CHARGE syndrome
An update

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Damien SANLAVILLE, Lyon
History

- **1979 (Hall-Hittner syndrome)**
  - Bryan Hall: 17 children with MCA and choanal atresia
  - HM Hittner: 10 MCA patients with coloboma

- **1981**
  - R Pagon: 21 patients
    - Coloboma
    - Heart disease
    - Atresia of choanae
    - Retarded growth and development
    - Genital hypoplasia
    - Ear anomalies / deafness
Epidemiology

- > 400 reports

- Canadian Pediatric Surveillance Programme (CPSP)
  - 1/8500

- North-America
  - 1/12500

- Europe
  - 1/110000 !!!

- Recurrence rate close to 1%
The typical presentation of CHARGE in NICU
Clinical aspects: face

- Square-shaped face
- Narrow bifrontal diameter
- Broad nasal bridge
- Small mouth with inverted V-shaped upper lip

- Facial asymmetry
  - Facial palsy
  - Dysplastic pinnae
- CL/P: 15-20%
The face (patients with CHD7 mutation)
Milder phenotype despite CHD7 mutation
Roma Dysmorpho - CHARGE syndrome
The eye

- Chorioretinal coloboma (75-90%)
  - with microphthalmia (40%)
  - often of posterior (fundoscopy +++)
  - Bilateral: 70-80%

- 20% of uveal coloboma have CHARGE
  - Most patients have preserved vision
  - Variable visual deficit
    - Photophobia (iris)
    - Loss of upper visual field (retina)
    - Low visual acuity (papilla)

- Risk of retinal detachment → regular follow up
Retinal coloboma (fetus)

Contrôle Normal

CHARGE

Roma Dysmorpho - CHARGE syndrome
ENT anomalies ( > 95%)

- External Ear Abnormalities
- Inner ear
  - labyrinthine dysplasia
    - complete absence of utricle and semicircular canals
    - with or without Mondini dysplasia of cochlea and saccule
  - Deafness; > 60% (conduct/mixed)
- Laryngomalacia
- Vocal Cord Paresis

- Choanal Atresia (35-65%) 
  - 1/3 to 2/3 of CA have CHARGE
Deafness

- By malformation of the auditive nerve VIII
- By malformation of the bony inner ear
- By malformation of the middle ear and ossicles
- By recurrent otites (facilitated if cleft or choanal atresia)
- Variable severity / asymmetry
Choanal atresia

- Prevalence: 1/5000 to 1/8000
- Females/Males: 2/1
- Unilateral 65-75%
- 75% with bilateral have CHARGE, or other syndromes
The ear

Tellier et al, 1998
The ear

Roma Dysmorpho - CHARGE syndrome
Agenesis of semi-circular canals

Morgan et al, 1993; Amiel et al, 2001
Cochlear functional anomalies

- Complete absence of nystagmic response to bithermal caloric stimuli
- Vestibulo-ocular responses
  - earth-vertical axis rotation: abolished
  - otolith vestibulo-ocular responses: preserved
- Delayed walking and balance disturbance
Reduced balances

- Delayed walking $> 2 \frac{1}{2}$ if vision OK
- Delayed walking $> 4$ if severe visual impairment
- "bizarre" way of moving without standing
- Unstable walking with falls and unusual position (spread legs,...)
- Tip toe, bare foot walking
- Importance of physical contact for postioning
- Difficulties in open space (loss of visual clues for vertical axis) vs. interior
Hypoplasia of SCC: visible on plain X ray in infancy

- Necessitates specific CT or MRI imaging
- Consequences
  - Contribute to deafness if associated with other anomalies
  - Reduced sense of head position
  - Reduced balance
Fig. 7. Chd7^{Gt/+} mice exhibit defects of the semicircular canals. Paint-filling of E16.5 fixed inner ears detects the lateral (lsc), posterior (psc), and anterior (asc) semicircular canals and part of the cochlea (co) in wild-type embryos (A) and absence of the lateral and posterior semicircular canals in Chd7^{Gt/+} (B, C). La, lateral ampulla; aa, anterior ampulla; pa, posterior ampulla.
GU malformations

- males: 80-90% - females: 15-25%
- Hypoplastic external genitalia
  - Micropenis and/or cryptorchidism : 80%
  - Hypoplastic labiae majorae : 1/3
- Urinary tract anomalies
  - 10-40%
  - Non-specific (renal ectopia, horseshoe kidneys, ureteral anomalies...)

03/08 Roma Dysmorpho - CHARGE syndrome
Other visceral anomalies

- Congenital heart defects (CHD)
  - 50 to 85% of cases
  - Conotruncal defects: 75%
    - Fallot tetralogy (1/3)
    - AVC, VSD, ASD, CoAo, PDA
    - Aberrant subclavian arteries

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Immune deficiency

- Uncommon and variable
  - impaired T-cell proliferation
  - T-cell lymphopenia
  - IgG2 subclass deficiency
  - Rarely: DiGeorge syndrome
Orthopedic problems

- Minor limb anomalies 1/3
- Spine
  - vertebral fusions
  - Hemivertebrae
  - abnormal cervico-cranial junction
- Scoliosis
  - 60% of patients beyond infancy
CNS malformations

- 55% to 85%
- Arhinencephaly or hypoplastic olfactory bulbs
  - Often overlooked but excellent sign
  - > 90% if MRI
  - Absence of reaction to disgusting odors
  - Interferes with eating
    - Absence of interest for « good smells »
    - Preferences for salty/spicy food
- Holoprosencephaly: rare
- Others
  - Forebrain: dysgenesis of the frontal lobe, agenesis of the septum pellucidum, nodular heterotopias, lissencephaly,…
  - Hindbrain: Dandy-Walker anomaly, vermis hypoplasia, stenosis of Sylvius aqueduct
Arhinencephaly

Control

A : olfactory groove  B : olfactory bulb

CHARGE

A : olfactory groove  B : olfactory bulb

Lin et al, 1990
Arhinencephaly

Normal control

CHARGE
Rhombencephalic dysfunction & cranial nerves

- All cranial nerves can be affected
- Congenital facial palsy usually asymmetric or unilateral: 50%-90%
- III and VI (2%)
- IX and/or X (31%)
  - Pharyngeal incoordination
  - Posterior palate weakness
  - Feeding and swallowing difficulties: 80%
  - Aspiration / choking: 30%
  - Distorted taste
- G-tube feeding/gastrostomy for months or years
  - may result in Moebius sequence.
Rhombencephalic dysfunction & cranial nerves

- Complex dysregulation of brainstem functions
- Thermal dysregulation
- Irregularities of cardiac rhythm
Hypothalamo-hypophyseal dysfunction

- Low normal BW & BL (10\textsuperscript{th} centile)
- Postnatal growth retardation
  - Feeding difficulties / surgery
  - Catch up after infancy
  - GH deficiency : rare
  - Osteoporosis in elder patients (malnutrition, steroids insufficiency)
- Hypothalomo-hypopituitary control of gonadotrophin varies during life
  - hypogonadotropic hypogadadism
  - Hormone substitution
  - Delayed/absent puberty : 2/3 of cases
Mental retardation

- Delayed early motor milestones
  - vestibular and visual impairments
  - Sitting > 1, walking: 24 and 36 months

- Mental retardation (MR)
  - IQ from normal (115) to severe MR
  - IQ < 70 in > 70% of cases
  - 50%: MRI evidences of anoxo-ischemic brain lesions
  - Correlated with extensive bilateral coloboma, microcephaly, and brain malformation
Behavior

- Relatively low adaptive behavior skills
- Significant motor impairments
- Common disturbances
  - obsessive-compulsive disorder
  - attention deficit disorder
- Inhability in verbal communication
  - Think that communication is central
  - But deafness and poor vision are problematic
  - Decreased ability to understand
  - Use non verbal system if necessary (ictograms, gestures)
- Autism
  - Secondary to combined sensory impairments?
  - Or “true” autism
Diagnostic criteria: R Pagon et al, 2001

- **Major criteria**
  - 1. Choanal atresia
  - 2. Ocular coloboma

- **Minor criteria**
  - 1. Heart defects of any type
  - 2. Atresia of the choanae,
  - 3. Retardation (of growth and/or of development),
  - 4. Genital anomalies
  - 5. Ear anomalies (abnormal pinnae or hearing loss)

- 4 criteria out of 6, and at least one major.
Clinical criteria

☐ Pagon’s criteria
  ■ Do not include radiological elements (CT/MRI)
  ■ Overlook neurological difficulties from brainstem dysfunction
  ■ The acronym is tricky, but not completely relevant
Blake criteria (1998):

Principle: 4M or 3M + 3 minor

Major
- 1. Coloboma
- 2. Choanal atresia
- 3. Characteristic ear abnormalities - external ear (lop or cup-shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects
- 4. Cranial nerve dysfunction - facial palsy (unilateral or bilateral), sensorineural deafness and/or swallowing problems
Blake criteria: minor

- 1. Genital hypoplasia - males: micropenis, cryptorchidism; females: hypoplastic labia; both males and females: delayed, incomplete pubertal development
- 2. Developmental delay
- 3. Cardiovascular malformations
- 4. Growth deficiencies - short stature, growth hormone deficiency
- 5. Orofacial cleft - cleft lip and/or palate
- 6. Tracheoesophageal-fistula - tracheoesophageal defects of all types
- 7. Characteristic face - sloping forehead, flattened tip of nose
Major (more specific)

1. Ocular coloboma ( > 80%)
2. Choanal atresia (50%)
3. Hypoplasia of semi-circular canals (> 95%)

Minor (less specific)

1. Rhombencephalic dysfunction (brainstem and cranial nerve III to XII anomalies, including sensorineural deafness) : > 90%
2. Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin defects) > 70%
3. Malformation of the ear (internal or external) > 80%
4. Malformation of mediastinal organs > 40%
5. Mental retardation >90%

Typical: 3M or 2M + 2m
Partial 2M + 1 m Atypical : 2M or 1M + 2m
CHARGE is a genetic syndrome, not an association

- Concordance in MZ twins
- Familial recurrences
- Increased paternal age
- 10 cases with (non recurrent) chromosomal anomalies
Etiologies

- Chromosome anomalies
  - del11qter & del13qter (coloboma, CHD, HPE)
  - Del22q11: rare +++

- Teratogens
  - thalidomide, retinoic acid, hydantoines, alcohol, maternal diabetes ???

- Genes
  - CHD7  58%-64%
  - SEMA3E (7q21)
    - 2 patients (Lalani): 1 t and one S703L
## Cytogenetics anomalies in CHARGE

### Table 1. Chromosome anomalies and clinical features in patients diagnosed with CHARGE association

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Ref</th>
<th>C</th>
<th>H</th>
<th>A</th>
<th>R</th>
<th>G</th>
<th>E</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XY,t(2;7)(p14;q21.11)</td>
<td>(19)</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4/6</td>
</tr>
<tr>
<td>45,XX,-3,-22, + der(3)t(3;22)(p25.1;q11.1)mat</td>
<td>(5)</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>girl</td>
<td>3/6</td>
</tr>
<tr>
<td>46,XY,+del(3)(pter p21.2::p12 qter)</td>
<td>(17)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6/6</td>
</tr>
<tr>
<td>46,XX,inv dup (14)(q22-q24.3)</td>
<td>(16)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6/6</td>
</tr>
<tr>
<td>46,XX,t(6;8)(6p8p:6q8q)</td>
<td>(18)</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>4/6</td>
</tr>
<tr>
<td>46,XY,-18,der(18)(2;18)(q37.3;q22.3)mat</td>
<td>(5)</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>4/6</td>
</tr>
<tr>
<td>46,XX, + 18</td>
<td>(14)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>4/6</td>
</tr>
<tr>
<td>46,XX,der(21)t (19;21)(q13.1;q22.3)mat</td>
<td>(12)</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>4/6</td>
</tr>
<tr>
<td>46,XX,del 22q11.2</td>
<td>(13)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5/6</td>
<td></td>
</tr>
<tr>
<td>46,X,der(X)t(X;2)(p22,1;q33)</td>
<td>(15)</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5/6</td>
</tr>
</tbody>
</table>

Present study

Patient 5  
Patient 7  

C: coloboma; H: heart defect; A: choanal atresia; R: retarded growth and/or anomalies of the central nervous system; G: hypogonadism; E: ear anomalies and/or deafness
Vissers et al. Nat Genet 2004

2,3 Mb
9 gènes
CHD7 gene

- 8q12.1
- cDNA 10 kb / 188 kb
- 38 exons: 37 coding exons and one non-coding exon
- 2997 aa
- Domains
  - 2 chromo (chromatin organization modifier)
  - 1 SNF2/SWI
  - 1 helicase
  - 2 BRK domains

03/08 Roma Dysmorpho - CHARGE syndrome
# Review of published molecular data

<table>
<thead>
<tr>
<th></th>
<th>Jongmans</th>
<th>Lalani</th>
<th>série Fr.</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Non sense</td>
<td>31 (45%)</td>
<td>28 (44%)</td>
<td>27 (36%)</td>
<td>86 (42%)</td>
</tr>
<tr>
<td>Frameshift</td>
<td>17 (25%)</td>
<td>19 (30%)</td>
<td>32 (43%)</td>
<td>68 (33%)</td>
</tr>
<tr>
<td>Splicing</td>
<td>13 (19%)</td>
<td>10 (16%)</td>
<td>7 (9%)</td>
<td>30 (14%)</td>
</tr>
<tr>
<td>Missense</td>
<td>8 (12%)</td>
<td>7 (11%)</td>
<td>8 (11%)</td>
<td>23 (11%)</td>
</tr>
</tbody>
</table>

|                 | 69        | 64        | 74        | 207     |

ATG  

TAA  

03/08 Roma Dysmorpho - CHARGE syndrome
## Clinical data on patients with a mutation

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
<th>+</th>
<th>-</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Colobome</td>
<td>47</td>
<td>10</td>
<td>82%</td>
</tr>
<tr>
<td>H</td>
<td>Cardiopathie</td>
<td>46</td>
<td>11</td>
<td>81%</td>
</tr>
<tr>
<td>A</td>
<td>Atrésie des Choanes</td>
<td>21</td>
<td>34</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>Fente labiale ou palatine</td>
<td>18</td>
<td>36</td>
<td>33%</td>
</tr>
<tr>
<td>R1</td>
<td>Retard croissance</td>
<td>25</td>
<td>27</td>
<td>48%</td>
</tr>
<tr>
<td>R2</td>
<td>Retard de développement</td>
<td>32</td>
<td>3</td>
<td>91%</td>
</tr>
<tr>
<td>G</td>
<td>Anomalie génitale</td>
<td>33</td>
<td>17</td>
<td>66%</td>
</tr>
<tr>
<td>E1</td>
<td>Anomalies de l'oreille externe</td>
<td>56</td>
<td>1</td>
<td>98%</td>
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<tr>
<td>E2</td>
<td>Surdité</td>
<td>39</td>
<td>2</td>
<td>95%</td>
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<td>E3</td>
<td>Anomalies des CSC</td>
<td>43</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Paralysie/ asymétrie faciale</td>
<td>34</td>
<td>7</td>
<td>83%</td>
<td></td>
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<tr>
<td>Arh/ anomsie</td>
<td>26</td>
<td>1</td>
<td>96%</td>
<td></td>
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<tr>
<td>Corps calleux</td>
<td>4</td>
<td>32</td>
<td>11%</td>
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<tr>
<td>Fosse postérieure</td>
<td>18</td>
<td>21</td>
<td>46%</td>
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<td>Autres anomalies SNC</td>
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<td>18</td>
<td>49%</td>
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<td>Oesophage</td>
<td>8</td>
<td>34</td>
<td>19%</td>
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<tr>
<td>Thymus</td>
<td>12</td>
<td>16</td>
<td>43%</td>
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<td>Reins</td>
<td>10</td>
<td>37</td>
<td>21%</td>
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<td>Extrémités</td>
<td>14</td>
<td>28</td>
<td>33%</td>
<td></td>
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<td>Squelettiques</td>
<td>15</td>
<td>27</td>
<td>36%</td>
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<tr>
<td>Retard langage</td>
<td>26</td>
<td>1</td>
<td>96%</td>
<td></td>
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<td>Retard moteur</td>
<td>28</td>
<td>0</td>
<td>100%</td>
<td></td>
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<tr>
<td>Troubles comportement</td>
<td>12</td>
<td>12</td>
<td>50%</td>
<td></td>
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<tr>
<td>Dysmorphie</td>
<td>43</td>
<td>3</td>
<td>93%</td>
<td></td>
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<tr>
<td>Difficultés alimentaires (DNTC)</td>
<td>39</td>
<td>0</td>
<td>100%</td>
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<tr>
<td>Polyhydramnios</td>
<td>13</td>
<td>27</td>
<td>33%</td>
<td></td>
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</tbody>
</table>

| Age paternel                                     | 34 ans 4 mois |
| Age maternel                                     | 30 ans 5 mois |
Clinical data on fetuses with a mutation

<table>
<thead>
<tr>
<th>Acronyme</th>
<th>Clinique</th>
<th>+</th>
<th>-</th>
<th>%</th>
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<tbody>
<tr>
<td>C : Colobome</td>
<td>7</td>
<td>5</td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>H : Cardiopathie</td>
<td>11</td>
<td>1</td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>A : Atrésie des Choanes</td>
<td>6</td>
<td>6</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>R1 : Retard croissance</td>
<td>0</td>
<td>12</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>R2 : Retard de développement</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G : Anomalie génitale</td>
<td>7</td>
<td>5</td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>E1 : Anomalies de l'oreille externe</td>
<td>12 0</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2 : Surdité</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3 : Anomalies des CSC</td>
<td>12</td>
<td>0</td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

| Malformations / Anomalies    |          |   |   |    |
| Oesophage                    | 3        | 9 |   | 25%|
| Thymus                       | 7        | 5 |   | 58%|
| Reins                        | 4        | 8 |   | 33%|
| Extrémités                   | 6        | 6 |   | 50%|
| Squelettiques                | 5        | 7 |   | 42%|

| Développement                |          |   |   |    |
| Retard langage               | 0        | 0 |   |    |
| Retard moteur                | 0        | 0 |   |    |
| Troubles comportement        | 0        | 0 |   |    |

| Autres                       |          |   |   |    |
| Dysmorphie                   | 12       | 0 |   | 100%|
| Difficultés alimentaires (DNCT) | 0 0 |     |
| Polyhydramnios               | 4        | 8 |   | 33%|

| Age paternel                 | 35 ans 9 mois |
| Age maternel                 | 29 ans 6 mois |
CHARGE mosaics

Germline mosaic

Somatic mosaic / expression variability?

Lalani et al. 2006
Familial CHARGE syndrome

Patient 1 at 12 years old
Patient 2 at 5 years old

- Coloboma of optic disc
- Vestibular dysfunction and hypoplastic semicircular canals
- Vestibular dysfunction
- Malformations of mediastinal organs
- Mental retardation
- Abnormal external ears
- Sensorineural deafness
Role of CHD7

- MI-2/CHD family of chromodomain proteins
  - Chromo domains
    - Recognition of lysine-methylated histone tails
  - SWI/SNF2
    - in proteins with DNA-dependent ATPase activity
  - Helicase domain
    - DNA strand separation during replication, repair, recombination

- Role in Nucleosome Remodeling and Deacetylation complex (NuRD)?
Role of CHD7

- CHD7 & Neural crest cell
  - Convincing: choana, coloboma, ear
  - Not clear: CHD, mental handicap
  - Unexplained / secondary
    - Growth retardation
    - Hypogonadism
CHD7 expression in human development (T Attié)

3 weeks

4 weeks

5 weeks

Embryo

Vitelline vesicle

Ubiquitous

CNS

CNS

Neural crest derivatives
Inner ear

03/08 Roma Dysmorpho - CHARGE syndrome
7 weeks

- Brain
- Foie
- Olfactive tracts
- CSC
- Retina

03/08 Roma Dysmorpho - CHARGE syndrome
8 ½ weeks

Nasal epithelium

Pituitary gland

- Expression correlated with CHARGE signs
- No cardiac expression
- Pituitary ?

03/08 Roma Dysmorpho - CHARGE syndrome
What about orphan CHARGE syndrome?

☐ No obvious clinical differences
☐ Diagnostic errors
  ■ Evolving criteria
☐ Missed mutations
  ■ 3’UTR, 5’UTR
  ■ Promotor
  ■ Undescribed exons
  ■ Small deletions (Kosaki et al.)
☐ Phenocopies
☐ Genetic heterogeneity?
Prenatal diagnosis

Roma Dysmorpho - CHARGE syndrome
Ears in 2D at 25 wg

Roma Dysmorpho - CHARGE syndrome
Hypoplasia of SCC

Normal control

CHARGE

03/08 Roma Dysmorpho - CHARGE syndrome
23 weeks
Arhinencéphaly

MRI

03/08 Roma Dyemorpho - CHARGE syndrome
Prenatal strategy for CHARGE syndrome

Common revealing signs
Digestive / Heart / Cleft / Brain malformations / Hydramnios

Ultrasound

External ear → 32 WG
SCC hypoplasia < 26 WG

MRI
Arhinencephaly
Vermis hypoplasia
SCC hypoplasia
Coloboma

< 26 WG

> 26 WG
Thank you for your attention

From: chargesyndrome.ca
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