Mosaic Down Syndrome: Meeting the needs of all your families through research, support, and awareness

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What is mosaicism?

A condition in which an individual has 2 or more genetically distinct cell lines derived from a single zygote but differing genetically because of a mutation or nondisjunction.
How does mosaicism arise?

= Two (disomic)  

= Three (trisomic)
What is the frequency of mosaicism for trisomy21/Down syndrome?

### Summary of studies with at least 1000 participants

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>% Mosaic</th>
<th>Population</th>
<th>Total</th>
<th>Ascertainment</th>
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<td>Iselius &amp; Lindsten</td>
<td>1981</td>
<td>1.7</td>
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<td>Hook, et al</td>
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<td>4.0</td>
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<td>Mandava, et al</td>
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<td>Mumbai, India</td>
<td>1,572</td>
<td>Postnatal</td>
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<td>Shin, et al</td>
<td>2010</td>
<td>1.9</td>
<td>USA</td>
<td>6,300</td>
<td>Unspecified</td>
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<td>England and Wales, UK</td>
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<td>Denmark</td>
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</tbody>
</table>
What is the prevalence of mosaicism for trisomy 21/Down syndrome?

Social Conditions for People With Down Syndrome: A Register-Based Cohort Study in Denmark
Jin Liang Zhu,1,2* Carsten Obel,1,3 Henrik Hasle,4 Sonja A. Rasmussen,5 Jiong Li,2 and Jørn Olsen2
1Research Program for Children’s Mental Health, Department of Public Health, Aarhus University, Aarhus, Denmark
2Section of Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark
3Section of General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark
4Department of Pediatrics, Aarhus University Hospital, Skejby, Aarhus, Denmark
5Centers for Disease Control and Prevention (CDC), Atlanta, Georgia


3.3% of people studied (ages 0-39 years)

Individuals with mosaicism:

- Attending secondary or post-secondary education (18%)
- Full time job (27.5%)
- Married (15%) or had a child (7%)
IMDSA is designed to support any family or individual whose life has been touched by mosaic Down syndrome by continuously pursuing research opportunities and increasing awareness in the medical, educational, and public communities throughout the world.

Brandy Hellard – IMDSA President
Brandy Snow – IMDSA President Elect
Researcher and Advisor – Colleen Jackson-Cook
What influences detection of mosaicism?

- Tissue(s) assessed
- Number of cells evaluated
- Assay used
- Clinical findings
Are there tissue-specific differences?

- Fertilized Cell
- Extra-embryonic tissue
  - Placenta
  - Chorion
  - Amnion
- Embryo
- Ectoderm
  - Epidermis
  - Eyes
  - CNS
  - Buccal mucosa
- Endoderm
  - Alimentary canal
  - Lungs
  - Liver
  - Pancreas
- Mesoderm
  - Bones
  - Cartilage
  - Muscle
  - Dermis
  - Urinary tract
  - Heart
  - Blood
  - Blood vessels
  - Reproductive system
- Blood
- Skin
- Buccal Mucosa
Which diagnostic test(s) is/are most effective for detecting mosaicism?
Diagnostic Tests

• Conventional GTG-banding will detect most cases (score 20-50 cells)

• FISH is “gold standard” for evaluation of mosaicism (score 100-1000 cells)

• Microarray useful tool; detects levels as low as 4%
What is the best method for detecting the presence of mosaicism?

What is the biological basis for the observed variation in health conditions and developmental progress?

What can we learn about aging and the risk to develop age-related conditions by studying people with mosaicism?

What is the frequency of depression in adolescents and adults with Down syndrome, can we develop tools to better assess depression in these individuals, and does risk for depression associate with risk for Alzheimer disease?
Study Participants

- To date, more than 135 individuals with mosaicism have been ascertained through:
  - Annual meetings of support groups (NDSC)
  - Support group newsletters
  - The International Mosaic Down Syndrome Association (IMDSA) website and meetings

- Criteria: Diagnosis of mosaic Down syndrome

- Also, controls having trisomy 21
Study Population Demographics

- Non-U.S. countries include: Australia, Canada, England, Ireland, Germany, & Portugal
- 47.6% males; 52.4% females
- Ages range from 3 months – 40 years
Assessment of traits and percentage of trisomic cells

• Physical Examination
• Medical Records
• Parental Questionnaire
• Photographs
Phenotypic Assessments Through the Use of Photographs (birth – current age)

11 year-old male proband

Ears appear to be slightly small in size but are of normal shape & position

- Mildly broad (but not flat) nasal bridge
- Also, subtle epicanthal folds

High-arched palate
(1) Blood sample

(a) Cultured Lymphocytes

(1) Standard GTG-banding

(2) FISH for aneuploidy

(b) Uncultured Blood Smear

FISH for aneuploidy

(2) Buccal Smear

(3) FISH for chromosome-specific telomere lengths

FISH for aneuploidy
Percentage of Trisomic Cells in Cultured (Lymphocytes) Compared to Uncultured (Buccal Mucosa and Lymphocytes) Cells

Buccal: 46.06 ± 3.44%
Cultured Blood: 30.13 ± 3.99%

Cultured Blood: 33.15 ± 4.72%
Uncultured Blood: 30.57 ± 3.80%
Is there a correlation between the % of trisomic cells present and the development and health outcome of people having mosaicism?
Correlations Between IQ Scores and Percent Trisomy in Buccal Mucosa and Blood Samples

- Significant inverse correlation between IQ scores and % trisomy in buccal samples.
- Trend toward lower IQ with higher % lymphocyte trisomy
Correlations Between CHD and Percent Trisomy in Buccal Mucosa and Blood Samples

(a) Lymphocytes

(b) Buccal

Percent trisomy

Number of Cases Studied

CHD
No CHD
"We are more alike than we are different"

Class 1: 20 individuals  
Class 2: 138 individuals*

Mean % Tri in Blood 
Class 1: 37.34%  
Class 2: 53.97%  
(p=0.0189)

Mean % Tri in Buccal 
Class 1: 34.54%  
Class 2: 53.37%  
(p=0.0119)

*Includes 54 full tri 21 individuals
Research Questions

What is the biological basis for the observed variation in health conditions, depression/stress, and developmental progress?

- Percentage trisomic cells
- Epigenetic differences
- Acquired chromosomal changes
Do individuals with mosaicism have depressive symptoms?

- 27% report high or very high emotional distress
- 27% risk for emotional disorder
- 38.5% diagnosed by professional with emotional disorder

Results from study by Ruth Brown, PhD  VCU
Do people with mosaicism feel stressed?

More than one third of all participants (36.36%) report high or very high stress.

Results from study by Ruth Brown, PhD, VCU
A specialized structure at the ends of chromosomes; maintains chromosomal integrity by preventing end-to-end fusions
Biological consequences?

- Stress
- Dementia
- Heart disease
- Depression
- Childhood Adversity
Model for Acquired Genetic & Epigenetic Changes

Immune System
- CRP
- Interleukins
- Cytokines

Telomerase

Telomere length

Oxidative Stress
- ROS production
- Base oxidation

Gene Expression
- Euploid
- Trisomic

Epigenetic Changes

Chromosome anomalies

Health or Developmental Alteration
Chromosome-Specific Telomere Lengths

Scoring

• 10 metaphase spreads
• Telomere average of 20 homologs
• Does the length of the tips of chromosomes (telomeres) differ in the trisomic compared to euploid cells of people who have mosaicism for trisomy 21/Down syndrome?
Telomere lengths in trisomic compared to euploid cells from a 2 yr old with mosaicism
Telomere lengths in euploid and trisomic cells

![Graph showing mean telomere length and age](image)
Model for Acquired Genetic & Epigenetic Changes

- **Immune System**
  - CRP
  - Interleukins
  - Cytokines

- **Telomerase**

- **Oxidative Stress**
  - ROS production
  - Base oxidation

- **Telomere length**

- **Gene Expression**

- **Chromosome anomalies**

- **Epigenetic Changes**

- **Euploid**
- **Trisomic**

- **Health or Developmental Alteration**
Acquired Chromosomal Instability (Somatic Cell)

Cytokinesis Block

- Isolate WBC
- 44 hr add Cyt B
- Harvest (no colcemid)

- Comparable to chromosomal data
- Less prone to artifacts
- Less labor intensive
- Limited selection pressure
Acquired Chromosomal Findings

Removing 21 from one cell

Removing 21 from both cells

Not involving chromosome 21
Does the chromosomal instability involve chromosomes other than 21 and how does this relate to the presentation of dementia?

Spectral Karyotyping
- Interphase
- 100 MN/person
Differences in pattern of chromosomes present in micronuclei from people having dementia compared to people without dementia
The study of heritable changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence, hence the name *epi-* (Greek: επί- over, above) -genetics. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism;[1] instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently.[2]
Genotypic variation also important in gene expression and modulating effects of “environmental” exposure

Fig. 5. A scheme for environmental driven epigenetic states and inter-individual phenotypic variance in behavior and susceptibility to disease in humans. From Szyf M, Weaver I, Meaney M (2007) Reprod Toxicol 24: 9-19.
Studies of cells/DNA/RNA from individuals with mosaicism can help to recognize effects of trisomy 21.
Studies of cells from individuals with mosaicism provide unique vision.

- Chromosome 21
- Genes not associated with chromosome 21
- Environmental
Studies of cells from individuals with mosaicism provide unique vision.

Chromosome 21
Genes not associated with chromosome 21
Environmental
Studies of cells from individuals with mosaicism provide unique vision.
Model for Acquired Genetic & Epigenetic Changes

Immune System

- CRP
- Interleukins
- Cytokines

Telomerase

Telomere length

Oxidative Stress

- ROS production
- Base oxidation

Chromosome anomalies

Epigenetic Changes

Gene Expression

Euploid

Trisomic

Health or Developmental Alteration
Differences in epigenetic patterns?

• 133 significant sites
• 63% sites within genes (most on chromosomes other than 21)
• May provide tool for understanding health/developmental traits

• Reversibility of epigenetic marks gives promise for treatment
IMDSA is designed to **support** any family or individual whose life has been touched by mosaic Down syndrome by continuously pursuing research opportunities and **increasing awareness** in the medical, educational, and public communities throughout the world.

Brandy Hellard – IMDSA President
Brandy Snow – IMDSA President Elect
Researcher and Advisor – Colleen Jackson-Cook
Why have *another* Ds organization specifically for mosaic Down syndrome?

- If you have a specific type of cancer you want to know all about that specific cancer; It’s the same with mosaic Down syndrome.

- Families having a loved one with mDs thirst for knowledge.

- Before IMDSA there was very little information available about mosaic Down syndrome.

- IMDSA also provides information to those families whose loved one has translocation or mosaic translocation Down syndrome.
What does IMDSA do?
Support, Information & Research

- Online support (Yahoo) email groups
- Online Facebook support groups
- Informative website (www.IMDSA.org)
- IMDSA Welcome and Professional Publications
- Student learning program
- Research program
- Toll-free hotline (1-855-IMDSA21)
- Family Connect program
- Awareness Campaigns – Gene’s Day and Raising for Research
- Conferences
How many families with mDs are in your community?

Our goal is to ensure that these families are connected and that their needs (both socially and medically) are being met.
• Unfortunately, many times families whose loved one has mosaic Down syndrome will feel isolated without other families to meet face-to-face.

• Many feel they do not belong in the Down syndrome community due to lack of acceptance.

• Many feel guilt or shame if their child achieves more than other children in the group with Down syndrome.
How you can best serve all of your families

• Provide support
  • IMDSA is an International organization, but we are not able to provide support at the local level. Because of this we encourage our families to become active with their local Down syndrome organizations

• Include factual and helpful information about mosaic Down syndrome on your website.
  • Try not to simply include a link or short paragraph with statistics

• Provide printed materials about mosaic Down syndrome
  • We have materials available to make available to you

• Train your staff on how to handle calls
  • We can help provide links to talks such as this that might help tremendously

• Your families and staff will follow your lead – be a leader

• Reference play groups based on stage of development rather than age
  • A birth to 3 years old might not be appropriate for both a child with Ds and a child with mDs

• Refer to IMDSA for any additional support and information for your organization or for the families

‘Cause it makes me that much stronger
So, thanks for making me a fighter!

I'm Ivonne.
I have mosaic Down syndrome.

Share this and help us spread awareness for mosaic Down syndrome
www.IMDSA.org
Information available for distribution

- Permission is granted to use any non-password protected information
  - Citing of IMDSA and all contact information is required

- Request brochures and other publications

- Call or email us to request resources or information
Please contact us:

www.imdsa.org
Toll-free phone number: 1-855-IMDSA21
Email: president@IMDSA.org

Also, we thank all the individuals who have generously helped with this research.

If you have families interested in participating in this research, please contact Colleen Jackson-Cook at 804-628-2992 or ccook@mcvh-vcu.edu

Life is what happens to you while you are busy making other plans. - John Lennon

I AM MARK.
I have mosaic Down syndrome.
Members of the IMDSA

Officers of IMDSA
Brandy Hellard – Past President
Kristina Welch – Past National Vice President
Brandy Snow – President Elect
Matt Ward – Vice President
Brian Chun – International Vice President
Elvis Cabral – Treasurer
Angie Satterfield - Secretary

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