
Simons Variation in Individuals Project

# Simons VIP & SETBP1 Society Family Meeting

January 13, 2018

# Introductions

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Lindsey Cartner

Dr. Wendy Chung

Jennifer Tjernagel

Dr. Siddhartha Srivastava

Haley Oyler

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# SETBP1 Society

Presented by Haley Oyler

# Thank You

- Simons VIP Connect
  - Dr Wendy Chung
  - Kaitlyn Singer
  - Lindsey Cartner
- Boston Children's Hospital
  - Dr Siddharth (Sid) Srivastava
- Our SETBP1 Families

SETBP1 SOCIETY

# SETBP1 Society's Mission

Provide support to individuals with SETBP1 disorder and their families, to promote discussion and fund research, and to bring awareness and education to the public!

SETBP1 SOCIETY

# SETBP1 Society's Focus

Find targeted treatments to improve the quality of life for individuals with SETBP1 disorder

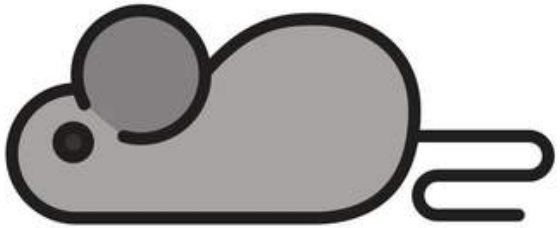
SETBP1 SOCIETY

# 2017 Highlights


SETBP1 SOCIETY

# 2018 Goals

- Fund 2 Projects
  - Biological Model of SETBP1 disorder



Mouse Model

OR

Human IPSC Model

  - Patient Stories from SETBP1 Families – A Diagnostic Journey Report
- How?
  - From 2017 Funds & Funds raised through the RARE Carousel of Possible Dreams fundraiser!

SETBP1 SOCIETY

# BE THE HOPE
# BE THE CHANGE

SETBPI SOCIETY


Simons Variation in Individuals Project

# Simons VIP & SETBP1 Society Family Meeting

Wendy Chung, MD, PhD

January 13, 2018

# Agenda

| | |
|---|---|
| 2:20 – 3:00 | SETBP1: What we know, Dr. Wendy Chung |
| 3:00 – 3:10 | Questions |
| 3:10 – 3:50 | Medications in SETBP1, Dr. Sid Srivastava |
| 3:50 – 4:00 | Questions |
| 4:00 | Meeting/Recording Ends |
| 4:00 – 5:00 | Optional Family discussion time |

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# Simons VIP Individuals with SETBP1 Mutation

- Total number of registered, consented participating families, n=5
- Total number of participants with medical history data, n=5
  - 5 male
  - Ages 6 – 14 years

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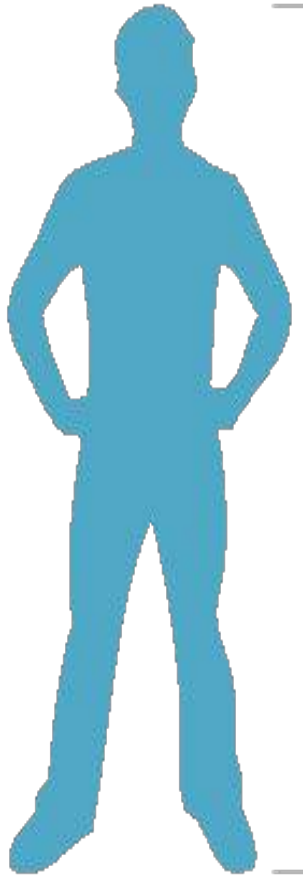
# Our Genome



**1 Genome** in a human

**46 Chromosomes** in a Genome

**20,000 Genes** in your chromosomes

**23** from Mom

**23** from Dad



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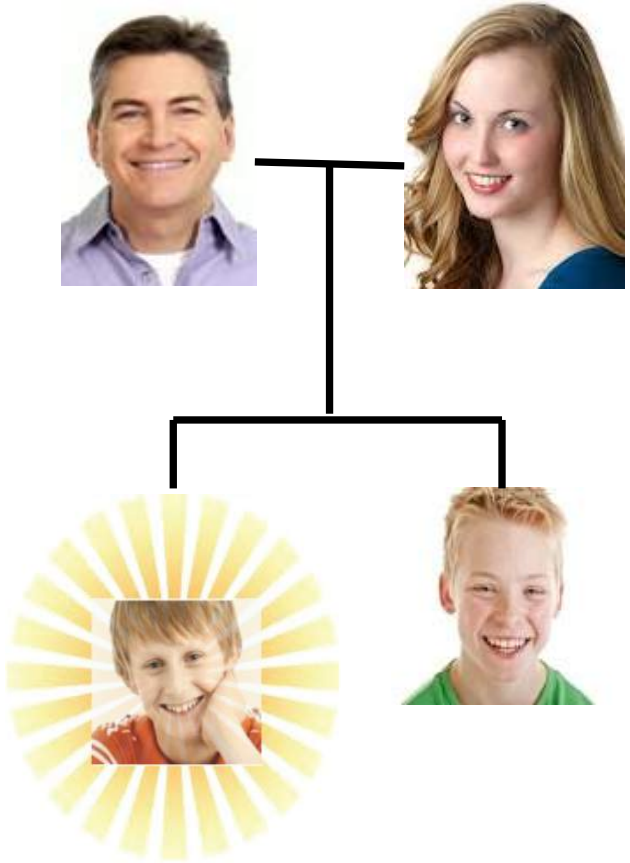
# Not all Genetic Conditions Run in Families
# De novo mutations are common children with neurodevelopmental problems



# When do de novo mutations occur?

- In the egg
- In the sperm
- At or shortly after conception
- No way to know
- Recurrence risk of 1% in future pregnancies

# SETBP1: one gene but two different conditions

- Gain of function mutations cause Schinzel-Giedion syndrome
- Loss of function mutations cause a different SETBP1 condition that is similar but with distinct differences
- Some loss of function mutations are due to deletions
- Some deletions are specific to SETBP1 but others also delete adjacent genes.  The more genes that are deleted, the greater the chance for additional features.
- It's not always possible to predict whether some genetic differences will lead to loss or gain of function

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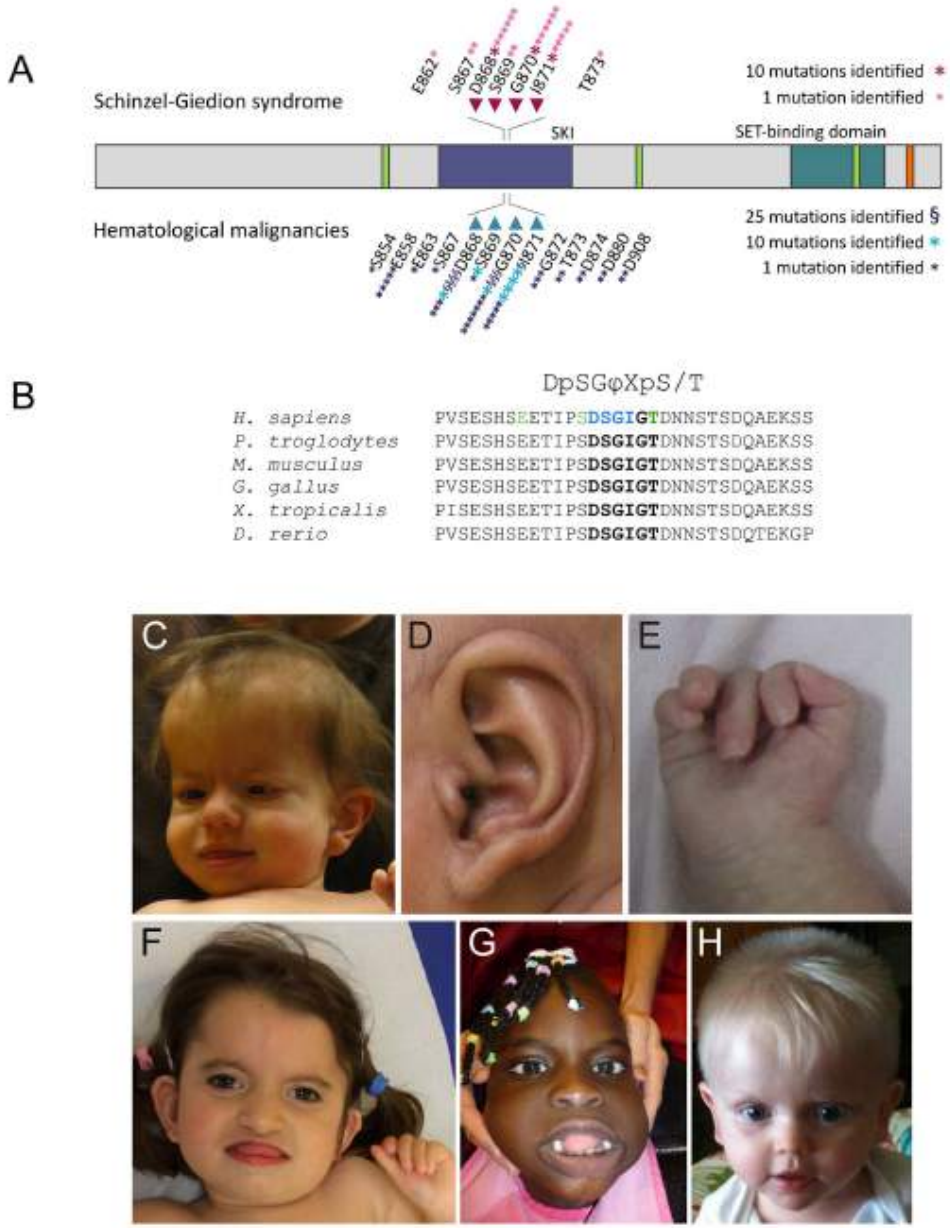
# SETBP1 mutations and Schinzel-Giedion syndrome




Acuna-Hidalfo R, et al. *PLoS Genet.* 2017 Mar 27;13(3):e1006683. doi: 10.1371

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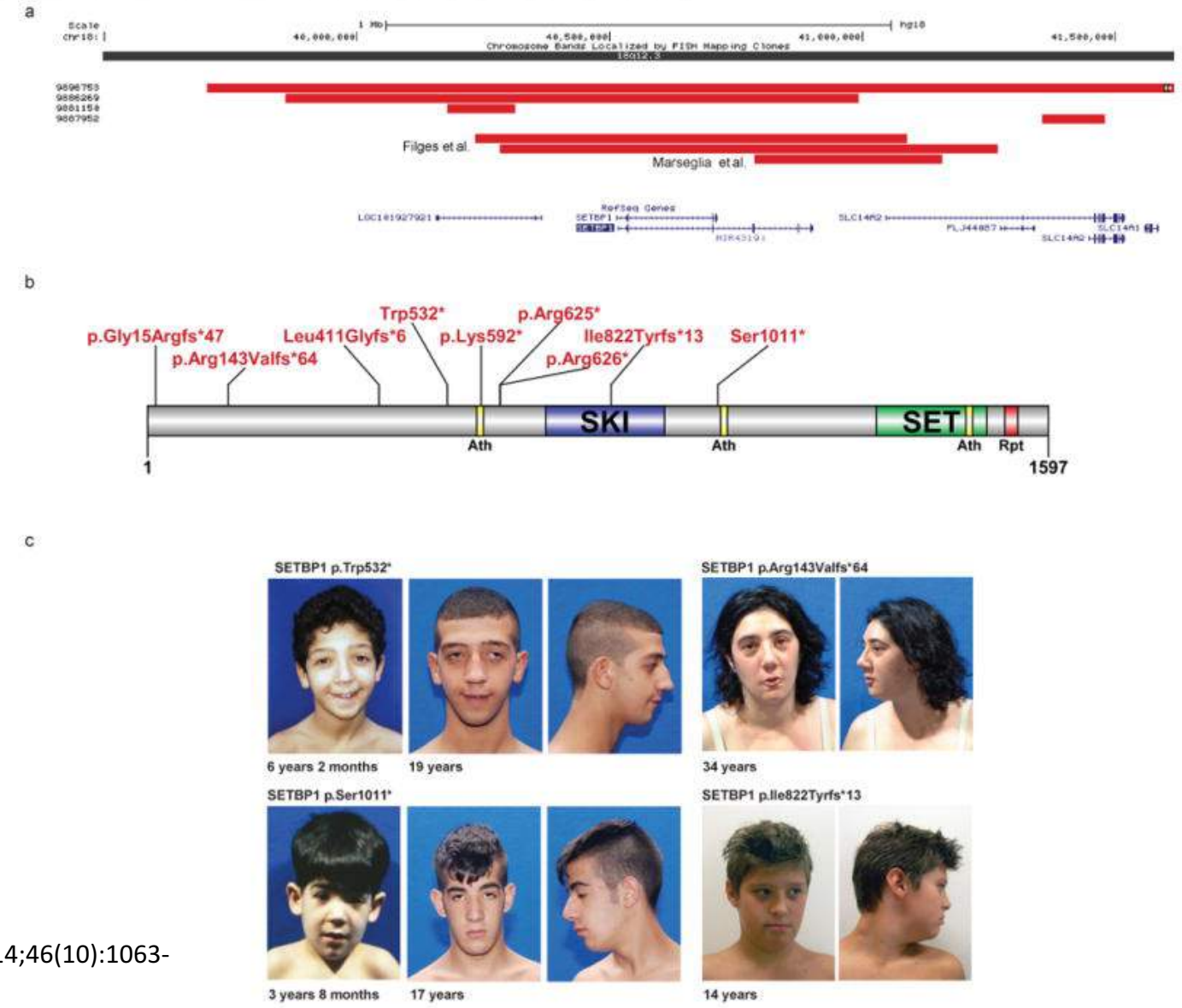
# Other SETBP1 mutations




Coe BP, et al. *Nature genetics*. 2014;46(10):1063-1071. doi:10.1038/ng.3092.

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**Table 4 Brief phenotypic description of cases with *SETBP1* loss-of-function variants**

| Case | Age at examination | Sex | Alteration | Inheritance | Cognitive | Hyperactive or ADHD | Social difficulties | Other behavioral difficulties | Speech delay | Motor delay | Facial dysmorphism | Seizures or EEG abnormalities |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DNA03-00335 | 14 years | M | p.Ile822Tyrfs*13 | *De novo* | Normal IQ | | | + | + | + | + | |
| DNA-008897 | 73 years | M | p.Leu411Glyfs*6 | | Profound ID | | + | + | + | + | + | |
| Troina 1274 | 19 years | M | p.Trp532* | *De novo* | Severe ID | | | + | + | + | + | – |
| Troina 1512 | 17 years | M | p.Ser1011* | *De novo* | Mild ID | + (3y 8m) | + | | + | + | + | – |
| Troina 3097 | 34 years | F | p.Arg143Valfs*64 | | Severe ID | | | | + | + | + | + |
| DNA11-21308Z | 36 years | F | p.Arg625* | | Mild to moderate ID | + | + | + | + | + | + | |
| DNA11-19324Z | 9 years | F | p.Arg626* | | 2- to 2.5-year delay at 9 years old | | | | + | – | + | – |
| DNA08-08272 | 9 years | M | p.Gly15Argfs*47 | | Mild ID | + | | + | + | + | + | + |
| Rauch *et al.* | 13 years | F | p.Lys592* | | Mild ID | + | + | | + | – | + | |
| 9886269 | 5 years | M | Deletion | *De novo* | Global delay | + | | | + | + | + | + |
| Marseglia *et al.* | 15 years | M | Deletion | *De novo* | Mild ID | + | + | + | + | + | + | + |
| Filges *et al.* pt. 1 | 7 years | M | Deletion | *De novo* | Moderate ID | | | | + | + | + | + |
| Filges *et al.* pt. 2 | 4 years | M | Deletion | *De novo* | | | | | + | + | + | |

ID, intellectual disability; EEG, electroencephalogram; M, male; F, female.

**Table 1. Major clinical findings in 51 individuals with germline mutations in *SETBP1*.** NA stands for "Not Assessed".

| Residue affected in SETBP1 | E862 | S867 | D868 | S869 | G870 | I871 | T873 | All degron-affecting mutations (868–871) | |
|---|---|---|---|---|---|---|---|---|---|
| Male(M):female(F) | 1F | 2F | 8F:7M | 2F | 5F: 10M | 6F:9M | 1M | 21F:26M | |
| **Craniofacial findings** | | | | | | | | | |
| Microcephaly | 1/1 | 1/2 | 10/12 | 1/2 | 10/13 | 8/11 | 0/1 | 29/39 | 74.4% |
| SGS facial gestalt | 0/1 | 2/2 | 15/15 | 2/2 | 15/15 | 15/15 | 0/1 | 47/47 | 100.0% |
| **Congenital anomalies** | | | | | | | | | |
| Hydronephrosis | 0/1 | 0/2 | 15/15 | 2/2 | 14/15 | 14/15 | 0/1 | 45/47 | 95.7% |
| Genital abnormalities | 1/1 | 0/2 | 14/15 | 1/2 | 14/15 | 12/13 | 0/1 | 41/45 | 91.1% |
| Cardiac defects | 0/1 | 1/2 | 10/15 | 1/2 | 4/13 | 5/13 | 0/1 | 20/43 | 46.5% |
| Tracheo/laryngomalacia | 0/1 | 0/1 | 3/4 | 0/2 | 3/8 | 2/2 | 0/1 | 8/16 | 50.0% |
| Inguinal hernia | 0/1 | 0/1 | 2/4 | 0/2 | 6/8 | 0/1 | 0/1 | 8/15 | 53.3% |
| Alacrima | 0/1 | 2/2 | 6/10 | 0/2 | 7/9 | 6/6 | 0/1 | 19/27 | 70.4% |
| **Neurodevelopmental anomalies** | | | | | | | | | |
| Developmental delay | 1/1 | 2/2 | 14/14 | 2/2 | 13/13 | 10/10 | 1/1 | 39/39 | 100.0% |
| Seizures | 0/1 | 2/2 | 15/15 | 2/2 | 13/14 | 12/13 | 0/1 | 42/44 | 95.5% |
| Spasticity and/or hypertonia | 0/1 | 1/1 | 4/4 | 1/2 | 8/10 | 4/4 | 1/1 | 17/20 | 85.0% |
| Vision impairment | 1/1 | 1/1 | 7/10 | 1/2 | 7/8 | 5/6 | 0/1 | 20/26 | 76.9% |
| Hearing impairment | 0/1 | 0/1 | 9/9 | 0/1 | 7/8 | 8/9 | 0/1 | 24/27 | 88.9% |
| Progressive failure to thrive | 0/1 | 0/1 | 10/11 | 1/2 | 13/13 | 8/9 | 0/1 | 32/35 | 91.4% |
| **Brain MRI/CT** | | | | | | | | | |
| Ventriculomegaly | 0/1 | NA | 6/12 | 2/2 | 11/14 | 7/14 | 0/1 | 26/42 | 61.9% |
| Underdeveloped corpus callosum | 0/1 | NA | 9/11 | 0/2 | 12/13 | 10/12 | 0/1 | 31/38 | 81.6% |
| Cortical atrophy or dysplasia | 0/1 | NA | 8/10 | 0/2 | 7/10 | 3/11 | 1/1 | 18/33 | 54.5% |
| Choroid plexus cysts | 0/1 | NA | 2/9 | 0/2 | 8/10 | 3/10 | 0/1 | 13/31 | 41.9% |
| **Radiological findings** | | | | | | | | | |
| Sclerotic base of skull or mastoid | NA | NA | 9/10 | 0/1 | 5/5 | 5/7 | NA | 19/23 | 82.6% |
| Hypoplastic distal phalanges | 0/1 | NA | 8/9 | 0/1 | 8/9 | 5/6 | NA | 21/25 | 84.0% |
| Broad ribs | 0/1 | NA | 10/13 | 2/2 | 6/7 | 9/9 | NA | 27/31 | 87.1% |
| Hypoplastic/underossified pubic bones | 0/1 | NA | 6/7 | 2/2 | 4/5 | 6/6 | NA | 18/20 | 90.0% |
| **Tumors** | 0/1 | 0/2 | 5/11 | 0/2 | 1/11 | 1/9 | 0/1 | 7/33 | 21.2% |

https://doi.org/10.1371/journal.pgen.1006683.t001

Acuna-Hidalfo R, et al. *PLoS Genet.* 2017 Mar 27;13(3):e1006683. doi: 10.1371

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# Variants in SETBP1 Mutations Observed

| Protein Change | Number of Individuals |
|---|---|
| His523LeuFs*32 | 1 |
| Gly588AspFs*42 | 1 |
| Arg589* | 1 |
| Ser608AlaFs*22 | 1 |
| Asp874Gly (uncertain) | 1 |

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# Developmental and Behavioral Diagnoses
## (5 children)

| Condition | Number of Children |
|---|---|
| Developmental Delay and Intellectual  Disability | 5 |
| Language Impairment | 5 |
| Autism Spectrum Disorder | 1 |
| ADHD | 4 |

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# Parent report of medical history

(5 individuals, ages 6-14 years)

# Newborn Birth Issues

| Medical Condition | Number of Children |
|---|---|
| Respiratory Distress | 1 |
| Jaundice | 2 |
| Requiring Phototherapy | 1 |

# Newborn Issues

| Medical Condition | Number of Children |
|---|---|
| Poor suck | 3 |
| Low tone/Floppy | 3 |
| Feeding difficulties | 2 |

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# Neurological Issues

| Medical Condition | Number of Children |
|---|---|
| Motor | |
| Uncoordinated | 1 |
| Low muscle tone | 4 |
| Small head size | 1 |
| Cerebral Palsy | 1 |
| Tremor | 1 |

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# Vision Problems

| Medical Condition | Number of Children |
|---|---|
| Nearsighted, Astigmatism | 1 |
| Farsighted | 1 |

* Corrected with glasses

# Gastrointestinal Issues

| Medical Condition | Number of Children |
|---|---|
| Reflux (heartburn) | 3 |
| Constipation | 1 |
| Diarrhea | 2 |

# Infections

| Medical Condition | Number of Children |
|---|---|
| Ear infections | 3 |
| Requiring PE tubes | 2 |

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# Lung Issues

| Medical Condition | Number of Children |
|---|---|
| Asthma | 1 |

# Heart Issues

| Medical Condition | Number of Children |
|---|---|
| Aortic Regurgitation | 1 |

# Kidney/Urinary Issues

| Medical Condition | Number of Children |
|---|---|
| Renal agenesis, Hydronephrosis | 1 |

# Genital Issues

| Medical Condition | Number of Children |
|---|---|
| Undescended Testicles | 3 |
| Hypospadias | 1 |

# Endocrinological Issues

| Medical Condition | Number of Children |
|---|---|
| Difficulty gaining weight | 2 |
| Short stature | 1 |

# Bone Issues

| Medical Condition | Number of Children |
|---|---|
| Scoliosis | 1 |

# Surgeries

| Medical Condition | Number of Children |
|---|---|
| Tonsillectomy | 1 |
| PE Tubes/Adenoidectomy | 2 |
| Cleft repair | 1 |
| Orchiopexy | 2 |
| Hypospadias repair | 1 |

# Special Diets

| Medical Condition | Number of Children |
|---|---|
| Gluten Free | 3 |
| Casein Free | 1 |
| Lactose Free | 2 |
| Specific Food Allergy | 1 |

# Current Medication Use
## (4 individuals)

| Medication | Number of Children |
|---|---|
| ADHD | 4 |
| Stimulants (Ritalin, Metadate, Focalin) | 3 |
| Non Stimulants (Clonidine, Guanfacine) | 2 |
| Antiepileptic (for tremors) | 1 |
| Reflux | 1 |
| Constipation | 1 |

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# Response to ADHD Medication

- Four children, ages 7-14 reported being on medication for ADHD
- Of these four, one indicated that **Metadate** was the most effective medication in treating his ADHD symptoms
- Another identified **Focalin** as the most effective ADHD medication tried
- Other medications taken long term (~3 years or more) include **Ritalin** and **Intuniv**. Longer-term use may indicate some success in the treatment of ADHD symptoms.

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# Range of Adaptive Functioning
# Based on parent report on Vineland Adaptive Behavior Scales-II
# Children ages 6 to 14 years

| Domain | Range of Functioning Level | Representative Skills |
|---|---|---|
| Expressive Language | 18 mos<br>To<br>5 years | Says one-word requests<br><br>Tells about experiences in detail |
| Self-Care | 2 ½ years<br>To<br>4 ½ years | Can use the toilet<br><br>Buttons small buttons correctly |

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# Unanswered Questions

- Some topics we hope to be able to more fully address over time:
  - Changes with age and long-term prognosis for individuals with a SETBP1 mutation
  - Acquisition and level of language
  - Developmental milestones
  - More details about effective treatments
  - The presence of autistic traits or “autism-like” features in the absence of a full ASD diagnosis
  - Sensory issues

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# Summary

- Developmental delay
- Language impairment
- ADHD
- Low muscle tone
- Undescended testicles
- Intestinal reflux

- Notable absence of seizures, regression, cancer

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# Gene Therapy & Genome Editing

- Promising individualized medicine

- Are we there yet?
  - Not quite for most conditions
  - Recent developments in research advanced the field

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# Gene editing

- Edit the genetic code making a new generation of medical treatments possible.
- Can be done precisely but there are challenges.
- New and untested in humans

# What can families do?

- Organize the families: family networking/Facebook page
- Family meeting
- Standardized clinical data collection
  - Genetic test reports
  - Medical history interview
  - Medical record review
  - Vineland
  - Sample biorepository (blood/skin) for researchers

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# Next steps

- Increase the number of identified individuals and confirm the correct diagnosis
  - Work other medical conditions doing the same thing
- Care until the cure
  - Understand the natural history and document it well
  - Learn practical tips from each other
- Understand molecular mechanism
- Develop reagents to enable researchers and make the reagents widely available
  - Cell lines
  - Mice
- Determine if the condition is reversible and if so when
- Learn from other diseases

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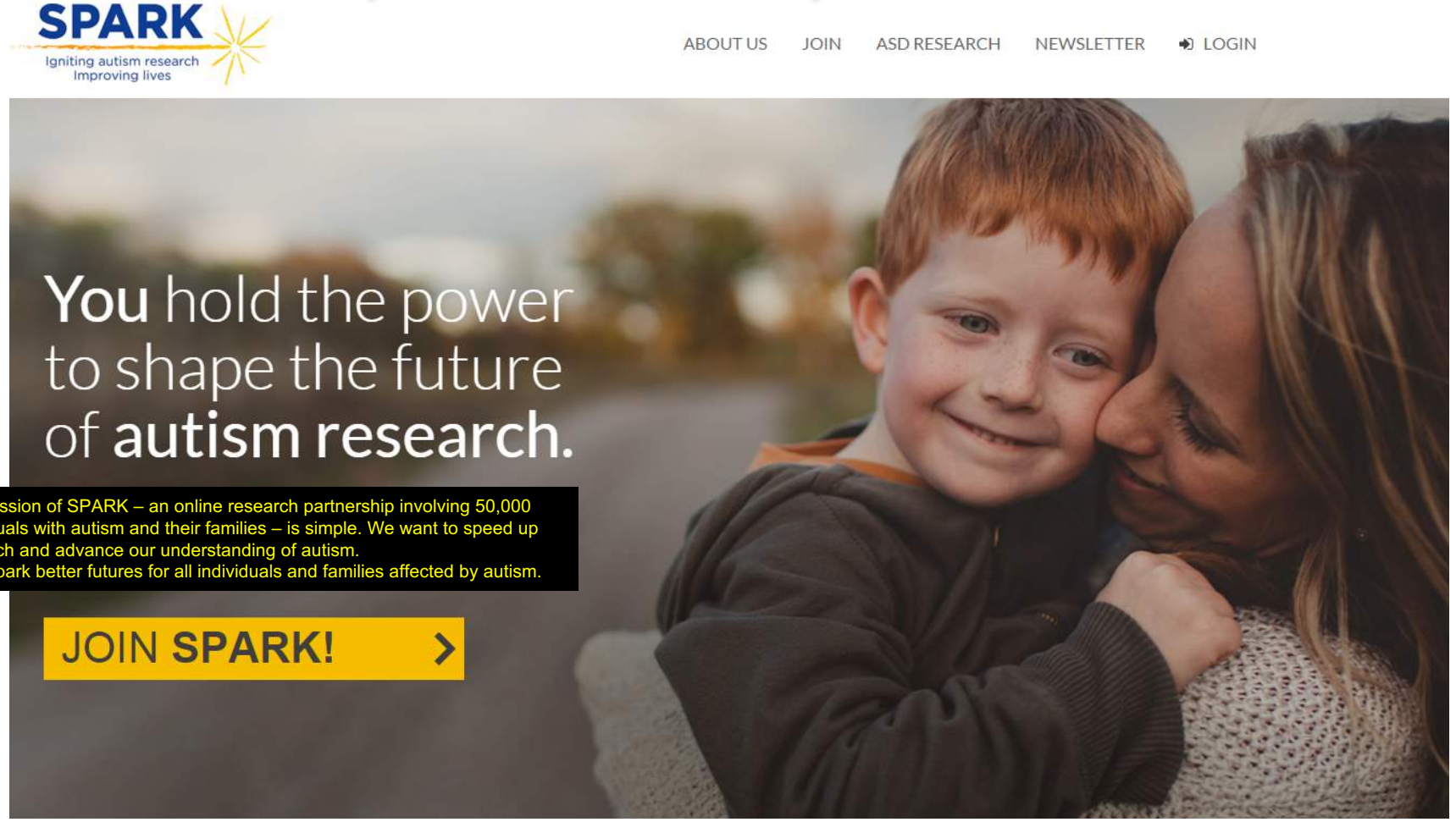
# SPARK will help to identify more families




**SPARKforAutism.org**

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# Questions?

# Medical Management of Neurodevelopmental Concerns in SETBP1 Disorder

**Siddharth Srivastava, M.D.**

**siddharth.srivastava@childrens.harvard.edu**

**Department of Neurology**

**Boston Children's Hospital**

**Simons VIP SETBP1 Virtual Family Meeting**

**January 13, 2018**

# Outline

- Background
- Motor Impairment
- Intellectual Disability
- Language Disorders
- Attention Deficit Hyperactivity Disorder
- Anxiety/Depression
- Aggression/Self-Injury
- Restrictive, Repetitive Behaviors
- Conclusions

# Warnings

- Non-medication interventions can be effective too, but I will try to focus on medications for this talk

- The information presented here is a combination of anecdotal and observational data from individuals  with SETBP1 Disorder, and extrapolated data from other neurodevelopmental disorders

- In general, there is a great need for **evidence-based** research on neurobehavioral interventions for SETBP1 Disorder

# Background

# SETBP1 Disorder

- SETBP1 Disorder is associated with distinct facial features and full spectrum of neurodevelopmental disorders
  - intellectual disability
  - attention deficit hyperactivity disorder
  - autism spectrum disorder
  - hypotonia
  - delayed motor development

# Significance

- Challenging behaviors and developmental concerns can affect the **quality of life** for individuals with SETBP1 Disorder and their families

- Addressing these concerns early on – through medications, therapies, or other interventions – may help optimize long-term neurodevelopmental outcomes

**Q3 - Is you child currently taking medication to manage developmental or behavioral challenges?**

56%

N = 5/9

# Development

Motor | Language | Socialization | Cognition | Behavior/Mood

***Cerebral Palsy***
***Hypotonia****
***Dyspraxia****

***Language Disorder****

***Autism***

***Intellectual Disability****

***ADHD****
***Anxiety/Depression****
***Aggression/Self-Injury****
***Repetitive Behaviors****

# Motor Impairment

# Motor Impairment

- Hypotonia
  - Hypotonia refers to low muscle tone
  - It is a non-specific finding

- Developmental coordination disorder (DCD) / Dyspraxia
  - DCD affects one's ability to  learn and execute coordinated motor skill
  - DCD significantly impacts a child's functioning
  - These difficulties are not due to cognitive/visual impairment

# Motor Impairment in SETBP1 Disorder

**Q1 - Which developmental/behavioral target symptoms are most important for medicational therapy to improve in your child? Select all that apply.**

| Answer | % | Count |
|---|---|---|
| Lack of effective communication | 10.87% | 5 |
| Sensory integration issues | 4.35% | 2 |
| Learning deficits | 13.04% | 6 |
| Sleep disturbances | 4.35% | 2 |
| Motor control/coordination challenges | 13.04% | 6 |
| Seizure control | 4.35% | 2 |
| Aggressive, self-injurious, and/or explosive behavior | 4.35% | 2 |
| Processing speed | 13.04% | 6 |
| Anxiety | 6.52% | 3 |
| Hyperactive, impulsive, and/or inattention behaviors | 15.22% | 7 |
| Restricted, repetitive behaviors | 4.35% | 2 |
| Depression and/or bipolar symptoms | 2.17% | 1 |
| Other (please specify) | 4.35% | 2 |
| Total | 100% | 46 |

67%

N = 6/9

# Motor Impairment in SETBP1 Disorder

“Global motor planning difficulties - Every aspect of my son’s life is impacted by his motor planning difficulties. It has impacted his ability to learn to sit up, crawl, walk, sign language, talk, run, play games, write, and learn any new skill.”

# Motor Impairment Treatment

**DCD / Dyspraxia**

- Occupational therapy
- Speech/language therapy
- Physical therapy/hippotherapy
- Assistive technology

**Hypotonia**

- Physical therapy/hippotherapy

# Intellectual Disability (ID)

# Cognition

- Cognition refers to our innate problem-solving abilities
- IQ testing is one way of assessing cognitive abilities

# IQ Testing

| WISC-IV Scale | Score |
|---|---|
| Verbal Comprehension Index | 60 |
| Perceptual Reasoning Index | 60 |
| Working Memory Index | 70 |
| Processing Speed Index | 70 |
| Full Scale IQ | 65 |

**Developmental Age = (Full Scale IQ * Actual Age) / 100**

For example, a 5 year old with a full scale IQ of 65 will have thinking skills of a 3.25 year old [(5 * 65) / 100]

# ID

- ID is defined by the following:
  - Full scale IQ < 70
  - Corresponding impairment in self-help skills

- IQ is not necessarily static

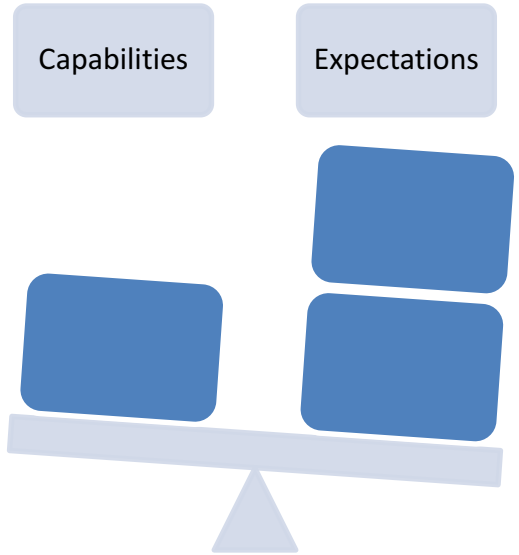
# ID in SETBP1 Disorder

- A wide range of ID can occur with SETBP1 Disorder
  - Mild: Full scale IQ 50 to 70
  - Moderate: Full scale IQ 35 to 50
  - Severe: Full scale IQ 20 to 35

- SETBP1 Disorder is non-progressive disorder

- There are no ID-specific treatments for SETBP1 Disorder

- An imbalance between academic expectations and intrinsic cognitive capabilities can create problems



# Language Disorders

# Language

Language affects our ability to interface with the rest of the world (e.g., socialize, communicate)

**Expressive Language**

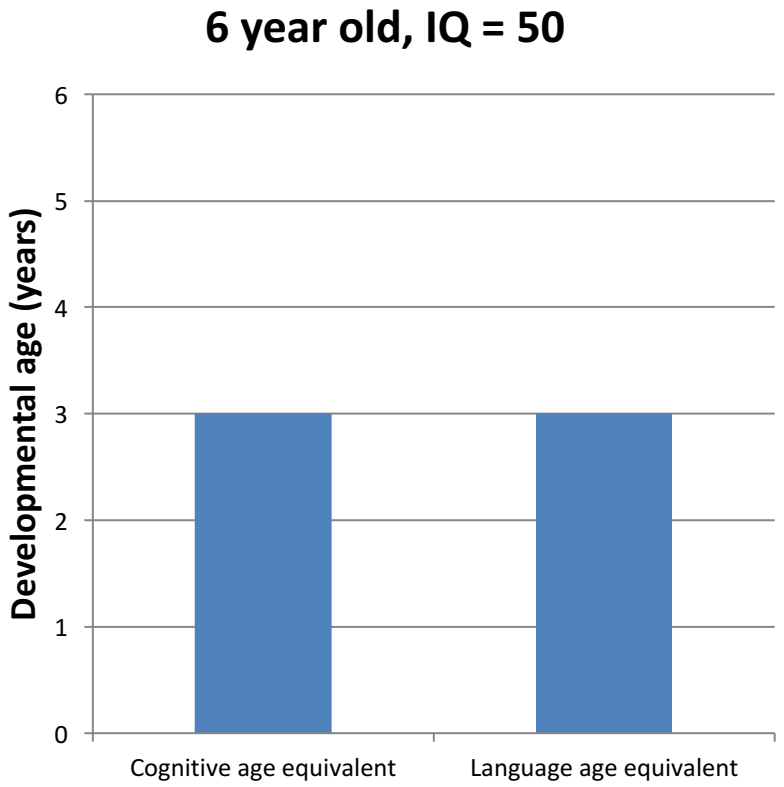
Ability to communicate

**Receptive Language**

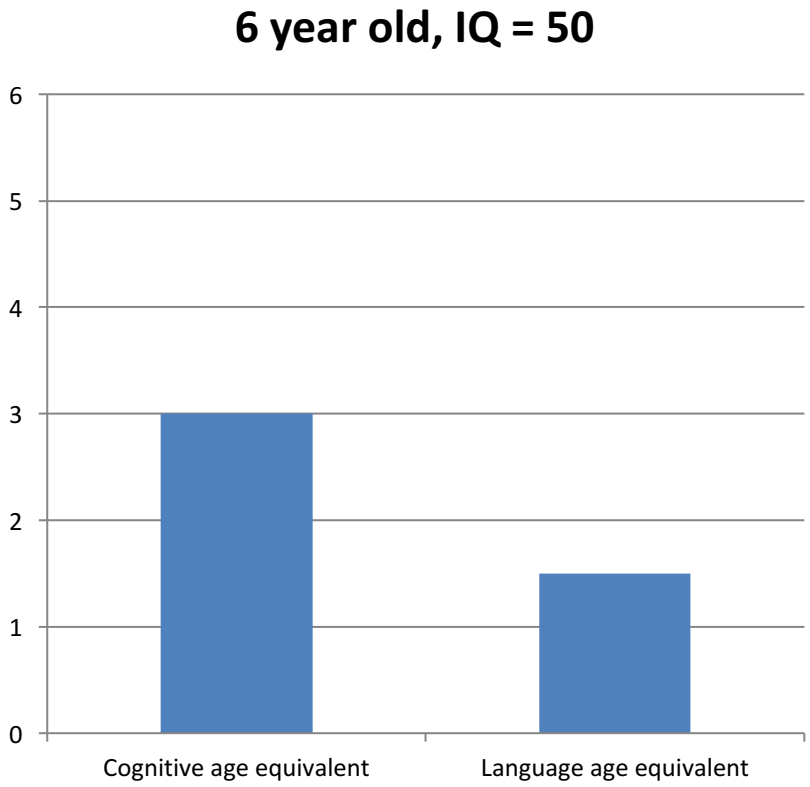
Ability to understand

# Language and Cognition

## Intellectual Disability




## Intellectual Disability PLUS Language Disorder



# Language in SETBP1 Disorder

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| Depression and/or bipolar symptoms | 2.17% | 1 |
| Other (please specify) | 4.35% | 2 |
| Total | 100% | 46 |

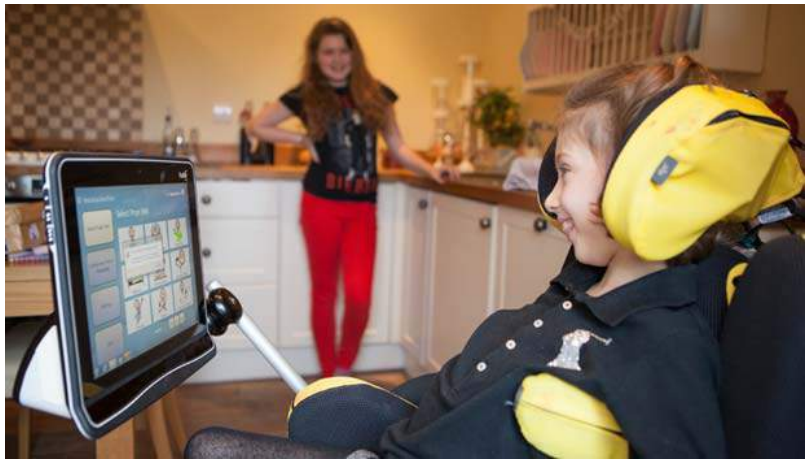
56%

N = 5/9

# Language Disorders Treatment

# AAC

- AAC refers to the use of special devices that allow children to communicate even in the absence of spoken speech
- These devices can be high tech or low tech
- AAC is especially useful for children who are non-verbal



# Attention Deficit Hyperactivity Disorder (ADHD)

# ADHD in SETBP1 Disorder

**Q1 - Which developmental/behavioral target symptoms are most important for medicational therapy to improve in your child? Select all that apply.**

| Answer | % | Count |
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| Anxiety | 6.52% | 3 |
| Hyperactive, impulsive, and/or inattention behaviors | 15.22% | 7 |
| Restricted, repetitive behaviors | 4.35% | 2 |
| Depression and/or bipolar symptoms | 2.17% | 1 |
| Other (please specify) | 4.35% | 2 |
| Total | 100% | 46 |

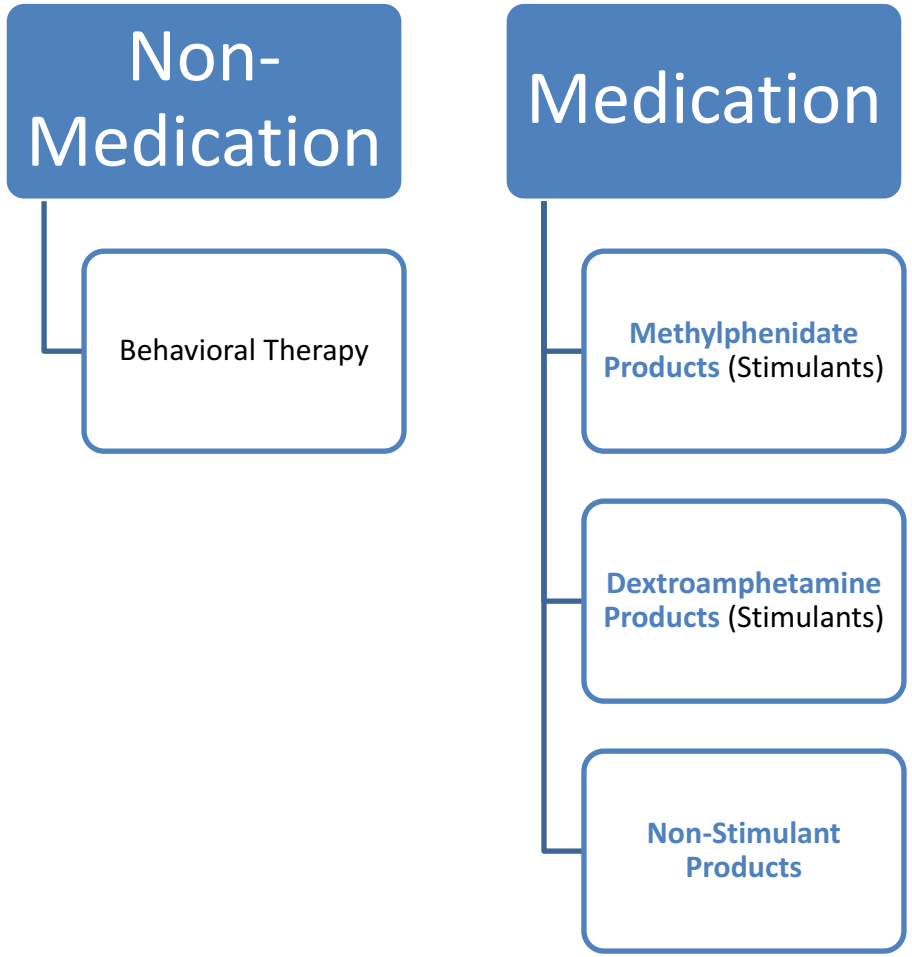
78%

N = 7/9

# ADHD

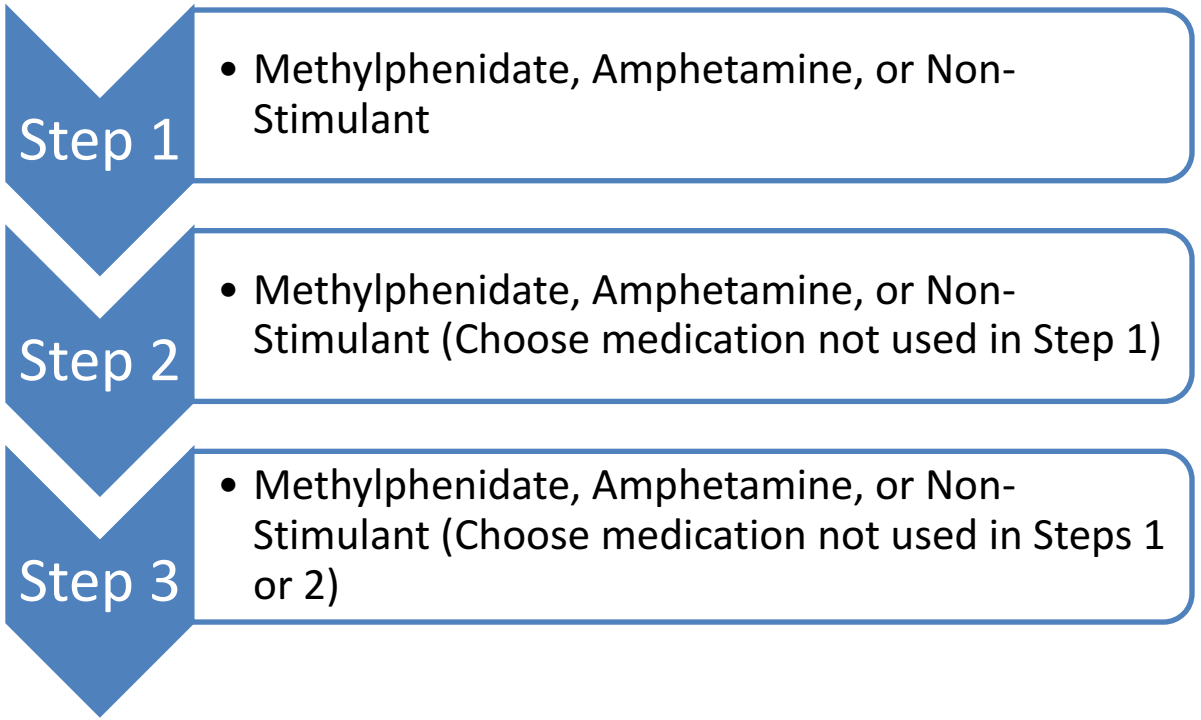
- ADHD is characterized by impairment of attention, distractibility, hyperactivity, and impulsivity
- Symptoms must be present in two or more settings (e.g., home, school)
- Symptoms must cause functional impairments (e.g., social, academic)

# ADHD Treatment



# ADHD Medications

## Treatment may require a trial-and-error approach



# ADHD Medications

- “Start low, go slow”
- Main side effects are decreased appetite, disrupted sleep
- Wait at least 1 week before deciding whether a new medication or dose change is ineffective

# ADHD Medications

| | Pill (can't crush/chew) | Capsule (can open up and sprinkle onto food) | Chewable Pill (can chew) | Liquid | Patch |
|---|---|---|---|---|---|
| **METHYLPHENIDATE PRODUCTS** | | | | | |
| Short Acting | Focalin<br>Ritalin | | Methylin Chewable | Methylin Solution | |
| Long Acting | Concerta<br>Ritalin SR | Focalin XR<br>Ritalin LA<br>Metadate CD | | Quillivant XR | Daytrana |
| **AMPHETAMINE PRODUCTS** | | | | | |
| Short Acting | Adderall | | | ProCentra | |
| Long Acting | Vyvanse<br>Dexedrine | Adderall XR | | | |
| **NON-STIMULANT PRODUCTS** | | | | | |
| Short Acting | Clonidine<br>Guanfacine | | | | |
| Long Acting | Gunfacine ER<br>Clonidine ER<br>Atomoxetine | | | | Clonidine patch |

# ADHD Medications

**Q9 - If your child had an improvement, please provide the specific medication name and a description of the improvements:**

"[stimulants]. These medications improve his hyperactive and impulsive behavior. "

"**Adderall**. Was on this for several years, kept him calm and focused"

"**Ritalin** and **Intuniv**. Better attention and focus at school. No real impact at home. Intuniv is very hard to swallow every morning."

From 4 individuals (7-14) in the Simons VIP registry, 1 indicated **Metadate** was most effective, and another indicated that **Focalin** was most effective

**Q5 - If your child had an adverse effect or poor response, please provide the specific medication name and description of adverse effect or poor response:**

"[stimulants]. He metabolizes them too fast. The dosage doesn't last as long as it should."

"Hyper sensibility with Vyvanse and Adderall"

# Anxiety/Depression

# Anxiety/Depression in SETBP1 Disorder

**Q1 - Which developmental/behavioral target symptoms are most important for medicational therapy to improve in your child? Select all that apply.**

| Answer | % | Count |
|---|---|---|
| Lack of effective communication | 10.87% | 5 |
| Sensory integration issues | 4.35% | 2 |
| Learning deficits | 13.04% | 6 |
| Sleep disturbances | 4.35% | 2 |
| Motor control/coordination challenges | 13.04% | 6 |
| Seizure control | 4.35% | 2 |
| Aggressive, self-injurious, and/or explosive behavior | 4.35% | 2 |
| Processing speed | 13.04% | 6 |
| Anxiety | 6.52% | 3 |
| Hyperactive, impulsive, and/or inattention behaviors | 15.22% | 7 |
| Restricted, repetitive behaviors | 4.35% | 2 |
| Depression and/or bipolar symptoms | 2.17% | 1 |
| Other (please specify) | 4.35% | 2 |
| Total | 100% | 46 |

33%

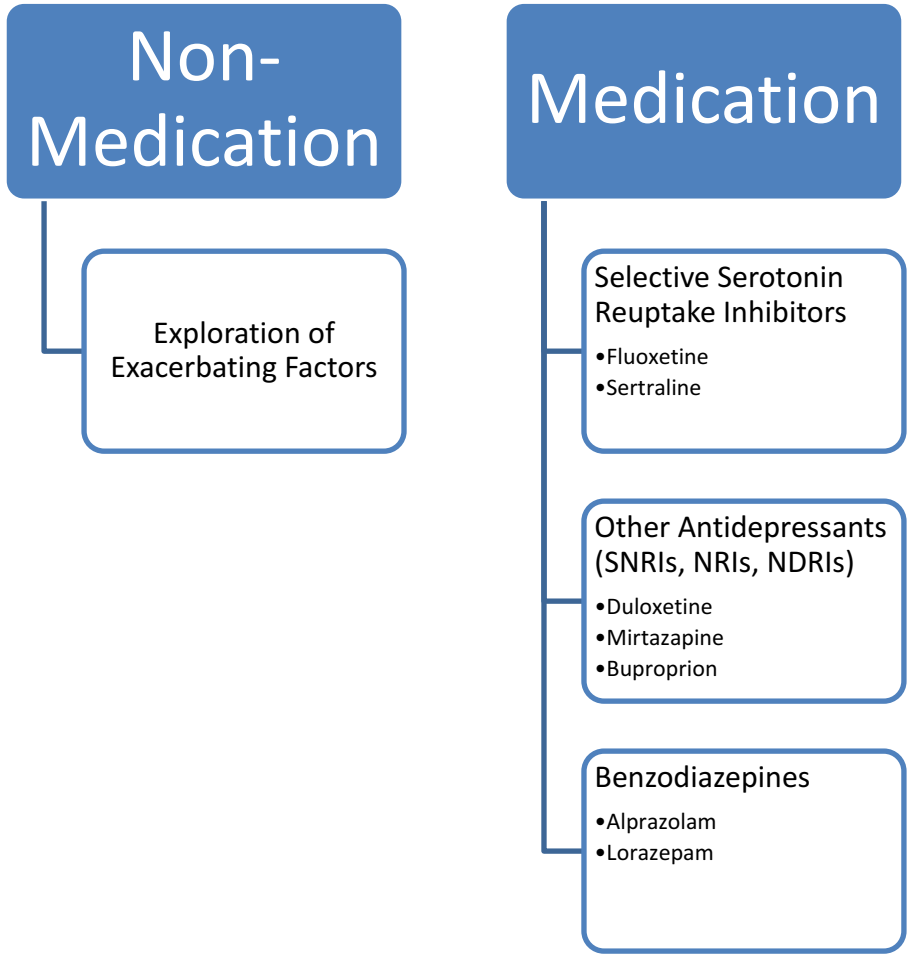
N = 3/9

# Anxiety/Depression

- Symptoms can include irritability, excessive worry, perseveration, social avoidance

- Anxiety and depression can be difficult to recognize, especially with increasing levels of intellectual disability associated with SETBP1 Disorder

# Anxiety/Depression Treatment



# Anxiety/Depression Medications

- A low-dose of a **selective serotonin reuptake inhibitors (SSRI)** may help anxiety and mood issues in SETBP1 Disorder

**CAVEAT:** SSRIs can lead to **behavioral activation** and **worsening agitation** in some individuals

- It may be prudent to avoid benzodiazepines for the management of anxiety due to risk of dependency and paradoxical agitation

# Aggression/Self-Injury

# Aggression/Self-Injury in SETBP1 Disorder

**Q1 - Which developmental/behavioral target symptoms are most important for medicational therapy to improve in your child? Select all that apply.**

| Answer | % | Count |
|---|---|---|
| Lack of effective communication | 10.87% | 5 |
| Sensory integration issues | 4.35% | 2 |
| Learning deficits | 13.04% | 6 |
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| Depression and/or bipolar symptoms | 2.17% | 1 |
| Other (please specify) | 4.35% | 2 |
| Total | 100% | 46 |

22%

N = 2/9

# Aggression/Self-Injury

- Aggressive/self-injurious behaviors include head-banging, hand-biting, and excessive scratching

- They can be a source of significant parental distress for families affected by SETBP1 Disorder

# Aggression/Self-Injury Treatment

- Aggressive, self-injurious behaviors require a full behavioral assessment  in order to identify triggers

- Sometimes undiagnosed medical problems – such as reflux, dental issues – can worsen aggression/self-injury

# Aggression/Self-Injury Medications

- **Second-generation neuroleptics (such as risperidone)** may be an option for SETBP1 Disorder

- Other second-generation neuroleptics to consider include aripiprazole, quetiapine, and olanzapine

- In some individuals, a mood stabilizer (valproate, lithium) may be beneficial, though the data is limited

# Aggression/Self-Injury Medications

**CAVEAT:** Second-generation neuroleptics are potent medications, with potential for serious side effects, such as **metabolic syndrome** and **weight gain**

- “Abilify (aripiprazole). Child became very, very violent”
- “with too much risperidone he became drowsy and absent”
- “Risperidone: asks for food all day”

# Restrictive, Repetitive Behaviors

# Restrictive, Repetitive Behaviors in SETBP1 Disorder

**Q1 - Which developmental/behavioral target symptoms are most important for medicational therapy to improve in your child? Select all that apply.**

| Answer | % | Count |
|---|---|---|
| Lack of effective communication | 10.87% | 5 |
| Sensory integration issues | 4.35% | 2 |
| Learning deficits | 13.04% | 6 |
| Sleep disturbances | 4.35% | 2 |
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| Other (please specify) | 4.35% | 2 |
| Total | 100% | 46 |

22%

N = 2/9

# Restrictive, Repetitive Behaviors

- Repetitive behaviors include stereotyped motor movements, insistence on sameness, and compulsive and ritualistic behaviors
- Repetitive behaviors occur with higher frequency in autism and severe intellectual disability, which can occur in SETBP1 Disorder
- Social demand and the presence of anxiety may worsen repetitive behaviors

# Restrictive, Repetitive Behaviors Medications

- A low-dose **SSRI (e.g. fluoxetine, sertraline)** may help repetitive behaviors in SETBP1 Disorder

**CAVEAT:** SSRIs can lead to **behavioral activation** and **worsening agitation** in some individuals

- For difficult cases leading to significantly disruptive behaviors, one could consider augmenting an SSRI with a second-generation neuroleptic (e.g. risperidone)

# Conclusions

- There is a spectrum of neurodevelopmental disorders associated with SETBP1 Disorder:
  - Intellectual Disability
  - ADHD
  - Language Disorder
  - Autism
  - Hypotonia
  - Motor impairment

- Identifying the target behavioral symptom(s) can help tailor medication management:
  - Hyperactivity
  - Anxiety/Depression
  - Aggression/Self-Injury
  - Repetitive Behaviors

- There is a great need to study what medications work and don’t work for individuals with SETBP1 Disorder

# SETBP1 Clinic

- Location: Boston Children's Hospital

- Goals:
  1. Optimize long-term neurodevelopmental outcomes
  2. Coordinate specialty care across multiple disciplines

- The clinic would help address:
  - neurological concerns (e.g., seizures)
  - developmental/behavioral concerns (e.g., autism, intellectual disability, and behavioral challenges)
  - educational concerns
  - questions about treatments (e.g., applied behavior analysis therapy and other developmental services)

- The clinic would form partners with physicians in other departments for referrals and coordination of care

- There would be opportunities to participate in research including bio banking

Boston Children's Hospital
Until every child is well™

# Acknowledgements


- Hayley Oyler and the SETBP1 families
- Dr. Wendy Chung and the Simons VIP Project
- Dr. Mustafa Sahin

# Questions?