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

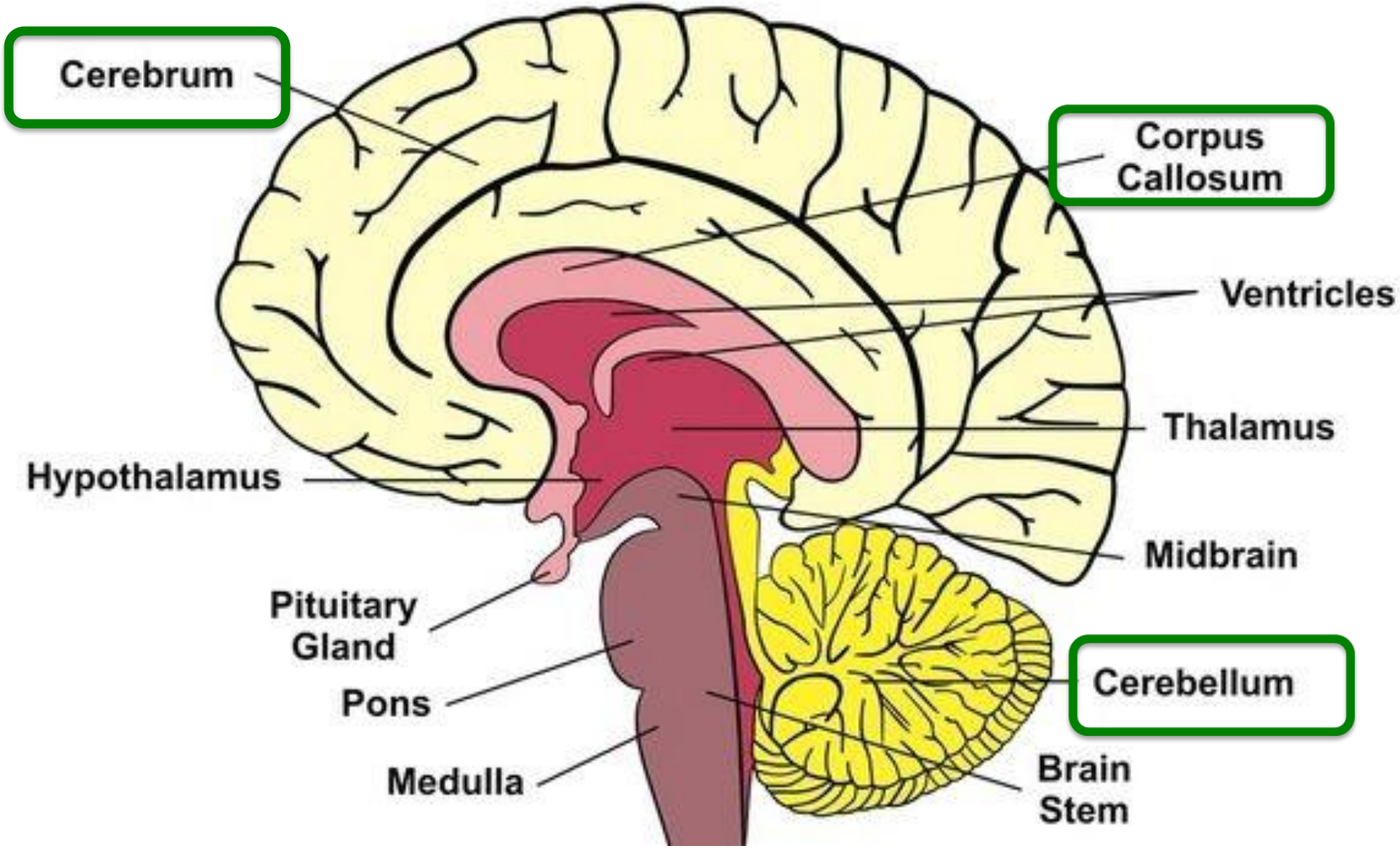
- Pulmonary Fibrosis
- Cancer
  - Head & Neck
  - Leukemia
  - Anogenital

- **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

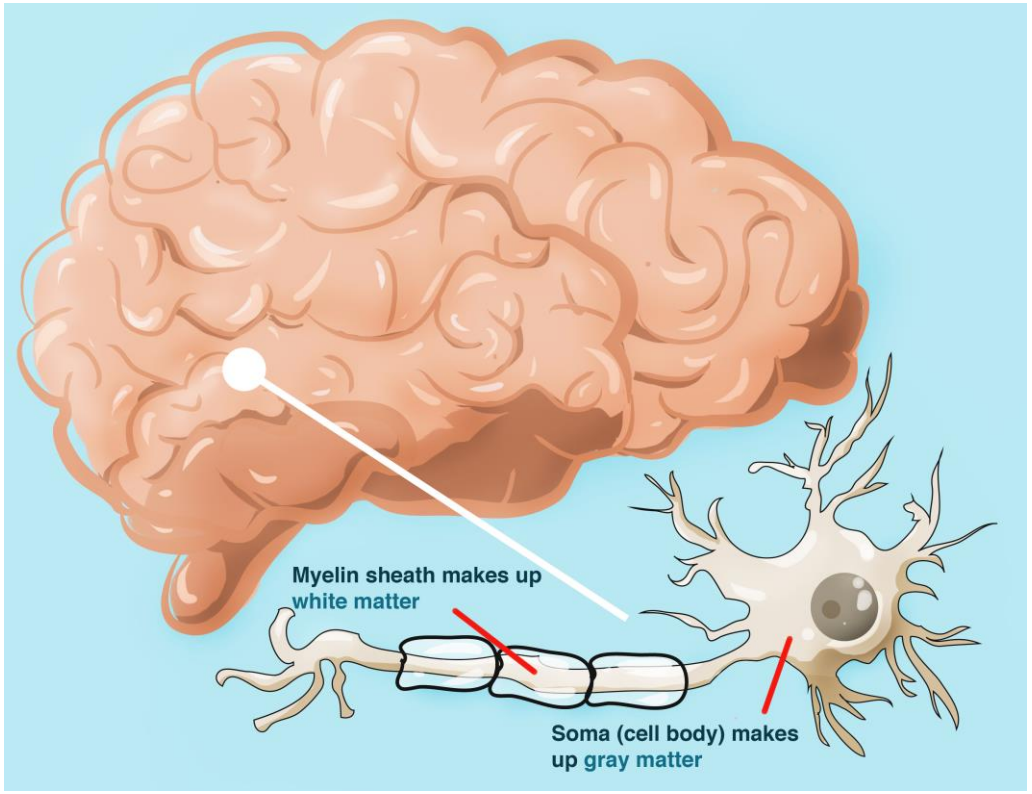
Traditional diagnosis:
Diagnostic Triad or 1 of the triad, + BMF + 2 other findings, Vulliamy et al, *Blood,* 2006, 107(7):2680-5

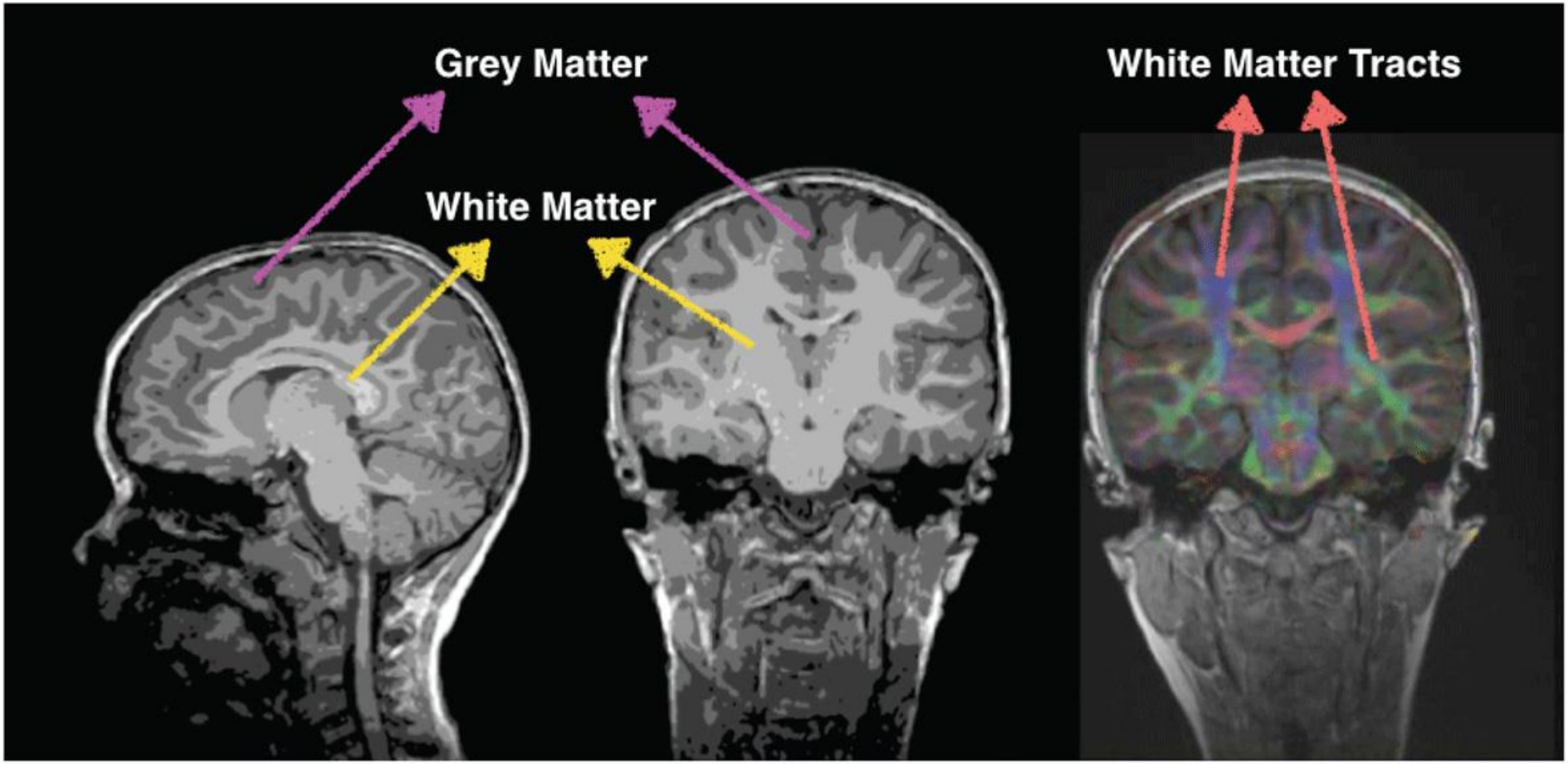
Brain Areas Affected by DC



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

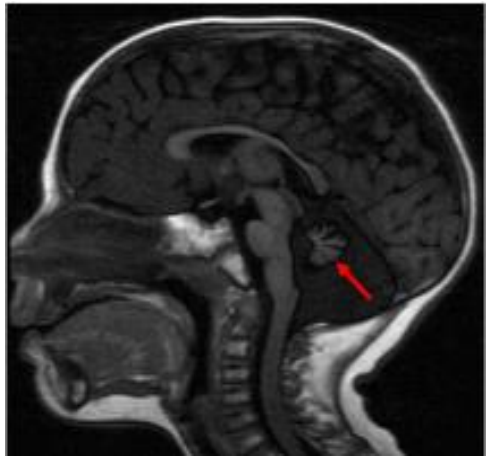
What brain MRI, neurologic, and psychiatric findings do we see in the National Cancer Institute DC Patients?

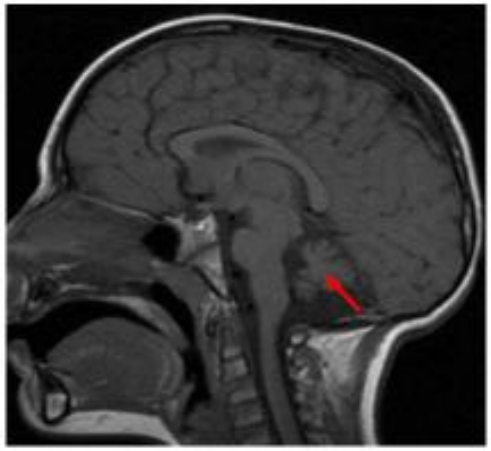
NCI DC Patients with Brain MRIs, 2001-2015

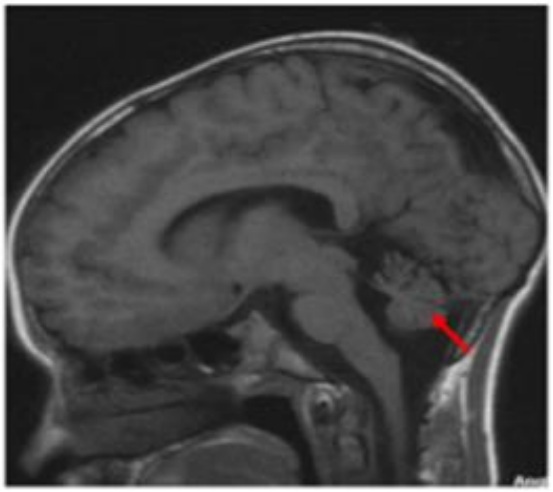
Characteristics (n=44)	Total (n=44)	XLR/AR (n=18)	AD (n=11)	TINF2 (n=9)	Unknown (n=6)
Age (yrs) at MRI					
Median	15	14	18	9	15
Range	1-60	2-46	1-60	1-24	6-31
Age group (yrs)					
0-9	16	6	3	5	2
10-17	10	4	3	1	2
18-29	11	6	1	3	1
30+	7	2	4	0	1
Sex					
Male	33	17	5	8	3
Female	11	1	6	1	3

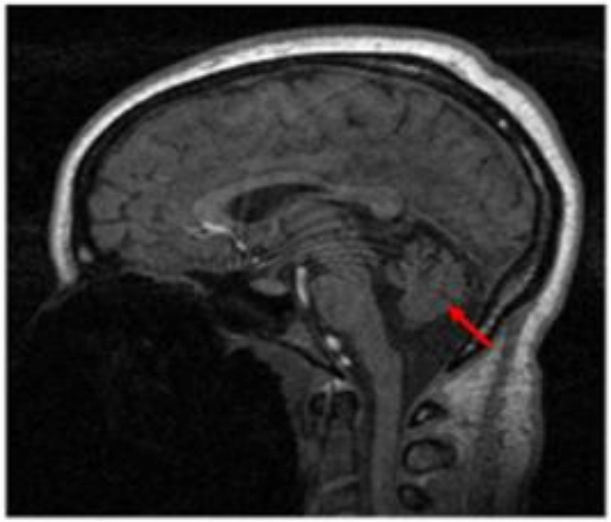
XLR:X-linked recessive inheritance, pathogenic variants in *DKC1*. AR: autosomal recessive, pathogenic variants in *RTEL1, PARN, ACD, TERT,* and *WRAP53*. AD: autosomal dominant, pathogenic variants in *TERT, TERC*, and *RTEL1*

Cerebellar hypoplasia exists in DC at varying levels of severity

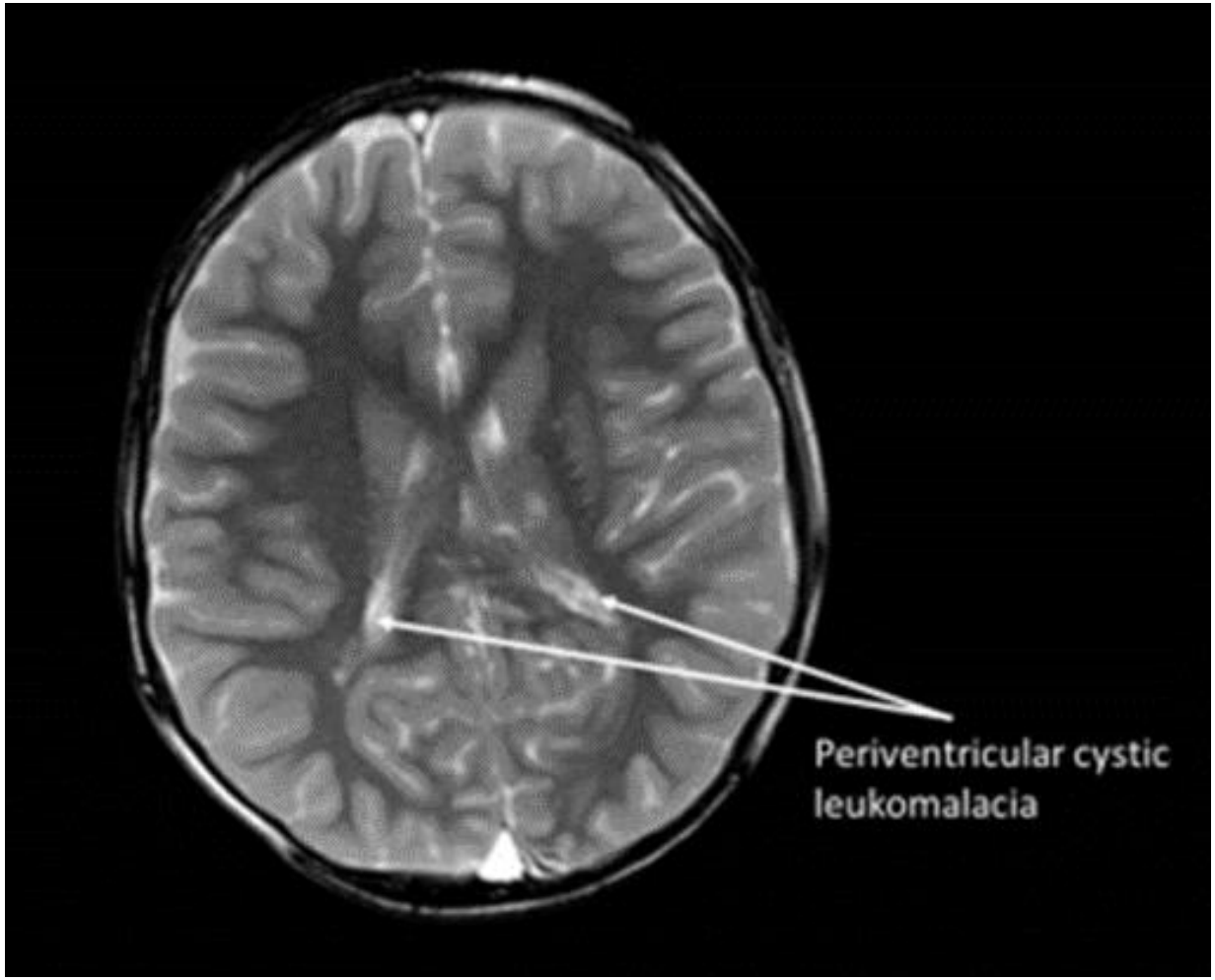








Example of abnormal cysts and a white matter abnormality in the brain MRI of a patient with DC



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%)*** **
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%)*** **
Cavum septum pellucidum abnormalities	79 (2.0%)	**20 (45.5%)*** **

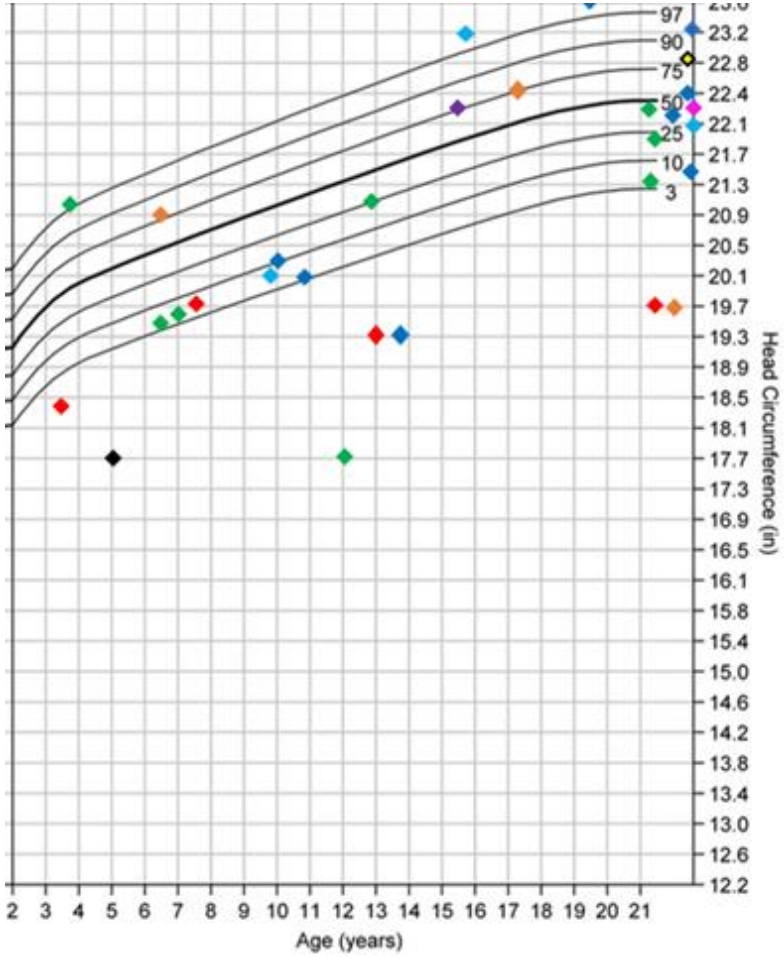
*Jansen et. al. “Incidental Findings on Brain Imaging in the General Pediatric Population.” *New England Journal of Medicine.* 2017.

***p<0.001

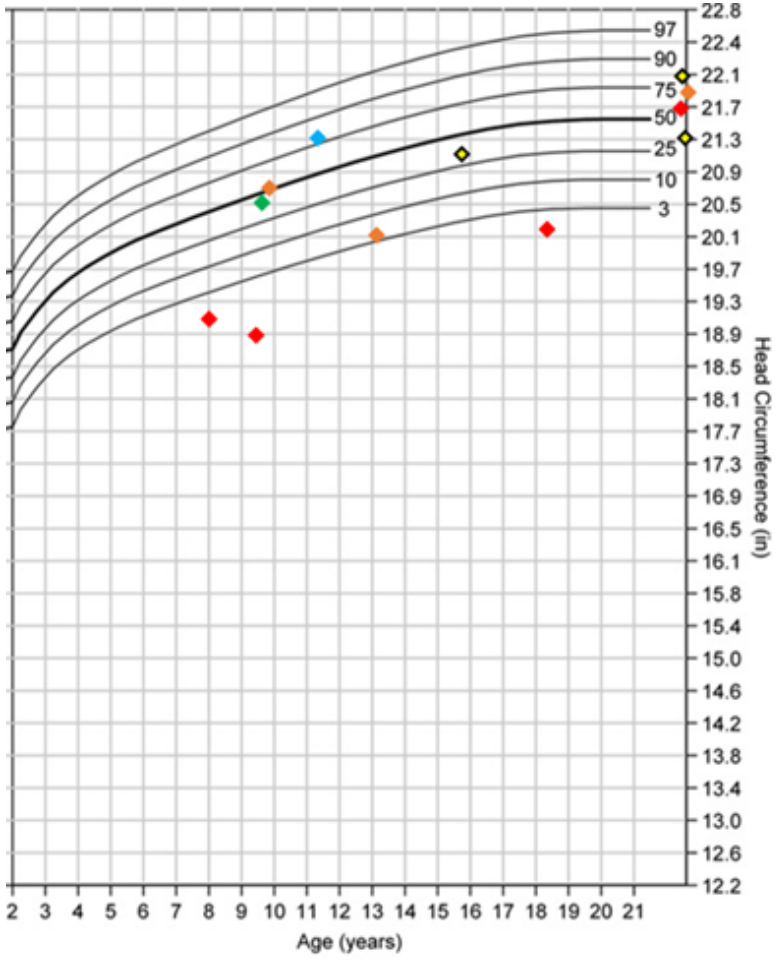
Head Size

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

Males



Females



Neurologic or Psychiatric Findings

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

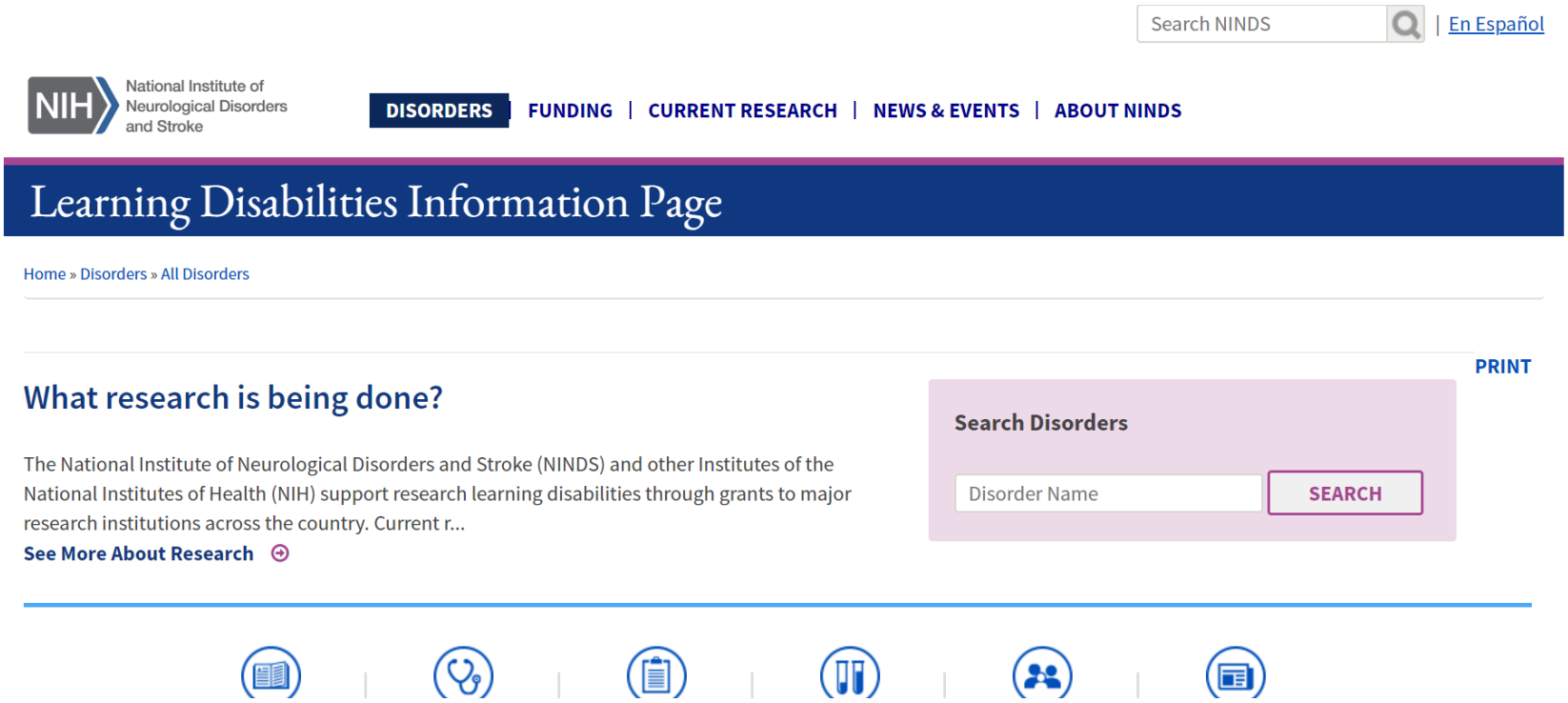
Management of Neurologic Complications

- 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

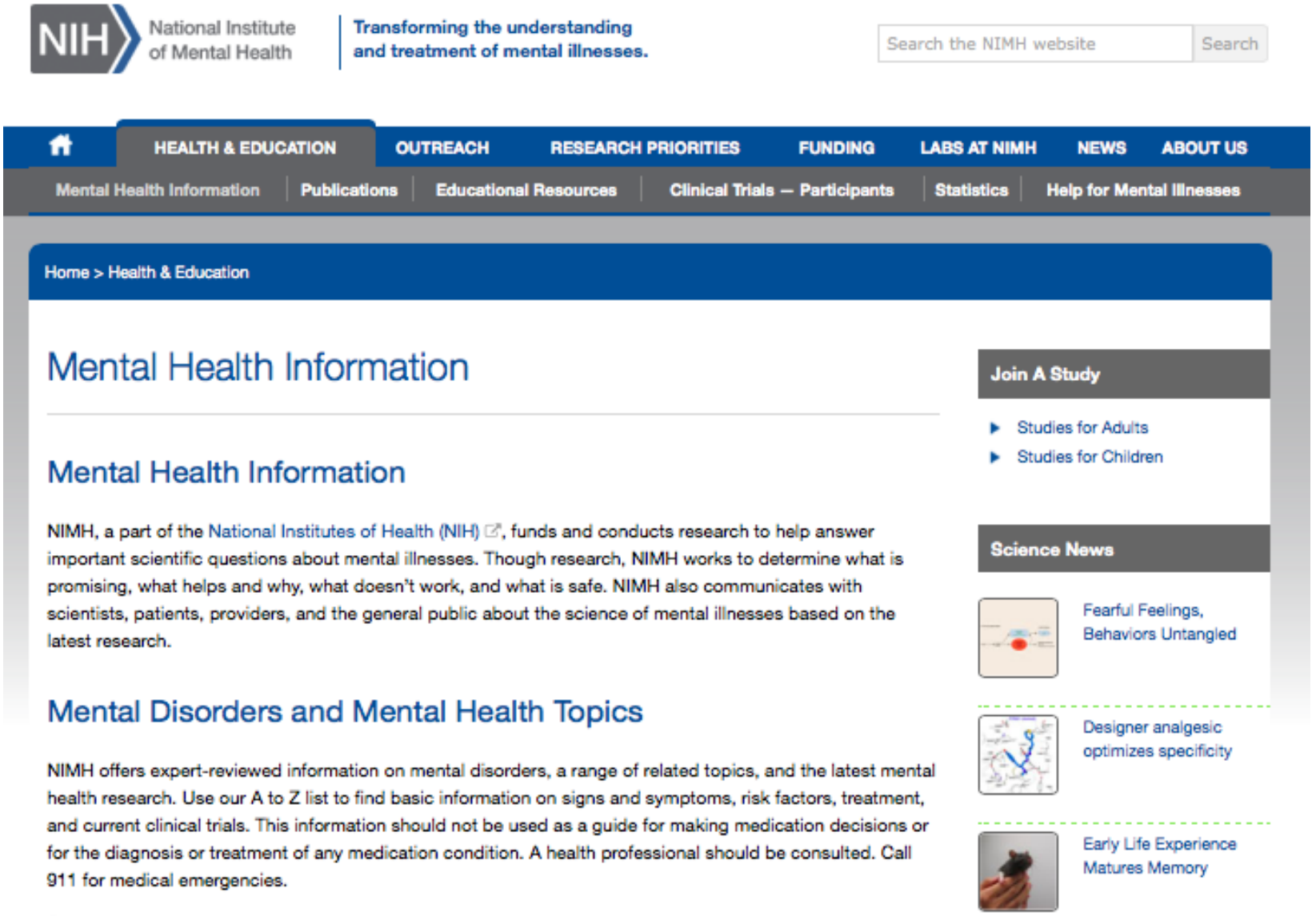
Management of Neurologic Complications



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

Resource:

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



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!

teamtelomere