# MDS phenotype

## Early clinical course

- **Prenatal**
  - Prenatal growth DEF 11/26
  - Polyhydramnios 13/24
- **Neonatal**
  - Neonatal resuscitation 06/20
  - Neonatal jaundice 08/21
- **Growth**
  - Postnatal growth DEF 18/24
  - Postnatal MIC 17/25
- **Other**
  - Heart malformation 06/27
  - Sacral dimple 14/19
  - GU anomalies in males 09/13

## Craniofacial malformations

- **Cranial abnormalities**
  - Prominent forehead 26/26
  - Bitemporal hollowing 06/26
- **Facial malformations**
  - Vertical furrowing 12/24
  - Short nose-upt nares 26/26
  - Epicanthal folds 08/22
  - Low-set ears 14/27
  - Malformed ears 10/25
  - Protuberant upper lip 24/25
  - Thin vermilion border 25/25
  - Small jaw 26/27
  - High-arched palate 14/20
MDS and LIS clinical course

• Pregnancy
  ▫ Prenatal US may show enlarged LV

• Newborn
  ▫ Most newborns appear normal
  ▫ Some are floppy and feed poorly

• Infancy
  ▫ Short tonic (stiffening) seizures 1-3 months
  ▫ Infantile spasm 3-6 months
  ▫ Delayed developmental milestones
MDS and LIS clinical course

• MDS facial phenotype
  ▫ Prominent forehead 26/26
  ▫ Short nose with upturned nares 26/26
  ▫ Protuberant upper lip 24/25
  ▫ Thin upper lip vermilion border 25/25
  ▫ Small jaw 26/27
MDS and LIS clinical course

• Cortical malformation
  ▫ Lissencephaly (classic, grade 1)
    27/27
  ▫ Corpus callosum hypoplasia
    17/23
  ▫ Cavum septi pellucidi
    17/22
  ▫ Midline calcification
    11/24
MDS and LIS clinical course

- **Early childhood (1 to 5 years)**
  - Continued mixed seizure types, decline in skills with poor seizure control
  - Poor feeding, GE reflux (acid reflux)
  - Developmental ceiling of 3-5 months
- **Later childhood (5 - 10 years)**
  - Worsening, intractable epilepsy, decline
  - Worse feeding, aspiration, recurrent pneumonia, feeding tubes
  - Mortality >50% by age 10 years
Lissencephaly and epilepsy

- Parent survey in 1994
  - Age 4 - 288 months, mean 60 months
    - Most less than 8 years (24/28 or 85%)
  - Sex ratio 15F:13M

- Prevalence of seizures (N = 28)
  - Seizures at any time 27 96%
  - Current seizures 25 89%
  - Infantile spasms 24 85%
  - Status epilepticus 12 44%
Lissencephaly and epilepsy

- Literature series

- Prevalence (N = 62)
  - Infantile spasms: 48 (77%)
  - Partial motor seizures: 07 (11%)

- Management
  - SZ often resistant to treatment
# MDS Cytogenetics

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>N=24</th>
<th>%</th>
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<tbody>
<tr>
<td>Familial rearrangements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reciprocal translocation</td>
<td>02</td>
<td>08</td>
</tr>
<tr>
<td>Pericentric inversion</td>
<td>01</td>
<td>04</td>
</tr>
<tr>
<td>De novo abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion (terminal or interstitial)</td>
<td>09</td>
<td>38</td>
</tr>
<tr>
<td>Dicentric translocation</td>
<td>01</td>
<td>04</td>
</tr>
<tr>
<td>Ring</td>
<td>01</td>
<td>04</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submicroscopic deletion</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>24</strong></td>
<td><strong>100</strong></td>
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MDS genomics

- Microdeletion syndrome
  - Co-deletion of LIS1 and YWHAE
Refinement of a 400-kb Critical Region Allows Genotypic Differentiation between Isolated Lissencephaly, Miller-Dieker Syndrome, and Other Phenotypes Secondary to Deletions of 17p13.3

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Deletions of 17p13.3, including the LIS1 gene, result in the brain malformation lissencephaly, which is characterized by reduced gyration and cortical thickening; however, the phenotype can vary from isolated lissencephaly sequence (ILS) to Miller-Dieker syndrome (MDS). At the clinical level, these two phenotypes can be differentiated by the presence of significant dysmorphic facial features and a more severe grade of lissencephaly in MDS. Previous work has suggested that children with MDS have a larger deletion than those with ILS, but the precise boundaries of the MDS critical region and causative genes other than LIS1 have never been fully determined. We have completed a physical and transcriptional map of the 17p13.3 region from LIS1 to the telomere. Using fluorescence in situ hybridization, we have mapped the deletion size in 19 children with ILS, 11 children with MDS, and 4 children with 17p13.3 deletions not involving LIS1. We show that the critical region that differentiates ILS from MDS at the molecular level can be reduced to 400 kb. Using somatic cell hybrids from selected patients, we have identified eight genes that are consistently deleted in patients classified as having MDS. In addition, deletion of the genes CRK and 14-3-3ε delineates patients with the most severe lissencephaly grade. On the basis of recent functional data and the creation of a mouse model suggesting a role for 14-3-3ε in cortical development, we suggest that deletion of one or both of these genes in combination with deletion of LIS1 may contribute to the more severe
Subject: question about chromosomes
Date: Sunday, January 6, 2008 8:43 AM
From: (mother)
To: William Dobyns <wbd@genetics.bsd.uchicago.edu>

Dear Dr. Dobyns,

We recently lost our angel - She was 17 months with MDS. She died from Lymphoblastic Leukemia. I have some questions if you can answer them it would be great. Have you ever had any other patients with MDS that have contracted Leukemia? This diagnosis was an absolute shock to our family. Entirely unexpected. I read that it can happen in children with chromosome problems. It would have been nice to know that this is a possibility. Her days leading to her diagnosis were painful and enduring. She received multiple blood draws (from her neck as there were no other veins available), as well as a blood transfusion (through her neck). We were trying to help her feel better as she was dangerously anemic. Finally, the person analyzing her blood sample noticed the "blasting" and positively confirmed the Lymphoblastic Leukemia. Here in New Mexico there is a doctor writing a paper about the link between the two conditions. But I was hoping to find a way to educate future parents in some way. I feel like we could have spared my daughter a lot of discomfort and pain if we had only known. And finally can a person have MDS with out having lissencephaly? Silly question but just curious. Thanks for taking the time to read my issues. Hopefully you can help us help others. Hope you and your family had a Safe and Happy Holiday.

Curiously hopeful~
------- ------- mommy of Angel ------- ------- -----
MDS and cancer

- **MDS and cancer with del 17p13.3**
  - Female with leukemia (ALL) age 15 mo and died 17 mo

- **MDS and cancer with del 17p13.3**
  - Male with gallbladder CA age 14 yr and died 16 yr (unrelated)

- **Rpa1**

- **Ovca1 (Dph1)**

- **Hic1**
  - Chen W et al. Heterozygous disruption of Hic1 predisposes mice to a gender-dependent spectrum of malignant tumors. Nature Genet 2003;33:197-
  - "Here we show that mice disrupted in the germ line for only one allele of Hic1 develop many different spontaneous malignant tumors, including a predominance of epithelial cancers in males and lymphomas and sarcomas in females."
Distal deletion 17p13.3 syndrome

chr17
Microdeletions including YWHAE in the Miller-Dieker syndrome region on chromosome 17p13.3 result in facial dysmorphisms, growth restriction, and cognitive impairment


_J. Med. Gen._
doi:10.111
Deletion 17p13.3
Distal deletion 17p13.3 syndrome

**Craniofacial and growth**
- Mild MDS-like face
  - High prominent forehead
  - Mild and variable
    - Broad nasal root
    - Epicanthal folds
    - Thin upper lip
  - Small jaw
- Growth
  - IUGR variable

**Development and brain**
- Developmental course
  - Mild DD, mild MR
- Brain
  - White matter hyperintensity
    - Periventricular WM
    - Perivascular spaces
  - CBL tonsillar herniation
    - Chiari 1 in some
Deletion 17p13.3 (polymorphism?)

Two smallest deletions with very different phenotypes!
Is distal 17p13.3 seen in MDS?
# MDS and deletion 17p13.3

## Deletion 17p13.3 with LIS1
- **MDS**
  - MDS facial dysmorphism
  - Severe DDMR and SZ
  - LIS grade 1
  - Variable features
    - CBL tonsillar herniation
    - Cancer
- **MDS-ILS overlap**
  - Same but LIS grade 3
- **ILS**

## Deletion 17p13.3 not LIS1
- **Distal deletion 17p13.3**
  - MDS-like dysmorphism
  - Mild-moderate DDMR
  - White matter hyperintensity
  - Variable features
    - CBL tonsillar herniation
    - Cancer