**



1.3-fold excess of rare CNVs (deletions and duplications) in patients compared to controls

# « Associated » Anorectal Malformation

- Association
  - VACTERL
    - Vertebral
    - Anal
    - Cardiac
    - Tracheo-Esophageal fistula
    - Renal
    - Limb
  - MURCS
    - MUllerian duct
    - Renal aplasia
    - Cervico-thoracic Somite dysplasia

Over diagnosed?

(44% in Hassink's series in 1996)

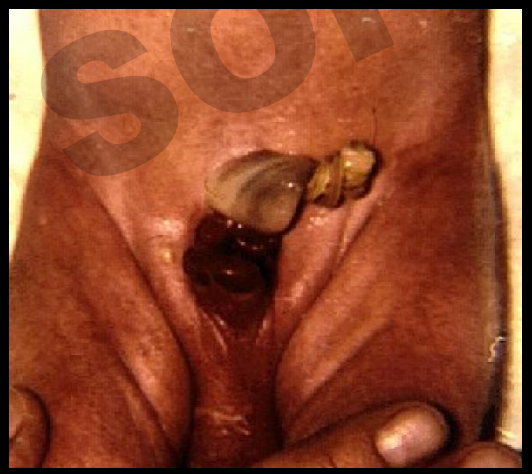
# « Associated » Anorectal Malformation

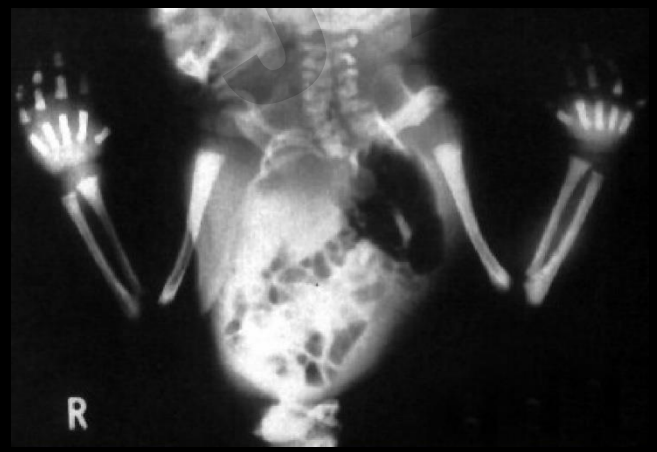
- Sequence
  - OEIS
  - Caudal regression
  - Sirenomelia
  - Axial mesodermal dyplasia (Goldenhar + caudal regression)
  - Klippel-Feil

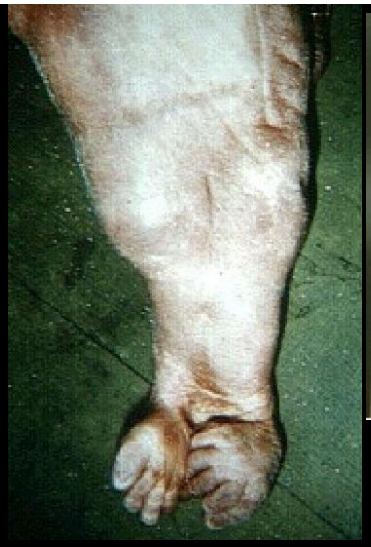
→

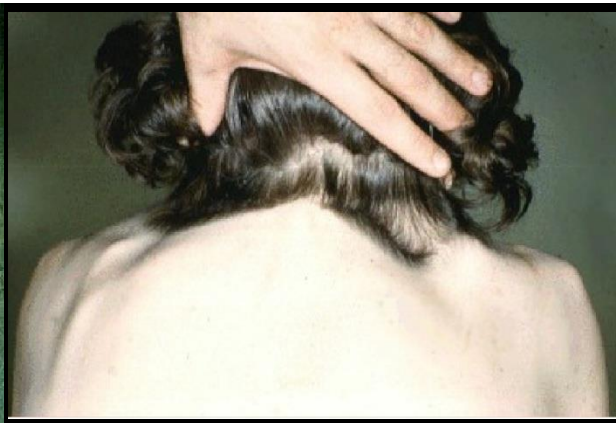
Omphalocele
Exstrophy of bladder
Imperforate anus
Spinal defect







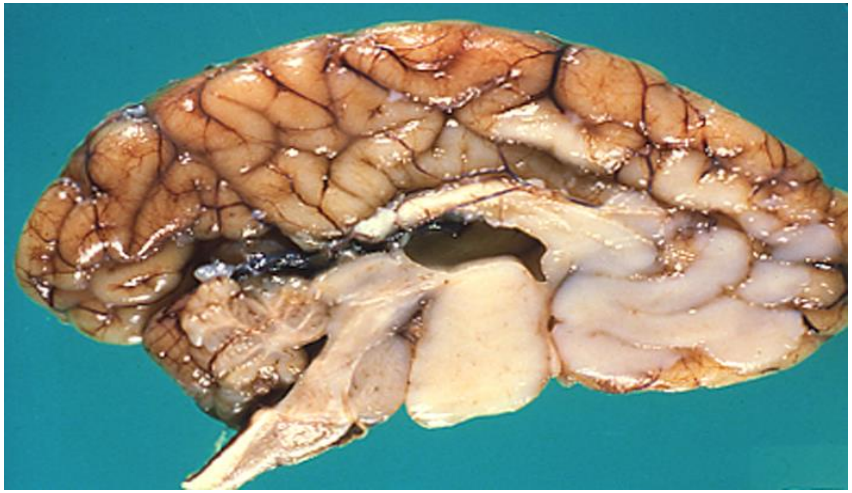


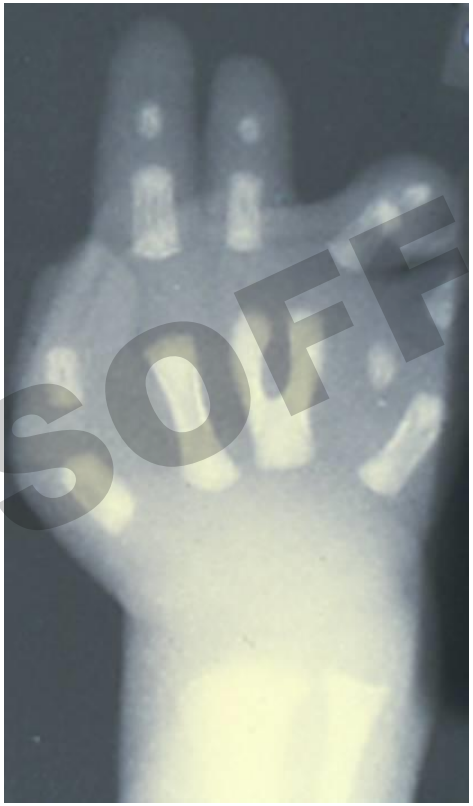
LDDB

# Syndromic Anorectal Malformations

| AD | AR | XLR-XLD |
|---|---|---|
| Currarino (*HLXB9*) | Johanson-Blizzard (*UBR1*) | G-Opitz (*MID1*) |
| Pallister-Hall (*GLI3*) | Dysostose spondylocostale | Lowe (*OCRL*) |
| Townes-Brocks (*SALL1*) | (*DLL3*,*MESP2*, *LNFG*) | Hétérotaxia (*ZIC3*) |
| Okihiro (*SALL4*) | Cotes courtes-polydactylie | FG (*MED12*) |
| Ulnar-mammary (*TBX3*) | Baller-Gerold (*RECQL4*) | Renpenning (*PQBP1*) |
| Rieger (*PITX1*) | Fraser (*FRAS1*, *FREM2*) | MIDAS (*HCCS*) |
| Thanatophore (*FGFR1-3*) | … | STAR (*FAM58A*) |
| Hirschsprung (*RET*) | | Christian |
| Feingold (*NMYC*) | | … |
| Kabuki (*KMT2D*) | | |
| …. | | |

# Pallister-Hall

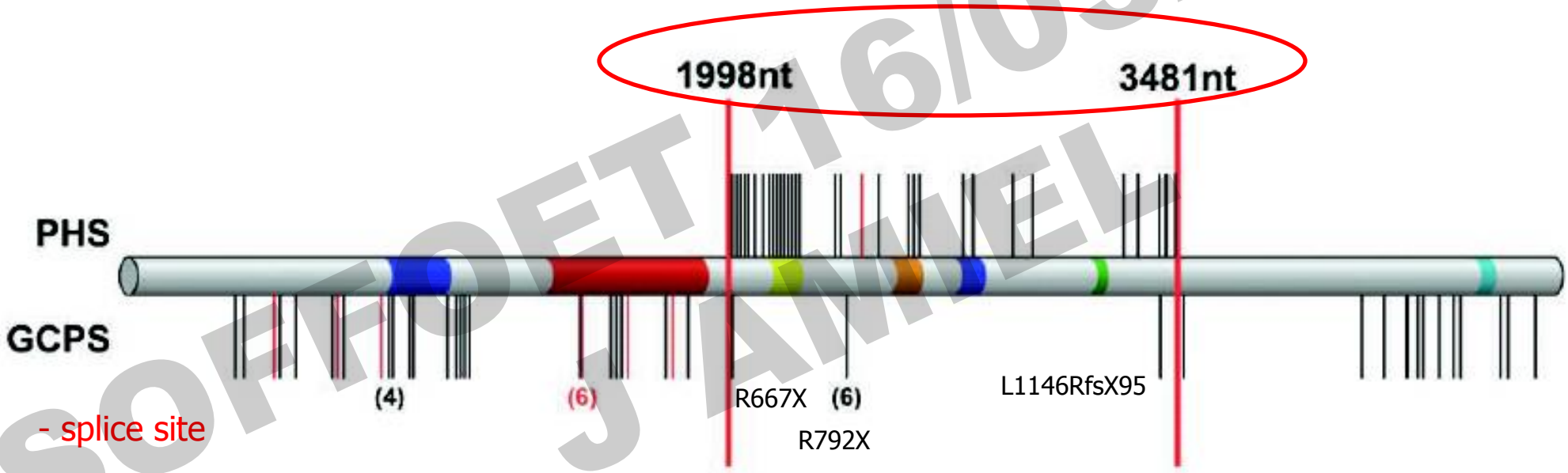




B. Gorlin Collection

- **IUGR,** short limbs
- **Hypothalamic Hamartoblastoma**
- **Polydactyly**
  Mesoaxial, postaxial (upper limbs)
  Postaxial or mesoaxial (lower limbs)
- **Anorectal malformation**
- **Genital anomalies**
- **Renal anomalies**
- **Cranio-facial anomalies**:
- **Laryngeal cleft**
- **Heart defects**
- **Skeletal anomalies**
- **Nail dysplasia**

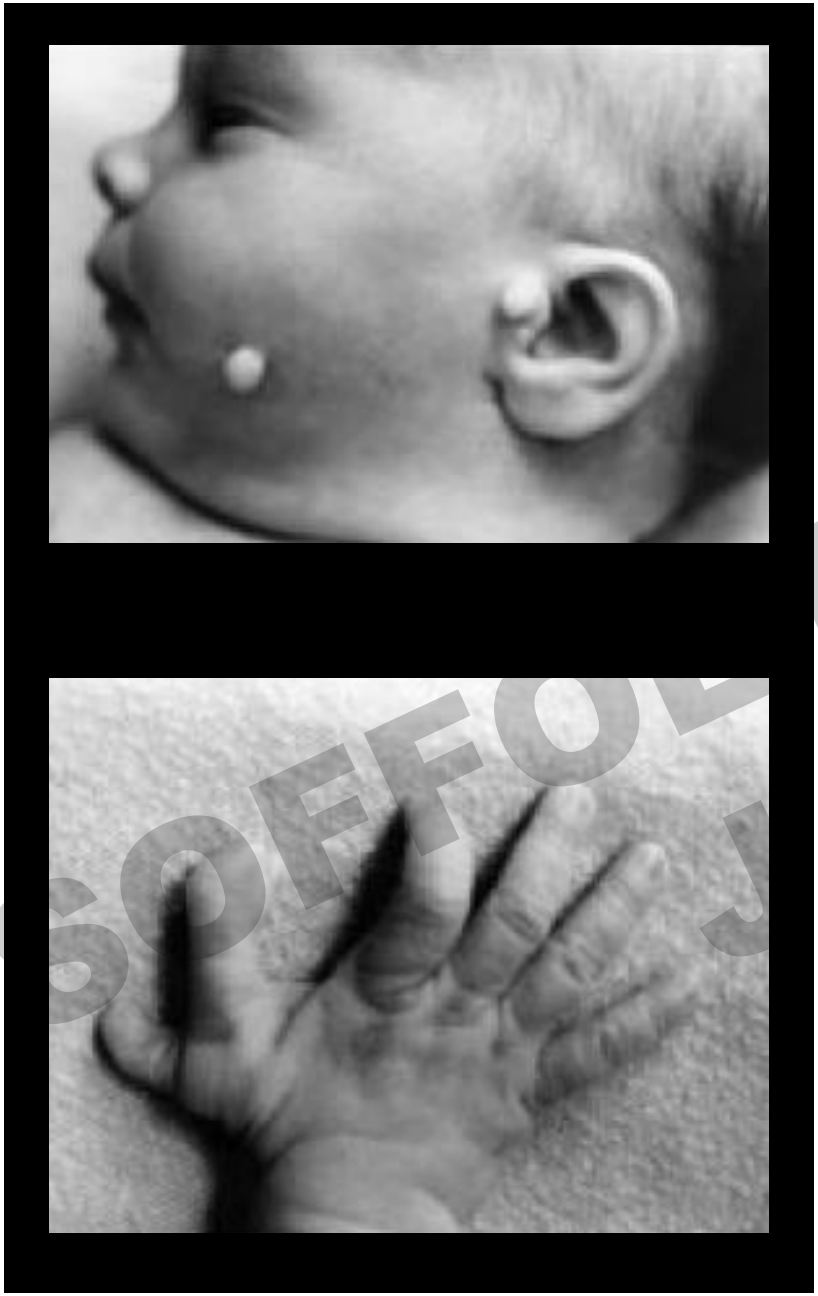
# Phenotype-Genotype Correlations at GLI3






*Am J Hum Genet* 2005; 76: 609–622

# Townes-Brocks



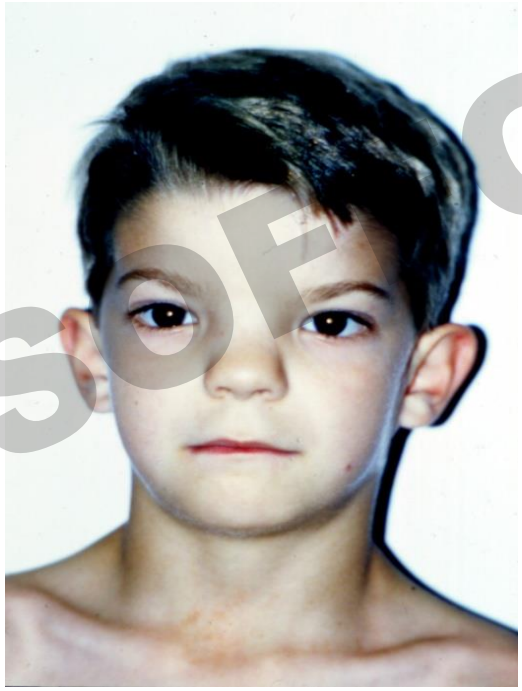
- Ear dysplasia, deafness
- Radial anomalies
- Anorectal malformations
- *Renal anomalies*

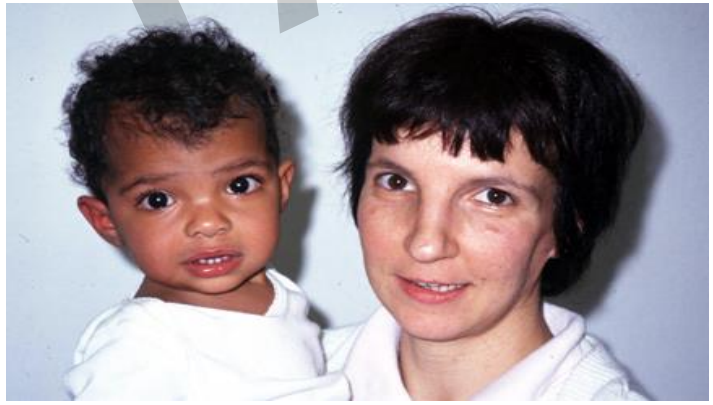
- AD
- *SALL1*

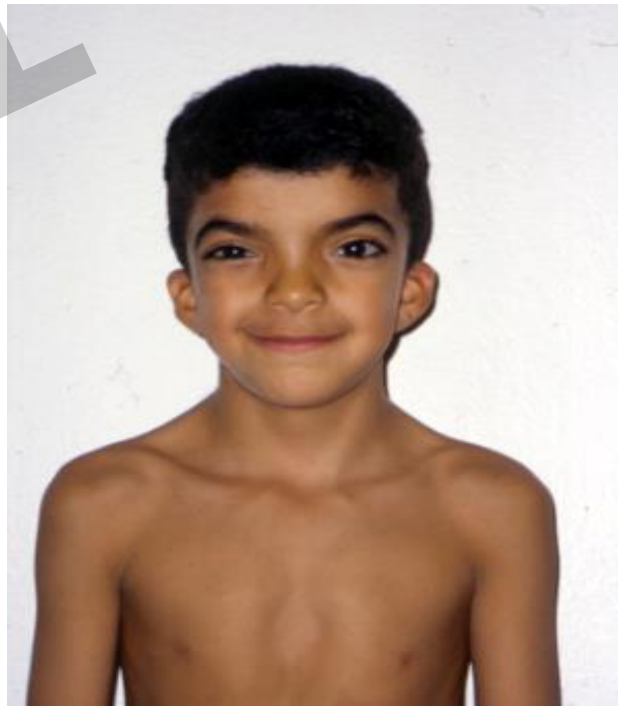
# Opitz (G syndrome)

- Hypertelorism
- Hypospadias
- Laryngeal cleft
- Anorectal malformation

- RLX / AD
- *MID1*



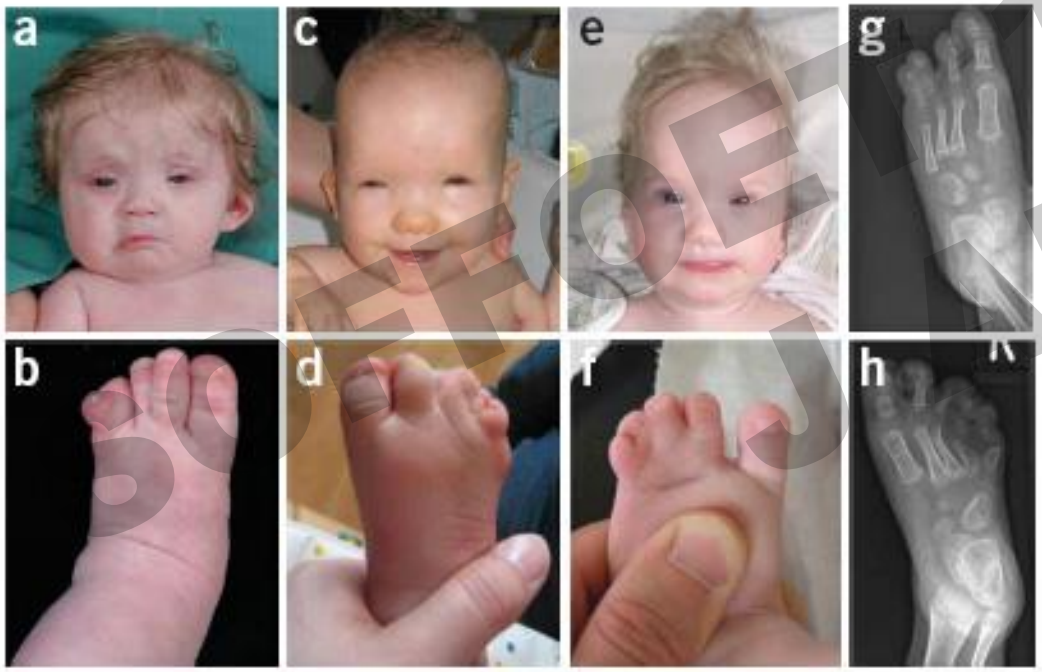


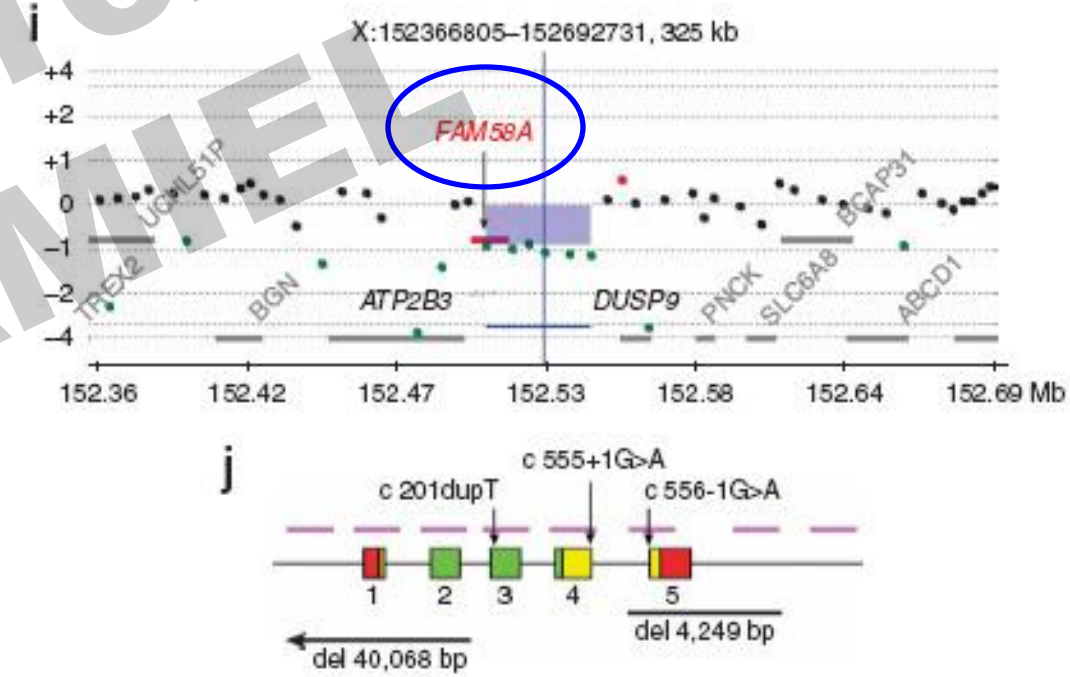


Pinson et al. ***J Med Genet*** 2004

# STAR Syndrome, XLD Condition

toe Syndactyly
Telecanthus
Anogenital malformation
Renal malformation



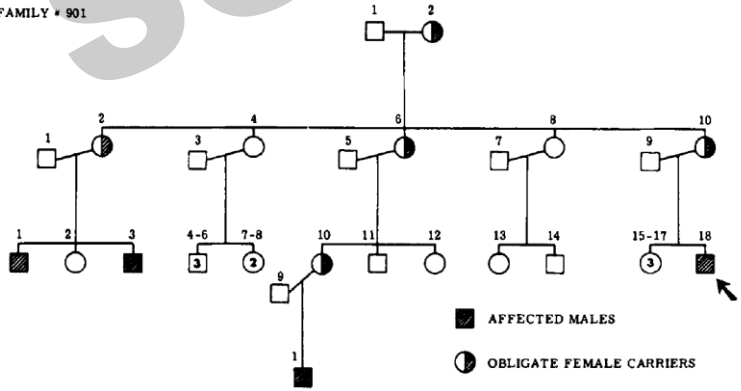

Unger el al. ***Nature Genetics*** 2008

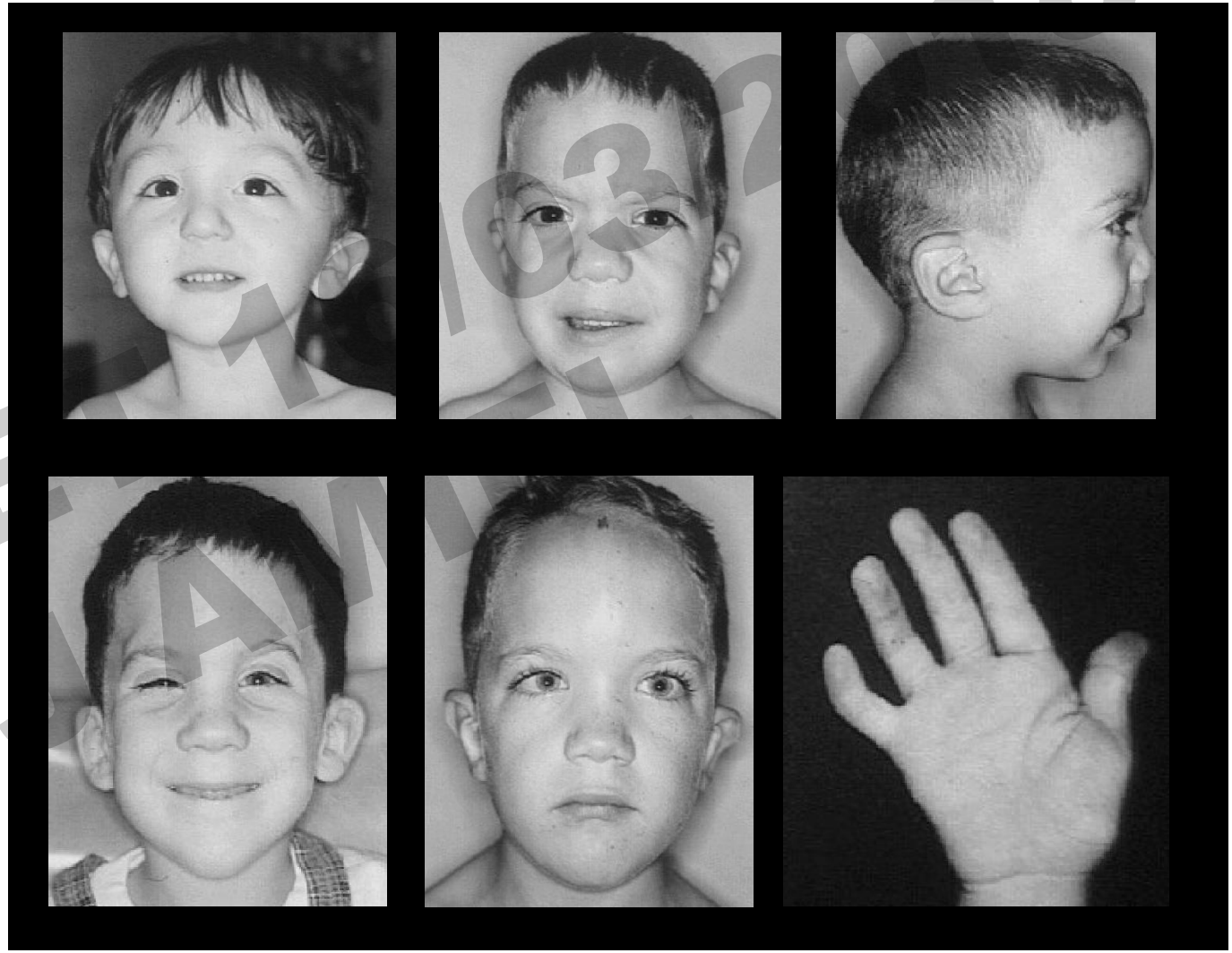
# Christian Syndrome, XLR

- XLR-ID

- Short stature
- Vertebral anomalies
- Anorectal malformation
- Brachy-clinodactylies
- Facial palsy
- Strabismus

- Xq27-qter



Christian et al. *Clin Genet* 1977
Dhouhy et al. *Hum Genet* 1987

# Association of Hirschsprung's disease and anorectal malformation: a systematic review

Alejandro D. Hofmann · Prem Puri



Retropective study of the literature from 1952 to 2013

- 38 articles, 90 cases: HD in 2% of the ARM, no sex biais
- Syndromes in 23 cases (55%)

| Type | Number |
|---|---|
| Currarino syndrome | 11 |
| Down's syndrome | 8 |
| Cat-eye-syndrome | 3 |
| Pallister-hall-syndrome | 1 |
| Total | 23 |

Hofmann and Puri. ***Ped Surg Int*** 2013

# « Associated » Anorectal Malformation

- Teratogenic

  Maternal Diabetes
  Thalidomide
  Alcool

  *Progesterone*
  (*maternal fever*)

# Anorectal Malformation and Animal Models

- Teratogens

  Adryamicine (rat and pig)
  ETU (rat)

  ] Low ARM

- Gli gene family and hindgut development in mice

  Gli2 $^{-/-}$ : low ARM
  Gli3 $^{-/-}$ : low ARM
  Gli2 $^{-/-}$,Gli3 $^{+/-}$ : high ARM

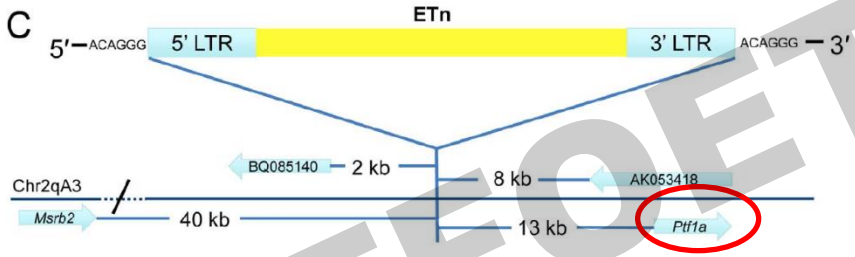


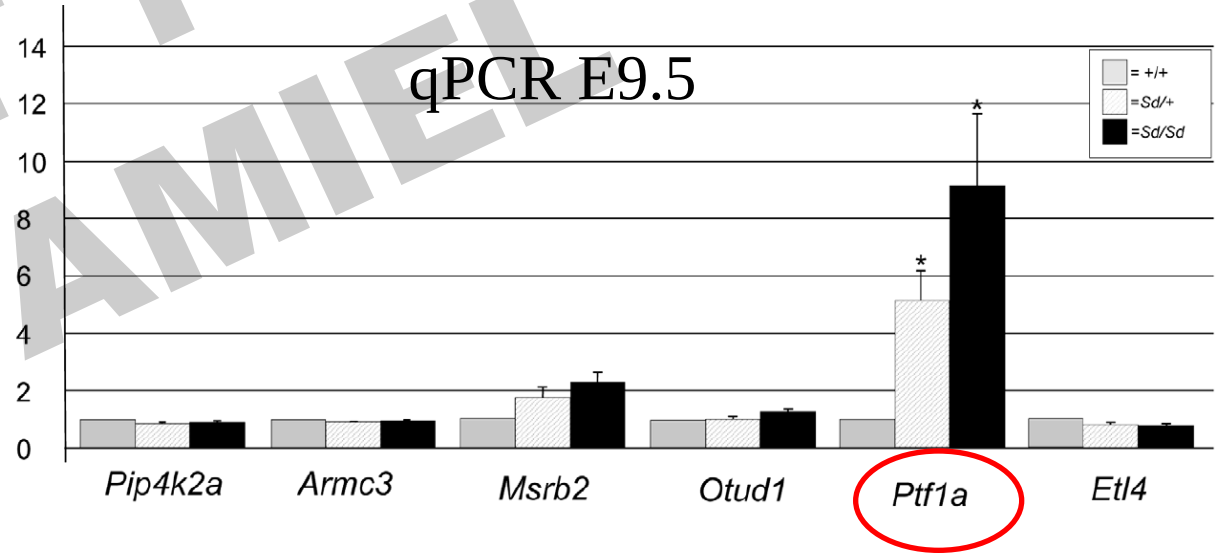
Kimmel et al. ***J Ped Surg*** 2000

# Anorectal Malformation and Animal Models

- Danforth's short tail (Sd) mice, semi dominant (vertebrae, urogenital, anal)

  Mice Model for caudal regression sequence




Pancreas specific TF1

Vlangos et al. *PLOS Genetics* 2013

# Mapping Loci Causing Susceptibility to Anal Atresia in Pigs, Using a Resource Pedigree

By Tetsuo Hori, Elisabetta Giuffra, Leif Andersson, and Haruo Ohkawa
*Tsukuba, Japan; Uppsala, Sweden; and Mito, Japan*

***J Ped Surg*** 2001



Incorporating *Mouse Genome*
**Mammalian Genome**
*Genes and Phenotypes*

2005

# Genetic analysis of anal atresia in pigs: evidence for segregation at two main loci

**Pamela Cassini,[1] Alberto Montironi,[1] Sara Botti,[1] Tetsuo Hori,[2] Haruo Okhawa,[2,3] Alessandra Stella,[1] Leif Andersson,[4] Elisabetta Giuffra[1]**

# Conclusion

- Frequent malformation
- Higher frequency in twins (isolated form and sequence)
- Sex biais
- Multiple congenital anomalies are frequent (hign ARM +++) chromosomal anomalies and sequence >> Syndromes
- A low recurrence risk for isolated forms

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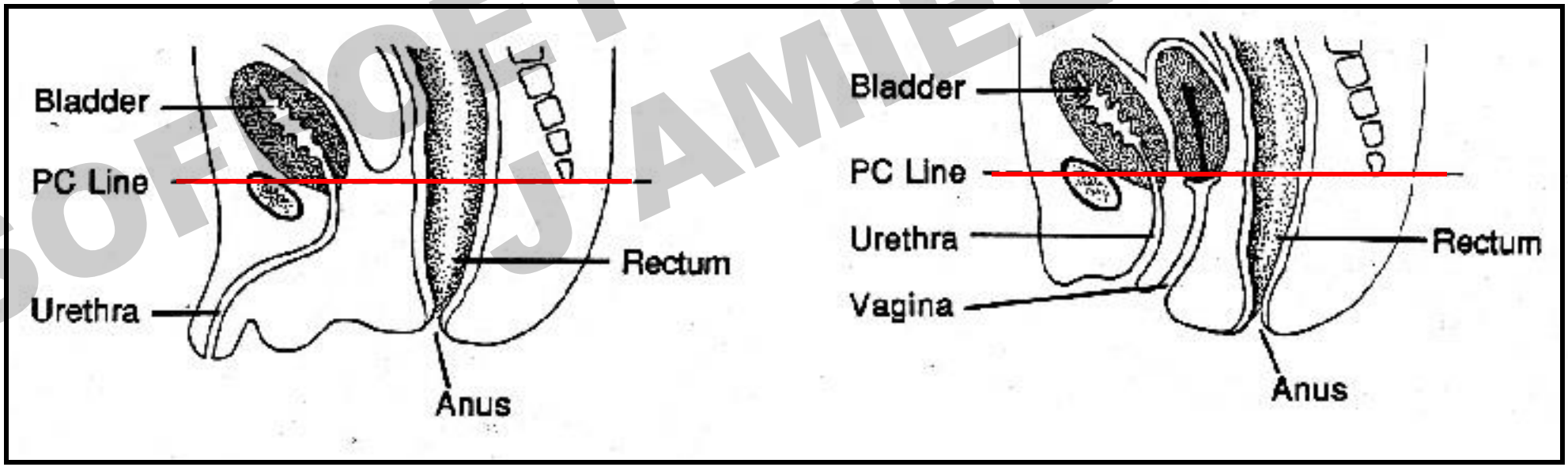
Hôpital Necker-Enfants Malades, Paris, France

# Malformation Anorectale : Définition

- Formation incomplète de l'intestin terminal

- Responsable d'une imperforation anale
  +/- fistule (recto-périnéale, recto-urogénitale)



# Malformation Anorectale : Bilan d'extension

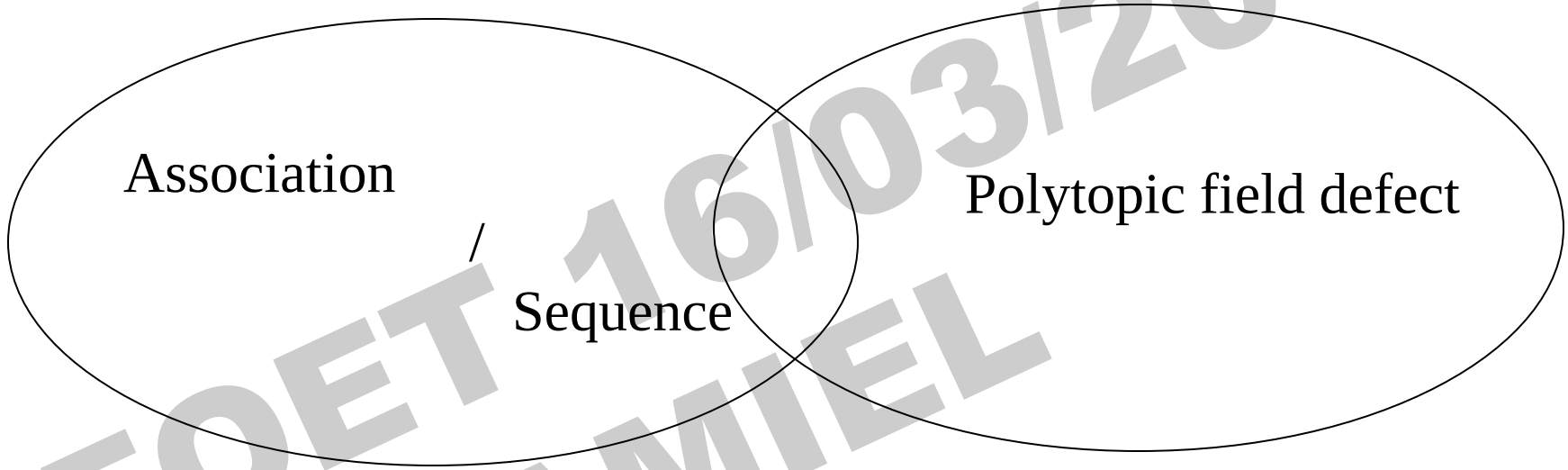
- Loco-régional
  Échographie pelvienne / rénale
  Uréthro-cystographie
  +/-IRM

## Contexte clinique et familial

- Radiographies de squelette

- Imagerie cérébrale
- Examen ophtalmologique
- Echographie cardiaque
- Caryotype

# Anorectal Malformation and Embryology



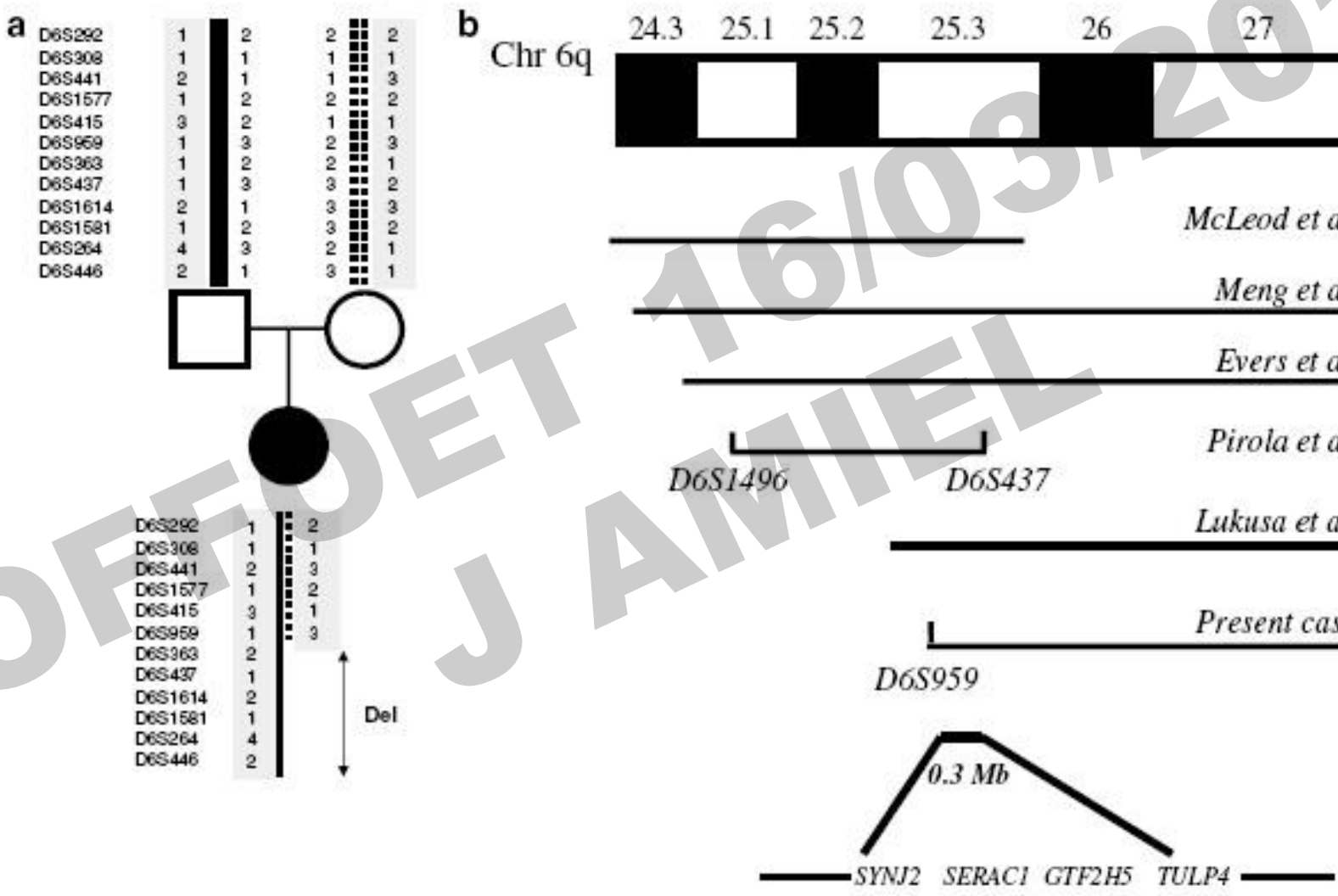

**Martinez-Frias et al. *Am J Med Genet* 1998;76:291-6**



- *Formes hautes / Formes basses*
  - Similar spectrum of associated malformations (except gastro-intestinal malformations)

(Boocock and Donnai. 1987)

# A Gene for Caudal Development in 6q25?






Titomanlio et al. ***Eur J Hum Genet*** 2006