Simons Searchlight is an international research program with the goal of accelerating science and improving lives for people with rare genetic neurodevelopmental disorders.
Priorities for Searchlight Data Collection

- Participant-centered
  - high-priority useful data

Facilitate investigation by researchers

Longitudinal

Feasible, scalable

Standardized, validated, sensitive measures
What are the **goals** of Simons Searchlight?

Our mission is to shed light on these conditions by collecting high quality natural history data and building strong partnerships between researchers, industry and families.

- Collect detailed **medical and behavioral histories** along with blood **samples**
- Synthesize the information you provide and share **results back to families**
- **Freely share data** and samples with qualified researchers
- **Connect** participants and researchers from around the world
- Promote better understanding of these genetic changes
Information for Families

- Personalized reports: SCQ, SRS, CBCL and Vineland located on your dashboard
- Summary snapshots on your gene page
- Presentations at conferences and meetings

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**Simons Searchlight Registry Update**

**December 2023**

**Participant Age at Most Recent Interview**

**Developmental & Behavioral Diagnoses**

**Neurological Problems**

**Gastrointestinal Problems**

**How to Participate**

Thank you for contributing to the Simons VIP study!

Please remember these results are based on your responses to an online computerized research survey. They are not monitored or evaluated by a professional, and they do not represent a clinical evaluation or clinical feedback. No questionnaire is 100 percent accurate. If you ever have any questions or concerns, please talk to your doctor.
Simons Searchlight participants can donate a blood sample

Blood collection steps

**Step 1:** A blood sample kit is mailed to you free of charge
**Step 2:** Make an appointment at a local Quest Labs to have the blood drawn
**Step 3:** The lab mails the kit back to Simons Searchlight

Questions? Email coordinator@simonssearchlight.org
How will the sample be used in research and why is this important?

Questions? Email coordinator@simonssearchlight.org
What are induced pluripotent stem cells (iPSCs)?

Simons Searchlight Participant → Blood Cells → iPSC Cells → Specialized Differentiated Cells → Disease Modelling

Treatments to make iPSC cells

Treatments to tell the iPSC cells to change into something else

Disease Modelling

Nerve Cells, Liver Cells, Other Tissue Cells

Drug Screening and Discovery

Questions? Email coordinator@simonssearchlight.org
The SETBP1 Registry in Simons Searchlight
Progress of Individuals with SETBP1

**STEP 1**
Sign up online.

**STEP 2**
Provide your genetic lab report.

**STEP 3**
Share your important medical history.

**STEP 4**
Fill out surveys.

**STEP 5**
Provide a blood sample if you are interested.

**STEP 6**
Update us every year.

We are a long-term study, gathering new information from you every year.

* All SETBP1 inclusive of SGS
**SETBP1 Biospecimens**

11 individuals contributed to the available biospecimens

<table>
<thead>
<tr>
<th>Available Sample</th>
<th>SETBP1 Carriers</th>
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<tbody>
<tr>
<td>Induced pluripotent stem cells (iPSCs)</td>
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<tr>
<td>Lymphoblastoid cell lines</td>
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<td>Whole blood DNA</td>
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<td>Saliva DNA</td>
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* All SETBP1 inclusive of SGS
## SETBP1 iPS Cells

<table>
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<tr>
<th></th>
<th>p. nomen</th>
<th># of Carriers</th>
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<tr>
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<td>2</td>
<td>p.Met470*</td>
<td>1</td>
<td>Available</td>
</tr>
<tr>
<td>3</td>
<td>p.His523Leufs*32</td>
<td>1</td>
<td>Available</td>
</tr>
<tr>
<td>4</td>
<td>p.Arg625*</td>
<td>1</td>
<td>Upcoming</td>
</tr>
<tr>
<td>5</td>
<td>p.Glu858Lys</td>
<td>1</td>
<td>Upcoming</td>
</tr>
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</table>

- Researchers worldwide can request (non- and for-profit), nominal fee $120/sample
- Request through SFARI Base
- Researchers can submit requests now

* All iPSc's inclusive of SGS


### Variants Observed in SETBP1-HD

#### 29 individuals

<table>
<thead>
<tr>
<th>Variant Category</th>
<th>Number</th>
<th>Coordinates</th>
<th>Variant Classification</th>
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<td></td>
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<tr>
<td></td>
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<td>p.Asp875Gly</td>
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<td>p.Trp274*</td>
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<td>p.Met470*</td>
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<tr>
<td></td>
<td></td>
<td>p.Ter1597Trpext*</td>
<td>Likely pathogenic</td>
</tr>
</tbody>
</table>

- Variants as of June 2022
- Does not include Schinzel Giedion Syndrome
- 13 VUSs in Simons Searchlight not shown
Variants Observed in SETBP1-HD

- Variants:
  - Missense variant:
    - p.Gln89*
    - p.Ala113Leufs*94
    - p.Lys152Trpfs*18
    - p.Gln178*
    - p.Pro208Glnfs*135
    - p.Trp274*
    - p.Met470*
    - p.His523Leufs*32
    - p.Arg530*
    - p.Ser540*
    - p.Pro559Aspfs*42
  - Frameshift/nonsense:
    - p.Glu585Lys
    - p.Gly588Aspfs*42
    - p.Arg589*
    - p.Ser608Alafs*22
    - p.Arg625*
    - p.Arg626*
    - p.Arg757Cysfs*23
    - p.Asp875Gly

- Functional regions:
  - A.T hook 1
  - SKI homologous region
  - A.T hook 2
  - SET binding domain
  - A.T hook 3
  - Repeat domain

- 13 VUS and 7 SGS variants in Simons Searchlight, not shown
Protein Structure of SETBP1
Quality of Life Survey
Notes: These graphics reflect the percentage of people who reported “Often” or “Very Often” for each question. We gratefully acknowledge Dr. Jenny Downs of the Telethon Kids Institute.
Quality of Life Inventory - Disability

(13 individuals with SETBP1)

**Family & Friends**
- Happy when they are understood: 92%
- Enjoys socializing at mealtimes: 92%
- Feels relaxed while making eye contact: 92%
- Enjoys interacting with others: 100%
- Initiates greetings with others: 85%
- Excited by upcoming activities: 85%
- Happy to be included: 92%

**Daily Life**
- Expresses their needs: 77%
- Makes own choices for activities: 85%
- Likes using technology: 69%
- Helps with routines: 62%
- Enjoys making things: 62%

Notes: These graphics reflect the percentage of people who reported "Often" or "Very Often" for each question. We gratefully acknowledge Dr. Jenny Downs of the Telethon Kids Institute.
Simons Searchlight SETBP1-HD Medical History Data

19 participants with pathogenic or likely pathogenic loss of function variants
Age at Most Recent Medical History Interview
(19 individuals)
Developmental and Behavioral Conditions (19 individuals)

- Language impairment: 18 (95%)
- Intellectual Disability/Developmental Delay: 16 (84%)
- Autism: 5 (26%)
- Anxiety: 3 (16%)
- ADHD: 9 (47%)
Neurological Problems
(19 individuals)

- Tic Disorder: 1 (5%)
- Small Head Size: 2 (11%)
- Movement Disorder: 1 (5%)
- Low Muscle Tone: 12 (63%)
- High Muscle Tone: 1 (5%)
- Coordination Problems: 5 (26%)
- Cerebral Palsy: 1 (5%)
Vision Problems
(19 individuals)

- Other: 1 (5%)
- Nearsighted: 2 (11%)
- Lazy Eye: 1 (5%)
- Farsighted: 7 (37%)
- Crossed Eyes: 2 (11%)
- Astigmatism: 1 (5%)

* 1 eye surgery for crossed eyes
Additional Medical Issues
(19 individuals)

- Scoliosis: 1 (5%)
- Kidney: 1 (5%)
- Heart: 1 (5%)
- Facial Cleft Repair: 1 (5%)
- Undescended Testicles: 3 (16%)
- Endocrinologic: 4 (21%)
- Gastro: 9 (47%)
- Vision: 12 (63%)
Medication Use (16 individuals)

- Sleep: 1 (6%)
- Antiepileptic drugs (AEDs): 2 (12%)
- Other: 1 (6%)
- Gastrointestinal: 2 (12%)
- Cannabidiol/Cannabis: 1 (6%)
- Attention, Hyperactivity: 7 (44%)
- Asthma, Respiratory, Allergy: 2 (12%)
- All Pain: 1 (6%)

(SIMONS SEARCHLIGHT)
Vineland Adaptive Behavior Scales
Developmental Growth Charts
(Vineland-3)
Expressive Language Development
(10 individuals)

Vineland Age Equivalent (in years)

Age at Evaluation

Uses single words to request
Personal Care Skills
(10 individuals)

Vineland Age Equivalent (in years)

Age at Evaluation

Dresses self

Feeds self with fork and spoon
Social Development
(10 individuals)

Vineland Age Equivalent
(in years)

Age at Evaluation

Shows interest in friends

Makes eye contact during social interactions
Gross Motor Development
(9 individuals)

Vineland Age Equivalent (in years)

Age at Evaluation

Hops/jumps
Walks without help

SIMONS SEARCHLIGHT
Child Behavior Checklist (CBCL)
Child Behavior Checklist
Behavioral and Emotional Concerns
Ages 1.5-5 Years (11 individuals)

- Aggression
- Sadness
- Anxiety
- Attention/Hyperactivity
- Oppositional Behavior

Scale:
- Little to no concern
- Mild
- Significant concern
Child Behavior Checklist
Behavioral and Emotional Concerns
Ages 6-18 Years (12 individuals)

- Aggression
- Sadness
- Anxiety
- Attention/Hyperactivity
- Oppositional Behavior

Looking at a very small number of children over time, behavior problems are not increasing for most children in the pre-teen/teen years.
Child Behavior Checklist

Top Behavioral and Emotional Concerns
Ages 1.5-5 Years (11 individuals)

- Quickly moves from one activity to the next
- Difficulty waiting
- Gets into everything
- Hyperactive
Child Behavior Checklist

Top Behavioral and Emotional Concerns
Ages 6-18 Years (12 individuals)
Summary: SETBP1-HD Medical and Behavioral Phenotypes

**Common issues**
- Language delay
- Intellectual disability and developmental delay
- ADHD
- Hypotonia (low muscle tone)

**Other issues**
- Autism
- Coordination problems
Thank you