Silver-Russell syndrome

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Silver-Russell syndrome

• Clinical features

• Genetic heterogeneity
  – mUPD7
  – 11p15 hypomethylation

• Epigenotype-phenotype correlation
Silver-Russell syndrome

• Two children with LBW, short stature and asymmetry described by Silver in 1953

• 5 further children with LBW, distinctive facial features and asymmetry (in 2) described by Russell in 1954

• Term Silver-Russell Syndrome used from 1970s

• Difficult clinical diagnosis
Silver-Russell syndrome

‘Classic’ SRS if ≥4 of:

• Intrauterine growth retardation
• Postnatal short stature
• Relative macrocephaly
• Triangular facial appearance
• Asymmetry

Price et al., 1999
Mean final height around -4.2 SDS
Silver-Russell syndrome: facial features

- Frontal bossing
- Low set posteriorly rotated ears
- Down-turned corners of the mouth
- Micrognathia/ dental crowding
Silver-Russell syndrome: Asymmetry

~1/3 patients with a clinical diagnosis of SRS are asymmetric

Price et al., 1999
Silver-Russell syndrome: Hands/feet

- 5th finger clinodactyly
- Later contractures
- 2/3 toe syndactyly
Silver-Russell syndrome: other problems

• Severe feeding difficulties
• Learning difficulties- usually mild
• Speech delay
• Hypoglycaemia/ sweating
• Male genital anomalies/ other anomalies
• Over investigation for failure to thrive
Genetic testing in SRS:

Genetically heterogeneous
  – mUPD7
  – 11p15 hypomethylation
mUPD7

- mUPD7 in 4/35 SRS patients (Kotzot et al. 1995)
- ~5-10% SRS patients
- Likely imprinting effect
- Two key candidate regions on chr 7
  - 7p11.2-p13
  - 7q31-qter
Human chromosome 7

7p11.2–p13
Duplicated in 2 SRS patients

IGFBP1
IGFBP3
GRB10
EGFR

SGCE

7q31–qter
Segmental mUPD in 1 SRS patient

MEST
CIT1
γ–2COP

Homologous mouse imprinted regions

Chromosome 11

Prenatal growth retardation
T41Ad

Grb10
U2af1
-rs1

Homologous to human 7p11.2–p13
Prenatal overgrowth
Homologous to human chromosome 5

Chromosome 6

Early embryonic lethality
T77H

Growth retardation
T6Ad

γ–2COP
Mit1
Mest

Sgce
Genetic testing in SRS: chromosome 11p15

• Few SRS patients described with maternally derived duplication of 11p15

• Could SRS be genetic opposite of BWS?
Imprinted gene cluster at 11p15.5

**IC1 DMR**
- Maternal allele unmethylated
- Paternal allele methylated

**IC2 DMR (KvDMR1)**
- Maternal allele methylated
- Paternal allele unmethylated

- Paternally expressed
- Maternally expressed
ICR1: H19/IGF2 expression

Maternal

IGF2

DMR

H19

CTCF

Paternal

IGF2

CH₃ CH₃ CH₃ CH₃

CH₃ CH₃

H19

CTCF
Genetic testing in SRS: chromosome 11p15

- 5/9 SRS patients found to have loss of methylation in ICR1 of the 11p15 region
- Results in over-expression of $H19$ and down regulation of $IGF2$

Gicquel et al., 2005
Genetic testing in SRS: chromosome 11p15

- More recent studies suggest 40-60% SRS patients have ICR1 hypomethylation
- Single case of SRS with maternal duplication of ICR2 (Schönherr et al., 2007)
- ~4% 11p15 hypomethylation patients have both ICR1 and ICR2 hypomethylation (Azzi et al., 2009)
Clinical features in patients with mUPD7 vs ICR1 abnormalities

• mUPD7
  – ? Milder form of SRS (Hannula et al., 2001)
  – Speech delay, severe feeding difficulties, sweating
Clinical features in patients with mUPD7 vs ICR1 abnormalities

- 11p15 methylation abnormalities
  - Not seen in children with IUGR without SRS features (Bartholdi et al., 2008)
  - SRS patients with ICR1 hypomethylation more likely to have ‘classic’ features than those with idiopathic SRS/ mUPD7 (Netchine et al., 2008)
  - Possible correlation between degree of loss of methylation and clinical severity and genital and skeletal abnormalities (Bruce et al., 2009)
Study of clinical features in SRS patients with known molecular abnormalities

- 64 SRS patients with known molecular abnormalities recruited, tested in UK/ Netherlands
  - 20 with mUPD7
  - 44 with abnormalities of 11p15 region
    - ICR1 hypomethylation (41)
    - Sibs with ICR1 hypomethylation (2)
    - 11p15 mat duplication (2)
    - Mosaic mUPD11 (1)
- Detailed, prospective clinical data collected
- Clinical features in mUPD7/ ICR1 hypomethylation patients compared
mUPD7 vs ICR1 hypomethylation

• Considerable overlap in clinical phenotype

• Wide variation in severity especially with ICR1 hypomethylation

• ICR1 hypomethylation patients generally more typical of SRS
## Clinical score

<table>
<thead>
<tr>
<th>Clinical score ≥4</th>
<th>ICR1 hypomethylation</th>
<th>mUPD7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>61%</td>
<td>20%</td>
<td></td>
<td>0.003</td>
</tr>
</tbody>
</table>

*(Price et al., 1999)*

- Intrauterine growth retardation
- Postnatal short stature
- Relative macrocephaly
- Triangular facial appearance
- Asymmetry
## Growth

<table>
<thead>
<tr>
<th></th>
<th>ICR1 hypomethylation</th>
<th>mUPD7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BWt ≤ 2SD</td>
<td>82%</td>
<td>70%</td>
<td>ns</td>
</tr>
<tr>
<td>Ht ≤ 2SD</td>
<td>57%</td>
<td>65%</td>
<td>ns</td>
</tr>
<tr>
<td>Relative macrocephaly</td>
<td>70%</td>
<td>90%</td>
<td>ns</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>68%</td>
<td>30%</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Growth: postnatal height SDS

Some evidence that mUPD7 patients tend to have higher birth length but are then more likely to lose height SDS in early childhood (Binder et al., 2008)
**Growth: postnatal height SDS**

<table>
<thead>
<tr>
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<th>ICR1 hypomethylation</th>
<th>mUPD7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in postnatal ht SDS*</td>
<td>53% (n=36)</td>
<td>78% (n=9)</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Excluding patients on GH

- mUPD7 patients may be more likely to lose height SDS in early childhood
- Some ICR1 patients showed ‘catch up’ growth
Facial features

• Most characteristic in early life
• In patients < 5 yr
  • ICR1 hypomethylation
    Frontal bossing
  • mUPD7
    Triangular face
    Low set, posteriorly rotated ears
• Variability in facial phenotype seen in both groups
Facial features

More characteristic in early childhood
## Development

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<th>ICR1 hypomethylation</th>
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<th>P-value</th>
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<tbody>
<tr>
<td>Global delay</td>
<td>20%</td>
<td>65%</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild</td>
<td>10%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5%</td>
<td>0%</td>
<td></td>
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</tbody>
</table>
## Development

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<th>ICR1 hypomethylation</th>
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<th>P-value</th>
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<tbody>
<tr>
<td>Gross motor delay*</td>
<td>26% (n=34)</td>
<td>7% (n=14)</td>
<td>ns</td>
</tr>
<tr>
<td>Speech therapy (≥2.5y)</td>
<td>32% (n=28)</td>
<td>67% (n=18)</td>
<td>0.03</td>
</tr>
<tr>
<td>Statement (≥3.5y)</td>
<td>9% (n=23)</td>
<td>25% (n=16)</td>
<td>ns</td>
</tr>
<tr>
<td>Behavioural problems</td>
<td>9%</td>
<td>20%</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Excluding those with global delay
Myoclonus dystonia in mUPD7

- Recent reports of myoclonus-dystonia in association with mUPD7 (Guettard et al., 2008; Stark et al., 2010)

- Mild dystonia/ myoclonic jerks

- Paternally expressed SGCE gene at 7q21

- 3/20 mUPD7 patients in study with movement disorders (infantile myoclonus/ L. arm tremor/ head jerking)
Human chromosome 7

Homologous mouse imprinted regions

Chromosome 11

- Mat
- Pat

Prenatal growth retardation
- Grb10
- U2af1-rs1

Homologous to human 7p11.2–p13
Prenatal overgrowth
Homologous to human chromosome 5

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IGFBP3
GRB10
EGFR

SGCE

Chromosome 6

- Mat
- Pat

Early embryonic lethality
- Sgce

Growth retardation
- γ-2COP
- Mit1
- Mest

7q31–qter
Segmental mUPD in 1 SRS patient

MEST
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## Congenital anomalies

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<th>ICR1 hypomethylation</th>
<th>mUPD7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 congenital anomaly</td>
<td>36%</td>
<td>10%</td>
<td>0.04</td>
</tr>
</tbody>
</table>
## Congenital anomalies

<table>
<thead>
<tr>
<th></th>
<th>ICR1 hypomethylation</th>
<th>mUPD7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft palate/ bifid uvula</td>
<td>7%</td>
<td>0%</td>
<td>ns</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>9%</td>
<td>0%</td>
<td>ns</td>
</tr>
<tr>
<td>Male genital anomaly</td>
<td>23% (n=22)</td>
<td>0% (n=5)</td>
<td>ns</td>
</tr>
<tr>
<td>Renal anomaly</td>
<td>0%</td>
<td>10%</td>
<td>ns</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>9%</td>
<td>5%</td>
<td>ns</td>
</tr>
<tr>
<td>Other skeletal anomaly</td>
<td>9%</td>
<td>0%</td>
<td>ns</td>
</tr>
</tbody>
</table>
No evidence seen for correlation between level of ICR1 hypomethylation and clinical severity

\[ p = 0.53 \]
Assisted reproductive technology

• Increased frequency of ART with BWS and Angelman syndrome (Maher, 2005)

• Evidence for an increased frequency of ART in association with SRS (Svensson et al., 2005)

• Our study: 5/44 patients with ICR1 hypomethylation conceived by IVF
Recurrence risk in SRS

• Usually sporadic

• Few reports of familial SRS associated with various modes of inheritance

• 4 families reported with recurrence of ICR1 hypomethylation (Bartholdi et al. 2009; Wakeling et al., 2010)

• Underlying molecular mechanism for recurrence in these families currently unknown

• Recurrence risk low in majority of cases
Idiopathic SRS

• Underlying molecular defect unknown in around 30-50%

• Small proportion may have cryptic chromosome rearrangements (*Bruce et al.*, 2009)

• Clinical assessment important to reduce heterogeneity in patients labelled as ‘idiopathic SRS’

• Underlying molecular mechanism?
  • IGF/ growth hormone (GH) axis
  • Other epigenetic mechanisms
Conclusions

• SRS is associated with mUPD7 or ICR1 hypomethylation in ~60% patients

• Difficult to clinically distinguish between mUPD7 and ICR1 hypomethylation

• mUPD7 patients generally less ‘typical’ for SRS

• Significant differences in the frequency of some features observed

• Low threshold for investigation of patients with features suggestive, but not typical, of SRS
Epigenotype–phenotype correlations in Silver–Russell syndrome

E L Wakeling, S Abu Amero, M Alders, et al.

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