Analysis of the phenotypes in the Rett Syndrome Networked Database

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Rett syndrome (RTT)

• Severe X-linked neurological disorder affecting almost exclusively girls

• Prevalence 1:10,000 born females

• Period of regression (6-12 months)

• Loss of purposeful hand use and spoken language

• One principal phenotype (classical RTT) and 3 atypical forms:
  - Zappella variant with some speech ability preserved (Zappella 1992);
  - congenital form (Rolando, 1985);
  - early onset epilepsy (Hanefeld 1985);

The severity varies from mild to more severe phenotypes.
Genes: \textit{MECP2} \rightarrow 90\% classic RTT, 50\% Z-RTT
\textit{CDKL5} \rightarrow early onset seizures variant
\textit{FOXG1} \rightarrow congenital variant

Proteins: MeCP2: Transcriptional regulator (e.g. BDNF)
cdkl5: Cyclin Dependent Kinase
FoxG1: Transcriptional regulator (e.g. fgf8)

There is only limited correlation between genotype and phenotype.
Rett Registries in Europe 2009
Database place: Paris

Name: SYRENE = Syndrome Rett network

Number of cases 232

Web interface: http://afsr.in2p3.fr/RETT/

Questionnaire written by clinicians (supervision of Nadia Bahi Buisson)

81 structured clinical items (yes; no; not known; not defined)
   grouped in 16 clinical fields

   plus 1 descriptive clinical item

12 structured genetic items
Database place: **Cardiff** (from Ellison Kerr database in Glasgow)

Name: **BIRSS** British Isles Rett Syndrome Survey

Number of cases: **821**

No web interface

Questionnaire written **by families**  (supervision of Angus Clark)

**271 structured clinical items**  (1=yes, 2=no; 3=not sure; 9=not known) grouped in 22 clinical fields

Longitudinal data

Plus **94 descriptive clinical items**

**6 structured genetic items**
Database place: Barcelona
Name: Barcelona Rett database
Number of cases: 383
No web interface
Data inserted by clinicians seeing patients
(supervision of Merce Pineda)

44 structured clinical items
plus 4 descriptive clinical items
4 structured genetic items
Database place: Siena
Name: Italian Rett database and biobank
Number of cases: 310
Web interface: http://www.biobank.unisi.it
Data inserted by clinicians seeing patients
  (supervision of Alessandra Renieri)
  20 structured clinical items (0=absent; 1=mild; 2=severe)
  17 structured genetic items including location and kind of samples
  plus 7 descriptive items
The Adaptor Approach of Rett syndrome registries

The example of clinical items related to head
<table>
<thead>
<tr>
<th>Item name</th>
<th>Spanish</th>
<th>Italian</th>
<th>BIRSS</th>
<th>SYRENE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stagnation head</td>
<td>Acquired microcephaly</td>
<td>Head</td>
<td>OFC fall</td>
<td>PC rallentissmant croissance</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td>2=postnatal microcephaly</td>
<td>1=yes, any evidence of fall from original centile</td>
<td>oui</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>1=deceleration of head growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>no</td>
<td>0=no deceleration</td>
<td>2=no evidence of fall from original centile</td>
<td>no</td>
</tr>
</tbody>
</table>
Harmonization

297 items: 281 clinical and 16 genetic grouped in 29 domains
(28 clinical and 1 genetic)
RETT NEWORKED DATABASE PRESENT SHAPE

293 clinical items and 16 genetic items

1911 patients from twelve countries

62 clinical and 7 genetic items constitute the minimum dataset
REGRESSION

Last updated on 07/03/2010 by: Pineda Merce

Regression Yes
Onset of Regression (months) Before 18 months
Regression Age (months) 1 years, 0 months
Behavioral Disturbance
Speech Regression Yes
Age of speech regression 3 years, 0 months
Regr Speech Note Lost propositive sentence skill at 36 months
Growth Failure No
Regr Hand Use Yes
Regr Hand Use Age 2 years, 0 months
Regr Hand Use Note
Hand Use Before Regression Normal for age
Regr Mob Yes
Regr Mob Age
Regr Mob Age
Regr Pers Cont Yes
Regr Pers Cont Age 3 years, 0 months

HAND SKILLS

Last updated on 07/03/2010 by: Pineda Merce

Handed
Labour at term Yes
Labour Concerns
Labour Concerns Note
Apgar Score

HEAD
Last updated on 31/08/2009 by: Villard Laurent
head score
OFC at birth in cm 34
Normal OFC at birth Yes
Month of OFC deceleration 0
OFC at birth in centile 0
OFC normal within 1 year
OFC with age (cm at examination) 51 cm at 132 months

WEIGHT
Last updated on 31/08/2009 by: Villard Laurent
Birth weight in gr 2850
Weight with age (gr) 32000 gr at 132 months
weight score

HEIGHT
Last updated on 31/08/2009 by: Villard Laurent
Height at birth in cm 50
Height with age (cm at examination) 100 cm at 132 months
HAND SKILLS
Last updated on 02/10/2010 by: Bruria Been-Zev
Handed ambidextrous
Purp Grasping
Grasping Age (months)
Purp Grasping Note
Hand Use Acquisition Yes
Hand Use Acquisition Age 0 years, 6 months
Hand Use Score Quite good hand use at 99 months
Hand skills regained
Hand skills regained age

HAND STEREOTIPY
Last updated on 02/10/2010 by: Bruria Been-Zev
Hand Stereotipy Score Mild or intermittent
Hand Stereotipy Age (months) 0 years, 5 months
Hand Stereotipy Type very mild hand clapping

FEEDING
Last updated on 02/10/2010 by: Bruria Been-Zev
Gastrointestinal Disturbances Absent
Feed Diff Three Months No
COMMUNICATIONS

Last updated on 02/10/2010 by: Bruria Been-Zev

Comm Non Verb Yes
Comm Non Verb Quality
Comm Facial Exp Yes
Comm With Meaningful Sound
Eye Contact Yes
Comm With Gestures Yes
Sign Language
Babble speech
Babble speech Age (months) 1 years, 0 months
Communication skill longitudinal assessment Not Known at 99 months
Phrases Score Complex phrases
Single words age acquired (months) 1 years, 6 months
Propositive sentences age acquired (months) 0 years, 3 months
Word in context Yes
Age of increasing words before 72 months
Age of increasing words Note
Speech Score Yes

MOTOR SKILLS

Last updated on 02/10/2010 by: Bruria Been-Zev

Head Control at (months)
GENETIC DATA

Last updated on by: Bieber Nielsen Jytte

Mutation in a gene: Yes

Screened Genes: MECP2

Methods used to screen:

Regions/Molecules screened:

Mutated Gene: MECP2

Mutation Type: missense

Nucleotide Change

AAChange: p.T158M

X Inactivation status: balanced

Inheritance

Parent of origin of mutation

Other genetic investigations

Normal Karyotype

Karyotype Result Note

CNVs found

SNPs found
The number and list of patients are displayed.

Search can be done in 46 items belonging to 25 different domains of the minimum data set.

It is possible to perform multiple searches at once.

The maximum number of items that can be selected simultaneously is 10.
Number of patients in archive: 1911

- Australia: 1
- Czech Republic: 0
- Germany: 0
- Denmark: 64
- Spain: 387
- Finland: 0
- France: 252
- United Kingdom: 255
- Croatia: 29
- Hungary: 58
- Israel: 93
- India: 3
- Italy: 607
- Poland: 0
- Portugal: 0
- Romania: 15
- Serbia: 50
- Russia: 0
- Sweden: 0
- USA: 96
How To Join

Are you a physician involved in Rett syndrome?
Are you willing to join us in this project on Rett database network?

If yes, please fill in and sign the password request form and send it to the administrator of the database network. You will receive the username and password by which you can insert your patients. Your center will be listed under the flag of your country.

If you are a parent of a Rett syndrome patient or patients association representative and you want to join us in this project on Rett database network, you need a physician responsible for inserting data.

Download the Password request Rett database network.doc (575 KB)

Database administrator:
Rossano Di Bartolomeo
3W Net Service S.a.s.
email: rossano@3wnet.net

Database coordinator:
Alessandra Renieri
University of Siena
e-mail: renieri@unisi.it
Access rules to Rett database network

There are three different levels of access:

1. **Public access**
   
   Public has access to the general information and to the description of content.

2. **Aggregated data access**
   
   Registered users have access to aggregated data only. Registered users have to disclose their identity, affiliation and have to agree to the data protection policy (HBGRD Human Biobanks and Genetics Research Databases guidelines).

3. **Full access**
   
   Access to individual data and statistical analysis is be given upon the submission of a research proposal to the scientific review board composed by the major contributors (more than 50 patients).
   
   The scientific review board may decide the term of access for example scientific collaboration, or acknowledgement or citation of the paper that describe the database (key contributors will be coauthors). Then there will be an approval by the local ethic committee of the University hosting the database.
Data coverage
Overview of RSND data
Mutations in MECP2
Mutations in CDKL
Mutations in FOXG1

Cumulative distribution

Percent cases

Clinical severity

- early truncating
- gene deletion
MECP2 (red) CDKL5 (blue) FOXG1 (green)
ONGOING STUDIES....
EXOME SEQUENCING IN 124 PATIENTS

**Study design**

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**Top extreme phenotype**
52 patients with severe classic RTT

**Bottom extreme phenotype**
63 patients with milder clinical condition

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**Table of Joined Clinical Score (modified from Renieri et al., 2009)**

<table>
<thead>
<tr>
<th>Head</th>
<th>postnatal microceph</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>decel heading</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>growth</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>none</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>below 3rd%</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-25%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;25%</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height</th>
<th>below 5rd%</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-25%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;25%</td>
<td>0</td>
</tr>
</tbody>
</table>

| etc...        |                     |   |
| Level of speech | absent            | 2 |
|               | single words       | 1 |
|               | phrases            | 0 |

| tot           | max. 36            |   |
Conclusions and perspectives

- Largest worldwide collection of Rett syndrome patients where clinical data is validated by experienced clinicians
- Open structure, available to all interested professionals and a searchable web interface made available for registered users
- Standardized and easily comparable clinical and genetic data
- Genotype/phenotype correlations
- Clinical trials

www.rettdatabasenetwork.org
THANKS FOR YOUR ATTENTION
A special thanks to Rett patients association and foundation for funding support and opportunities.

We also thanks all the centers that have inserted patients and that contributed to website development and update.
Rett Networked Database

Scientific Review Board of the Rett Networked Database: Alessandra Renieri (Coordinator), Francesca Mari (University of Siena, Siena, Italy), Laurent Villard (Université de la Méditerranée and Inserm, Marseille, France), Nadia Bahi-Buisson (University Paris V Descartes, Paris, France), Angus Clarke, Anna Hryniewiecka-Jaworska (Cardiff University, Wales, UK), Mercedes Pineda, Ana Roche Martinez (Hospital Sant Joan de Déu, Barcelona, Spain), Bruria Ben-Zeev (Sheba Med Center, Ramat-Gan, Israel). Members: Edvige Veneselli, Maria Pintaudi (University of Genova, Italy), Silvia Russo, Francesca Cogliati (Istituto Auxologico Italiano, Milan, Italy), Aglaia Vignoli (Ospedale San Paolo, Milano, Italy) Giorgio Pini (Versilia Hospital, Viareggio, Italy), Milena Djuric (University of Belgrade, Serbia), Jytte Bieber Nielsen, Kirstine Ravn (Glostrup, Denmark), Vlatka Mejaški-Bošnjak (University of Zagreb, Croatia), Béla Melegh, Polgár Noémi (University of Pécs, Hungary), Dana Craiu (Carol Davila University of Medicine, Bucharest, Romania), Aleksandra Djukic (Montefiore Medical Center, Albert Einstein College of Medicine, New York, USA).
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