Birth Defects and Childhood Cancer: Harnessing the Power of the Gabriella Miller Kids First Pediatric Research Program

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Baylor College of Medicine

Baylor College of Medicine

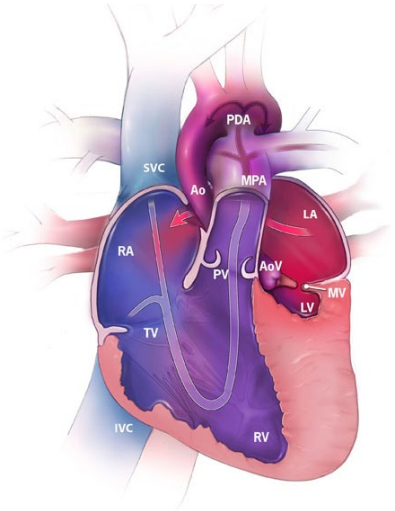
Texas Children's Cancer Center

Birth defects

- **Definition**: structural or functional anomalies present at the time of birth

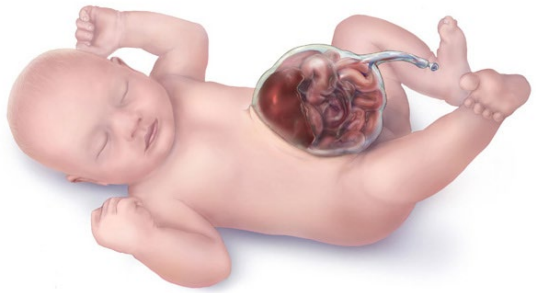
- Nomenclature
  - Anomalies
  - Malformations
  - Birth defects

- >100s of birth defects



Hypoplastic left heart syndrome

Anencephaly

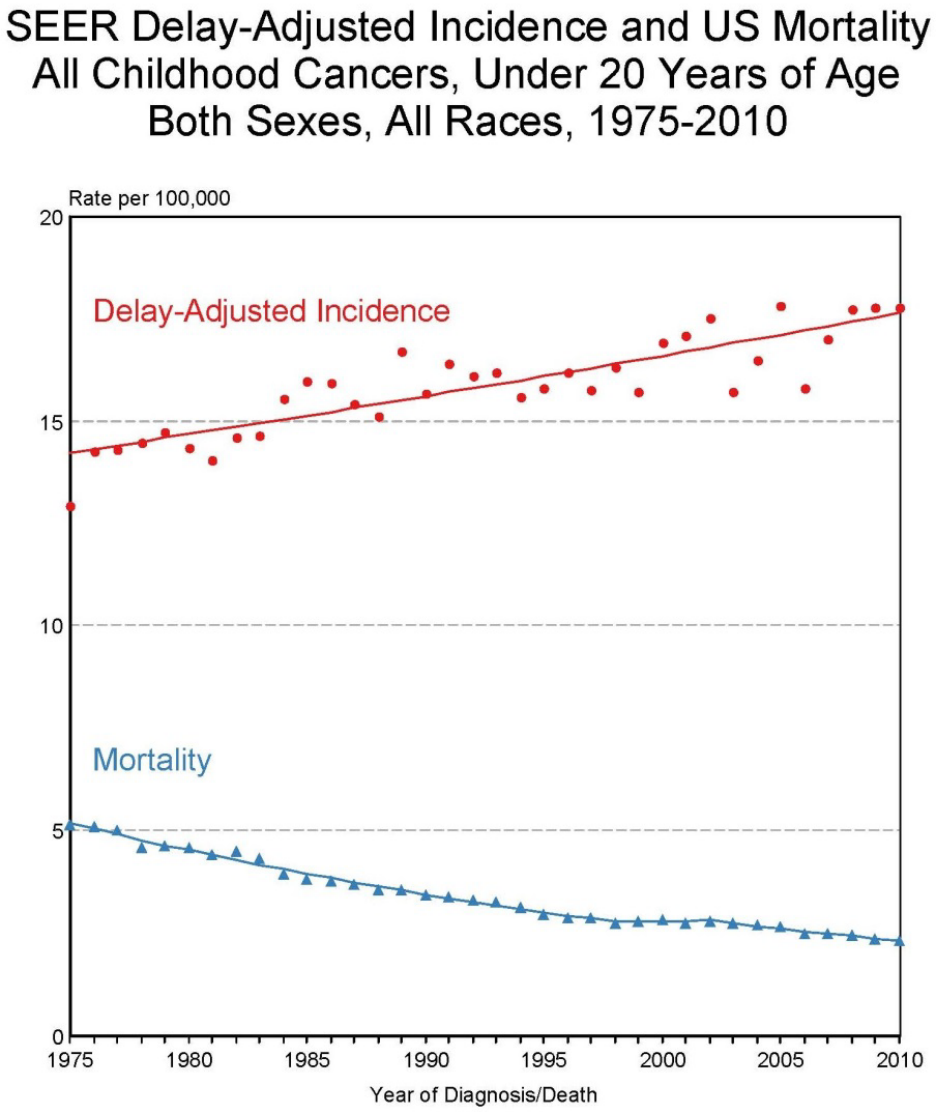


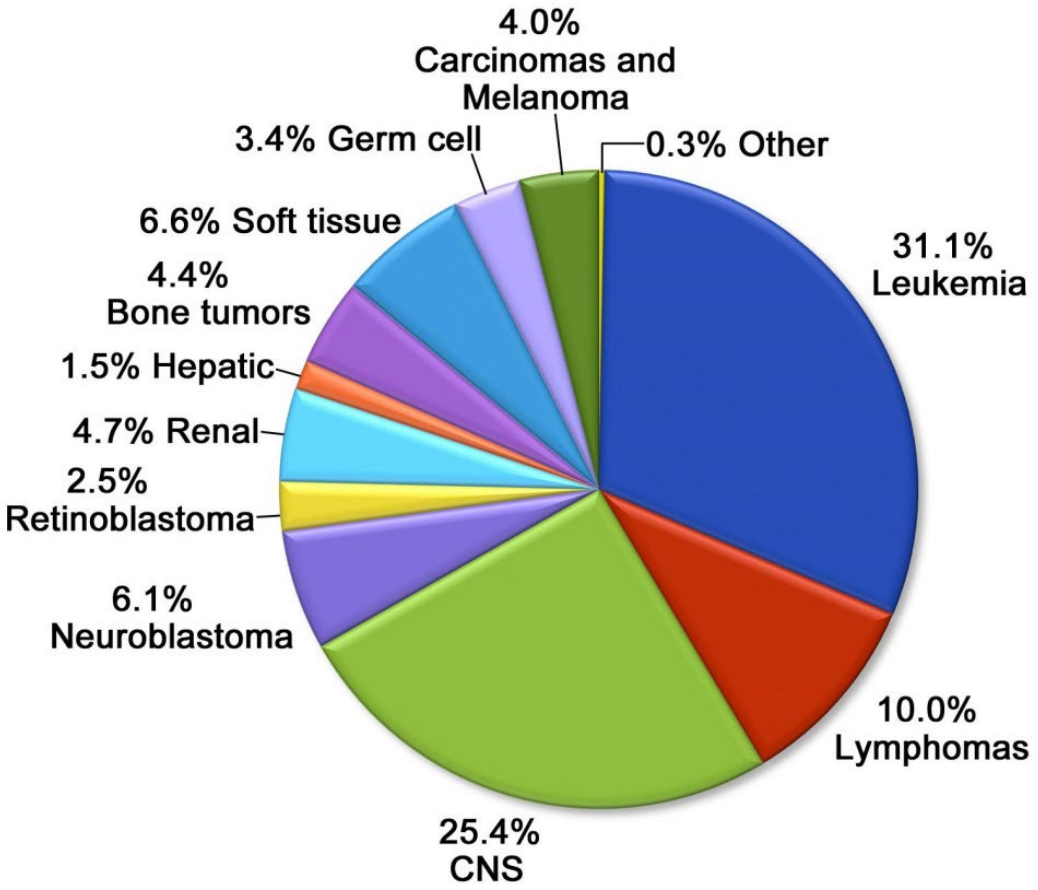
Omphalocele

Down syndrome

https://www.cdc.gov/ncbddd/birthdefects/types.html

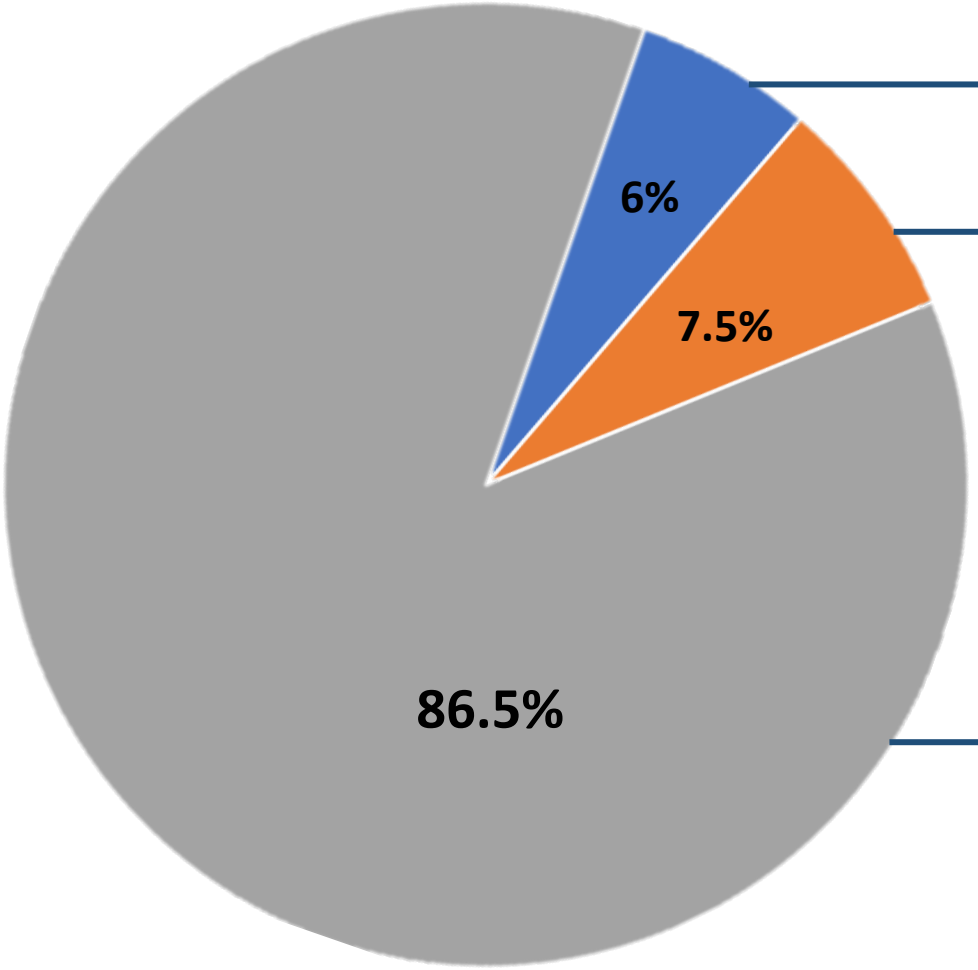
Childhood cancer





Data from the Surveillance, Epidemiology, and End Results (SEER) Database

Birth defects and cancer risk



Chromosomal anomalies
Example: Trisomy 21 and acute lymphoblastic leukemia

Single gene defects
Example: Costello syndrome and rhabdomyosarcoma

Non-syndromic birth defects
Multifactorial; cancer risk largely unknown

March of Dimes; Taub JW, *J Pediatr Hematol Oncol*. 2001; Genetics Home Reference

(Some) research questions

1. Which birth defects are associated with which cancers?

2. Do specific birth defect-cancer associations represent undiscovered Mendelian syndromes?

3. Why do some children with birth defects develop cancer while others do not?

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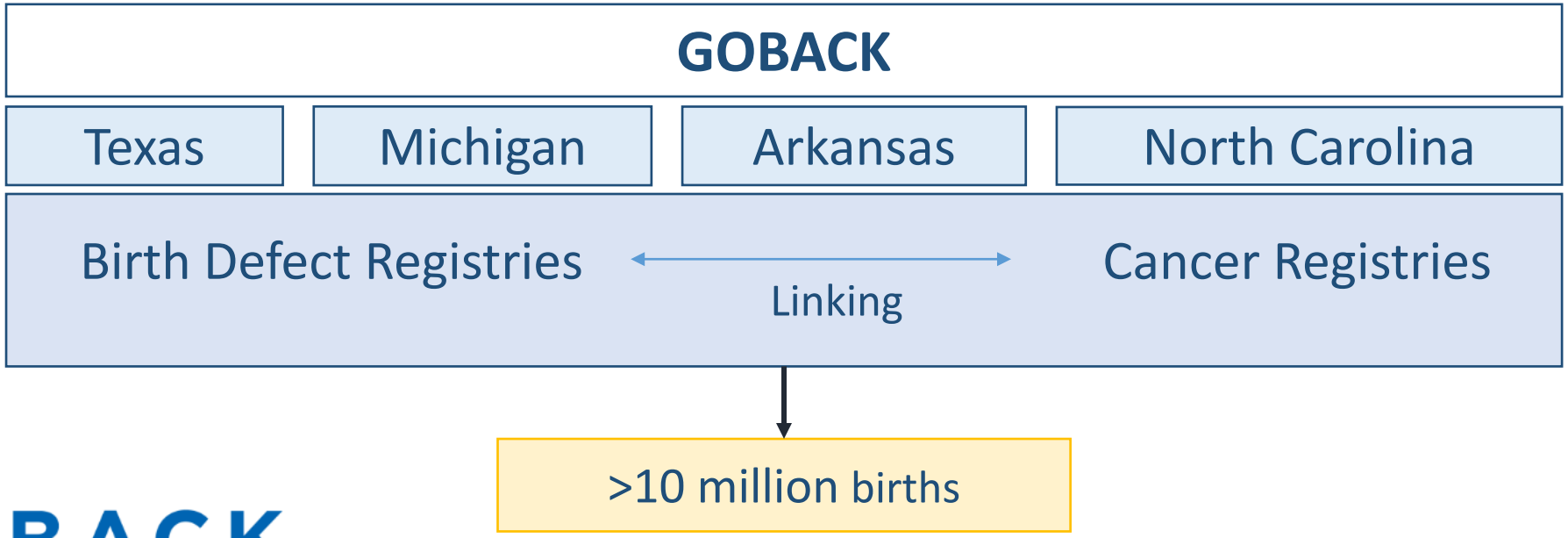
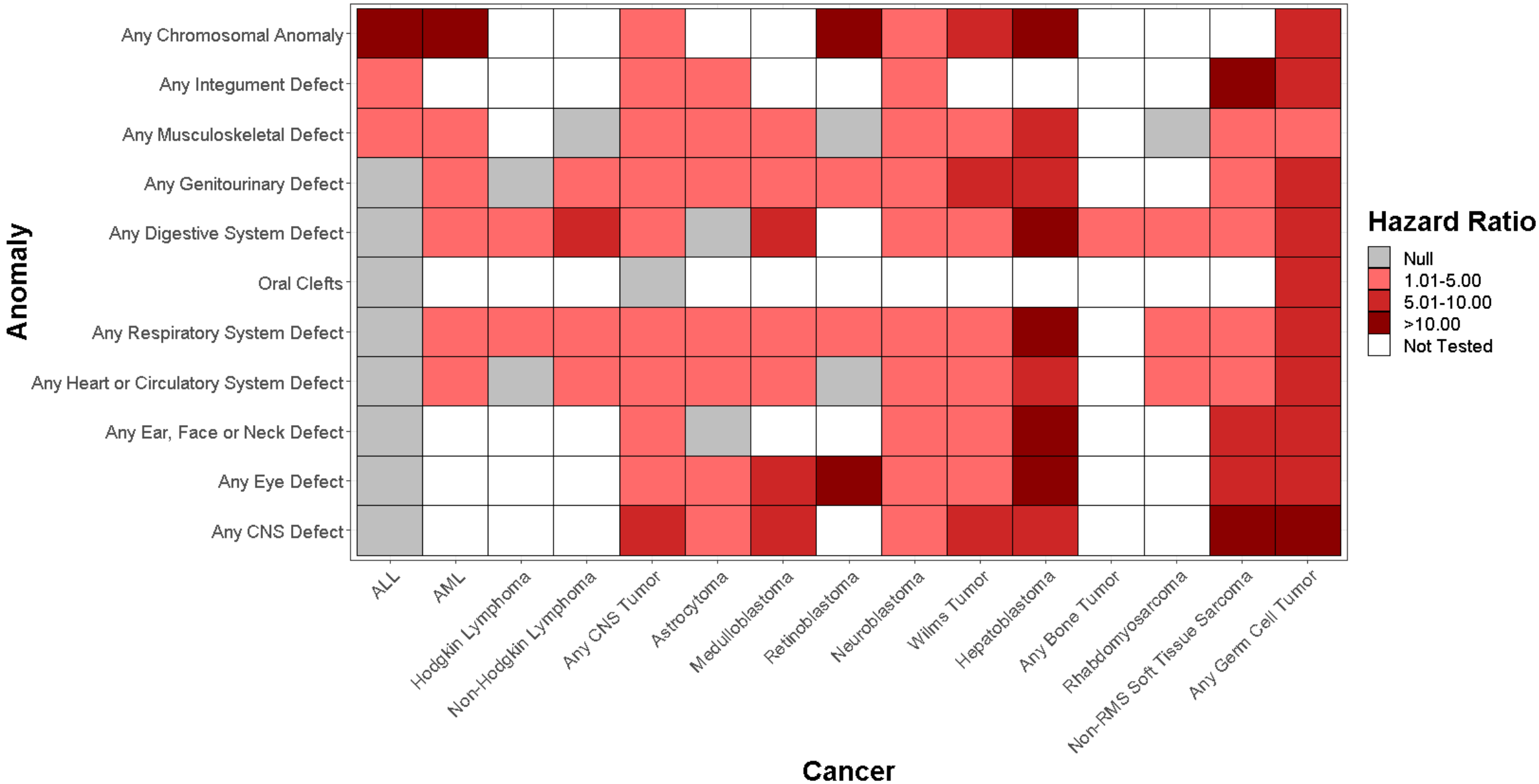
GOBACK (Genetic Overlap Between Anomalies and Cancer in Kids) Study



GOBACK
TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids


Anomaly
Any Chromosomal Anomaly
Any Integument Defect
Any Musculoskeletal Defect
Any Genitourinary Defect
Any Digestive System Defect
Oral Clefts
Any Respiratory System Defect
Any Heart or Circulatory System Defect
Any Ear, Face or Neck Defect
Any Eye Defect
Any CNS Defect
ALL
AML
Hodgkin Lymphoma
Non-Hodgkin Lymphoma
Any CNS Tumor
Astrocytoma
Medulloblastoma
Retinoblastoma
Neuroblastoma
Wilms Tumor
Hepatoblastoma
Any Bone Tumor
Rhabdomyosarcoma
Non-RMS Soft Tissue Sarcoma
Any Germ Cell Tumor
Cancer
Hazard Ratio
Null
1.01-5.00
5.01-10.00
>10.00
Not Tested

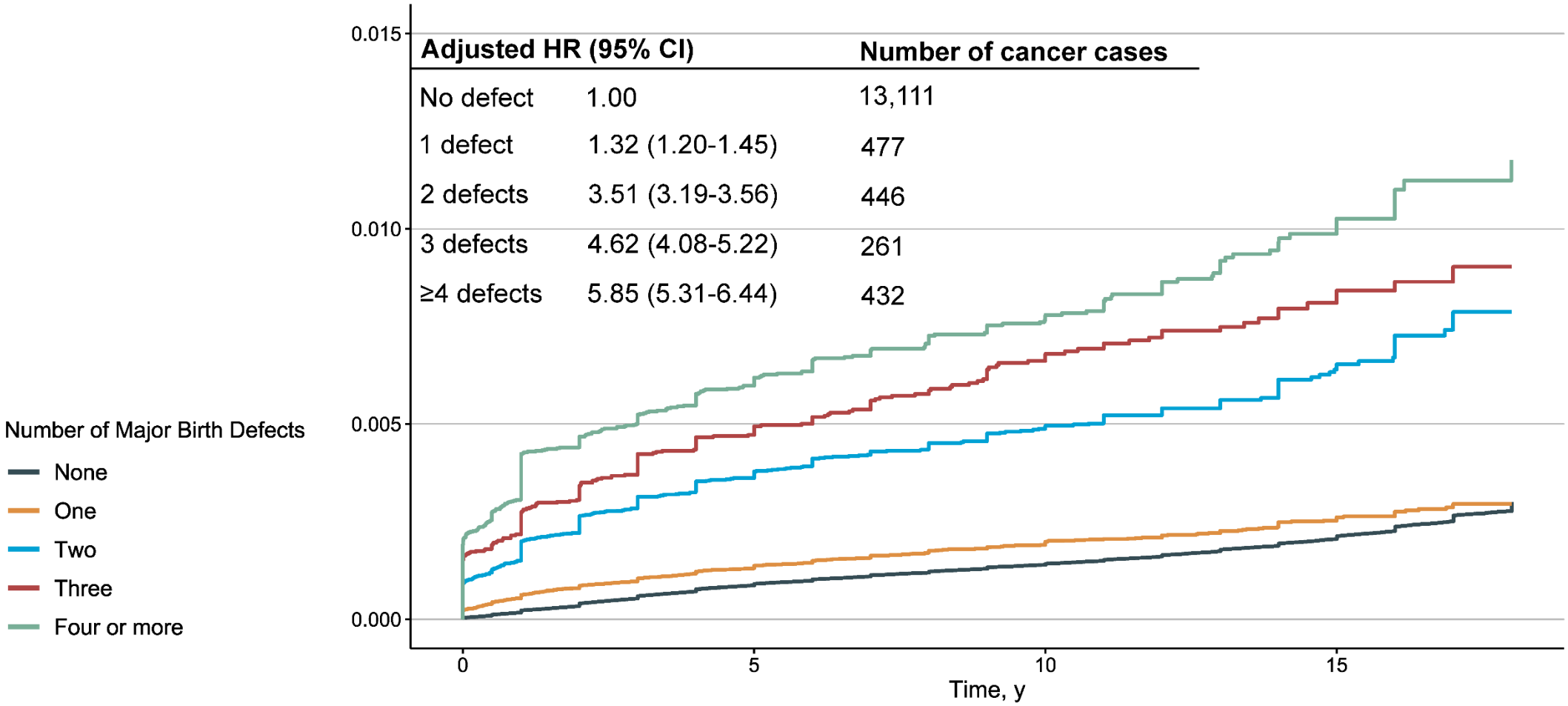
Non-syndromic birth defects and childhood cancer

Birth Defect	Cancer	HR (95% CI)[1]
Ventricular septal defect	Hepatoblastoma	10.6 (5.8-19.2)
Pulmonary valve atresia	Hepatoblastoma	22.6 (9.1-55.7)
Pulmonary valve atresia	Neuroblastoma	7.6 (3.8-15.3)
Left ventricular outflow tract defects	Neuroblastoma	7.8 (3.5-17.3)
Biliary atresia	Non-Hodgkin lymphoma	164.2 (77.8-346.8)
Craniosynostosis	Hepatoblastoma	9.7 (4.3-22.2)
Choanal atresia	**Acute leukemia**	**9.2 (3.8-22.1)**

1. Adjusted for maternal age, child's sex and state of birth. Models including hepatoblastoma are adjusted for birthweight. Models including ventricular septal defect are adjusted for birthweight and gestational age.

JAMA Oncol. 2019 Jun 20;5(8):1150-8

Cancer risk increased for children with multiple non-syndromic birth defects



JAMA Oncol. 2019 Jun 20;5(8):1150-8

GOBACK family cohort

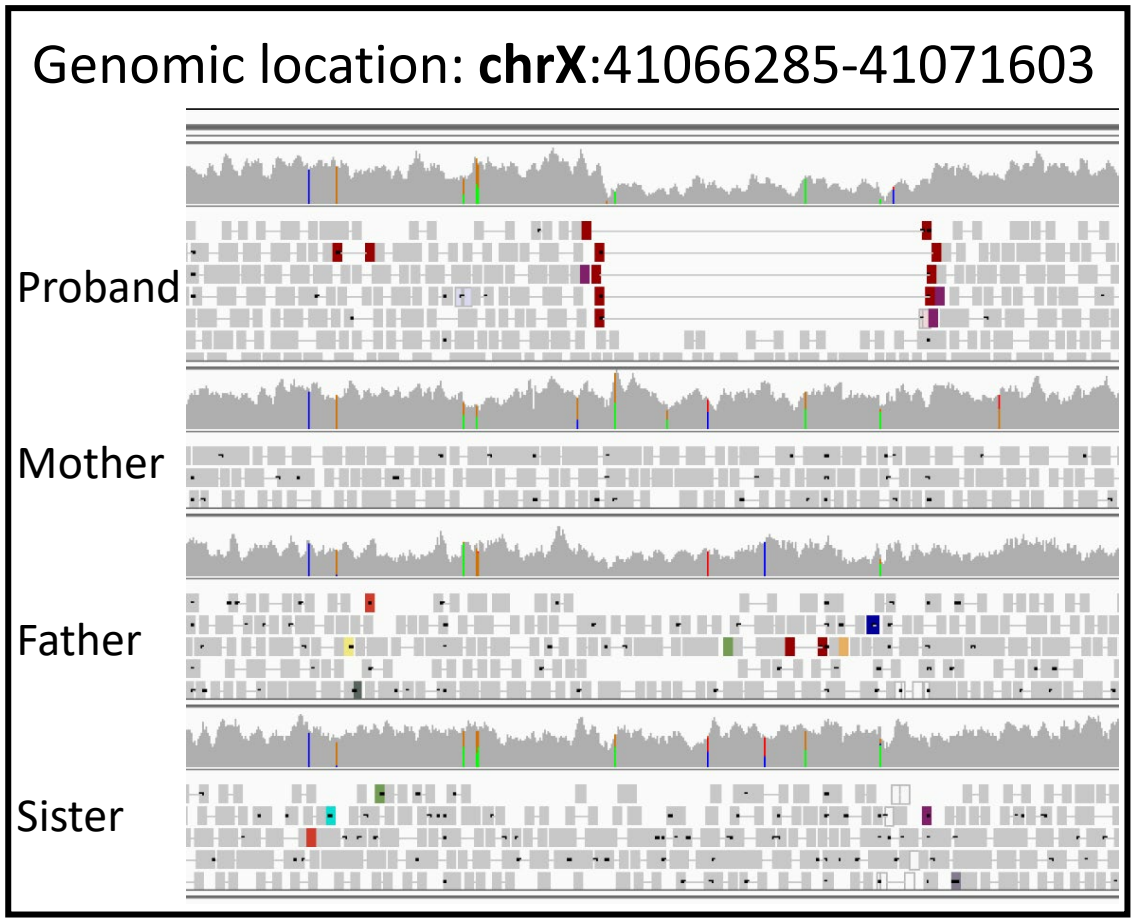
GOBACK
TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

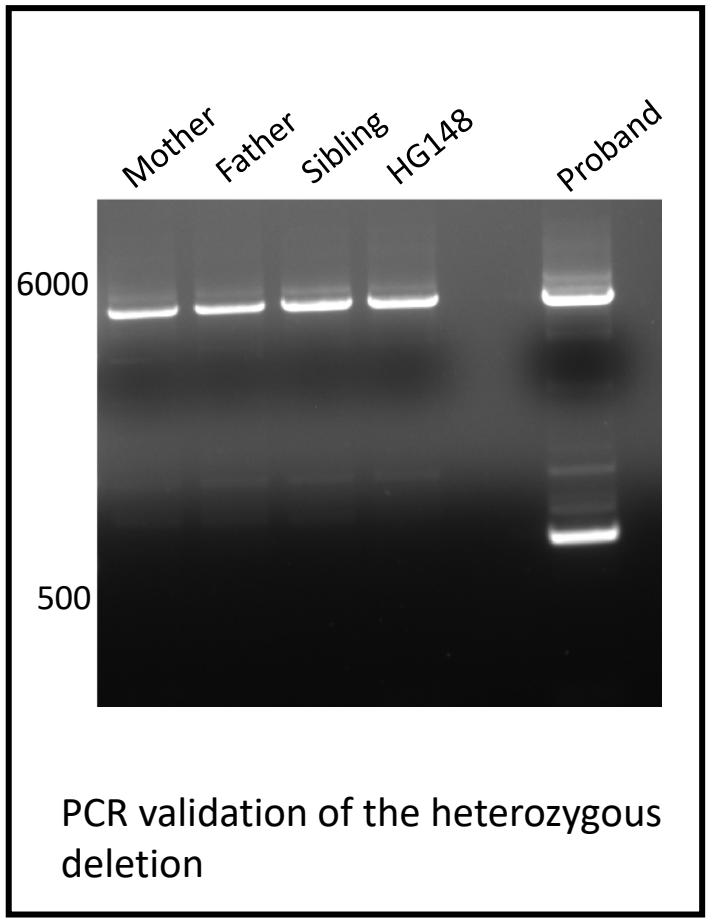

Sharon Plon, MD, PhD


Aniko Sabo, PhD

De novo heterozygous 5kb deletion in *USP9X*

Saumya Sisoudiya

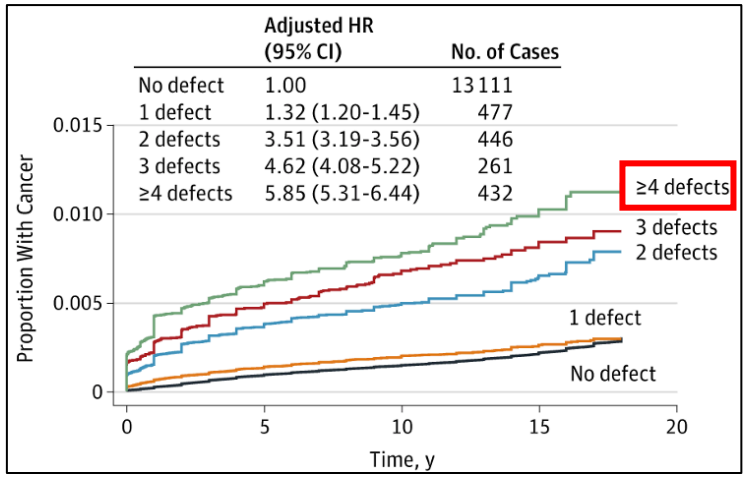




PCR validation of the heterozygous deletion

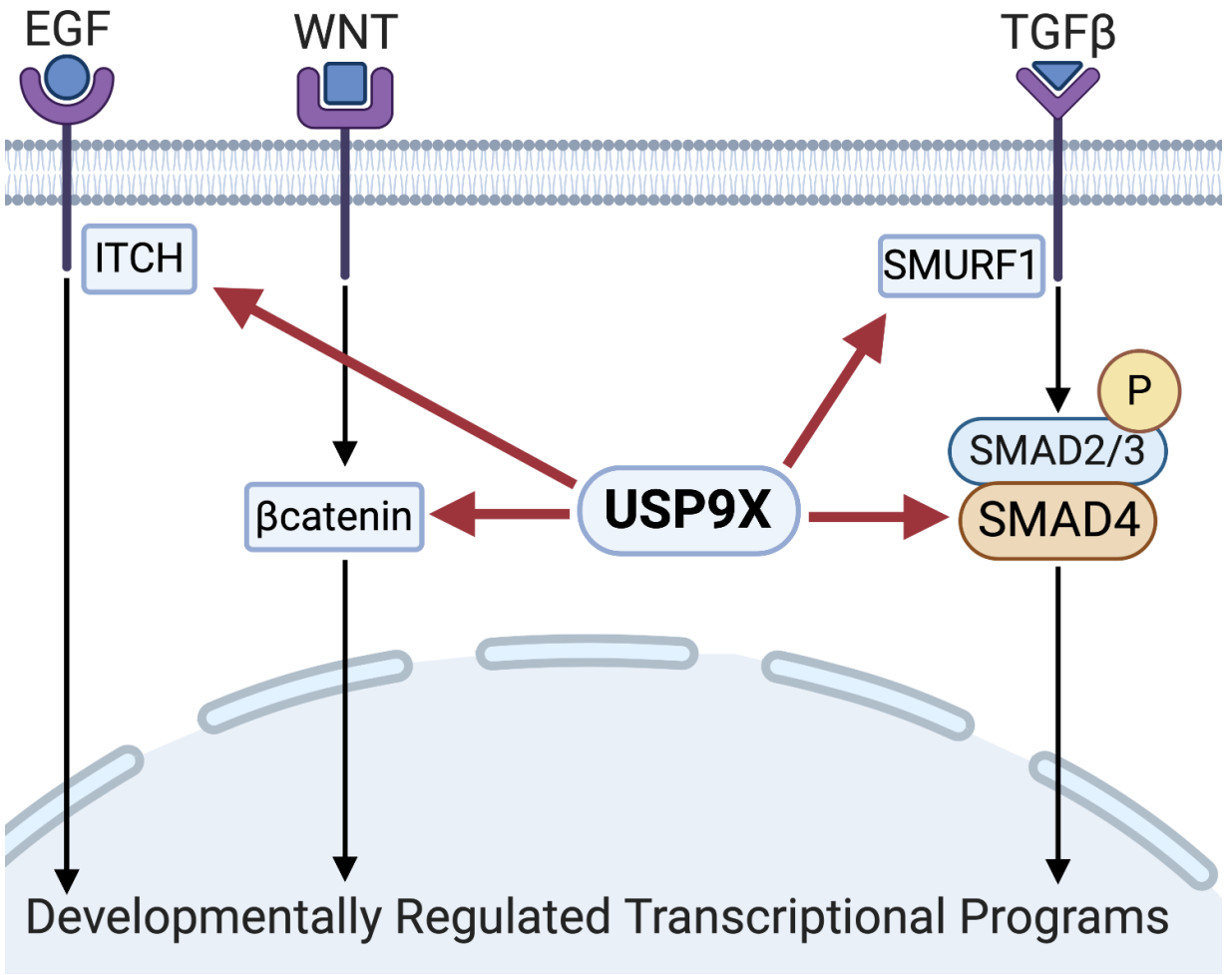
Female proband: multiple birth defects and leukemia

- Birth defects
  - Coloboma
  - Heart defects
  - **Choanal atresia**
  - Growth Retardation
  - Genital anomalies
  - Ear anomalies
- Cancer: **Precursor B-lymphoblastic leukemia**



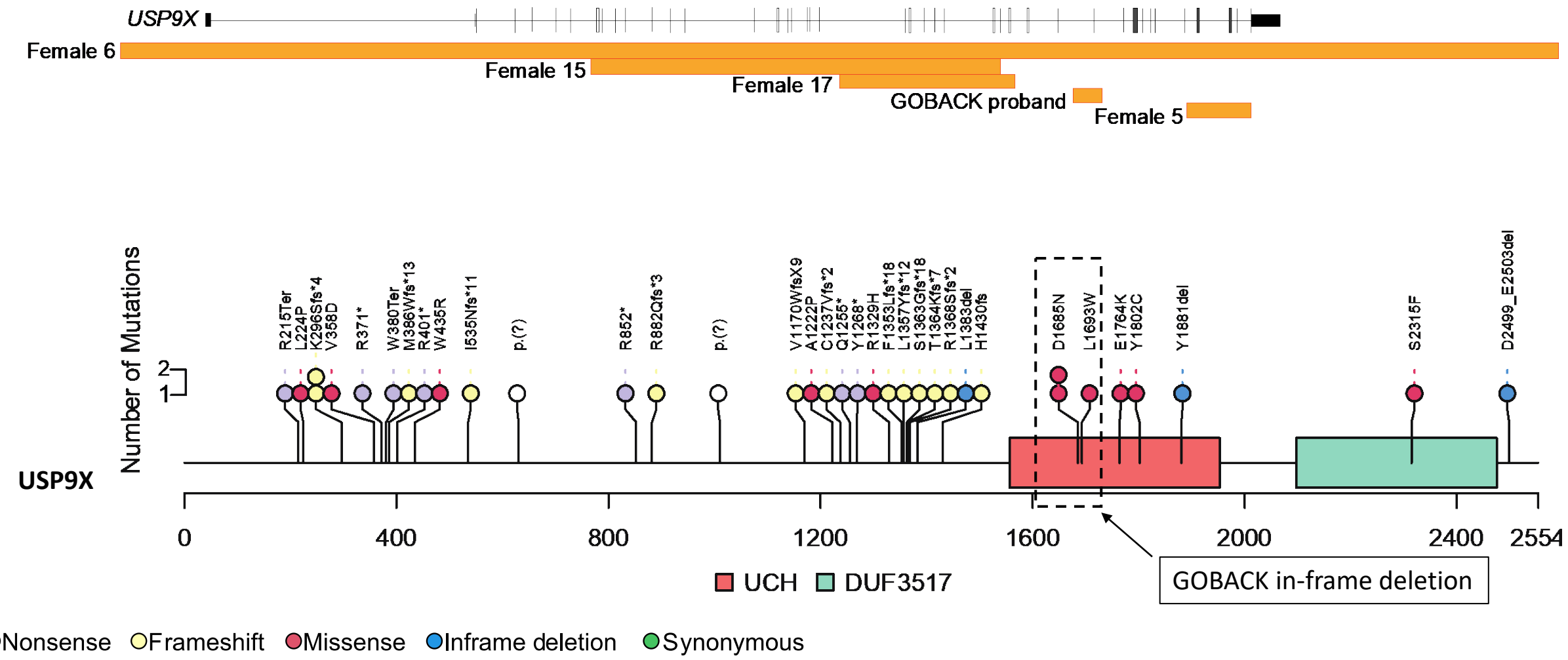
Birth defect	Cancer	HR (95% CI)
Choanal atresia	Acute leukemia	9.2 (3.8-22.1)

USP9X involved in several developmental and cancer pathways



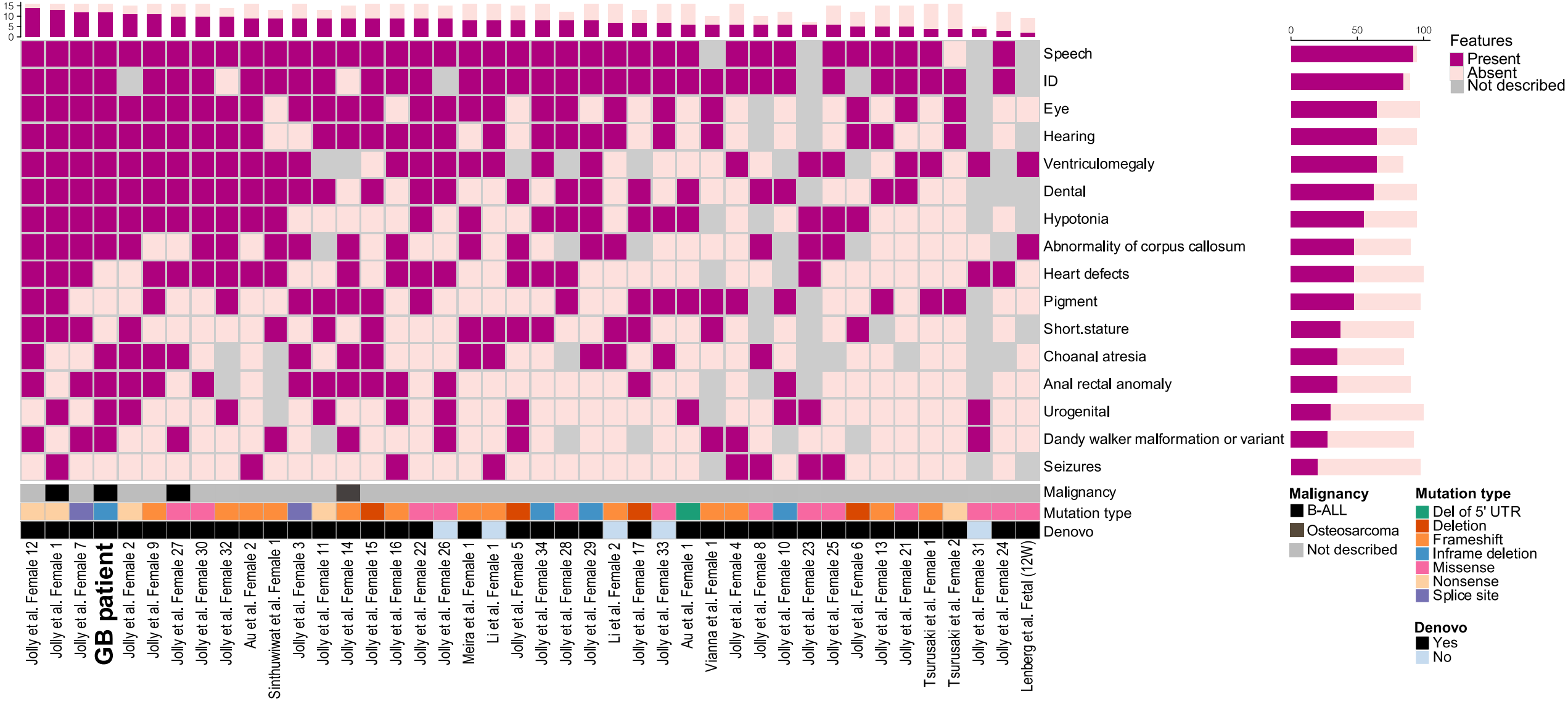
Adapted from Murtaza et. al., *Cell and Mol Life Sci.*, 2015
Created with BioRender.com

Germline LoF/missense variants in *USP9X* are associated with a female-specific syndrome with developmental delay and multiple birth defects: 42 cases

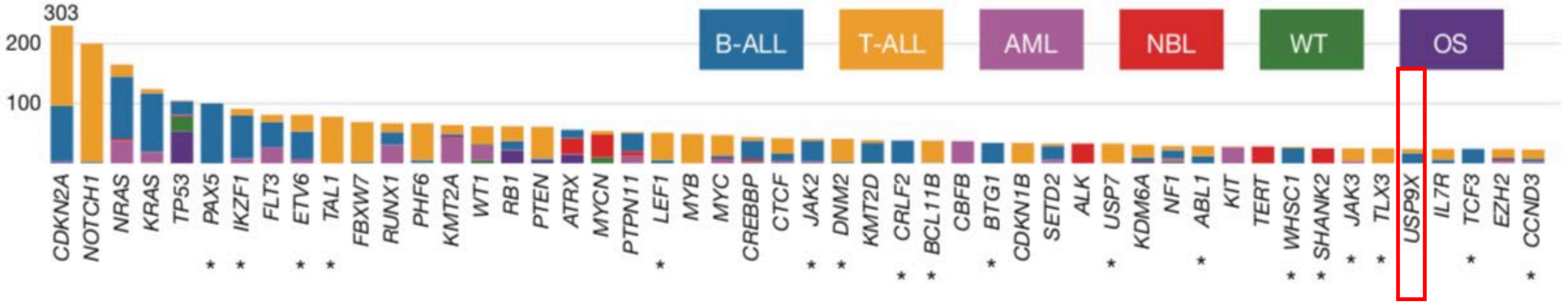


Jolly et al., 2016, Au et al., 2017; Tsurusaki et al., 2019; Sinthuwiwat et al., 2019; Lenberg et al, 2019; Vianna et al., 2020; Jolly et al., 2020; Meira et al., 2021; Li et al., 2022

Females with LoF variants present with the core phenotypic features of the syndrome



USP9X somatically mutated in childhood cancers



Ma et al, Nature, 2018

USP9X is a novel ALL susceptibility gene associated with a CHARGE-like syndrome

Next steps: Kids First GOBACK X01

Leverage Children's Oncology Group Project:EveryChild (PEC)

CHILDREN'S ONCOLOGY GROUP

1. Determine the frequency of known cancer predisposition variants among children with congenital anomalies and cancer

2. Identify variants that underlie novel anomaly-cancer predisposition syndromes and describe the landscape of somatic alterations in these children

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

Sharon Plon
Logan Spector

GOBACK TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

APEC14B1, Project EveryChild
Future Contact: optional information

PROJECT:EVERYCHILD

Patient Contact Information Child/Patient Initials _____ COG ID_____

Patient's Address: _____
Street Address

Patient's Address: _____
City (State/Province) (Zip /Postal Code)

Phone Number: _____ Country: _____ Email _____

*Driver's license number:*_____ *Driver's license Issued state:* _____ (If applicable)

Parent/Guardian Future Contact Information

Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____
First Parent or Guardian date of birth

Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify_____

Parent/Guardian Future Contact Information

Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____
Second Parent or Guardian date of birth

Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify

Other Key Contact Information

Key Contact: _____ _____ _____
First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____
Key contact date of birth, if known

Email address:_____

Please indicate the language spoken in the home, circle all that apply English French Spanish Other, specify

APEC14B1, Project EveryChild Registry

PROJECT:EVERYCHILD

1. Where was the patient born?

City State/Prov. Zip/Postal Code Country

2. Was this patient a single or multiple birth?
☐ **Single** ☐ **Twins** ☐ **Triplets or more**
2a. If twin, specify: Identical Fraternal Unknown
2b. If twin, specify sex:
☐ Both female ☐ Both male ☐ Male/female

	Not sure	Yes	No
3. Was patient conceived through use of in vitro fertilization?	☐	☐	☐
4. Was cord blood banked at birth?	☐	☐	☐
5. Has anyone in the patient's immediate family (biological mother, father, brothers, sisters) ever had cancer? If yes, please record information below.	☐	☐	☐

My child's... *What types of cancer?*

☐ Mother →
☐ Father →
☐ Full brother →
☐ Full sister →
☐ Son →
☐ Daughter →

6. Please indicate the name and relationship of at least one parent/guardian.

Parent or guardian: First Name Last name

Circle relationship: **Mother Father Grandparent Sibling**
Guardian Other relationship, specify: _____

7. Does the patient have any structural birth defects known at this time?

	Not sure	Yes	No
Cleft lip	☐	☐	☐
Cleft palate	☐	☐	☐
Clubfoot	☐	☐	☐
Gastroschisis	☐	☐	☐
Heart defect	☐	☐	☐
Other specify: _____	☐	☐	☐

8. Does the patient have any known genetic disorder?

	Not sure	Yes	No
Down Syndrome	☐	☐	☐
Li Fraumeni Syndrome	☐	☐	☐
Neurofibromatosis Type I	☐	☐	☐
Other specify: _____	☐	☐	☐

9. Does the patient have any known autoimmune diseases?

	Not sure	Yes	No
Juvenile Idiopathic Arthritis	☐	☐	☐
Celiac disease	☐	☐	☐
Diabetes mellitus (Type I)	☐	☐	☐
Inflammatory bowel diseases (Crohn's or Ulcerative colitis)	☐	☐	☐
Other specify: _____	☐	☐	☐

10. Which these describe the patient? Check all that apply.

[ ] - White
[ ] - African American
[ ] - American Indian, Aleutian, Eskimo
[ ] - Asian specify: _____
[ ] - Other specify: _____
[ ] - Unknown
[ ] - Non-Spanish, non-Hispanic
[ ] - Mexican (incl Chicano)
[ ] - Puerto Rican
[ ] - Cuban
[ ] - South or Central American (except Brazil)
[ ] - Other Spanish/Hispanic origin includes European

Please return to hospital or clinic staff. *Phone:* _____ *FAX:* _____ ***Thank you for your information!***

Kids First GOBACK Sequencing

- 700 blood and 500 tumor DNA samples for whole genome sequencing (WGS) at 30X coverage
- 500 tumor DNA samples for exome sequencing at 100X coverage
- 120 tumor RNA samples for transcriptome sequencing

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GOBACK TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

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Parent/ Guardian: _____ _____ _____
First Name Middle Name Last Name

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First Parent or Guardian date of birth

Email address:_____

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First Name Middle Name Last Name

Address: _____
Street Address

Address: _____
City (State/Province) (Zip /Postal Code)

mm / dd / yyyy Phone number _____ Country _____
Second Parent or Guardian date of birth

Email address:_____

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Key Contact: _____ _____ _____
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	Not sure	Yes	No
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4. Was cord blood banked at birth?	☐	☐	☐
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☐ Daughter →

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Other specify: _____	☐	☐	☐

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Diabetes mellitus (Type I)	☐	☐	☐
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[ ] - Cuban
[ ] - South or Central American (except Brazil)
[ ] - Other Spanish/Hispanic origin includes European

Please return to hospital or clinic staff. *Phone:* _____ *FAX:* _____ ***Thank you for your information!***

Kids First GOBACK R03

1. Collect extensive phenotypic and clinical data from children with congenital anomalies and cancer enrolled in Project:EveryChild

2. Integrate phenotypic and clinical data from Project:EveryChild into the Gabriella Miller Kids First Pediatric Data Resource Center

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

Allison Heath
Adam Resnick

GOBACK TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

GOBACK conclusions

- Birth defects are associated with an increased risk for childhood cancer, especially embryonal tumors and germ cell tumors
- Birth defects account for ~10% of childhood cancers
- WGS of informative families
  - Yield new genetic insights about birth defects and childhood cancer
  - *USP9X*: a novel leukemia susceptibility gene

Gabriella Miller Kids First PEDIATRIC RESEARCH PROGRAM

GOBACK TO THE BASES
Genetic Overlap Between Anomalies and Cancer in Kids

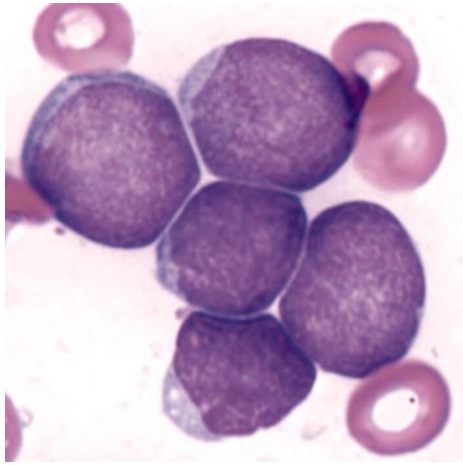
Down syndrome-associated leukemia

Baylor College of Medicine

Texas Children's Cancer Center

Down syndrome (DS) and leukemia

- First reported 1930
- First systematic study in 1957
- ~20-fold increased risk
- Cumulative risk of 2% by age 5
- Comprises ~2% of childhood acute lymphoblastic leukemia (ALL) and 10% of childhood acute myeloid leukemia (AML)



Hasle et al, Lancet 2000

DS-ALL questions

- Why does ALL arise more often in children with DS?
- Does ALL differ between children with and without DS?
- Are there germline genetic variants associated with the ALL susceptibility in children with DS?

Baylor College of Medicine

Texas Children's Cancer Center

Genetic epidemiology of DS-related conditions

Project Number:	1 X01 HL145686-01	**Contact PI / Project Leader:**	Lupo, Philip J (Contact); Rabin, Karen R; Sherman, Stephanie L.; Yang, Jun J
Title:	Genomic Analysis of Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome	**Awardee Organization:**	Baylor College Of Medicine

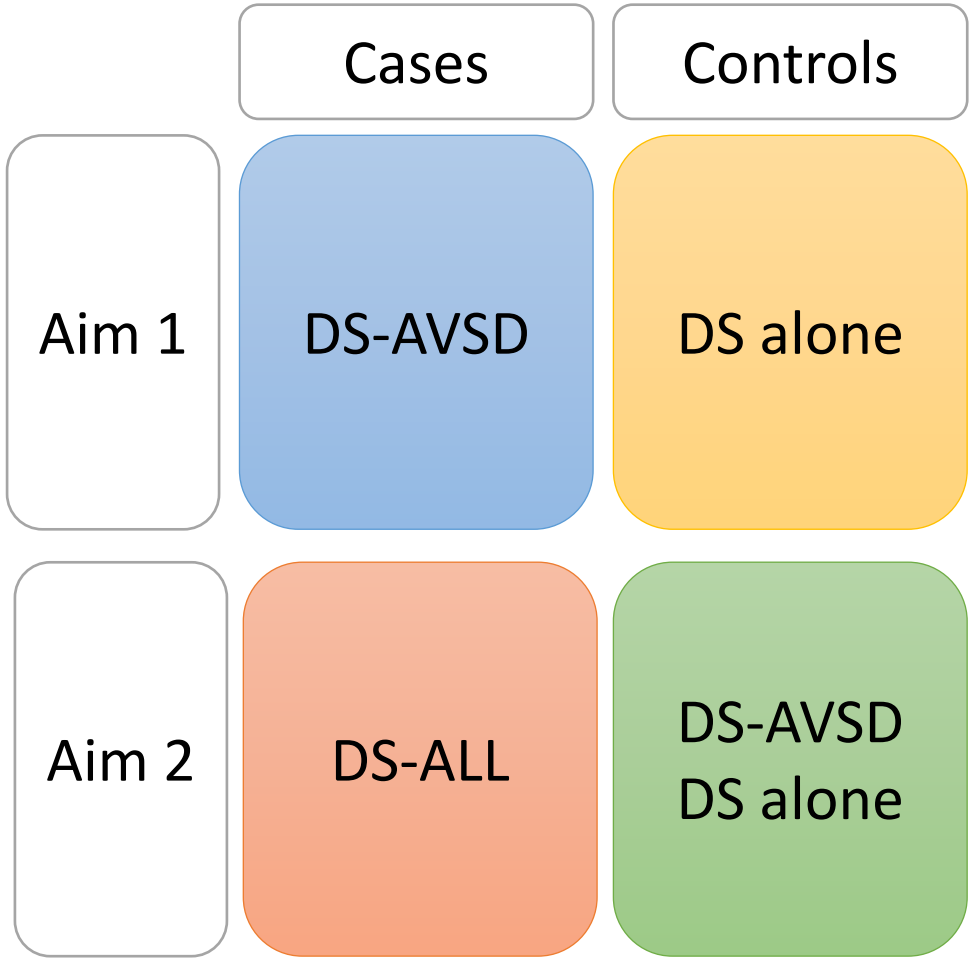
Abstract Text:

Abstract: DESCRIPTION (provided by applicant): Down syndrome (DS), which occurs due to trisomy 21, is one of the strongest risk factors for both congenital disease (CHD) and acute leukemia. For instance, children with DS have a 2000-fold increased risk of atrioventricular septal defects (AVSD) and a 20-fold increased risk of acute lymphoblastic leukemia (ALL). An important and innovative aspect of the Kids First program

***Sequencing of this project is partially supported by the Investigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project

Aims

1. Identify genetic variants underlying AVSD in children with DS
2. Identify genetic variants underlying ALL in children with DS
   - Particular attention to rare, structural, and chromosome 21 variants
   - Evaluation of relationship between germline and somatic features (WGS of paired leukemia-germline samples)



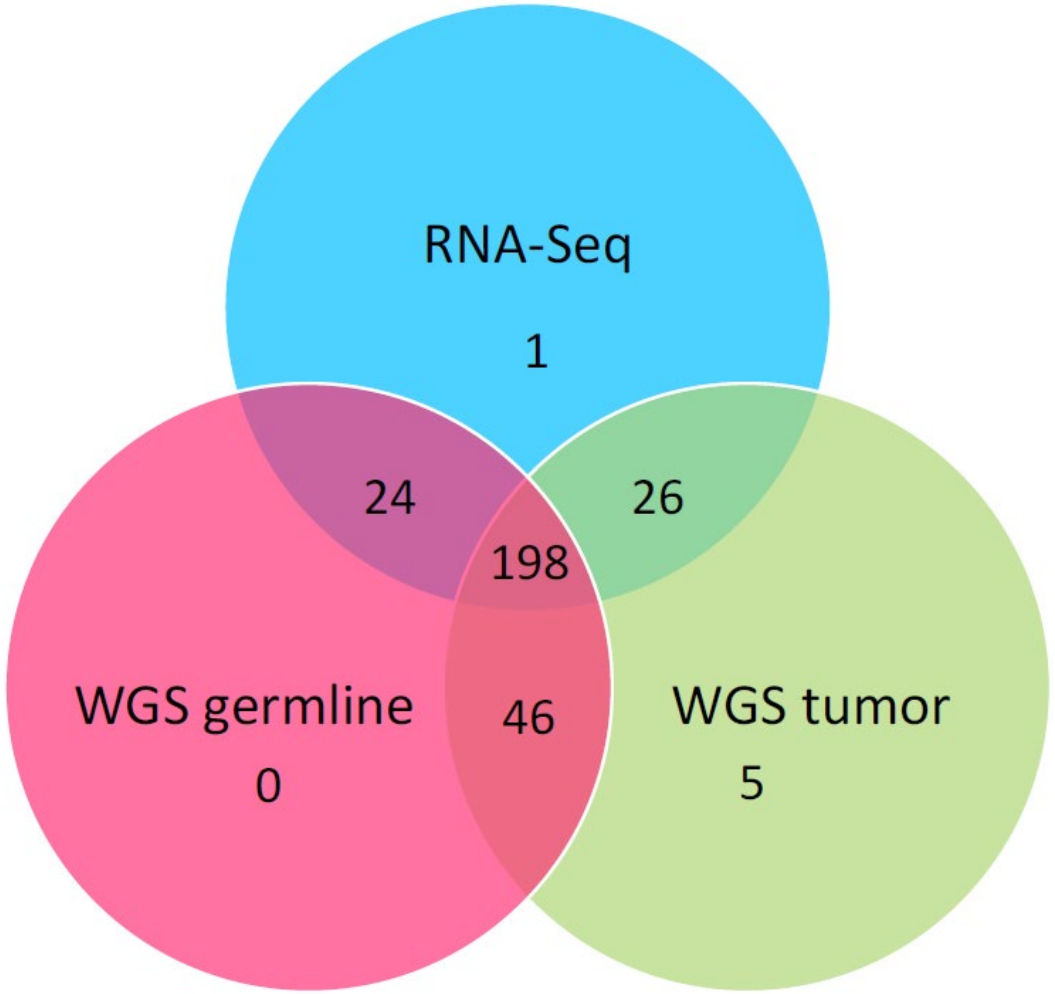
blood®
Available online 5 April 2023
In Press, Journal Pre-proof What's this?

Regular Article

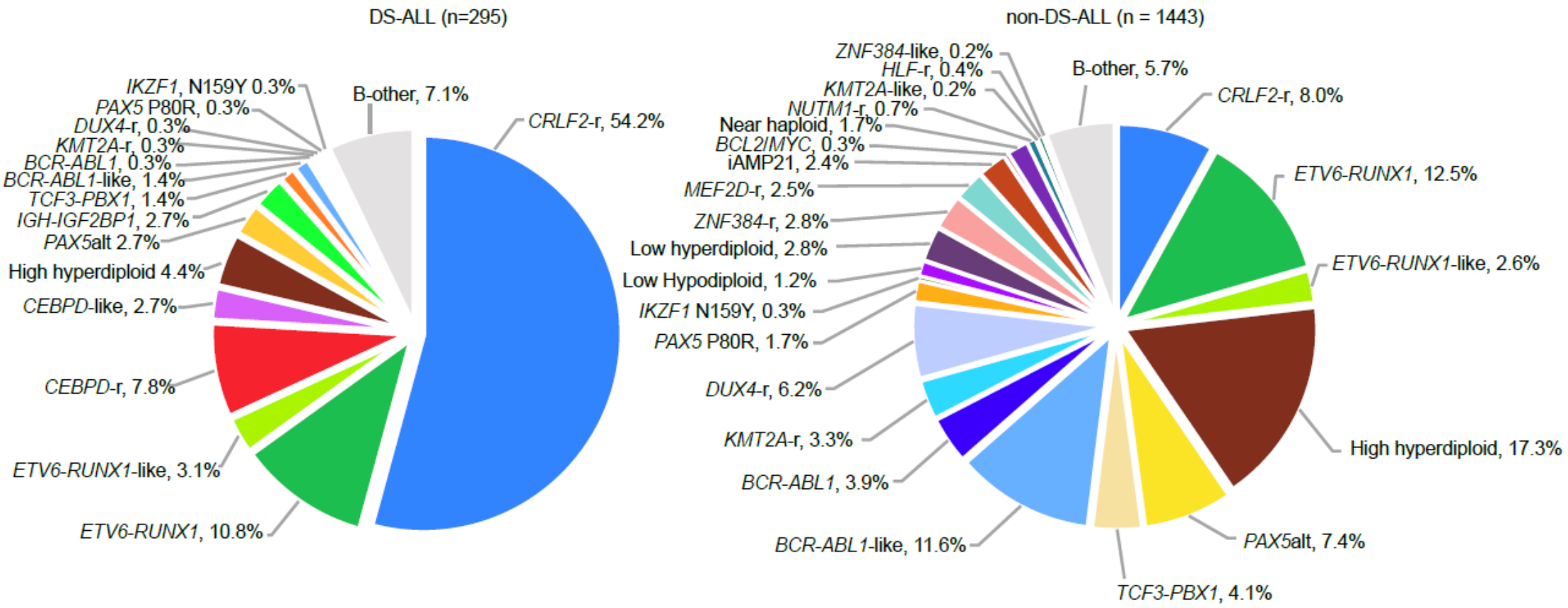
Genomic landscape of Down syndrome-associated acute lymphoblastic leukemia

Zhenhua Li [1] *, Ti-Cheng Chang [2] *, Jacob J. Junco [3] *, Meenakshi Devidas [4], Yizhen Li [1], Wenjian Yang [1], Xin Huang [5], Dale J. Hedges [2], Zhongshan Cheng [2], Mary Shago [6], Andrew J. Carroll [7], Nyla A. Heerema [8], Julie Gastier-Foster [3 9], Brent L. Wood [10], Michael J. Borowitz [11], Lauren Sanclemente [3], Elizabeth A. Raetz [12], Stephen P. Hunger [13 14], Eleanor Feingold [15], Tracie C. Rosser [16], Stephanie L. Sherman [16], Mignon L. Loh [17], Charles G. Mullighan [18], Jiyang Yu [5], Gang Wu [2 18], Philip J. Lupo [3], Karen R. Rabin [3] **, Jun J. Yang [1 19 20] **

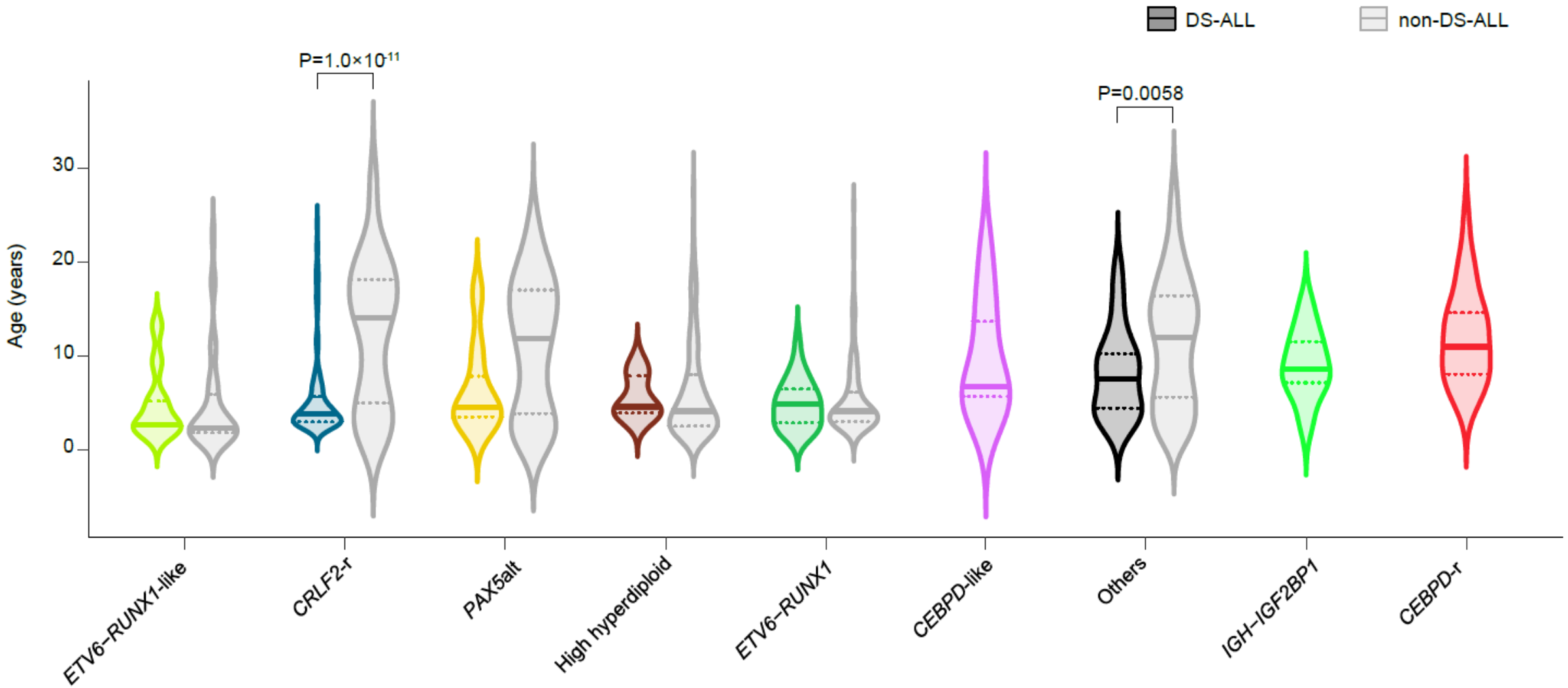
DS-ALL WGS study



ALL subtype classification by DS status

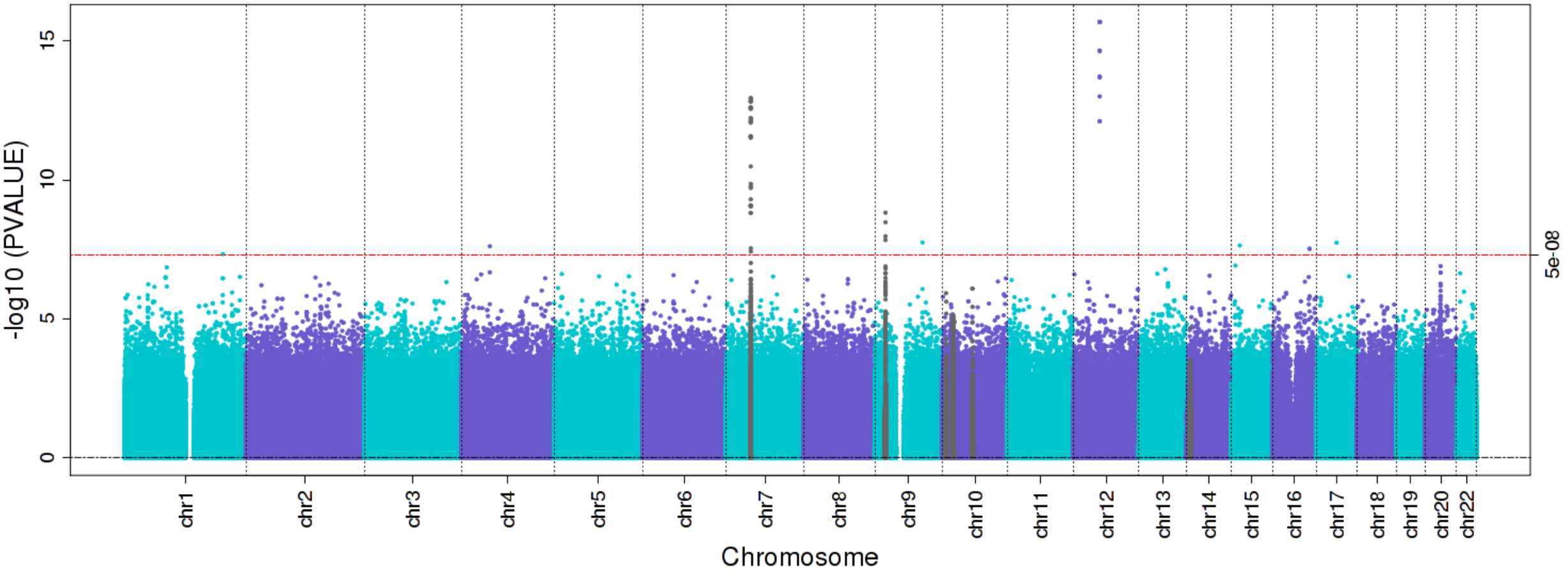


- Age at diagnosis was younger for those with DS-ALL compared to those with non-DS-ALL
- This was especially true for *CRLF2-r*



Preliminary DS-ALL germline findings

DS-ALL GWAS identifies novel (blue/purple) and known (gray) loci



Top variants associated with DS-ALL

Locus	RSID	CHR	POS, b38	Risk allele	DS-ALL freq	DS freq	OR (95% CI)	P-value	SNPs in Locus P<5e-8
LAD1 (intron 1)		1	201,394,520	C	0.0113	0.0003	2.04 (1.58-2.63)	4.6E-08	1
4q13.1	rs17290452	4	58,639,220	T	0.0992	0.0472	1.17 (1.11-1.23)	2.4E-08	1
IKZF1 (downstream)	rs28462675	7	50,406,172	G	0.4051	0.2618	1.11 (1.08-1.14)	1.1E-13	37
CDKN2A (exon)	rs3731249	9	21,970,917	T	0.0751	0.0280	1.23 (1.15-1.32)	1.5E-09	4
PTCSC2 (intron)		9	97,746,216	A	0.0127	0.0003	2.01 (1.58-2.56)	1.8E-08	1
***PCBP2* (intron 1)**		**12**	**53,452,389**	**T**	**0.0227**	**0.0000**	**2.24 (1.85-2.72)**	**2.1E-16**	**22**
GOLGA8B (upstream)		15	34,603,388	A	0.0142	0.0010	1.83 (1.48-2.27)	2.3E-08	1
CHST6 (upstream)		16	75,497,610	T	0.0142	0.0010	1.82 (1.48-2.26)	3.0E-08	2
KRT222-KRT24		17	40,688,678	T	0.0142	0.0000	2.03 (1.58-2.59)	1.8E-08	1

DS-ALL conclusions

- Distinct spectrum of subtypes in DS-ALL
  - *CRLF2-r* >50%
  - Other subtypes in non-DS ALL are under-represented
- DS-ALL patients are younger than non-DS ALL patients: onset of *CRLF2-2* ALL is almost 10 years earlier in children with DS
- Novel and known germline variants play a role in DS-ALL susceptibility

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DS-ALL future directions

- **Germline analyses of DS-ALL**
  - Further evaluate novel loci
  - Assess rare and structural variants
  - Evaluate relationship between the inherited germline and somatic features

- **Conduct deep phenotyping of children with DS-ALL**
  - Identify the role of co-occurring birth defects on DS-ALL features and outcomes
  - Linkages with COG and other data sources (e.g., National Death Index)

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Birth defects, childhood cancer, and Kids First: Overall conclusions

- Evaluating the overlap between birth defects and cancer provides novel insights into develop and carcinogenesis

- Insights into factors influencing cancer among children with birth defects may guide improved genetic counseling, surveillance, and treatment interventions

- Kids First has…
  - Accelerated the timeline of birth defects-childhood cancer discoveries
  - Provided a springboard for new funding opportunities
  - Fostered collaborative research

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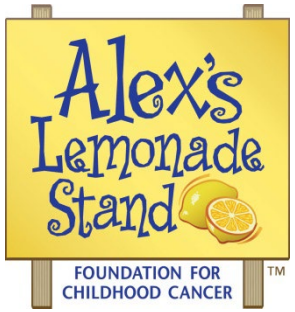
CHILDREN'S ONCOLOGY GROUP



INCLUDE PROJECT

GOBACK TO THE BASES

Genetic Overlap Between Anomalies and Cancer in Kids

Email: GOBACK_Study@bcm.edu | T 1-855-474-4520

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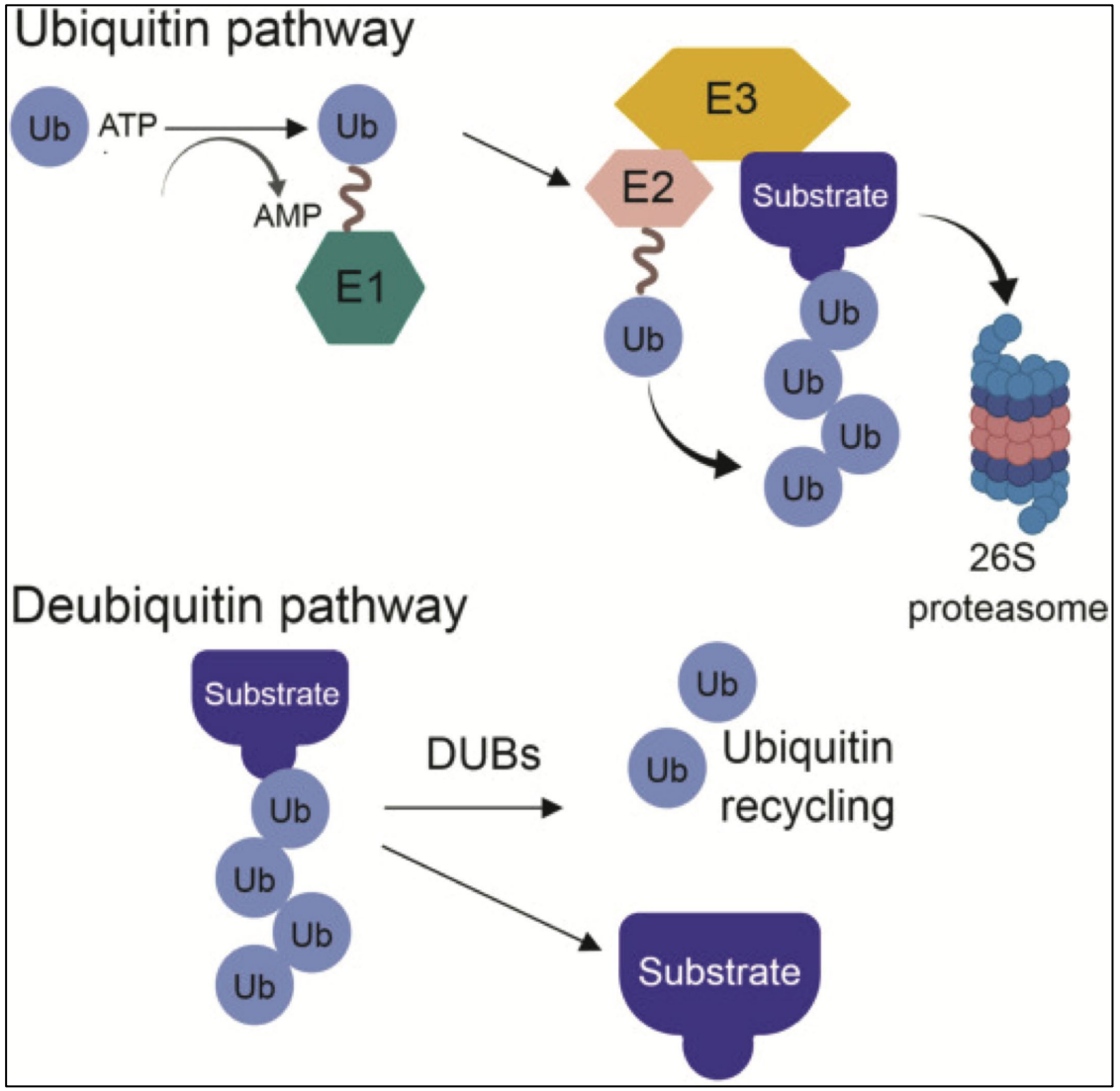
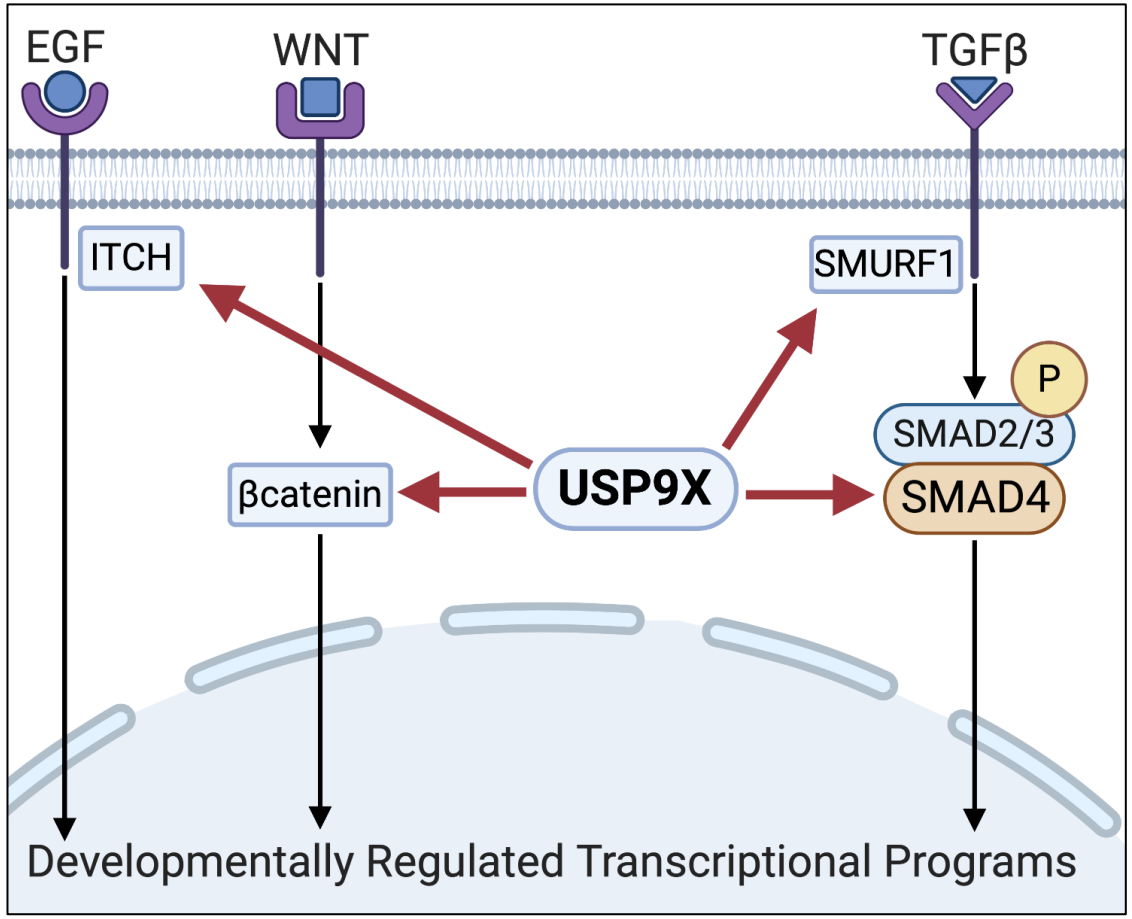
USP9X codes for a highly conserved deubiquitinase





Adapted from Murtaza et. al., *Cell and Mol Life Sci.*, 2015

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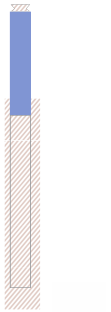
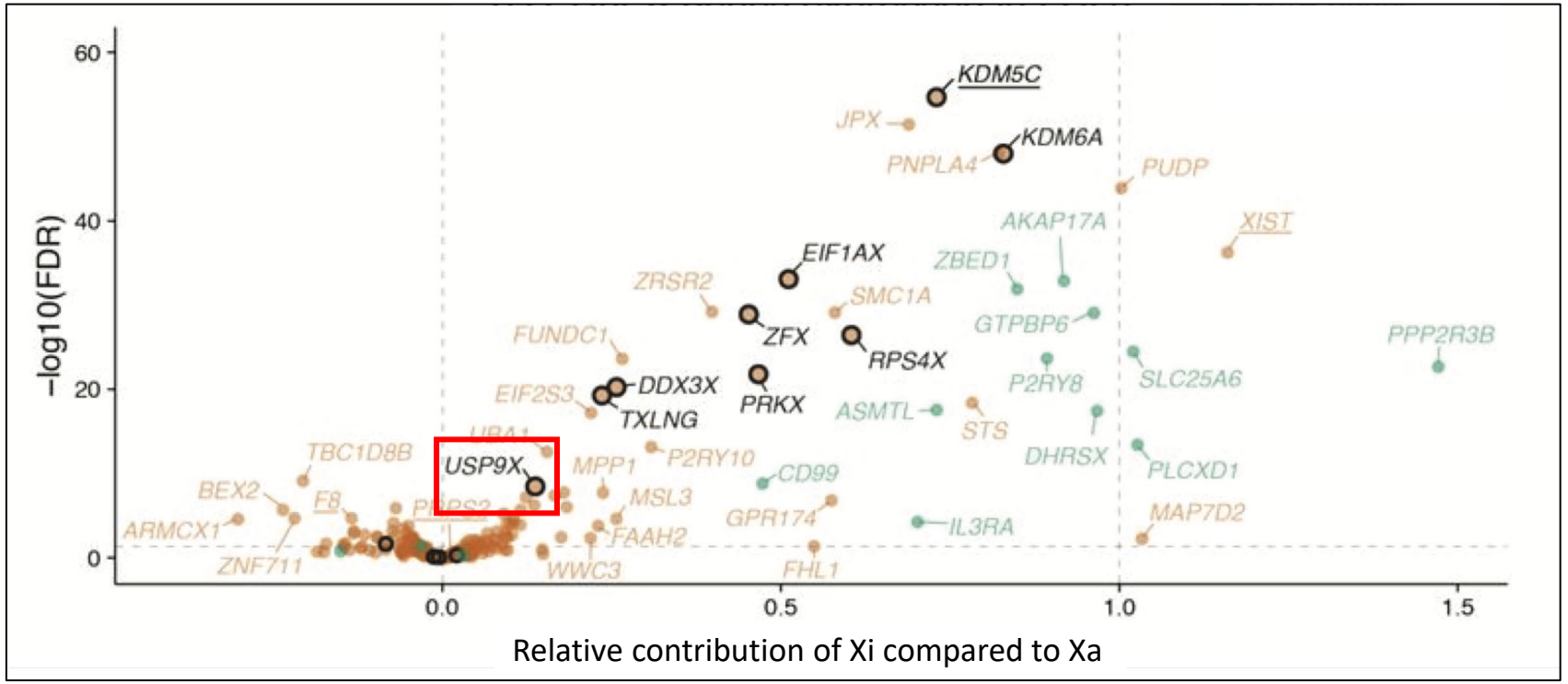
USP9X is expressed from active X (X_a) as well as the inactive X (X_i) chromosome in humans





Roman et. al., 2021