Weill Cornell Medicine

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Bloom Syndrome

Past, present, future

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Disclosure

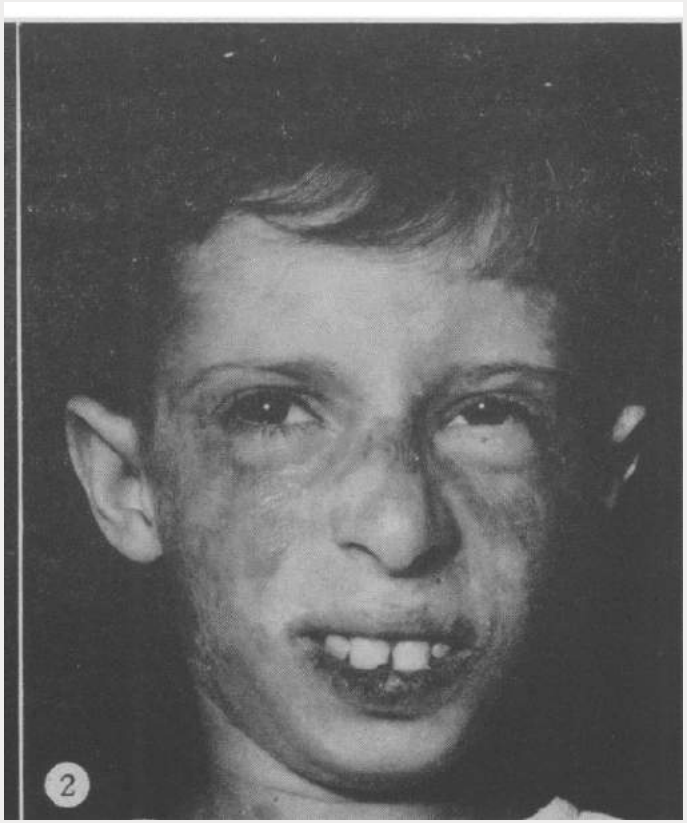
I do not have a financial interest in commercial products or services related to the subject of this talk.

What I will cover

- Background
- Bloom Syndrome Registry
- Completed work
- Ongoing work
- Future directions

Brief history of Bloom Syndrome

- 1954 report by David Bloom
- 3 children with growth deficiency and rash
- First reported patient was of Ashkenazi background
- Suggested a syndrome



Brief history of Bloom Syndrome

1965 - spontaneous chromosome breakage

1969 – first 27 patients published

1974 – increased sister chromatid exchange

1995 – *BLM* gene is a RECQ helicase

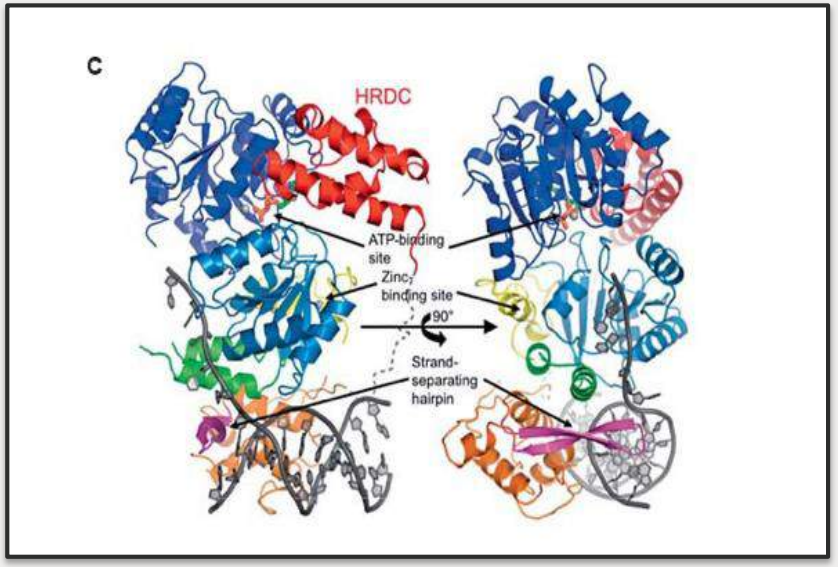
BLM functions

Helicase function unwinds DNA for replication, transcription

Maintains genome stability

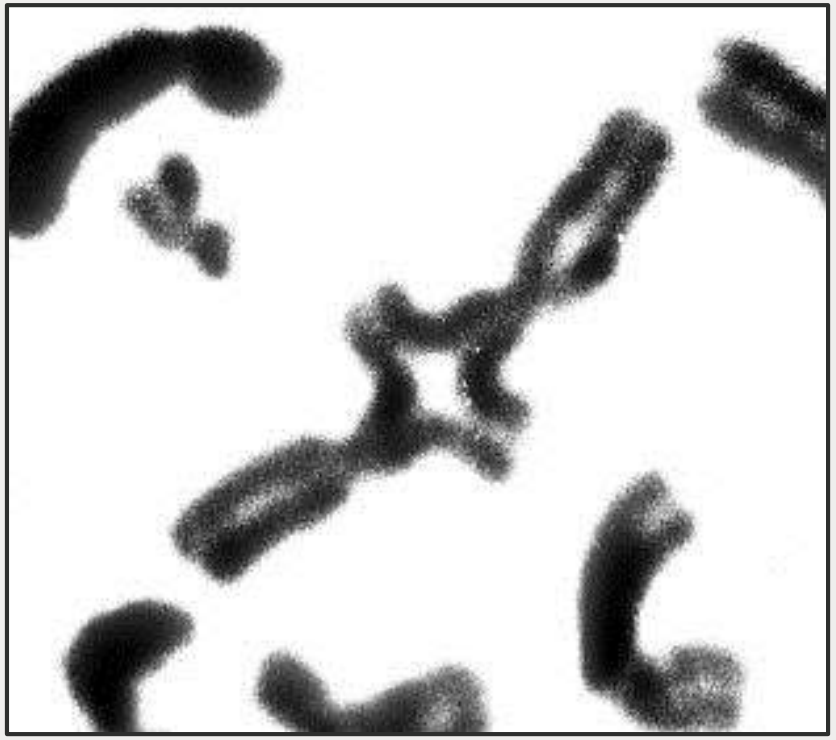
Suppresses homologous recombination

Repairs damaged DNA



BLM mutations

- Result in complete loss of *BLM* function
- Most common gene abnormality is *BLM*^{Ash} (c.2207–2212delATCTGA- insTAGATTC)
- 65 different mutations identified, many recurrent
- Present on all continents and many ethnic groups
- Mutation information available on 164 of 277 people in the BSR



Patient Registries

- Observational study design
- Uniform data collection
- Specified outcomes
- Scientific, clinical and policy purposes

Registries for evaluating patient outcomes:
https://www.ncbi.nlm.nih.gov/books/NBK208619/

Bloom Syndrome Registry

- REDCap database of persons with Bsyn
- 277 registrants from over 15 countries
- Biological samples on 161 individuals, mostly with trio samples
- 11 tumor samples
- Survey enabled

Completed work

- Two comprehensive reviews of Bloom syndrome published
- Health supervision recommendations
- Feeding and nutrition

Growth and feeding

Feeding difficulty in infancy

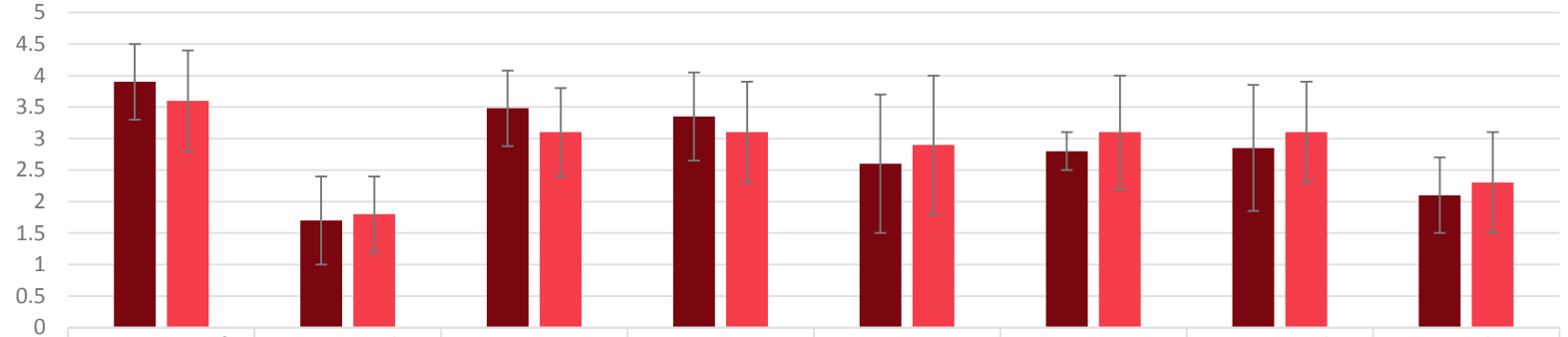
Gastroesophageal reflux common

Appetite decreased in older persons

Feeding and nutrition

- Survey based assessment of feeding patterns and behaviors
- Subjects: children ages 2 to 12 years of age
- Child Eating Behavior Questionnaire
- 8 domains such as emotional over/undereating, enjoyment of food
- Feeding Assessment Questionnaire
- Appetite, food preferences, eating problems

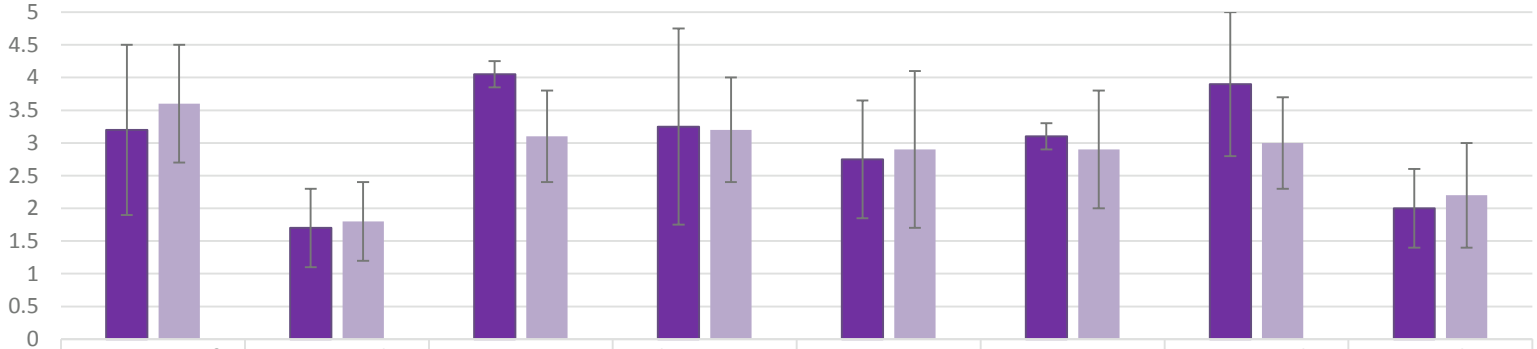
Child Eating Behavior Questionnaire (Male)



	Enjoyment of food	Emotional Overeating	Satiety Responsiveness	Slowness in Eating	Desire to Drink	Food Fussiness	Emotional Undereating	Food Responsiveness
Bloom Male average	3.9	1.7	3.48	3.35	2.6	2.8	2.85	2.1
Male Average	3.6	1.8	3.1	3.1	2.9	3.1	3.1	2.3

Bloom Male average Male Average

Child Eating Behavior Questionnaire (Female)



	Enjoyment of food	Emotional Overeating	Satiety Responsiveness	Slowness in Eating	Desire to Drink	Food Fussiness	Emotional Undereating	Food Responsiveness
Bloom Female Average	3.2	1.7	4.05	3.25	2.75	3.1	3.9	2
Female Average	3.6	1.8	3.1	3.2	2.9	2.9	3	2.2

Bloom Female Average Female Average

FAQ Findings - Growth

63% with birth weight <3% and 100% under 10th %

89% diagnosed with failure to thrive or slow growth

67% have weight below 3%, 78% at or under 10%

67% have height at or under the 3%

FAQ Findings

Feeding:

- 56% report their child has poor appetite
- 56% report child eats limited variety of foods
- 78% report child is slow to feed
- 100% of parents report that there is NOT a physical disability affecting feeding

Feeding Support:

- 56% of patients take a nutritional supplement (fortified milk, Pediasure)
- 33% of the children had G-tubes placed

Ongoing work

Time to event analysis

Ionizing radiation

Whole genome analysis

Time to event analysis

Cancer onset and survival

Gender differences

Genotype differences

Ionizing radiation

Radiation is highly toxic in some chromosome instability disorders

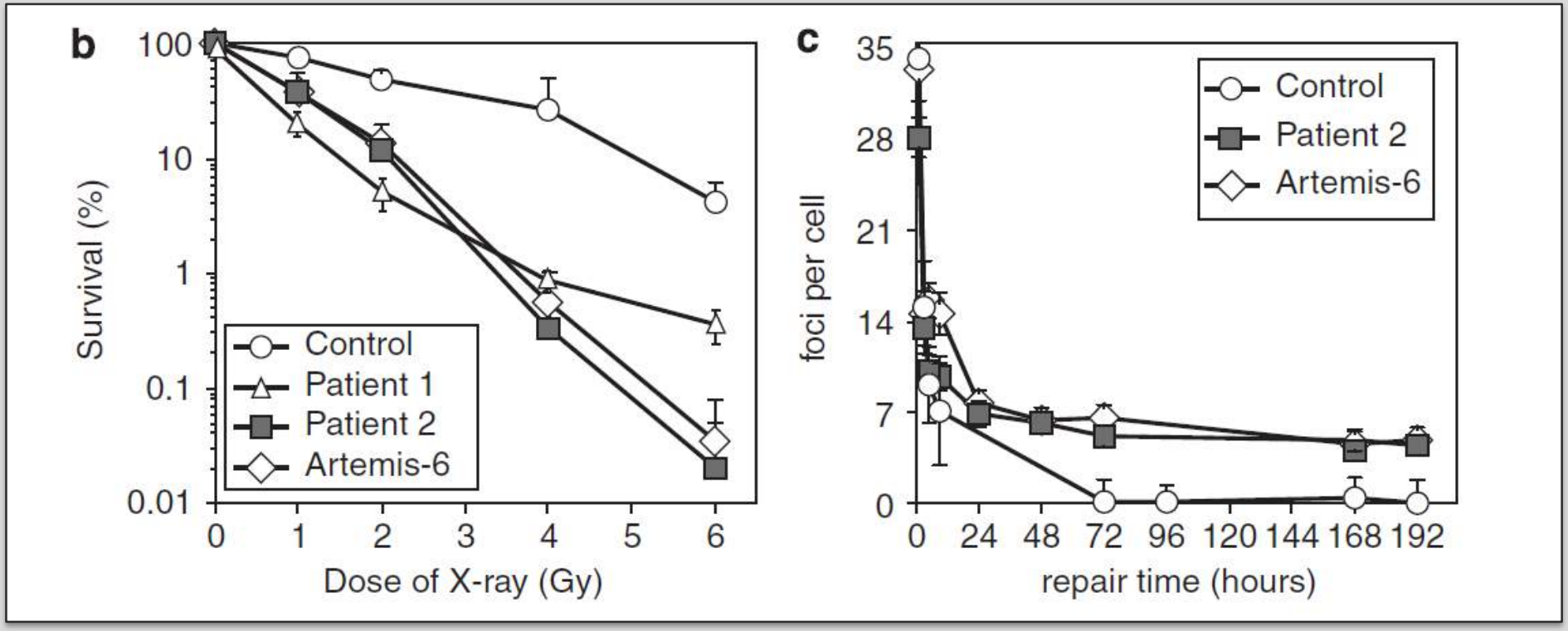
Several reports of severe local toxicity and mucositis in Bsyn patients

IR and risk for secondary malignancies?

Ionizing radiation sensitivity

Clonogenic survival assay

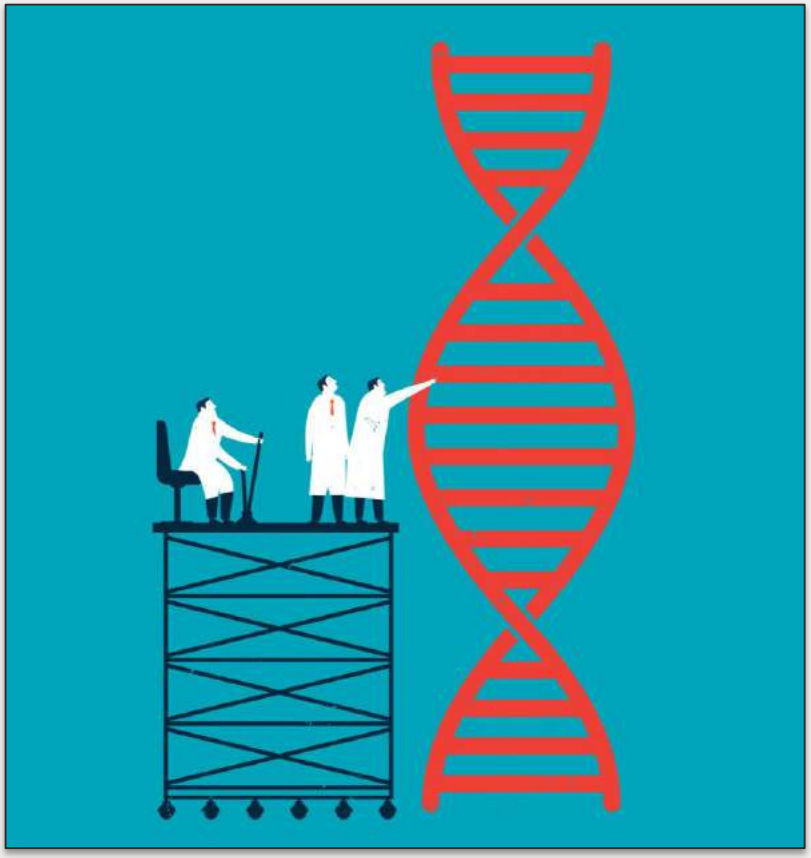
γH2AX assay



Ijspeert et al. Genes Immun 2011; 12:434-444

Whole genome sequencing

- Cells from 3 oldest and 3 youngest in BSR
- Low pass coverage to detect loss or gain of chromosome material
- High pass coverage to detect single gene changes



Future Directions

- Tumor analysis
- Longitudinal samples
- Health supervision effectiveness
- *BLM* pathway disorders
- Facial phenotyping
- Building infrastructure

Analysis of Bloom tumors

WES/WGS of Bloom tumors has not been reported

The mutation landscape of some tumors implicates DNA repair pathways

These tumors may be sensitive to some therapies such as PARP inhibitors

Use the signature to identify therapeutic targets

Longitudinal samples

- Surveys
- Multiple samples on each person
- Whole genome sequencing
- Exosome analysis

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ORIGINAL ARTICLE

Health supervision for people with Bloom syndrome

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ARTICLE

Mutations in *TOP3A* Cause a Bloom Syndrome-like Disorder

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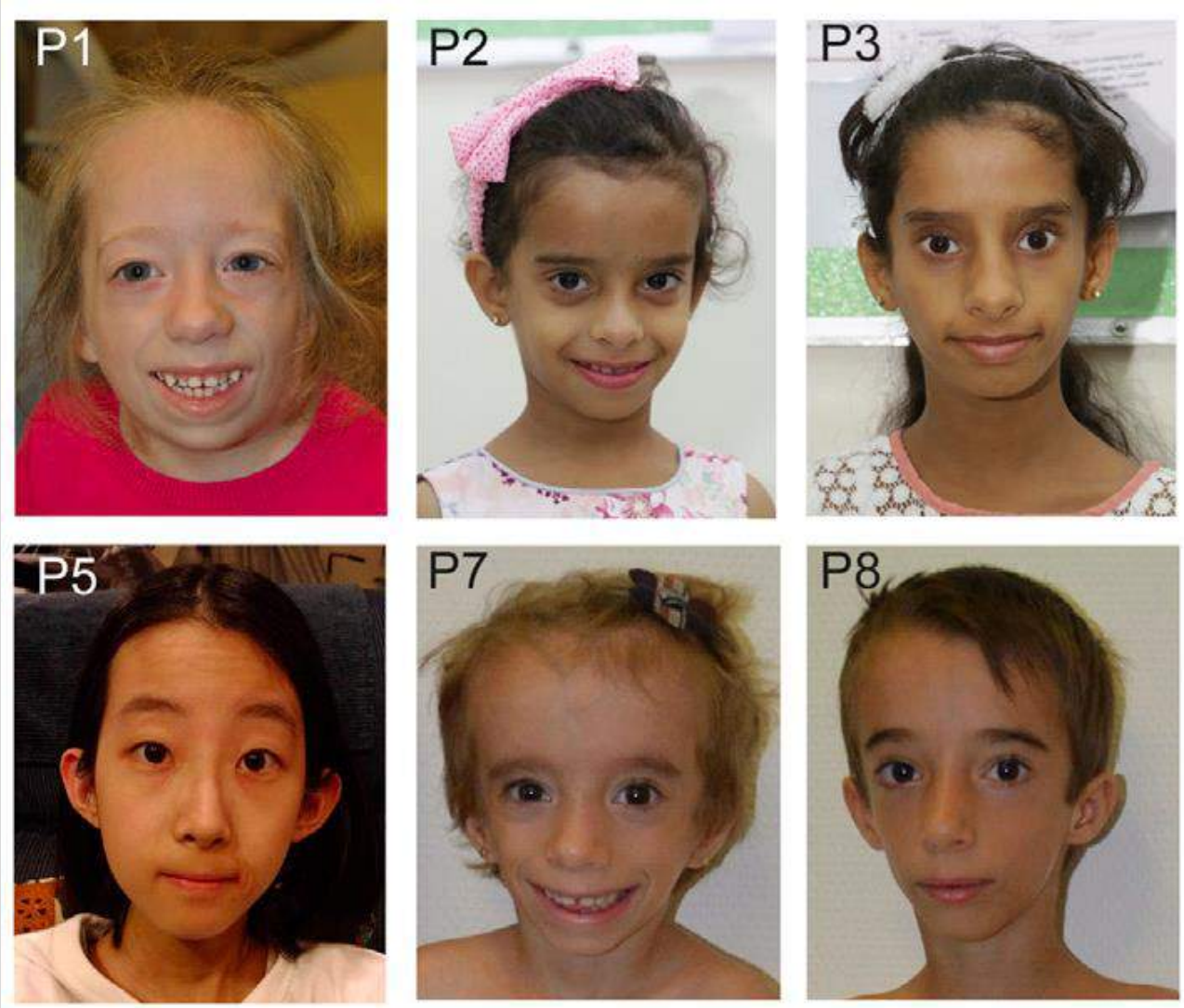
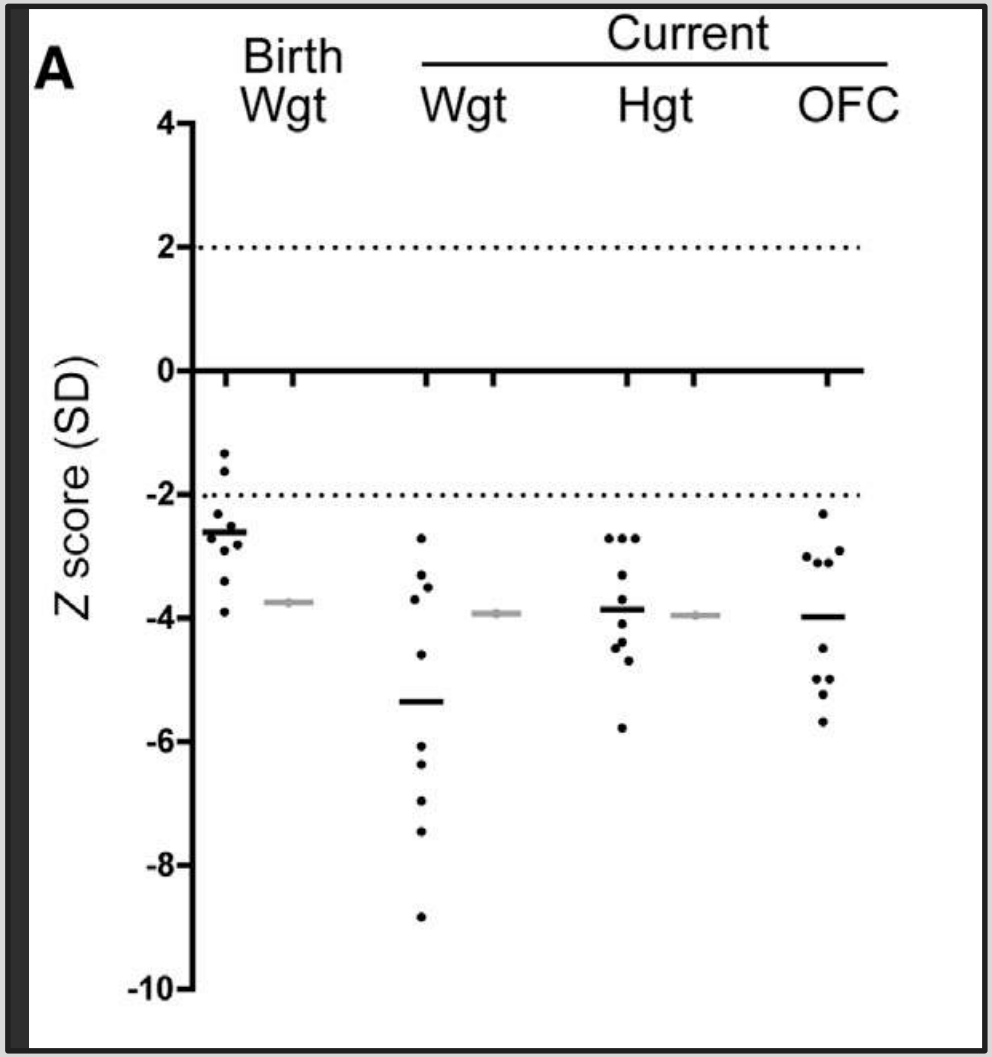
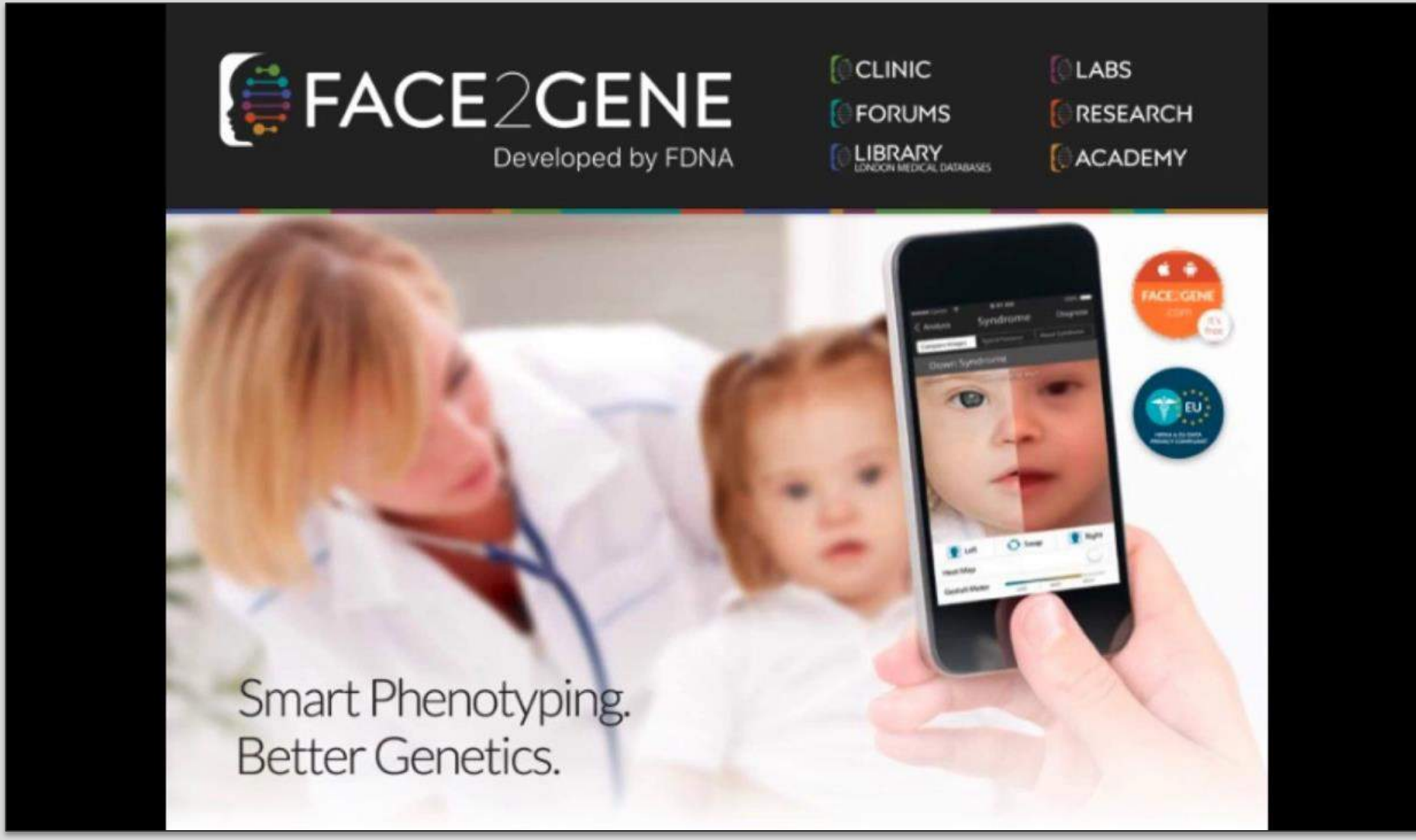
Bloom syndrome, caused by biallelic mutations in *BLM*, is characterized by prenatal-onset growth deficiency, short stature, an erythematous photosensitive malar rash, and increased cancer predisposition. Diagnostically, a hallmark feature is the presence of increased sister chromatid exchanges (SCEs) on cytogenetic testing. Here, we describe biallelic mutations in *TOP3A* in ten individuals with prenatal-onset growth restriction and microcephaly. *TOP3A* encodes topoisomerase III alpha (TopIIIα), which binds to BLM as part of the BTRR complex, and promotes dissolution of double Holliday junctions arising during homologous recombination. We also identify a homozygous truncating variant in *RMI1*, which encodes another component of the BTRR complex, in two individuals with microcephalic dwarfism. The *TOP3A* mutations substantially reduce cellular levels of TopIIIα, and consequently subjects' cells demonstrate elevated rates of SCE. Unresolved DNA recombination and/or replication intermediates persist into mitosis, leading to chromosome segregation defects and genome instability that most likely explain the growth restriction seen in these subjects and in Bloom syndrome. Clinical features of mitochondrial dysfunction are evident in several individuals with biallelic *TOP3A* mutations, consistent with the recently reported additional function of TopIIIα in mitochondrial DNA decatenation. In summary, our findings establish *TOP3A* mutations as an additional cause of prenatal-onset short stature with increased cytogenetic SCEs and implicate the decatenation activity of the BTRR complex in their pathogenesis.

TOP3A



TOP3A growth

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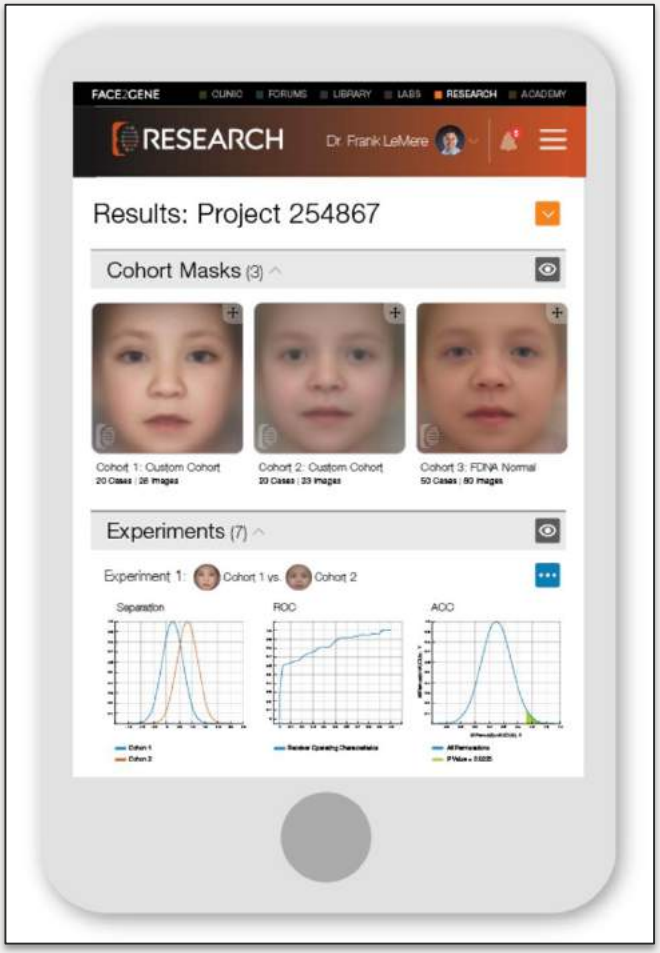
Digital phenotyping

Computer recognition software analyzes facial features

Composite image created

Image analysis by age, gender, ethnicity, genotype



Building infrastructure

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