Rubinstein-Taybi Syndrome

A short overview of genetics and research

4th International RTS Conference

Birmingham, May 2016

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Academic Medical Center, Amsterdam, The Netherlands
Topics

- Genes
- Defining RTS
- Growth
- Natural history site
- Keloids
- Tumours
- Behavior
Basics

Genes

nucleus (center)

chromosomes

cell
Basics

- Two genes in RTS
  a. CREBBP
     located on chromosome 16
     60-65%
  b. EP300
     located on chromosome 22
     5-10%
### Differences CREBBP – EP300

<table>
<thead>
<tr>
<th>Feature</th>
<th>CREBBP (n=308)</th>
<th>EP300 (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>small head</td>
<td>54%</td>
<td>86%</td>
</tr>
<tr>
<td>more hair</td>
<td>76%</td>
<td>52%</td>
</tr>
<tr>
<td>typical smile</td>
<td>94%</td>
<td>47%</td>
</tr>
<tr>
<td>broad thumbs</td>
<td>96%</td>
<td>70%</td>
</tr>
<tr>
<td>thumb not straight</td>
<td>49%</td>
<td>2%</td>
</tr>
</tbody>
</table>
## Differences CREBBP – EP300

<table>
<thead>
<tr>
<th></th>
<th>CREBBP (n=308)</th>
<th>EP300 (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild delay</td>
<td>14%</td>
<td>61%</td>
</tr>
<tr>
<td>more delay</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>marked delay</td>
<td>36%</td>
<td>7%</td>
</tr>
<tr>
<td>autism</td>
<td>49%</td>
<td>25%</td>
</tr>
<tr>
<td>pm pre-eclampsia</td>
<td>3%</td>
<td>21%</td>
</tr>
</tbody>
</table>
What about the other ~30%?

- mosaicism (= change in CREBBP/EP300 cannot be detected in blood): infrequent

- one candidate (unpublished)

- studies for other genes
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Defining RTS

Changes

- new “screening” DNA techniques
- unexpected gene changes
- is this still RTS?
Defining RTS

CREBBP mutation

But RTS??
All CREBBP mutation

Defining RTS

Leonie Menke

Defining RTS

- one has RTS if one has clinically RTS

- need for definition

- internationally accepted
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Growth

- growth curves 1990
- diagnoses not confirmed
- variation insufficiently considered
- change growth over time
Growth

- contact support groups
- n=92
- corrections secular trends / ethnicity
- subsequent check
Growth Charts for Individuals with Rubinstein–Taybi Syndrome

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¹Department of Pediatrics, Emma’s Children’s Hospital/Academic Medical Center, Amsterdam, The Netherlands
²Spanish Rubinstein-Taybi Association, Madrid, Spain

Growth

Boys

boys
Growth

Girls
Growth

Weight

girls

BMI
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Natural History Site

- information!

- what will the future bring

- future therapies
Natural History Site

- many rare disorders, few doctors
- and the true specialists are…
- Internet
- Wiki
Natural History Site

- once (!) all early data
- pdf
- follow-up questionnaires
- behavior
- translations in 8 languages
Natural History Site

- wikipedia

wiki = Hawaiian for fast
Natural History Site

- waihonapedia

waihona = Hawaiian for treasure
Natural History Site

European Journal of Medical Genetics

Building treasures for rare disorders

Melanie Baas\textsuperscript{a,1}, Sylvia Huisman\textsuperscript{a,1}, John van Heukelingen\textsuperscript{b}, Gerritjan Koekkoek\textsuperscript{c}, Henk-Willem Laan\textsuperscript{d}, Raoul C. Hennekam\textsuperscript{e,∗}

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\textsuperscript{b} Pitt-Hopkins Parents Support Group, IJmuiden, The Netherlands
\textsuperscript{c} Cornelia de Lange Syndrome Support Group, IJmuiden, The Netherlands
\textsuperscript{d} Marshall-Smith Syndrome Foundation, The Hague, The Netherlands
\textsuperscript{e} Department of Paediatrics and Translational Genetics, AMC, University of Amsterdam, The Netherlands

Phenotype and natural history in 101 individuals with Pitt-Hopkins syndrome through an internet questionnaire system

Channa F. de Winter¹⁺, Melanie Baas²⁺, Emilia K. Bijlsma³, John van Heukeligen⁴, Sue Routledge⁵ and Raoul C. M. Hennekam²⁺
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- Genes
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- Behavior
Keloids

Van de Kar, Br J Dermatol 2014;171:615

Dr Cecilie Bredrup session
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Tumor chance in RTS

- CREBBP known to be involved in cancer
- Miller / Rubinstein 1995: ‘risk elevated’
- no reliable data
Tumor chance in RTS

- pathologist Prof De Jong
- study started 2012
- still not ready
- likely: risk ~20%

  young age leukaemia

  adults: all kinds

  reacting on therapy in RTS as in non-RTS
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Behavior

- 24/7
- influence on daily life
- lecture Prof Chris Oliver
- session Prof Didier Lacombe
Behavior: MRI

- mouse model RTS

normal mouse

CBP knock-out mouse (‘Rubinstein-Taybi mouse’)
Behavior: MRI

- mouse model RTS
- MRI studies

Behavior: MRI

- mouse model RTS
- MRI studies
- but in man?

**Call for help!**

If a brain MRI has been made (age not important
If a change in CREBBP or EP300 has been found
If you allow me to ask for a copy from the hospital

Please email me at r.c.hennekam@amc.uva.nl

David Moratal
Behavior: progression?

Ponder, Nature 2001;411:336

Ahmad Aziz
Martine van Belzen
Behavior: progression?

- CBP has brain functions
- function: clearing ‘used’ proteins
- in some more ‘used’ proteins, in others less
- determined by genes

compare - CREBBP mutation
- genes that regulate protein use
- behavior