Kids First
PEDIATRIC RESEARCH PROGRAM
Data Resource Center
Introduction
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Data Coordination Core

- Ensures that curated genomic and clinical data can be brought together into one common format
- Collaborates with the University of Chicago's Bionimbus, which is a National Institute's of Health (NIH) Trusted Partner
- Meets all required core-NIH standards and established data quality, security and service protocols

Data Resource Portal Core

- Cloud-based, collaborative workspace
- Provides data analysis tools to allow access by the world-wide research community
- Allows researchers to instantly search large collections of clinical and genomic data
- Allows patients & families to search for information about a specific disease type, diagnosis, or researcher within the Kids First Data Resource Center

Administration & Outreach Core

- Engages with patient families & foundation advocates across the pediatric cancer and structural birth defects communities
- Provides support & programmatic coordination across the Kids First Data Resource Center
- Manages content, branding & messaging for Kids First educational resources
- Identifies new commitment makers and partners to increase the impact of the Kids First DRC
Kids First Data Resource Platform

**Kids First DRC Mission**

**Kids First Vision**: Alleviate suffering from childhood cancer and structural birth defects by fostering collaborative research to uncover the etiology of these diseases and supporting data sharing within the pediatric research community.

**The Research Challenge**

Pediatric Cancer → Development
Kids First DRC Mission

Kids First Vision: Alleviate suffering from childhood cancer and structural birth defects by fostering collaborative research to uncover the etiology of these diseases and supporting data sharing within the pediatric research community.
The Research Challenge
Platform Design Principle

Starting Point: Scientific Method

The Unmet Need
Starting Point: Scientific Method
<table>
<thead>
<tr>
<th>Observation</th>
<th>Hypothesis</th>
<th>Experiment</th>
<th>Analysis</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Ideas       | • Measurements  
  • Raw Data.  
  • Data-driven  
  • Causation vs. correlation  
  • Testable.  
  • Reductionist  
  • Controlled Variables  
  • Interpretations  
  • Integration of past knowledge and iterative experiments  
  • Theory or Translation to impact | Ideas | Ideas | Ideas | Ideas |

The Unmet Need

Gabrielle Miller and Diffuse Intrinsic Pontine Gliomas

DIPG

- Nine months median survival
- No known cures or therapies
Gabriella Miller and Diffuse Intrinsic Pontine Gliomas

"stop talking and start doing."
"Talk is b------t!"
“stop talking and start doing.”
“Talk is b------t!”
DIPG

- Nine months median survival
- No known cures or therapies
A new model for accelerated research
The genomic landscape of diffuse intrinsic pontine glioma and pediatric midline high-grade astrocytoma

Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma

Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma
Fibrodysplasia ossificans progressiva Research

Investigator #2

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<thead>
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<th>Experiment</th>
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</tr>
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Data ➔ Conclusion

A recurrent mutation in the BMP type 1 receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva.

[Reference Image]

[Image of fibrodysplasia]
A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva

Eileen M Shore1–3, Meiqi Xu1,2, George J Feldman1,2, David A Fenstermacher4–6, Tae-Joon Cho7, In Ho Choi7, J Michael Connor8, Patricia Delat9, David L Glaser1,2, Martine LeMerrer10, Rolf Morhart11, John G Rogers12, Roger Smith13, James T Triffitt14, J Andoni Urtizberea15, Michael Zasloff1,2,16,17, Matthew A Brown14,18 & Frederick S Kanlan1,2,19
Developmental Biology Research

Investigator #3

Observation  Hypothesis  Experiment  Analysis  Conclusion

Data  Conclusion

Dorsomorphin inhibits BMP signals required for embryogenesis and trio metabolism.

Paul B Xu²,³, Oliveria Dellaire²,³, Daniele Reddick²,³, Jakki H. Fan²,³, Bing Yang²,³, Deng Li², Min Su²,³, Hongtao Li²,³, Summer E. Young¹,³, Nestor D. Gislon²,³, and Nestor T. Herranz²,³

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³Institute for Regenerative Medicine and Translational Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01655, USA.
Dorsomorphin inhibits BMP signals required for embryogenesis and iron metabolism

Paul B Yu\textsuperscript{1,2,6}, Charles C Hong\textsuperscript{1,5,6}, Chetana Sachidanandana\textsuperscript{1,6}, Jodie L Babitt\textsuperscript{3}, Donna Y Deng\textsuperscript{1}, Stefan A Hoyng\textsuperscript{1}, Herbert Y Lin\textsuperscript{3}, Kenneth D Bloch\textsuperscript{1,4}, and Randall T Peterson\textsuperscript{1,2}

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A New Model

Lab/Institution Boundaries redefined

DATA → INFORMATION → KNOWLEDGE → IMPACT
Lab/Institution Boundaries *redefined*
Kids First
PEDIATRIC RESEARCH PROGRAM
Data Resource Center

A new model for accelerated research

kidsfirstdrp.org
The genetic basis for CDH: MYRF as a genetic cause of multiple congenital anomalies

Wendy Chung, MD PhD
Kennedy Family Professor of Pediatrics and Medicine
Columbia University
Congenital diaphragmatic hernia

- ~1/2500 birth
- ~30% of mortality
- ~40% -50% non-isolated (complex)
  - congenital heart disease
  - developmental delay
  - gastroesophageal reflux disease (GERD) and feeding difficulties
  - hearing loss
Genetic Evidence for CDH

• Chromosome anomalies
• Single gene disorder
  - Mathew-Wood syndrome, Fryns syndrome, Pallister Killian syndrome etc.
• Familial aggregation
  - Twin studies
• Mouse studies elucidated the role of several genes in diaphragm development
Genetic Causes of CDH are Largely Unknown

- Chromosome conditions
- Copy number variants
- Single Genes Disorders (inherited versus de novo)
- Multiple Gene Disorders
- Other
Study protocol

• **Eligible subjects**
  – Children and fetuses with CDH and their parents/other affected family members

• **Protocol**
  – Collection of blood from proband and biological parents
  – Over 100 data points on prenatal history, NICU stay, surgical report, and family history

• **Prospective cohort**
  – Collection of skin and diaphragm at time of surgery
  – Pulmonary Hypertension assessment at 1 and 3 months
  – 2 year developmental assessment
  – 5 year developmental assessment
Genetic Characterization

• Karyotype

• Chromosome microarray

• Exome sequencing
16/256 (6.3%) of CDH cases with chromosomal anomalies

• 3 aneuploidies ( 2 Trisomy 21, 1 trisomy 18)
• 2 unbalanced translocations
• 11 patients with de novo CNVs
Deletions of 8p23.1 associated with CDH

Wat et al., 2009 [51]
Slavotinek et al., 2005 [53]
Shimokawa et al., 2005 [16]
Faivre et al., 1998 [54]
Whole exome sequencing in familial CDH
GATA4

- A zinc finger transcription factor that controls gene expression and differentiation in a variety of cell types.
- Located at 8p23.1-p22 where there is a recurrent microdeletion associated with both congenital heart disease and CDH (Wat et al. 2009).
- ~14% of mice with heterozygous $Gata4^{+/\Delta ex2}$ had diaphragm defects.
GATA4 c.754 C>T p.R252W genotype
III.4 Father

II.3 Grandfather
Not all Genetic Conditions Run in Families

De novo mutations are common in autism, schizophrenia, intellectual disabilities, seizures, birth defects, syndromes
De novo variants often cause CDH

• ~6% of CDH patients carry pathogenic CNVs

• ~20% of non-isolated and ~10% isolated CDH patients explained by damaging de novo coding SNVs/indels
Silent Variants

mRNA

<table>
<thead>
<tr>
<th>AUG</th>
<th>AAG</th>
<th>UUU</th>
<th>GGC</th>
<th>GCA</th>
<th>UUG</th>
<th>CAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td>Lys</td>
<td>Phe</td>
<td>Gly</td>
<td>Ala</td>
<td>Leu</td>
<td>Gin</td>
</tr>
</tbody>
</table>

Protein

Silent Variants
• Don’t change the amino acid sequence
Missense Variants

- Changes the amino acid sequence
- This is not always a problem
Nonsense Variants

- Truncated a protein
- Generally thought to cause a problem with the protein
- We think they are likely gene disrupting
Burden of coding LGD and damaging \textit{de novo} variants in CDH patients

\[ p = 9.05 \times 10^{-6} \]

\[ * p < 0.001 \]

Damaging variants are enriched in constrained genes.
Higher enrichment of damaging variants in complex cases and female cases

\[ *p = 2.51 \times 10^{-4} \]

\[ *p < 0.001 \]
“Female Protective Model”

Population mean

Minimal disease liability sufficient to cause NDD or birth defects

Proportion of population

Increasing disease liability for NDD or birth defects

Affected individuals
### De novo variants of MYRF identified in CDH and CHD patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Diaphragm defect</th>
<th>Heart defect</th>
<th>Genital defect</th>
<th>Other malformations</th>
<th>Status</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>L CDH</td>
<td>ASD, VSD, TOF</td>
<td>B/L Undescended testis</td>
<td>None</td>
<td>Deceased</td>
<td>p.G81Wfs*45</td>
</tr>
<tr>
<td>Male</td>
<td>L CDH</td>
<td>ASD, VSD</td>
<td>None</td>
<td>None</td>
<td>Deceased</td>
<td>p.V679A</td>
</tr>
<tr>
<td>Male</td>
<td>L CDH</td>
<td>HLHS</td>
<td>Ambiguous genitalia</td>
<td>Intellectual disability</td>
<td>Alive</td>
<td>p.R695H</td>
</tr>
<tr>
<td>Female</td>
<td>L CDH</td>
<td>VSD</td>
<td>No internal genital organs</td>
<td>Accessory spleen</td>
<td>Deceased</td>
<td>p.G435R</td>
</tr>
<tr>
<td>Male</td>
<td>Right eventration</td>
<td>Abnormal aorta, aortic valve</td>
<td>Undescended testis</td>
<td>Abdominal Abnormalities</td>
<td>Deceased</td>
<td>p.Q403H</td>
</tr>
<tr>
<td>Female (identical twin)</td>
<td>L CDH</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Deceased</td>
<td>p.V636Sfs*5</td>
</tr>
<tr>
<td>Female (identical twin)</td>
<td>None</td>
<td>HLHS</td>
<td>None</td>
<td>None</td>
<td>Deceased</td>
<td>p.V636Sfs*5</td>
</tr>
<tr>
<td>Female</td>
<td>None</td>
<td>Abnormal aorta, aortic valve</td>
<td>NONE</td>
<td>General Skeletal Abnormalities, Short stature,</td>
<td>Alive</td>
<td>p.L479V</td>
</tr>
<tr>
<td>Male</td>
<td>None</td>
<td>Abnormal aorta</td>
<td>Ambiguous genitalia</td>
<td>None</td>
<td>Deceased</td>
<td>p.F387S</td>
</tr>
</tbody>
</table>
Myelin Regulatory Factor

- Transcription factor that controls gene expression
- Initially appreciated to play a role in the brain
- Now appreciated to cause cardiac urogenital syndrome
Noncoding variants also play a role

Significant signals suggest variants including SNVs and indels in these combination profile may have higher frequency in patients of CDH than in control populations.
Conclusions

• Exome and genome analysis of trios is a tool to identify genetic causes of CDH
• *De novo* genetic variants account for ~20% of complex CDH cases and ~10% of isolated CDH cases
• There is evidence that the genetic architecture of CDH may differ by gender
• Some genes causing CDH also cause other congenital anomalies
• Over 100 genes are predicted to be implicated in CDH and much larger cohorts are needed to fully understand the genetics of CDH
Thank You to the 1200 + DHREAMS Families
Acknowledgments

Surgeons
Vincent Duron
Gudrun Aspelund
Mark Arkowitz (p)
David McCulley
Ken Azarow
Amy J Wagner
Brad Warner
David Schindel
Samuel Soffer
George Mychaliska
Robert Cusick
Melissa Danko
Dai Chung (p)
Mahmoud ElFiky
Przemyslaw Kosinski
Foong Yen Lim
Jason Fisher
Emrah Aydin
Caroline Maloney
Michelle Kallis
Benjamin Wadowski
Brian Bucher
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Kate Ackerman
Xin Sun

Funding (>500)
1X01 HL132366-01
1P01HD068250-01
1P01HD068250-06A1
R01 HD057036-01A1
Gabriella Miller Kids First Pediatric Research Program
CHERUBS
CDHi
CDHUK
ACDHO
Global CDH
Breath of Hope
Help4CDH
National Greek Orthodox Ladies Philoptochos Society, Inc.
Fore Hadley Foundation
The Wheeler Foundation
The Vanech Foundation
Larsen Family
Brountzas/Kostaridis Family
Wilke Family
Henley Family
Guzman and Padolina Family
Orowitz Family
Schwartz Family
>100 donations from families of <$500
Questions

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Coordinators: Julia Wynn jw2500@columbia.edu
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How did Kids First get started?

- Initiated in response to the [2014 Gabriella Miller Kids First Research Act](#):
  - Signed into law on April 3, 2014
  - Ended taxpayer contribution to presidential nominating conventions
  - Transferred $126 million into the Pediatric Research Initiative Fund
  - Authorized appropriation of $12.6 million per year for 10 years to the NIH Common Fund for pediatric research; first appropriation was for FY2015
What is the Program’s vision?

Alleviate suffering from childhood cancer and structural birth defects by fostering collaborative research to uncover the etiology of these diseases and supporting data sharing within the pediatric research community.
Why study childhood cancer and structural birth defects together?

Congenital anomalies associated with increased risk of childhood cancer

Norwood, *PLOS ONE*, 2017
Who is part of Kids First?

Kids First is an NIH Common Fund program coordinated by a **trans-NIH Working Group**, which is chaired by four institutes:

- **Eunice Kennedy Shriver** National Institute of Child Health and Human Development (NICHD)
- National Human Genome Research Institute (NHGRI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Cancer Institute (NCI)

Other Working Group Representation:

- NIDCR
- NIAAA
- NIDDK
- NEI
- NIAID
- ORIP
- NIDA
- NINDS
- NIEHS
- NIAMS
- NCATS
- CDC
Who is part of Kids First?

The Kids First program has implemented two major initiatives, thus far:

- **X01 Childhood Cancer & Structural Birth Defects Cohorts**
- **Kids First Sequencing Centers**
Who is part of Kids First?

Data Coordination Center
- Clinical & phenotypic data harmonization using ontologies
- Genomic data harmonization against latest reference build with an optimized and scalable pipeline

Administration & Outreach
- Coordinate and communicate across the DRC
- Engage the broader community including researchers, physicians, patients, and foundation advocates

Data Resource Portal
- Develop interface to enable users of all skill levels to browse, visualize, and analyze across Kids First and related data
- Develop analytic frameworks and cloud-based workspaces to enable collaborative analysis and empower research
Who is part of Kids First?

Sequencing Centers

BROAD INSTITUTE

HudsonAlpha Institute for Biotechnology

St. Jude Children's Research Hospital

Baylor College of Medicine

HGSC Human Genome Sequencing Center

McDonnell Genome Institute

> 26,000 genomes
Who is part of Kids First?
X01 Cohort Projects/Datasets

- 26 projects
- ~10,000 patients (+ family members and tumors)
- 4 X01 cycles (3 more planned!)
- 7 released datasets

Disorders of Sex Development (FY15)
Congenital Diaphragmatic Hernia (FY15, 16, 17)
Ewing Sarcoma (FY15, 17)
Orofacial Clefts; Caucasian (FY15), Latin American (FY16), Asian & African (FY17)
Osteosarcoma (FY15)
Structural Heart & Other Defects (FY15, 16, 18)
Syndromic Cranial Dysinnervation Disorders (FY15)
Cancer Susceptibility (FY16)
Adolescent Idiopathic Scoliosis (FY16)
Familial Leukemia (FY16)
Hearing Loss (FY16)
Neuroblastomas (FY16)
Craniofacial Microsomia (FY17)
Enchondromatoses (FY17)
Hemangiomas, Vascular Anomalies & Overgrowth (FY17, 18)
Nonsyndromic Craniosynostosis (FY17)
Patients with both childhood cancer and birth defects (FY17)
Bladder Exstrophy (FY18)
Cornelia de Lange Syndrome (FY18)
Esophageal Atresia and Tracheoesophageal Fistulas (FY18)
Kidney and Urinary Tract Defects (FY18)
Intracranial Germ Cell Tumors (FY18)
Microtia (FY18)
Fetal Alcohol Spectrum Disorders (FY18)
Myeloid Malignancies + overlap with Down syndrome (FY18)
Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome (FY18)
Who is part of Kids First?

NIH Collaborators

Disorders of Sex Development (FY15)
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Intracranial Germ Cell Tumors (FY18)
Microtia (FY18)

NIAAA & INCLUDE Project
(INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome)

Fetal Alcohol Spectrum Disorders (FY18)
Myeloid Malignancies + overlap with Down syndrome (FY18)
Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome (FY18)
### Who is part of Kids First?

**NIH Collaborators**

#### Disorders of Sex Development (FY15)

- Congenital Diaphragmatic Hernia (FY15, 16, 17)
- Ewing Sarcoma (FY15, 17)
- Orofacial Clefts; Caucasian (FY15), Latin American (FY16), Asian & African (FY17)
- Osteosarcoma (FY15)

#### Structural Heart & Other Defects (FY15, 16, 18)

- Syndromic Cranial Dysinnervation Disorders (FY15)

#### Cancer Susceptibility (FY16)

- Adolescent Idiopathic Scoliosis (FY16)
- Familial Leukemia (FY16)
- Hearing Loss (FY16)
- Neuroblastomas (FY16)
- Craniofacial Microsomia (FY17)

#### Enchondromatoses (FY17)

- Hemangiomas, Vascular Anomalies & Overgrowth (FY17, 18)
- Nonsyndromic Craniosynostosis (FY17)
- Patients with both childhood cancer and birth defects (FY17)
- Bladder Exstrophy (FY18)
- Cornelia de Lange Syndrome (FY18)
- Esophageal Atresia and Tracheoesophageal Fistulas (FY18)
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- Intracranial Germ Cell Tumors (FY18)
- Microtia (FY18)
- Fetal Alcohol Spectrum Disorders (FY18)
- Myeloid Malignancies + overlap with Down syndrome (FY18)
- Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome (FY18)

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**Knockout Mouse Phenotyping Project (KOMP2)**

Who is part of Kids First?

Collaborations

X01 Childhood Cancer & Structural Birth Defects Cohorts

Kids First Sequencing Centers
Who is part of Kids First?

Collaborations &

The Kids First Community

X01 Childhood Cancer & Structural Birth Defects Cohorts

Kids First Sequencing Centers
How do I access data?

Anyone can register & login to the portal to filter, search, visualize datasets.

**Individual-level sequence data**

Individual-level sequence data

• To learn more about submitting dbGaP Data Access Requests (DARs) watch:
  https://www.youtube.com/watch?v=39cba0gF2tw&index=3&t=503s&list=PLoXwgZflAe4aMwWpVQU_WVeWHzyhI3BCu
How does Kids First support data sharing?

- Prioritize sequencing of datasets that can be broadly accessed and used by the research community, including combining data from different disease areas (based on consents).
- Created FAQs that explain the genomic data sharing process and provides helpful resources: https://commonfund.nih.gov/kidsfirst/FAQ
- Formed a Kids First Data Access Committee (DAC), run by the NCI Office of Data Sharing, to streamline the access process for Kids First datasets.
- Engaging in trans-NIH discussions to explore ways to support research across programs and datasets (e.g. NHLBI, NCI, Common Fund).
- The Kids First Data Resource Portal, workspaces, and tools are designed support collaboration and cross-analyzing a variety of datasets.
How are Kids First datasets (X01 cohorts) selected?

1. Researchers apply to have DNA (and RNA) samples from childhood cancer and/or structural birth defects cohorts sequenced by Kids First sequencing centers

2. X01 proposals are evaluated by a scientific peer review panel

3. The Kids First Working Group evaluates proposals based on the following factors, and selections are finalized by Kids First Working Group Co-Chairs.
   - Scientific and technical merit (determined by scientific peer review)
   - Broad data sharing and use (ability to combine data across diseases)
   - Value of incorporating the dataset into the Data Resource to empower research among the pediatric research community
   - Balance of childhood cancers and birth defects; conditions not previously sequenced are prioritized
   - Informative study design and sufficient clinical and phenotypic data
   - Availability of samples in timely manner
   - Sample quality in terms of suitability for sequencing
What funded opportunities are available?

- Apply for the Kids First cohort sequencing opportunity (X01)

- Analyze Kids First data with support from:

- To receive updates about future Kids First opportunities, sign up for the listserv:
How else can I get involved with Kids First?

• Search data available through the Kids First Data Resource Portal: https://portal.kidsfirstdrc.org/
• Connect with and provide feedback to the DRC: support@kidsfirstdrc.org
• Contact the program for questions or feedback: kidsfirst@od.nih.gov
Where can I learn more about X01 Cohort Projects?

Abstracts provided on the NIH Kids First Common Fund Website
https://commonfund.nih.gov/kidsfirst/x01projects

FY17 X01 Projects for the Gabriella Miller Kids First Program

**Title:** Whole genome sequencing of nonsyndromic craniosynostosis

**Contact PI / Project Leader:** Simeon Boyd

**Awardee Organization:** University of California Davis

**Abstract:**

**Abstract: DESCRIPTION** (provided by applicant): Craniosynostosis (CS), the premature fusion of one or more cranial sutures, is a common, major structural birth defect occurring in about 1 in 2,600 live births. About 85% of infants with CS present with nonsyndromic craniosynostosis (NCS) without associated birth defects or developmental delays. NCS is a heterogeneous condition with presumed multifactorial etiology and its causes remain largely unknown. Primary prevention strategies for NCS are limited. Our International Craniosynostosis Consortium (ICC) has advanced understanding of the genetic etiology for sagittal NCS (sNCS). Through our previous NIH-NICHD funding (R01 DE016866), we successfully conducted the first genome-wide association study (GWAS) for sNCS and identified robust associations to loci near BMP2 and BBS9, both biologic plausible genes involved in skeletal development. A similar GWAS with 415 case-parent trios with metopic NCS (mNCS) is in progress, as is an additional GWAS of over 800 coronal NCS (cNCS) case-parent trios. Additionally, others reported that whole exome sequencing (WES), SMAD6 mutations were found in 7% of probands in a cohort of sNCS, mNCS, or combined NCS cases. Importantly, among 17 NCS cases with SMAD6 mutations, 14 had T-C mutation (rs1884912) downstream of BMP2, suggesting a two-loci inheritance model. This discovery of an epistatic interaction between BMP2 and SMAD6 through use of GWAS and WES approaches explains only a small proportion of all NCS cases. Along with the data generated from the completed and ongoing GWAS’s, we believe that whole genome sequencing (WGS) is the next important step towards identifying causal variants in NCS cases, because it has the power to discover rare and common variants missed by other high-throughput technologies. We hypothesize that WGS will identify novel genetic factors beyond those identified with GWAS’s that contribute to the etiology of NCS. In this application, we propose to investigate 800 case-parent trios (200 cases each with sNCS, cNCS, and mNCS) and 20 multiplex families (11 with sNCS and 9 with mNCS) using WGS for discovery of all types of germline variants (de novo and inherited single nucleotide variants, insertions/deletions and structural variations). Somatic mutations contribute to the etiology of cancer and have been reported in some structural birth defects. These variants will confirm WGS or be novel. Database and sample data will be stored at NCI for detection of genetic markers.
Where can I learn more about Kids First Investigators?

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Investigator profiles available on the Kids First DRC website

Elizabeth Engle
Children's Hospital Corporation
Research Focus: Congenital Cranial Dysinnervation Disorders

Mary Marazita
University of Pittsburgh
Research Focus: Human Genetics of Complex Traits

Kenan Onel
University of Chicago

Joshua Schiffman
University of Utah

Christine Seidman
President and Fellows of Harvard College

Eric Vilain
University of California Los Angeles
Where can I learn more about available datasets?

Details provided on the Kids First DRC website
https://kidsfirstdrc.org/support/studies-and-access/
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- [https://kidsfirstdrc.org/](https://kidsfirstdrc.org/)
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