Micromapping of very rare anemias: The model of Congenital Dyserythropoietic Anaemia (CDA)

Prof. emeritus Hermann Heimpel FRCPath
The German registry on CDAs

Hermann Heimpel described CDA for first time in 1966
Deutsches Register für Congenitale Dyserythropoietische Anämien (CDA)

Hermann Heimpel, Elisabeth Kohne, Hubert Schrezenmeier Ulm

German Registry of Congenital Dyserythropoietic Anemia (CDA)
Congenital Dyserythropoietic Anemias (CDAs): Definition

- Evidence of a congenital and/or hereditary disorder - history, family studies.

- Evidence of ineffective erythropoiesis - blood count, bilirubin, haptoglobin, serum transferrin receptor, reticulocytes (inadequate), bone marrow

- Characteristic morphological abnormalities of erythrocytes and erythroblasts - light and electron microscopy

- Exclusion of hemolytic anemias, disorders of hemoglobin synthesis and megaloblastic anemias
<table>
<thead>
<tr>
<th>CDA type</th>
<th>I</th>
<th>II HEMPAS</th>
<th>III familial</th>
<th>III sporadic</th>
<th>Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Autosomal-recessive</td>
<td>Autosomal-recessive</td>
<td>Autosomal-dominant</td>
<td>Variable</td>
<td>Autosomal-recessive or x-linked</td>
</tr>
<tr>
<td>Cases reported</td>
<td>~180</td>
<td>&gt; 600</td>
<td>3 families</td>
<td>&lt; 20</td>
<td>~80</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene Locus</td>
<td>CDAN1 15q (15.1.3)</td>
<td>SEC23B 20p11.23-20p12.1</td>
<td>Unknown 15q (21-25)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dysmorphologies</td>
<td>Skeleton, Others</td>
<td>Variable, rare</td>
<td>B-Cells Retina</td>
<td>Variable</td>
<td>CNS Others</td>
</tr>
</tbody>
</table>
Micromapping of very rare anemias: The model of CDA
Methodological Problems

• General: Each case is one family!

• Case identification: Clinical and morphological phenotype, and/or:
  CDA I: Electron microscopy /mutation in CDANI
  CDA II: Electron microscopy/ specific abnormality of pattern in SDS-Page of red cell membranes / mutation in SEC23B
  CDA III: Morphological analysis of erythroblasts and evidence of dominant heredity

Variants: See general definitions of CDA – No CDA I, II, III

• Case notification: Recognition of multiple publications of identical cases, or enrollment of identical cases in more than one registry
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Case acquisition

All cases collected in the German Registry on CDAs 1967 – 2011 include:

- Own observations (Germany, Austria, Switzerland)
- Correspondence with Physicians/Scientists asking for advice
- Transfer of data from CDA-registries (Naples, Milano, Paris, Oxford, Barcelona)
- Case reports from the literature (Pubmed)
- Ongoing project: CDAs worldwide
Frequency of **CDA I and II** in Europe (2009)

Micromapping of very rare anemias
The CDAs Worldwide Project Hypothesis

• The prevalence of the CDAs, in contrast to thalassemias, sickle cell disease or G6PD variants, is **not** dependent on environmental factors such as malaria.

• The prevalence of the CDAs unlike many other hereditary disorders, is dependent on:
  - The awareness of the disease in the medical system in different countries/regions
  - The diagnostic facilities in the medical system in different countries/regions
  - The consanguinity rates in different countries/regions

• Definite proof of the hypothesis requires mutational analysis of cases from different countries/regions.
Micromapping of very rare anemias:  
The CDAs Worldwide Project Hypothesis Work Plan

1. Transfer of data from CDA registries Naples, Milano, Paris, Barcelona: Update of Data published in 2010
2. Correspondence with Physicians/ Scientists who asking for advice after 2009
3. Identification of corresponding members of the all countries by national societies of hematology or pediatric hematology (in progress)
4. Distribution of short questionnaires to corresponding members
5. Evaluation of questionnaires and additional correspondence
6. Calculation of parameters (prevalence, period prevalence, incidence of neonates with CDA, gene frequency)
7. Micromapping according to regions/countries)
8. Publication of results
Micromapping of very rare anemias:
The CDAs Worldwide Project Hypothesis Work Plan

- NATIONAL / REGIONAL CORRESPONDING MEMBERS
- CDA - REGISTRIES
- ENERCA
- Orphanet
- RARE DISEASES EXPERT CENTRES