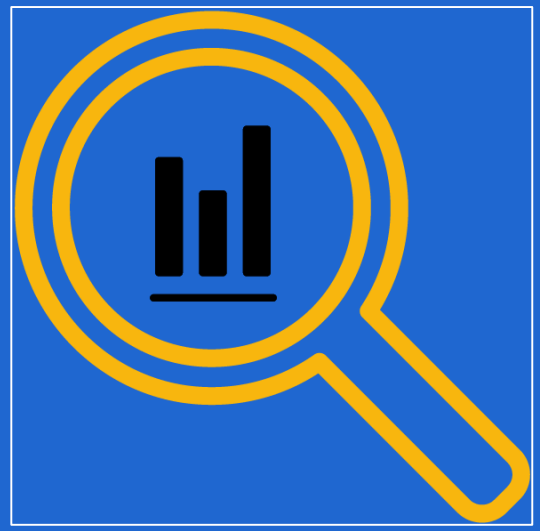
SIMONS SEARCHLIGHT

SLC6A1 Meeting

Jennifer Bain, M.D., Ph.D.

December 5, 2019

What is the goal of Simons Searchlight?



Collect detailed medical and behavioral histories along with blood and saliva samples

Synthesize the information and share results back to families

Freely share data and samples with qualified researchers

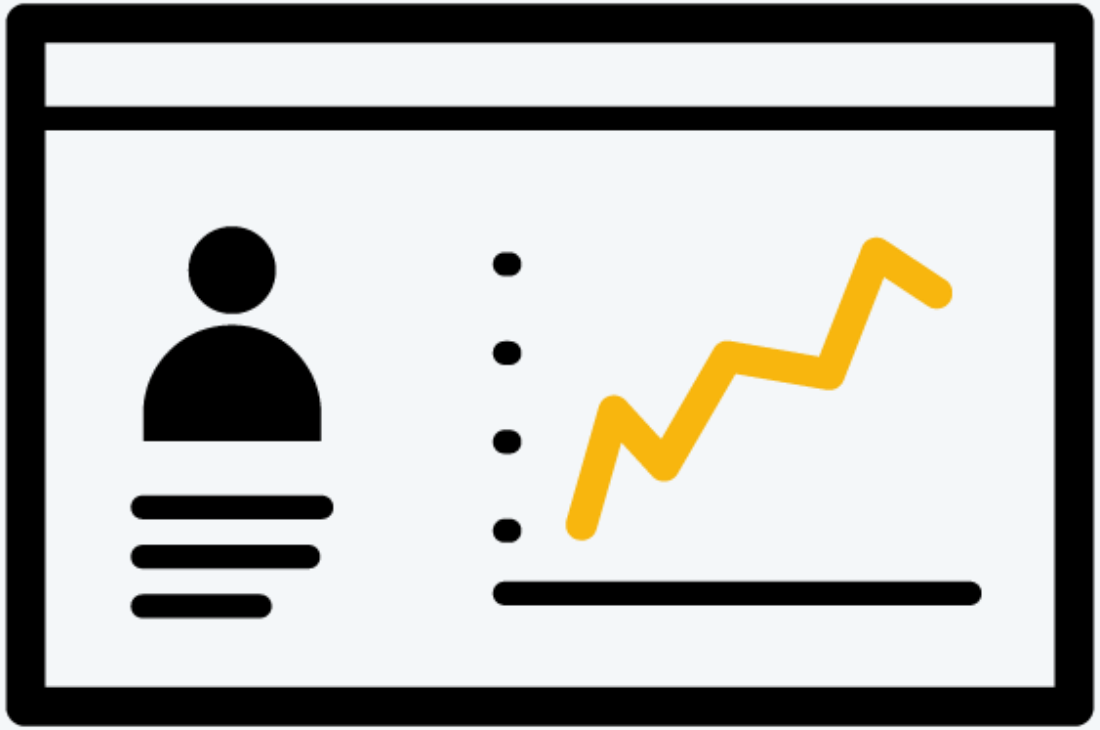
Connect participants around the world

Promote better understanding of these genetic changes

SIMONS SEARCHLIGHT

How has Simons Searchlight changed over time?

- The study began in 2011 and focused on families living with **one** specific genetic change.
- The first participants traveled to study centers to provide medical, behavioral and neuropsychiatric data to researchers.
- Today, families living with one of more than **170** different genetic changes can provide their data to researchers from home.



Data Collection

What information is collected?	Whose information is collected?		
	Individuals with the genetic change	Parents	Siblings
Medical records			
• Clinical Genetic Lab Results	X	X	X
Phone Interviews			
• Medical History Interview	X		
• Previous Diagnosis interview	X		
• Adaptive functioning interview – Vineland Adaptive Behavior	X		
Online surveys			
• Seizure History	X		
• Background History	X		
• Child/Adult Behavior Checklist	X	X	X
• Social Responsiveness Scale	X	X	X
• Social Communication Questionnaire	X		X
• Other surveys in development	X		

Simons Searchlight SLC6A1 Registry

Simons Searchlight Individuals with SLC6A1 Mutation

- 7 VUS and 1 with additional variant in PTPN11

Variants in SLC6A1 observed (n=40)

Missense mutations	
Arg44Gln	Ala288Val (2)
Arg44Trp	Gly307Arg
Glu101Gly	Asn327Ser
Gln106Arg	Ser331Gly (2)
Gly111Arg (2)	Val342Met (2)
Leu251Pro	Gly362Arg (2)
Ser295Leu	Val511Met
Gly297Arg	Trp532Ter
Phe297Arg	

Likely gene disrupting mutations
Val115Tyrfs*22
Gln291*
Leu408Trpfs*26
Arg419Alafs*15
Trp532*

Deletions
Leu390 - Leu392 del
Phe294 del
Thr217_Ile220del
Intragenic deletion

Splice site mutations
IVS4-2A>C
1695+1G>A

VUS	
Ala357Thr	953+13A>C (2)
Gly78Ala	
Asp482Glu	
Ala334Ser	
Phe386del	

Simons Searchlight
SLC6A1
Medical History Data

27 individuals

Age 20 months through adulthood

* 4 VUS and 1 PTPN11 not included in the data

Common Developmental and Behavioral Diagnoses in SLC6A1 participants (n=27)

Condition	Percent of individuals (n)
Intellectual disability/ developmental delay*	81% (22)
Autism spectrum disorder	30% (8)
Regression due to seizures	22% (6)
Attention deficit/hyperactivity disorder	19% (5)
Obsessive compulsive disorder	7% (2)
Anxiety	7% (2)
Oppositional defiant disorder	7% (2)
Dysthymia	4% (1)
No psychiatric or behavioral diagnosis	4% (1)

* 13 of whom have language impairment/disorder or speech delay

Eye, Vision, & Hearing Problems

Condition	Percent of individuals (n)
Near sighted	15% (4)
Strabismus (crossed eyes)	11% (3)
Astigmatism	7% (2)
Other (not specified)	7% (2)
Hearing problem	7% (2)

Neurological Issues

Condition	Percent of individuals (n)
Hypotonia	78% (21)
Movement disorders (e.g. tremor, ataxia)	56% (15)
Clumsy	15% (4)
Hypertonia	7% (2)
Macrocephaly	7% (2)
Microcephaly	7% (2)
Tics	4% (1)

Seizure History

Condition	Percent of individuals (n)
Seizures	78% (21)
Absence	59% (16)
Drop attacks	41% (11)
Myoclonic	33% (9)
Febrile seizures	22% (6)
Simple partial	4% (1)
Infantile spasms	4% (1)
Generalized tonic-clonic	4% (1)

- Age of seizure onset: 5 months - 2 years
- Most effective medications reported in a subset of 9: valproate (2), clobazam, zarontin
- Allergy reported to Lamictal (3)

Gastrointestinal Issues

Condition	Percent of individuals (n)
Constipation	30% (8)
Gastric reflux (heartburn)	19% (5)
Diarrhea	4% (1)

Infections

Condition	Percent of individuals (n)
Otitis media (middle ear infections)	59% (16)
Requiring ear tubes	15% (4)
Pneumonia	11% (3)
Urinary tract infection	4% (1)

Respiratory Issues

Condition	Percent of individuals (n)
Asthma	7% (2)

Growth, Hormone, and genital Issues

Condition	Percent of individuals (n)
Difficulty growing/gaining weight	4% (1)
Hypothyroidism (underactive thyroid)	4% (1)
Undescended testes	4% (1)
Penis chordae	4% (1)
Ovarian cysts	4% (1)

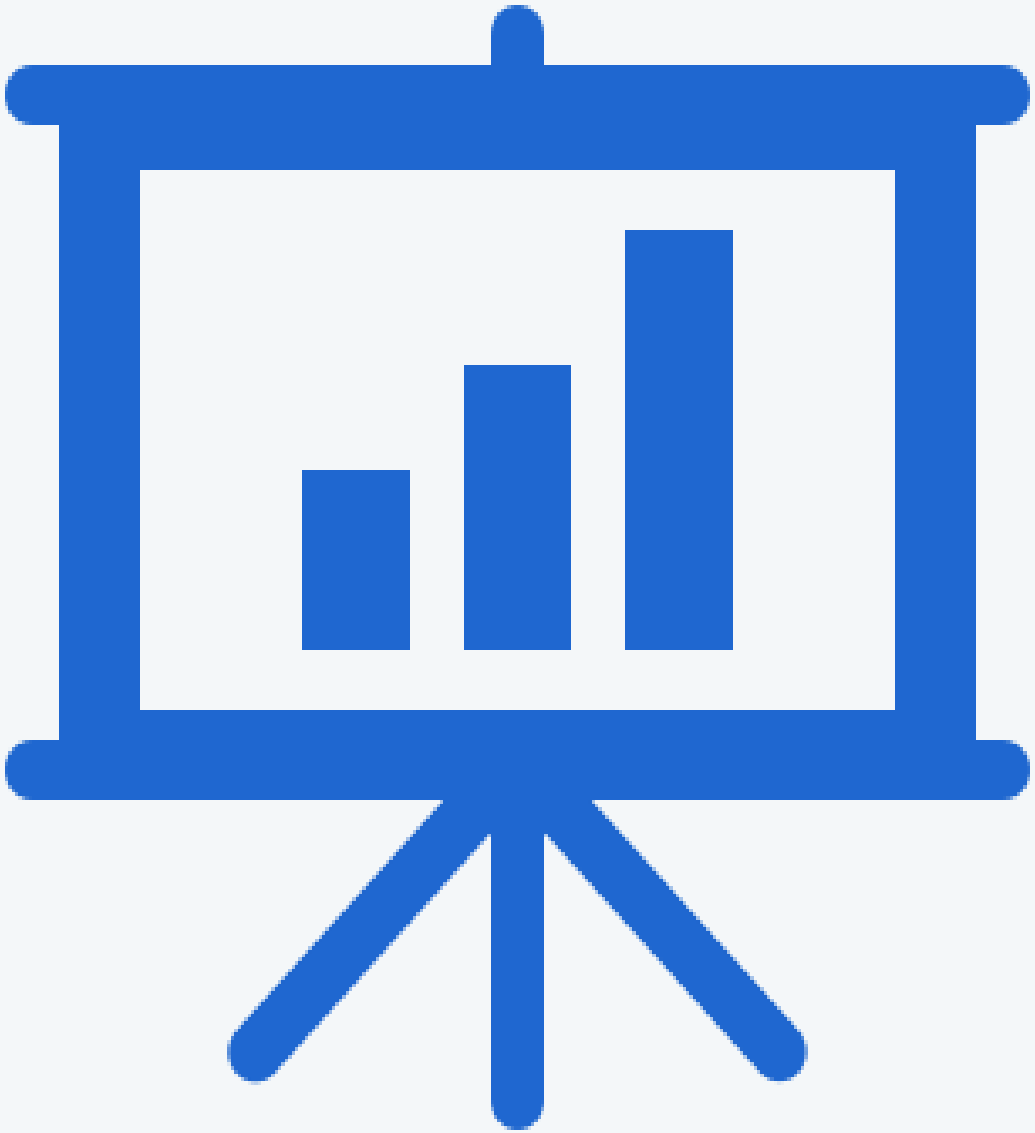
Bone Abnormalities

Condition	Percent of individuals (n)
Scoliosis	7% (2)
Plagiocephaly (flattened skull in infancy)	4% (1)
Pes planus (flat feet)	4% (1)
High arched palate	4% (1)
Pectus excavatum (caved in chest)	4% (1)

Surgeries

Condition	Percent of individuals (n)
ENT (ear tubes, adenoidectomy, and/or tonsillectomy)	19% (5)
Broken bone	19% (5)
Tongue tie repair	11% (3)
Eye	8% (1)
Hernia Repair	4% (1)

Summary of SLC6A1



Common issues

- Seizures
- Developmental delay or intellectual disability
- Movement disorders (e.g., tremor, ataxia)
- Hypotonia
- Autism spectrum disorder