

# Brain MRI, Neurologic and Psychiatric Findings in the NCI DC Cohort

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# A few definitions

- **Neurology** – medical specialty dealing with the structure, function and disorders of the nervous system
- **Psychiatry** – the practice or science of diagnosing and treating mental disorders

# A few definitions

- **Developmental delay** – when a child does not reach their developmental milestones at the expected time
  
- **Intellectual and Developmental Disabilities** – present at birth and negatively affect the trajectory of the individual's physical, intellectual, and/or emotional development. These conditions may affect multiple body parts or systems

# Medical problems may develop at different ages, with different severity, or not at all

- Nail dystrophy
- Oral leukoplakia
- Skin Pigmentation

• Bone Marrow Failure

• Pulmonary Fibrosis

• Cancer

- Head & Neck
- Leukemia
- Anogenital

▪ Liver Fibrosis

▪ Gastrointestinal

- Non-specific enteropathy
- Esophageal stenosis & webs

▪ Urogenital

- Urethral stenosis

▪ Ophthalmologic

- Lacrimal duct stenosis
- Exudative retinopathy

▪ Neurologic

- Microcephaly
- Cerebellar hypoplasia
- Development delay
- Psychiatric

▪ Orthopedic

- Osteoporosis
- Avascular necrosis

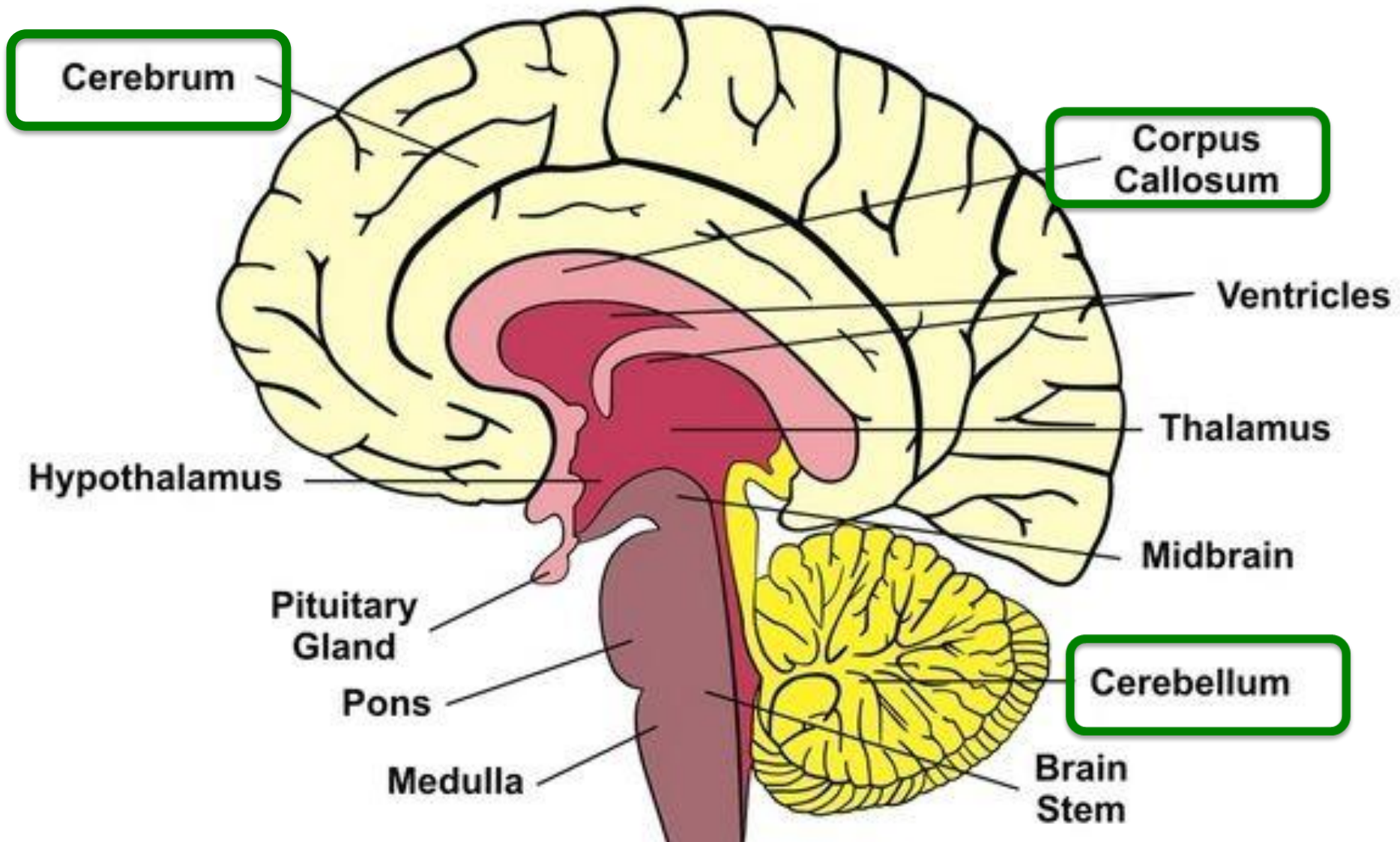
▪ Hair

- Early graying
- Early alopecia

Traditional diagnosis:

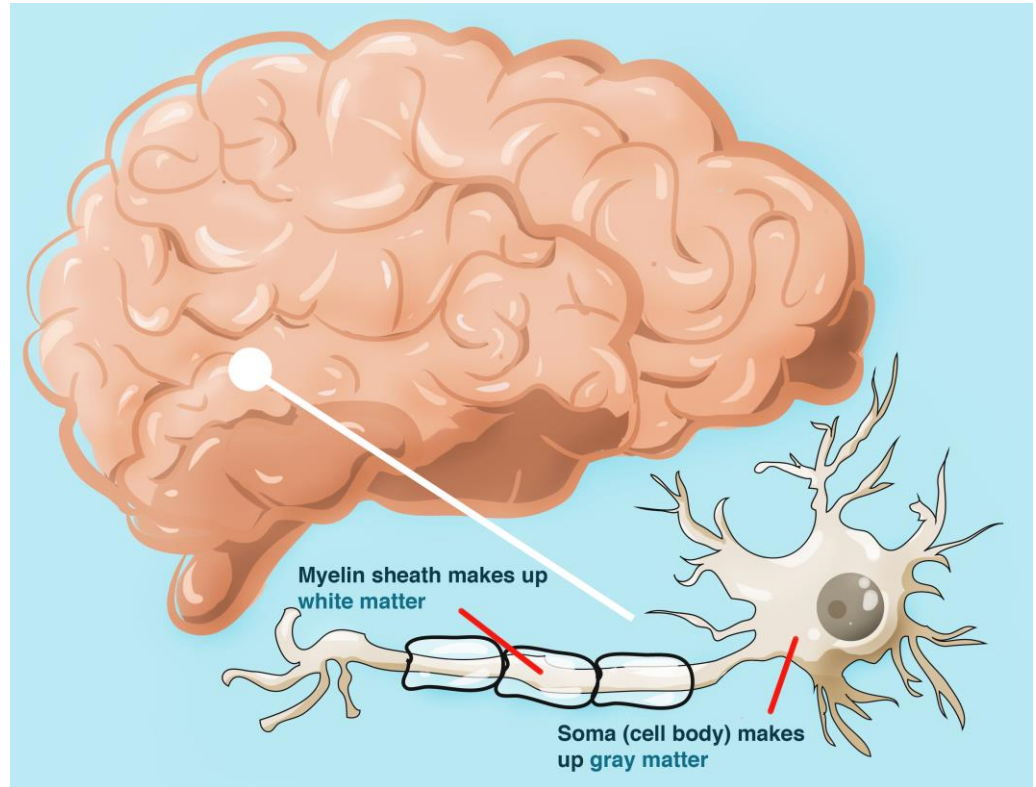
Diagnostic Triad or 1 of the triad, + BMF + 2 other findings, Vulliamy et al, *Blood*, 2006, 107(7):2680-5

# Brain Areas Affected by DC



# Grey vs. white matter

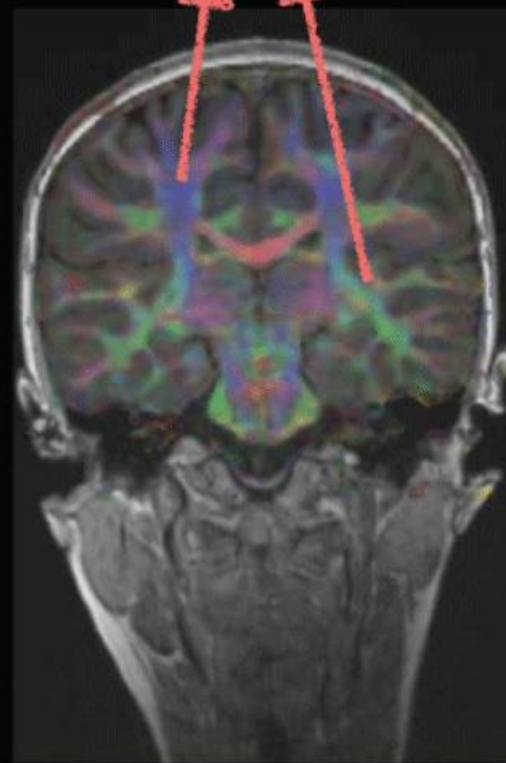
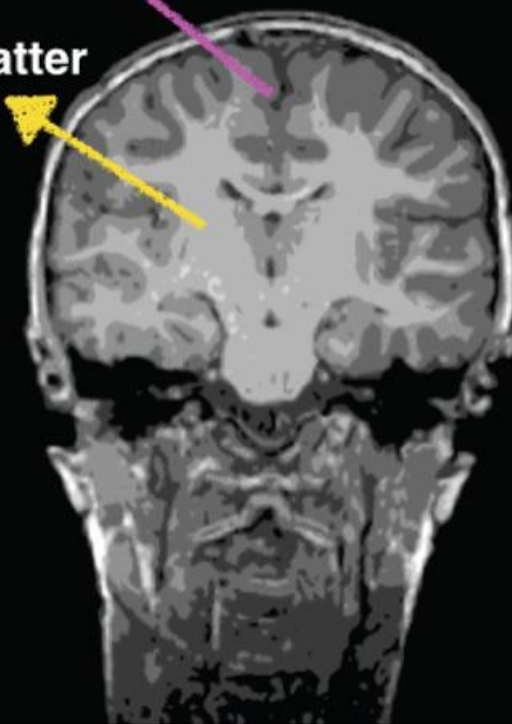
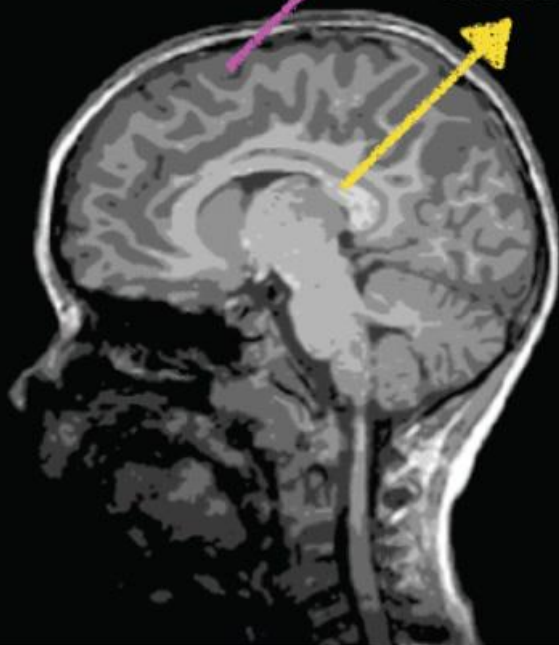
- Grey matter: consists mainly of neuronal cell bodies, from which nerve impulses originate
- White matter: consists largely of nerve fibers; its main role is to transmit nerve impulses



**Grey Matter**

**White Matter**

**White Matter Tracts**



# Clinical Variants of DC

- **Hoyeraal Hreidarsson (HH) Syndrome**

- Cerebellar hypoplasia (small cerebellum) may result in lack of coordinated muscle movement (ataxia)
  - Uncoordinated/unstable walking, uncoordinated movements, trouble speaking
- Small head (microcephaly)
- Developmental Delay

- **Revesz Syndrome**

- Intracranial calcifications
  - Need to rule out other causes such as infection or history of bleeding
- Small head (microcephaly)
- Developmental Delay

- **Coats Plus/CRMCC**

- Intracranial calcifications and/or cysts
- Leukodystrophy (white matter abnormality)



# Research Question

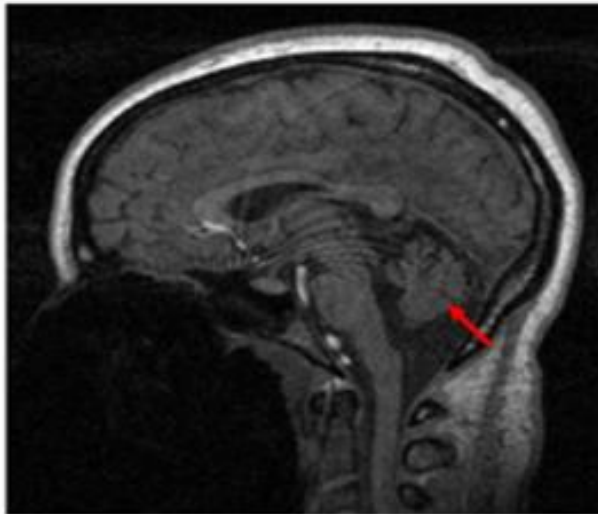
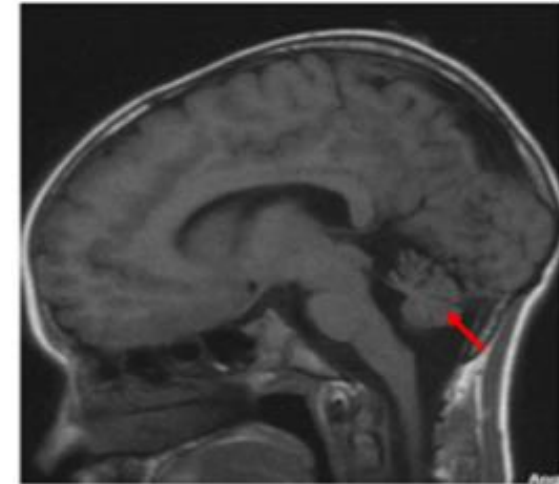
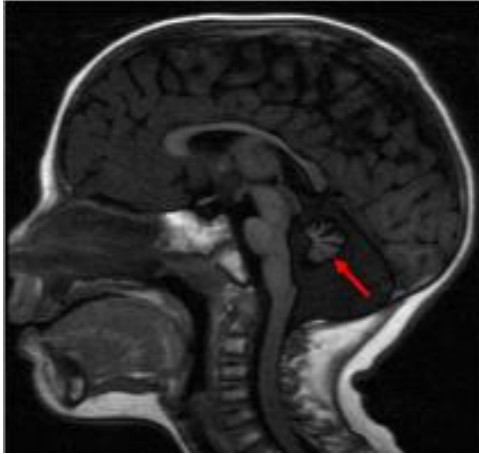
*What brain MRI, neurologic, and psychiatric findings do we see in the National Cancer Institute DC Patients?*

# NCI DC Patients with Brain MRIs, 2001-2015

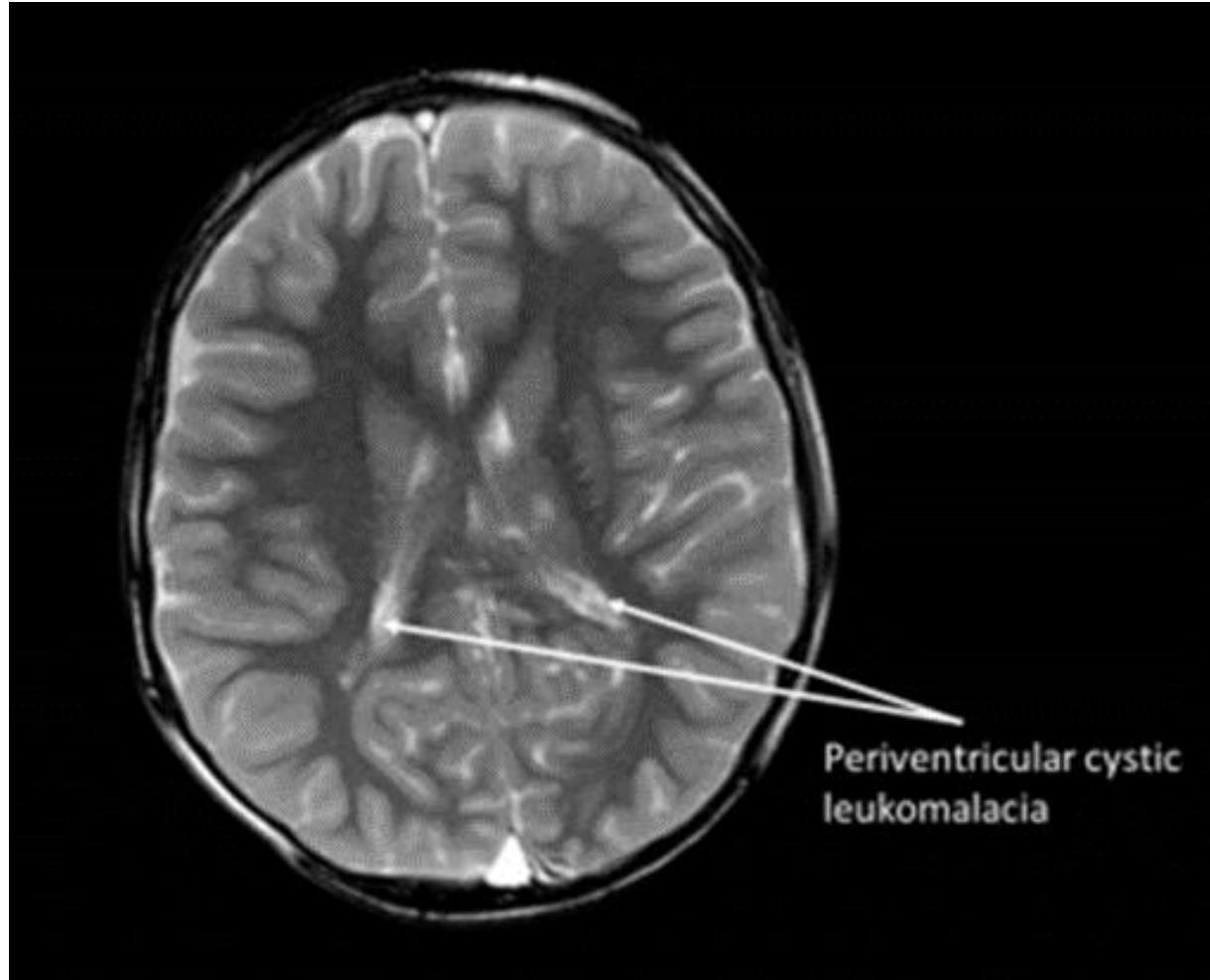
Characteristics (n=44)	Total (n=44)	XLR/AR (n=18)	AD (n=11)	TINF2 (n=9)	Unknown (n=6)
<b>Age (yrs) at MRI</b>					
Median	15	14	18	9	15
Range	1-60	2-46	1-60	1-24	6-31
<b>Age group (yrs)</b>					
0-9	16	6	3	5	2
10-17	10	4	3	1	2
18-29	11	6	1	3	1
30+	7	2	4	0	1
<b>Sex</b>					
Male	33	17	5	8	3
Female	11	1	6	1	3

XLR: X-linked recessive inheritance, pathogenic variants in *DKC1*. AR: autosomal recessive, pathogenic variants in *RTEL1*, *PARN*, *ACD*, *TERT*, and *WRAP53*. AD: autosomal dominant, pathogenic variants in *TERT*, *TERC*, and *RTEL1*

# Cerebellar hypoplasia exists in DC at varying levels of severity



# Example of abnormal cysts and a white matter abnormality in the brain MRI of a patient with DC



# Summary of Brain MRI Findings

- 25 of 44 (57%) patients had a brain MRI finding

Brain MRI Finding	Percentage
Cerebellar Hypoplasia/Atrophy	25/44 (32%)
Cerebral Atrophy/Delayed Myelination (White Matter Abnormality)	10/44 (23%)
Abnormal Cysts	12/44 (27%)
Corpus Callosum/Colpocephaly	8/44 (18%)

# Incidental Brain MRI Findings Unaffected People vs. Patients with DC

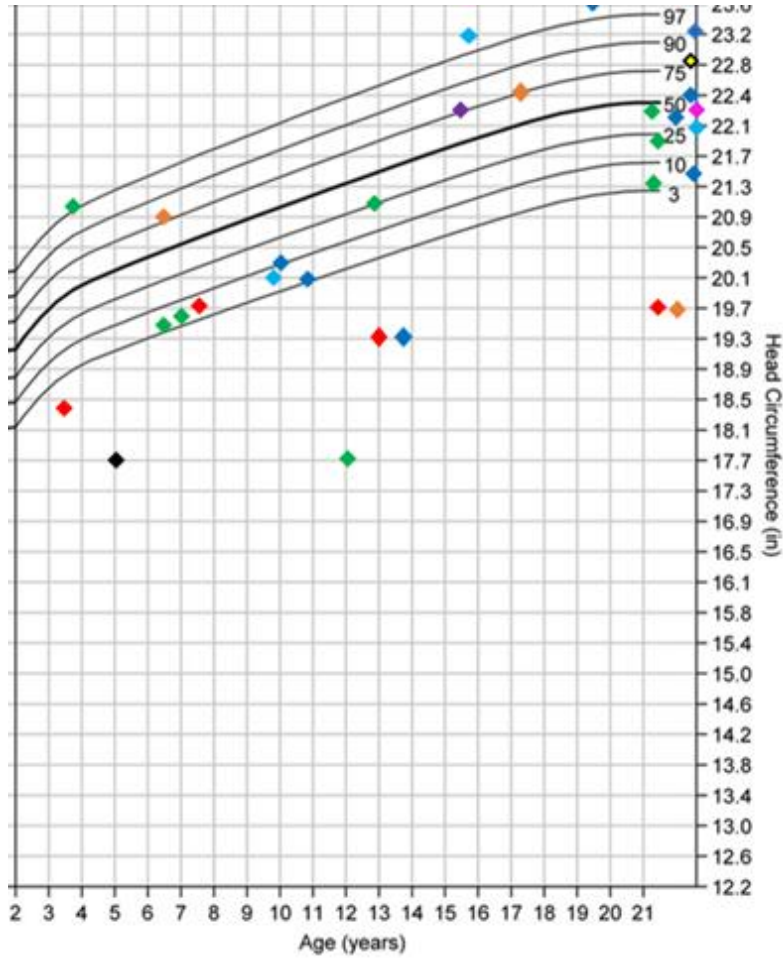
Finding	Unaffected People (n=3966)*	NCI Patients (n=44)
Mega Cisterna Magna	104 (2.6%)	11 (25.0%) <sup>***</sup>
Arachnoid cyst	86 (2.2%)	2 (4.5%)
Pineal gland cyst	665 (16.8%)	3 (6.8%)
White matter abnormalities	8 (0.2%)	7 (15.9%) <sup>***</sup>
Cavum septum pellucidum abnormalities	79 (2.0%)	20 (45.5%) <sup>***</sup>

\*Jansen et. al. "Incidental Findings on Brain Imaging in the General Pediatric Population." *New England Journal of Medicine*. 2017.

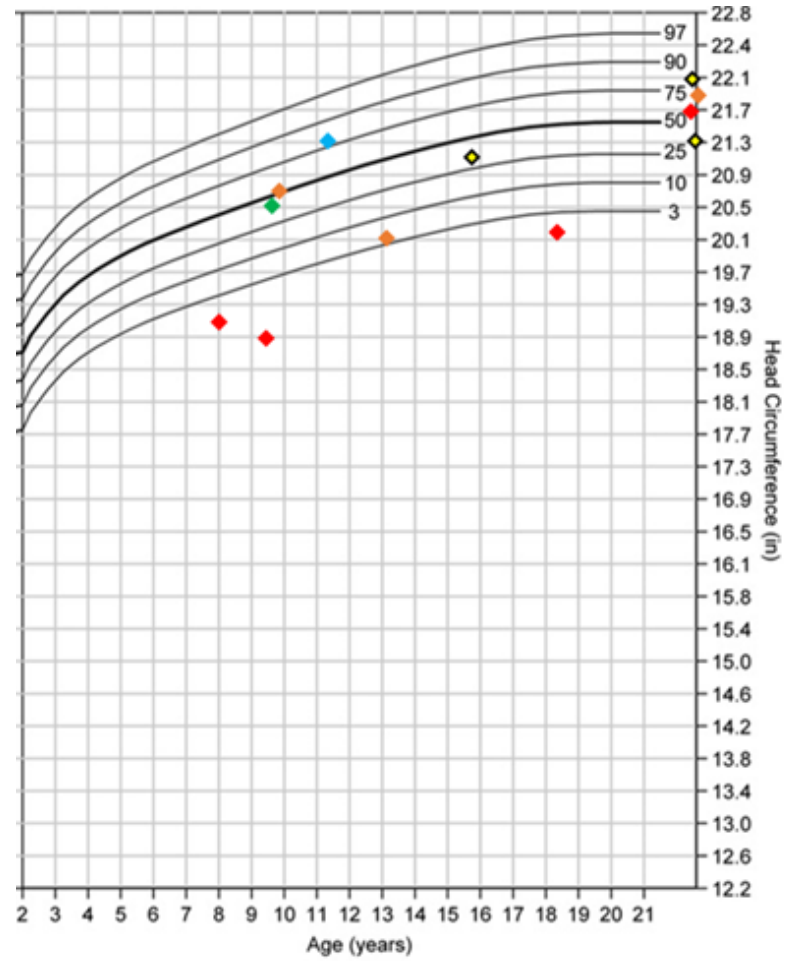
\*\*\*p<0.001

# Head Size

## Males



## Females



- ◆ ACD
- ◆ RTEL1
- ◆ TERC
- ◆ TINF2
- ◆ DKC1
- ◆ WRAP 53
- ◆ TERT
- ◆ PARN
- ◆ Unknown

# Neurologic or Psychiatric Findings

	Overall (n=44)		
	Pediatric (n=26)	Adults (n=18)	Total (n=44)
<b>Neurologic</b>	17 (65%)	4 (22%)	21 (48%)
<b>Developmental Delay</b>	15 (57%)	4 (22%)	19 (43%)
<b>Neuro-motor</b>	14 (54%)	2 (11%)	16 (36%)
<b>Psychiatric</b>	4 (15%)	8 (44%)	12 (27%)

We collaborated with a neurologist and psychiatrist in these assessments



# Summary

- 77% (34 out of 44) had a brain MRI, neurologic, or psychiatric finding
- Younger patients had more neurologic findings
  - More likely to have AR/XLR as genetic cause
  - Neuro-motor findings and cerebellar hypoplasia
  - Microcephaly
- Older patients had more psychiatric findings, primarily mood disorders
- Shorter telomeres were associated with more neurologic findings

# Recommendations for People with DC

## *(a.k.a. How can this help you?)*

- Routine screening for neurologic and psychiatric conditions
- Referral to specialty mental health services
- Early neuropsychological assessment for intellectual disability, pervasive developmental disorders, and learning disorders
- ***This study highlights the need for thorough evaluations***

# Management of Neurologic Complications


- Early intervention is key
- Evaluation by a neurologist and a brain MRI are recommended at diagnosis of DC, HH, RS, or related telomere biology disorder
- Work closely with pediatrician
- Evaluation by a developmental and behavioral pediatrician

# Management of Neurologic Complications

- Ask your school system, in writing, for an evaluation of your child, even if a baby, toddler, or preschooler
- Work with your school to develop an Individual Education Plan (IEP) or a 504 plan, as needed

Self-Advocacy:  
Know Yourself,  
Know What You  
Need, Know How  
to Get It

# Management of Neurologic Complications

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The National Institute of Neurological Disorders and Stroke (NINDS) and other Institutes of the National Institutes of Health (NIH) support research learning disabilities through grants to major research institutions across the country. Current r...

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<https://www.ninds.nih.gov/Disorders/All-Disorders/Learning-Disabilities-Information-Page>

# Resource:

<http://www.nimh.nih.gov/health/topics/index.shtml>



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### Mental Health Information

NIMH, a part of the [National Institutes of Health \(NIH\)](#), funds and conducts research to help answer important scientific questions about mental illnesses. Through research, NIMH works to determine what is promising, what helps and why, what doesn't work, and what is safe. NIMH also communicates with scientists, patients, providers, and the general public about the science of mental illnesses based on the latest research.

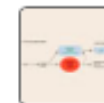
### Mental Disorders and Mental Health Topics

NIMH offers expert-reviewed information on mental disorders, a range of related topics, and the latest mental health research. Use our [A to Z list](#) to find basic information on signs and symptoms, risk factors, treatment, and current clinical trials. This information should not be used as a guide for making medication decisions or for the diagnosis or treatment of any medication condition. A health professional should be consulted. Call 911 for medical emergencies.

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# Caregivers need support too

- Parents of children with neurodevelopmental abnormalities often experience more stress, depression, and poorer health.

Dykens et al, Pediatrics 2014;134(2):e454-e463

- Peer mentors can help
- Seek out the support of your community!

