THE RING 14 SYNDROME: CLINICAL AND MOLECULAR DEFINITION OF A RARE CONDITION

Marcella Zollino

Genetica Medica, Università Cattolica Sacro Cuore, Roma

4th European Course on Clinical Dysmorphology, Rome 2011
Ring 14
structural rearrangement of one chromosome 14 to form a ring
Chromosome 14

- Coding genes: 700
- Imprinted genes: cluster at 14q32.2
  
  **MEG3**: maternal monoallelic expression
  **DLK1, RTL1, DIO3**: paternal monoallelic expression

*Figure 1. Schematic map of the 14q32.2 imprinted region. Loci on chromosome 14 represent markers used for microsatellite polymorphism analysis. Paternally expressed genes are shown in blue, maternally expressed genes in red, and...*
Chromosome 14

**UPD(14)pat**
- MR
- seizures
- typical skeletal anomalies

**UPD(14)mat**
- Prader-Willi-like phenotype
- mild MR
- precocious puberty
Ring chromosome 14

- First described in 1971 (Gilgenkrantz et al)

- A rare genetic condition, over 50 cases reported
  - Psychomotor delay
  - Seizures
  - Hypotonia
  - Microcephaly
  - Retinitis pigmentosa
  - Characteristic face

- Limited clinical and genetic characterization

- Pathogenic mechanisms unknown
Ring chromosomes: mechanisms of origin

Non Homologous End Joining (NHEJ)

Deleted ring

end-to-end fusion

Undeleted ring
Ring inv dup/del
Ring: Mitotic instability

Interweaved rings

Double ring

+ ring

SCE
Pathogenic mechanisms

Positional effect

• Telomere position effect (TPE): gene silencing in the proximity of the telomere
Positional effect

Heterochromatin spreading: silencing of genes within the proximal 14q region
SUBJECTS: 42

• 27 Ring 14
  15 males/12 females
  Aged: 3-36 years

• 10 linear 14q deletions
  5 males/5 females
  Aged: 1-33 years

• 1 balanced translocation t(10;14)(q25.3;q12)

• 4 unbalanced translocations
  → proximal 14q (q11) deletion: 2 subjects
  → distal 14q (q32) duplication: 2 subjects
Genetic Tests

PERIPHERAL BLOOD LYMPHOCYTES

1. **R banding (100 cells)**

2. **Array-CGH** (Agilent, 44k or 244k)

3. **Microsatellite segregation analysis**
1) R-Banding (100 cells)

Mosaicism with monosomy 14: 27/27 100%

46,r(14)/45,-14
46, r(14) [80%]/45, -14 [20%] mosaicism in all patients
2) a-CGH

- Complete rings 5/27 19 %
- Deleted rings 20/27 74 %

**Deletion size:** 0.3-5 Mb

*MEG3 and DLK1* preserved

- Ring with deletion + duplication (2.7 and 9.4 Mb) 2/27 7 %
Genetics: results

3) Microsatellite segregation analysis

UPD(14) never detected
Heritability: most de novo

1/27: low mosaicism in the healthy father

Parental origin: 70% paternal, 30% maternal

↓

no different clinical outcome
To summarize

- *De novo occurrence*
- *Mosaic status with monosomy 14*
- *Paternal origin*
- *Rings: deleted only, complete, deleted and duplicated*
- *No imprinting disturbances*

are the more relevant genetic features
Clinical signs

Ring 14: perinatal period

Pregnancy  uneventful
           IUGR uncommon

Delivery  at term
           normal
           (caesarean section uncommon)

Birth  normal weight
       (low BW in rings with large 14q deletions)
       normal length
       head circumference normal
       microcephaly possible
Ring 14: facial characteristics

- High forehead
- Linear eyebrows
- Hypolastic supraorbital ridges
- Deep set eyes
- Short palpebral fissures/ hypotelorism
- High nasal bridge
- Long/asymmetric face
- Full cheeks
- Small downturned mouth
- Ear anomalies
Deletion within the ring
No detectable deletion within the ring 14
Ring 14 : Physical anomalies

Major malformations absent
Minor skeletal anomalies (scoliosis)
Café-au-lait spots
Ocular anomalies
Ring 14: ocular anomalies

- Strabismus
- Myopia
- Abnormal macula
- ABNORMAL RETINAL PIGMENTATION
- Retinitis pigmentosa (1 subject)
- Glaucoma
Hypotonia 23/27

Seizures

severe 24/27

usually drug-insensitive

mild 3/27 (undeleted rings:2
del (4Mb)+dup(9.4Mb):1

Ring 14 : neuropsychology
Ring 14: neuropsychology

Intellectual disability  25/27
  moderate to severe

Normal intelligence/mild ID  2/27
  complete ring
  mild seizure disorder
Ring 14: behavior

- Quiet
- Autistic traits
- Hypercinetic/aggressive
- Social, loving
- Episodes of self aggressiveness

IN GENERAL

Good natured behavior, with iperactivity and occasional aggressiveness, autistic component
Ring 14 : CNS anomalies (brain MRI)

- Diffuse supratentorial hypoplasia
- Ventricular dilatation
- Corpus callosum anomalies (agenesis or hypoplasia)
- Hyppocampal abnormalities
Ring 14 : natural history

- Physical evolution:
  Facial characteristics: worsening, but can be stable
  Short stature
  Microcephaly
  Scoliosis

- Susceptibility to infections
Ring with deletion
Ring with deletion

M.A.
Ring without deletion
Ring without deletion
Ring 14: natural history

- Seizure disorder
  - Onsent: 3-6 months
  - 6 weeks-3 years
  - Decrease/stop possible: 10-12 years

- Precocious puberty possible
To summarize

- **EPILEPSY**
- **Intellectual disability**
- **Susceptibility to infections**
- **ABNORMAL RETINAL PIGMENTATION**
- **Behavior disorders**

are the more relevant clinical signs
Ring 14: prognostic factors

- Deletion within the ring
- Monosomic cell line (inverted correlation)
- Severity of the seizure disorder
Ring 14: pathogenesis

- Candidate genes?
- “ring” effects?
Linear 14q deletions

Distal

2 ys

8 ys

del(14)q31.3q32.2

32 ys

del(14)q24.3q32.12

Proximal

del(14)(q11.2)

del(14)(q11.1q11.2)
Linear 14 q deletions proximal

- **EPILEPSY**
- **Intellectual disability**
- **RETINAL ANOMALIES**
Linear 14 q deletions

distal

• Intellectual disability
• Scoliosis
• Behavior disorders
• Susceptibility to infections
Extent and mapping of different deletions

Deletions within rings
Duplication within rings
Linear deletions

* Breakpoint in t(10;14)
<table>
<thead>
<tr>
<th></th>
<th>Ring 14</th>
<th>Linear 14q deletions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Seizures</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ID</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Susceptibility to infections</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Behavior disorders</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acquired microcephaly</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Phenotypic map

- Visual impairment
- Epilepsy
- Microcephaly
- MR (+/-)
- Brain abnormalities

- Susceptibility to infections
- MR (+)
- Behavior disorders
- Scoliosis

Genes
- 14q11.2q12
  - NRL
  - RPGRIP1
  - FOXG1
- 14q32
  - IGH
### Linear 14q Proximal Deletions

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(14)(q11.2)</td>
<td>del(14)(q11.1q11.2)</td>
<td>Balanced t(10;14) (q25.3;q12)</td>
</tr>
</tbody>
</table>

FISH: FOXG1 not included

<table>
<thead>
<tr>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonia</td>
</tr>
<tr>
<td>Microcephaly</td>
</tr>
<tr>
<td>MR</td>
</tr>
</tbody>
</table>

**Impaired FOXG1 expression?**
Future: "Omics"

MATERIAL
- fibroblast cell lines 4
- mRNA from fresh blood samples 10
- lymphoblastoid cell lines 35

METHODS
- focus on FOXG1
- transcriptome
Collaborations

Giovanni Neri,
Laura Seminara, Daniela Orteschi, Stefania Ricciardi, Marina Murdolo,
Giuseppe Gobbi, Simona Giovannini, Elvio Della Giustina,
Paola Martinelli, Angela Scarano

Istituto di Genetica Medica, Università Cattolica del S. Cuore, Roma;
Neuropsichiatria Infantile, Ospedale Maggiore, Bologna;
Neuropsichiatria Infantile, Arcispedale S. Maria Nuova, Reggio Emilia
ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support of the “Associazione Ring 14”

We also thank the patients and the families for participating in this study
Lymphoblastoid cell lines

Real time PCR mRNA *FOXG1*

<table>
<thead>
<tr>
<th></th>
<th>t(10;14)</th>
<th>deleted ring</th>
<th>linear del</th>
<th>complete ring</th>
<th>controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>RQ</td>
<td>50</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
Real time PCR mRNA FOXG1  skin fibroblasts