Overview of DBA & DBAR

Adrianna Vlachos, MD
The Feinstein Institute for Medical Research
Zucker School of Medicine
Cohen Children's Medical Center

1st Adult DBA Meeting
September 28-29, 2019

Feinstein Institute for Medical Research
Northwell Health

Cohen Children's Medical Center
Northwell Health

DBA is an Inherited Bone Marrow Failure Syndrome

Inherited –
inherited from a parent,
OR, if sporadic, able to be passed on to your children

Bone Marrow – where all the blood cells are made

Failure – the blood cells fail to be produced

Syndrome – condition characterized by a set of associated symptoms and DBA is not only about anemia

Feinstein Institute for Medical Research
Northwell Health

DBAR

DBA is an Inherited Bone Marrow Failure Syndrome (IBMFS)

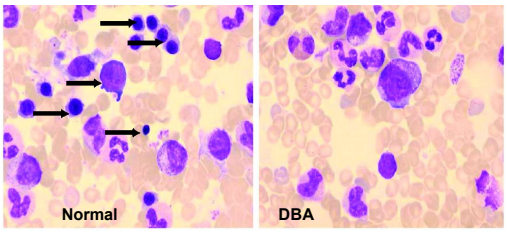
Clinical Features of all IBMFS
- Bone Marrow Failure
- Congenital Anomalies
- Cancer Predisposition

****Patients can present for the first time and be diagnosed in adulthood****

Feinstein Institute for Medical Research
Northwell Health

DBAR

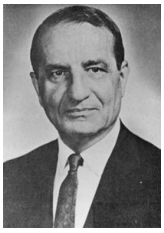
Diamond Blackfan anemia
Bone marrow smear



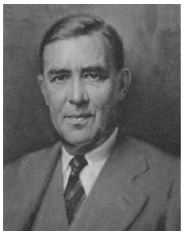
Feinstein Institute for Medical Research
Northwell Health

Diamond Blackfan Anemia

Louis Diamond



Kenneth Blackfan



Josephs H. *Medicine.* 1936;15:307
Diamond L, Blackfan K. *Am J Dis Child.* 1938;56:464

Feinstein Institute for Medical Research
Northwell Health

"Classic" Definition of DBA

- Moderate to severe macrocytic anemia
  - Macrocytic = large red cells = increased MCV
- Reticulocytopenia
  - = low reticulocyte count
- Normocellular bone marrow with a paucity of red cell precursors
  - = normocellular = normal number of cells overall (at diagnosis)
  - = low or absent early red cells
- Usual presentation at less than 1 year of age

Diamond LK, Wang WC, Alter BP. *Adv Pediatr.* **1976**;22:349-78.

Feinstein Institute for Medical Research
Northwell Health

"Modern" Diagnostic Criteria

- **Definitive but not essential**
  - *Ribosomal protein (RP)* mutation – Autosomal Dominant
  - *GATA1* – X-Linked Recessive
  - *TSR2* mutation – X-Linked Recessive
  - other mutations yet to be described
- **Major**
  - Positive family history
  - Anemia, reticulocytopenia, reduced red cell precursors in the bone marrow
- **Minor**
  - Elevated erythrocyte adenosine deaminase activity
  - Congenital anomalies
  - Elevated fetal hemoglobin
  - Macrocytosis
  - Age less than 1 year
  - No evidence of another IBMFS (FA, SDS, etc)
  - No evidence of parvovirus infection

Vlachos, et al. *Br J Haematol*. 2008;142:859-76.

Feinstein Institute for Medical Research
Northwell Health

D B A R

Diamond Blackfan Anemia Registry (DBAR) of North America

- The DBAR was established in 1991

28 years old!

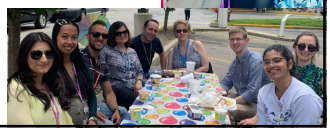
- **MISSION of the DBAR**
  - To develop a demographic, clinical and laboratory database in order to facilitate the study of
    - the epidemiology of DBA
    - the biology of DBA
- The DBAR is a **dynamic** tool for studying DBA

Feinstein Institute for Medical Research
Northwell Health

D B A R

Our Translational DBA Team

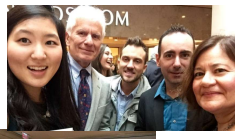
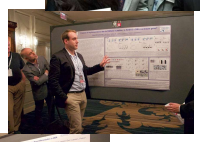
- Feinstein Institute for Medical Research/ Cohen Children's Medical Center
  - **Adrianna Vlachos, MD**
  - **Jeffrey M. Lipton, MD, PhD**
  - Eva Atsidaftos, MA
  - Johnson Liu, MD
  - Maryam Hussain, MPH
  - Maria Florento
- Lawrence Wolfe, MD – pediatric hematology
- Phyllis Speiser, MD – pediatric endocrinology
- Yael Toby Harris, MD - endocrinology
- Tara Kim, MD - endocrinology
- Sandeep Jauhar, MD - cardiology

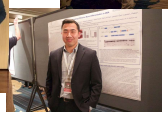


Feinstein Institute for Medical Research
Northwell Health

Our Translational DBA Team

- Feinstein Institute for Medical Research/ Cohen Children's Medical Center
  - **Lionel Blanc, PhD**
  - Julien Papoin, MS
  - Brian Dulmovits, MD-PhD student
  - Jimmy Hom, MD-PhD student
  - Elena Brindley, MD-PhD student
  - Ryan Ashley, MD-PhD student



Feinstein Institute for Medical Research
Northwell Health

DBAR Scientific Advisory Board

- Adrianna Vlachos, MD
- Jeffrey Lipton, MD, PhD

- Dawn Baumgardner, DBAF
- David Bodine, PhD – National Institutes of Health
- Irma Dianzani, PhD – Univ of Piemonte Orientale, Italy
- Steven Ellis, PhD – Univ of Louisville
- Jason Farrar, MD – Univ of Arkansas

Feinstein Institute for Medical Research
Northwell Health

Collaborators

- **NIH/NHGRI**
  - David Bodine, PhD
  - Kelly O'Brien, PhD
  - Jens Lichtenberg, PhD
  - Jessica Kang, BS
- **University of Arkansas**
  - Jason Farrar, MD
- **University of Louisville**
  - Steven R Ellis, PhD
- **NIH/NCI**
  - Blanche Alter, MD, MPH
  - Philip Rosenberg, PhD
- **Jackson Laboratory**
  - Luanne Peters, PhD
- **Children's Hospital Boston**
  - Len Zon, MD
  - George Daley, MD, PhD
  - Akiko Shimamura, MD, PhD
- **St Mary's Hospital, UK**
  - Josu De La Fuente, MD
- **University of Piemonte Orientale, Novara (Italy)**
  - Irma Dianzani, PhD

Feinstein Institute for Medical Research
Northwell Health

Diamond Blackfan Anemia Registry

- 7 per million live births = 20-40 new patients per year
- Enrollment – 821 total
  - 788 in North America (US, Canada, Mexico)
  - 33 international patients
- male/female – 411:410

Feinstein Institute for Medical Research
Northwell Health

21

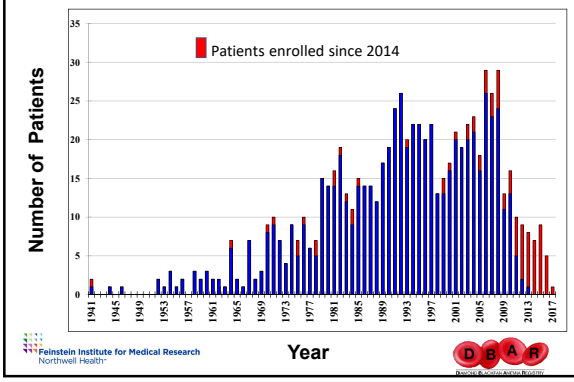
Diamond Blackfan Anemia Registry of North America

- 677 alive
  - Median age: 20 yr (9 mo – 69 yr)
- 111 dead
  - Median age: 23 yr (3 wk – 69 yr)
- Median age of presentation of anemia
  - 2 months (range, birth to 12 yrs)
- Median age of diagnosis of DBA
  - 4.5 months (range, birth to 28yr10mo)
- 113 patients have undergone SCT in the DBAR
  - Median age at SCT: 8yr (5mo – 53yr)

Feinstein Institute for Medical Research
Northwell Health

22

Patient Distribution By Birth Year



Feinstein Institute for Medical Research
Northwell Health

D B A R

Statistics of the DBAR

- Anemia
  - 10% at birth
  - 50% by 3 mo of age
  - 75% by 6 mo of age
  - 90% present by 1 yr of age
- Median age of presentation of anemia
  - 3 months (range, birth to 12 yrs)
- Median age of diagnosis of DBA
  - 4 months (range, birth to 53yr)

… 10% present in adolescence and adulthood

Feinstein Institute for Medical Research
Northwell Health

Diamond Blackfan Anemia Registry

- 111 deceased
  - Causes
    - Treatment Related (67%)
      - Stem cell transplant-related complications
      - **Iron overload**
      - Infections/sepsis
      - Venous access device complication
    - DBA Related (22%)
      - Malignancy (colon cancer and myeloid leukemia)
      - Severe aplastic anemia
    - Unknown (11%)
      - Pulmonary embolism
      - Stroke

Feinstein Institute for Medical Research
Northwell Health

Gene Discovery in DBA

- ***RPS19*** is the first gene found to be mutated in a patient with DBA

  Gustavsson P, *et al. Nat Gen.* **1997**;16:368–371.

- DBAR's collaboration for gene discovery with
  - Children's Hospital Boston – ***RPS24***

    Gazda HT, *et al. Am J Hum Gen.* **2006**;79:1110–1118.
  - Johns Hopkins Hospital – ***RPL35a***

    Farrar J, *et al. Blood.* **2008;** 112:1582-92.
- Establishment of the DBA DNA Repository
  - started July 2006; collect DNA and cells from patients and their family members

Feinstein Institute for Medical Research
Northwell Health

New Discovery: A New Class of Disorders

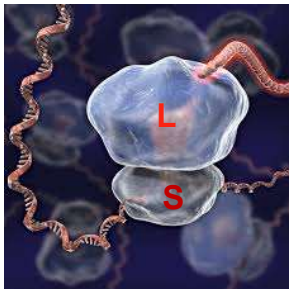
RPS – Ribosomal Protein Small subunit
RPL - Ribosomal Protein Large subunit

Diamond Blackfan anemia is the first human disorder of Ribosome Biogenesis and/or Function

Ribosomopathy

Feinstein Institute for Medical Research
Northwell Health

Ribosomopathy



Ribosomes are structures in the cell. The ribosome is made up of a large and a small subunit. Each subunit is made up of multiple ribosomal proteins. The ribosomal subunits join and read the messenger RNA to make proteins.

Feinstein Institute for Medical Research
Northwell Health

Resequencing Study

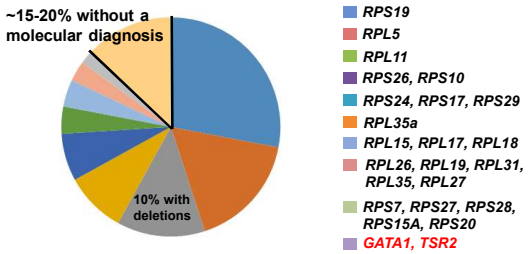
NIH National Heart, Lung, and Blood Institute

- NHLBI DNA Resequencing Grant
  - awarded January 2008
  - in collaboration with the J. Craig Venter Institute
  - resequencing the 80 genes of large and small ribosomal subunit proteins
  - We found multiple ribosomal proteins to be mutated in DBA.
  - We also found some ribosomal proteins to be deleted in DBA.

Feinstein Institute for Medical Research
Northwell Health

Gene Discovery Studies

- 22 RP genes and 2 non-RP genes have been found to cause DBA in 80-85% of patients



Feinstein Institute for Medical Research
Northwell Health

D B A R

Gene Mutations in Patients in DBAR

Gene	% of cases
RPS19	46%
*RPS26**	13%
RPS17	6%
*RPS24**	4%
*RPS10**	2%
*RPS7**	<1%
RPS27	<1%
RPS20	<1%

Gene	% of cases
*RPL5**	13%
*RPL11**	7%
*RPL35a**	5%
*RPL15**	<1%
*RPL35**	<1%
*RPL31**	<1%
TSR2	<1%
GATA1	<1%

Not found in DBAR: *RPS15A, RPS28, RPS29, RPL17, RPL18, RPL19, RPL26*, RPL27*

Feinstein Institute for Medical Research
Northwell Health

D B A R

Congenital Anomalies in DBA Patients

- 50% of all patients
  - 50% cranio-orofacial
  - 40% upper extremity
  - 40% genitourinary
  - 30% cardiac
- 20% with more than one anomaly (not including short stature)

Feinstein Institute for Medical Research
Northwell Health

D B A R

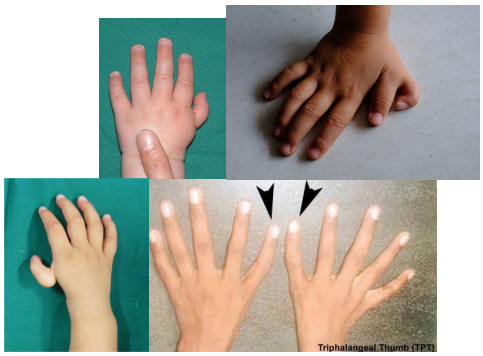
Genotype-Phenotype Correlations

- Patients with orofacial clefting represent a distinct group
  - Mutations in *RPL5, RPL11* and *RPS26* (and *TSR2*) are associated with cleft palate
  - *RPL11* with thumb anomalies
- Assists in genetic screening

Gazda HT, *et al. Am J Hum Genet.* **2008**;83:769-80.
Doherty L, *et al. Am J Hum Genet.* **2010**;86:222-8.
Gripp KW, et al. *Am J Med Genet A.* **2014**;164A:2240–2249.

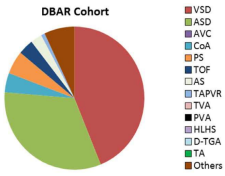
Feinstein Institute for Medical Research
Northwell Health

Upper Limb Anomalies



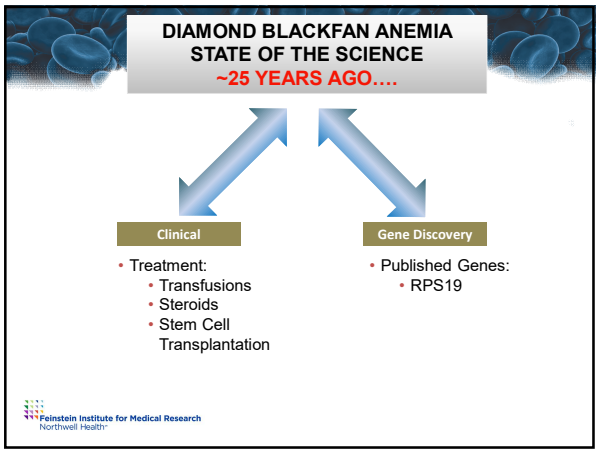
Congenital Heart Disease in DBA

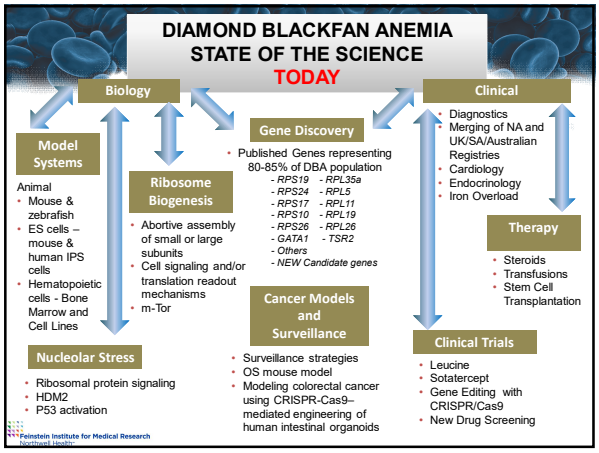
14.9%

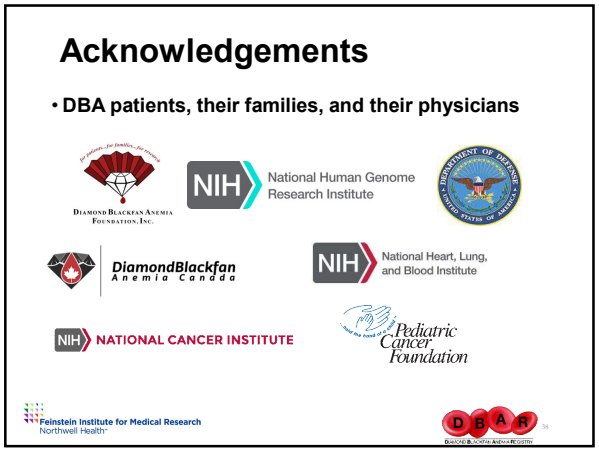


Most common defects are ventricular septal defects followed by atrial septal defects, also known as **"holes in the heart"**

Feinstein Institute for Medical Research
Northwell Health


DIAMOND BLACKFAN ANEMIA
STATE OF THE SCIENCE
~25 YEARS AGO….
Clinical
Gene Discovery
• Treatment:
• Transfusions
• Steroids
• Stem Cell Transplantation
• Published Genes:
• RPS19
Feinstein Institute for Medical Research
Northwell Health


DIAMOND BLACKFAN ANEMIA
STATE OF THE SCIENCE
TODAY
Biology
Clinical
Model Systems
Animal
• Mouse & zebrafish
• ES cells – mouse & human IPS cells
• Hematopoietic cells - Bone Marrow and Cell Lines
Ribosome Biogenesis
• Abortive assembly of small or large subunits
• Cell signaling and/or translation readout mechanisms
• m-Tor
Gene Discovery
• Published Genes representing 80-85% of DBA population
- RPS19 - RPL35a
- RPS24 - RPL5
- RPS17 - RPL11
- RPS10 - RPL19
- RPS26 - RPL26
- GATA1 - TSR2
- Others
- NEW Candidate genes
Cancer Models and Surveillance
• Surveillance strategies
• OS mouse model
• Modeling colorectal cancer using CRISPR-Cas9–mediated engineering of human intestinal organoids
Nucleolar Stress
• Ribosomal protein signaling
• HDM2
• P53 activation
• Diagnostics
• Merging of NA and UK/SA/Australian Registries
• Cardiology
• Endocrinology
• Iron Overload
Therapy
• Steroids
• Transfusions
• Stem Cell Transplantation
Clinical Trials
• Leucine
• Sotatercept
• Gene Editing with CRISPR/Cas9
• New Drug Screening
Feinstein Institute for Medical Research
Northwell Health


Acknowledgements
• DBA patients, their families, and their physicians
Diamond Blackfan Anemia Foundation, Inc.
NIH National Human Genome Research Institute
DiamondBlackfan Anemia Canada
NIH National Heart, Lung, and Blood Institute
NIH NATIONAL CANCER INSTITUTE
Pediatric Cancer Foundation
Feinstein Institute for Medical Research
Northwell Health
DBAR