DeSanto-Shinawi (DESSH) Syndrome-Overview

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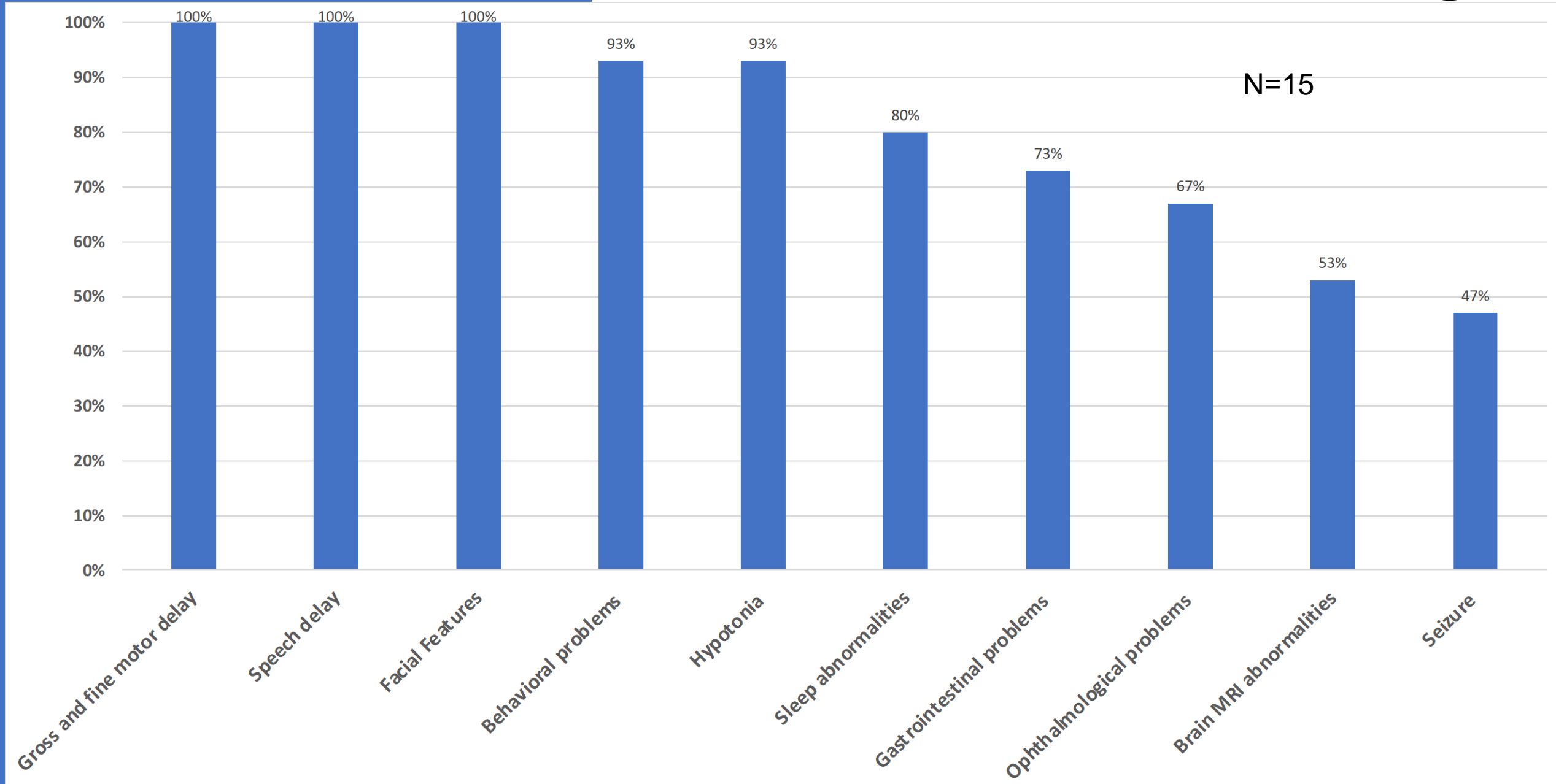
Background

- DeSanto-Shinawi (DESSH) syndrome is an ultra rare genetic condition that was first described in 2015. It is characterized by the following cardinal features:
  - Variable degree of developmental delay and intellectual disability
  - Behavioral abnormalities
  - Decreased muscle tone (hypotonia) & other neurological findings (seizures)
  - GI abnormalities: feeding problems & constipation
  - Eye abnormalities
  - Facial differences

DESSH Clinic 2022- Main Clinical Findings



Prevalence of DESSH syndrome

The prevalence of DESSH syndrome is unknown

~45 individuals with this disorder have been described in the medical literature

However, there are many individuals (total≃100) who are being studied & characterized. Worldwide: ~200-250

We anticipate many more to be identified through exome and genome sequencing

DESSH Clinic 2022- general DESSH Clinic- general

- 15 patients (8 females and 7 males)
- Mean age: 9.27+/- 4.26 years (Range: 3y1mo – 18y4mo).
- Method of diagnosis:
  - Clinical exome sequencing- 13 patients
  - Neurodevelopmental expanded panel- 1 patient
  - Chromosomal microarray analysis (CMA)- 1 patient
- 12 patients had completed parental testing: 11 had *de novo* variants, and 1 had a maternally inherited variant

Natural History: Clinical and Neurobehavioral Characteristics of DESSH Syndrome-1

- The newborn and infancy periods are frequently characterized by:
  - Nonspecific feeding and gastrointestinal problems (such as constipation, feeding difficulties and gastroesophageal reflux)
  - Decrease muscle tone (hypotonia)
  - Eye abnormalities, such as strabismus and refractive errors (nearsightedness, astigmatism), and cortical visual impairment
  - Recurrent respiratory infections can also occur (with or without immune deficiency)
  - A few cases with short stature +/- low blood glucose

Natural History: Clinical and Neurobehavioral Characteristics of DESSH Syndrome-2

- When children get older, developmental delay and neurobehavioral difficulties become more apparent:
  - Gross motor delay is very common; independent walking usually starts around 20-30 months of age
  - Difficulty with fine motor tasks are also common
  - Language acquisition is delayed in almost all individuals with DESSH syndrome (single words 20 mo and sentences 3-4 yo)
  - Potty training is typically delayed (3-8 yo)

Clinical and Neurobehavioral Characteristics of DESSH Syndrome-3: Cognitive Disability

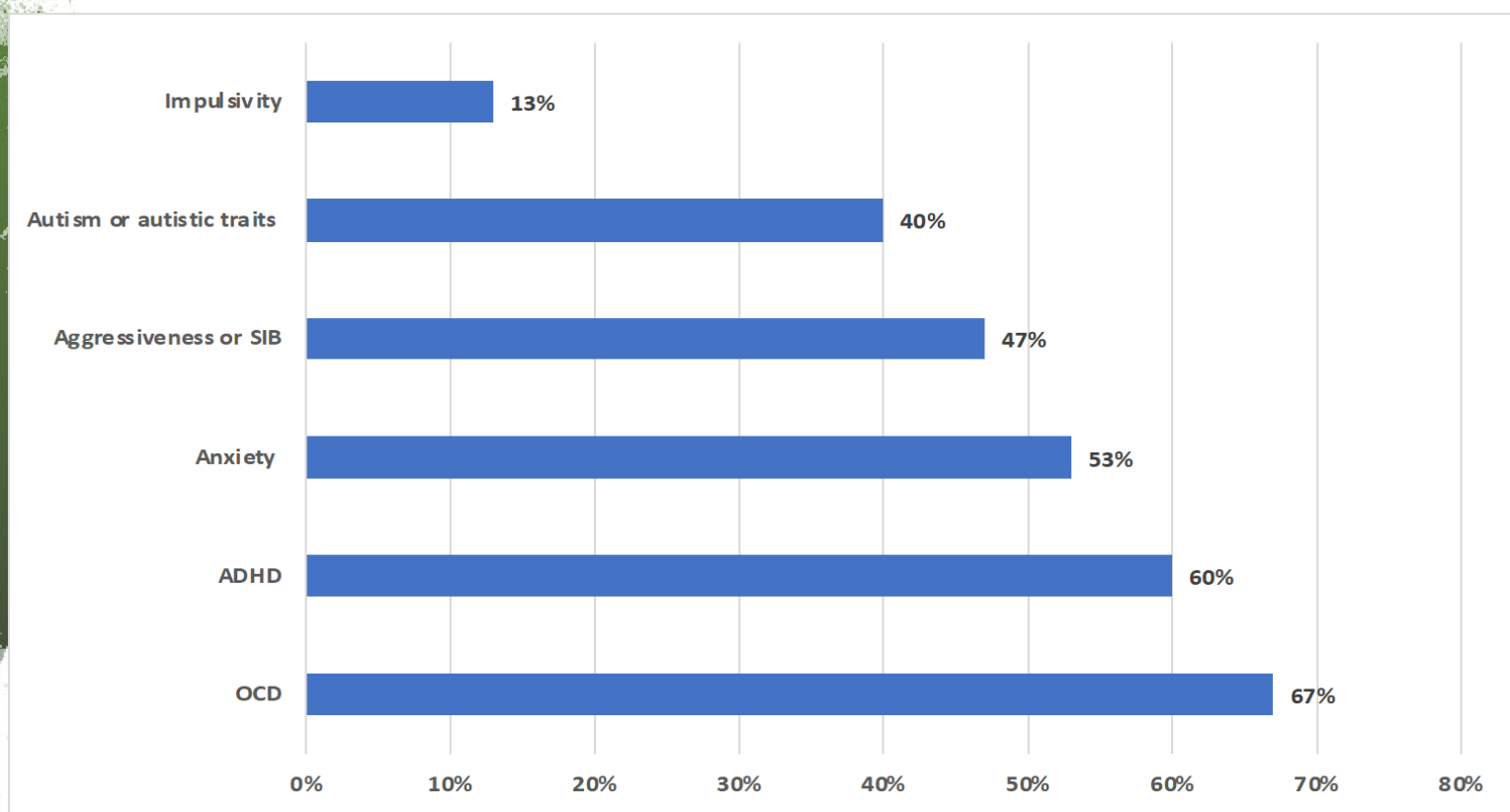
- Cognitive disabilities range from mild to moderate. Formal intelligence testing can be normal in a few patients
  - Most patients with formal cognitive testing displayed mild to moderate ID (mean IQ=66; range:51-81; n=7; 2 patients diagnosed with moderate ID using other tools)

Clinical and Neurobehavioral Characteristics of DESSH Syndrome-4: Behavioral Problems

- Behavioral abnormalities and/or mental illness are prominent component of DESSH syndrome:
  - Inconsolable crying in infancy (colicky baby)
  - Attention deficits and/or hyperactivity
  - Aggressive behaviors (including SIB)
  - Impulsivity and stubbornness
  - Autism/autistic features
  - Anxiety
  - OCD
  - Sleep problems (falling asleep, awakening, sleep apnea)

Clinical and Neurobehavioral Characteristics of DESSH Syndrome-4: Behavioral Problems

- Prevalence of behavioral problems in individuals with DESSH syndrome:



DESSH Clinic 2022

Neurological Findings

Hypotonia (delayed motor skills; drooling)

Seizures (47%, 2022 data; ~25%): tonic-clonic, absence, and febrile seizures (can be in sleep; EEG can be normal). Age of onset: 2 mo-15 yo. Possibly correlate with more severe developmental and cognitive outcome

Brain neuroimaging may reveal nonspecific abnormalities [7/13 (53%), 2022 data]: ventriculomegaly , corpus callosum abn.

Patients with epilepsy are more likely to have abnormal brain MRI findings

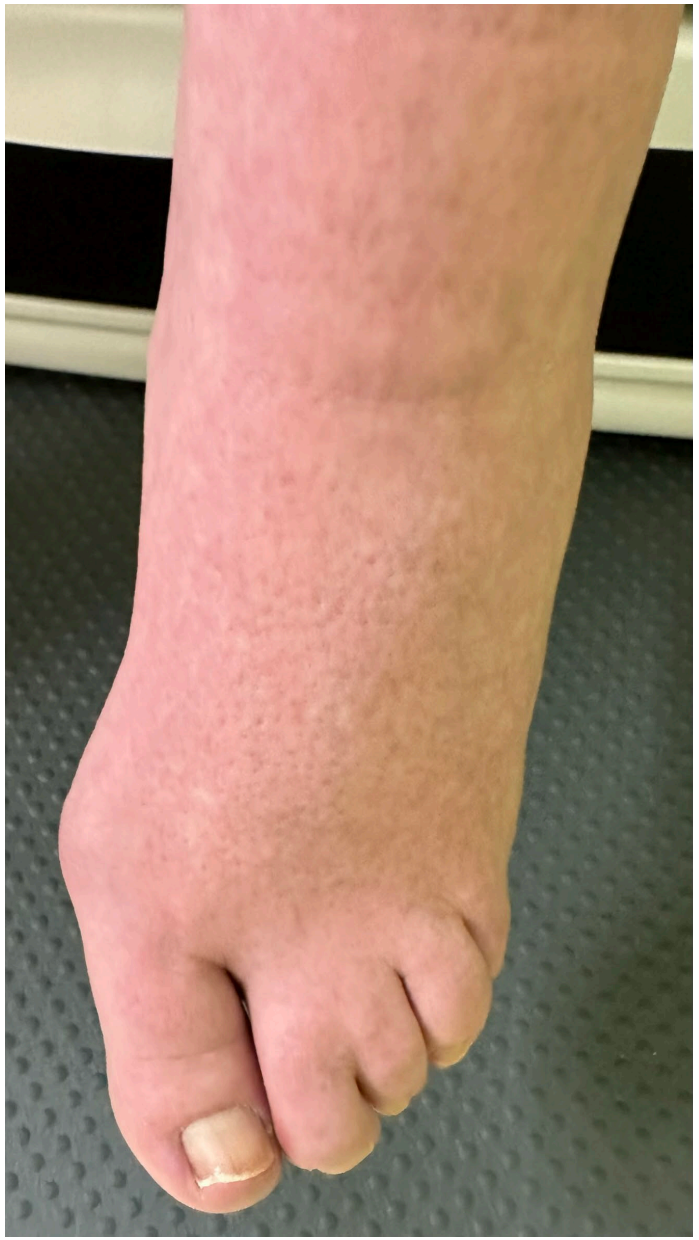
Facial Differences in DESSH Syndrome

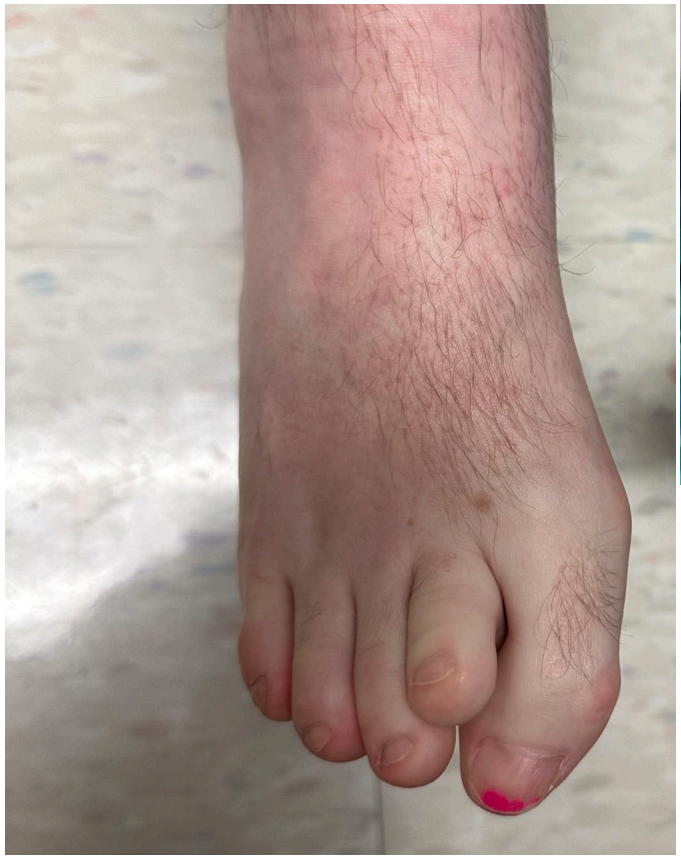
- Many but not all individuals with DESSH syndrome exhibit recognizable facial features
- Common findings include:

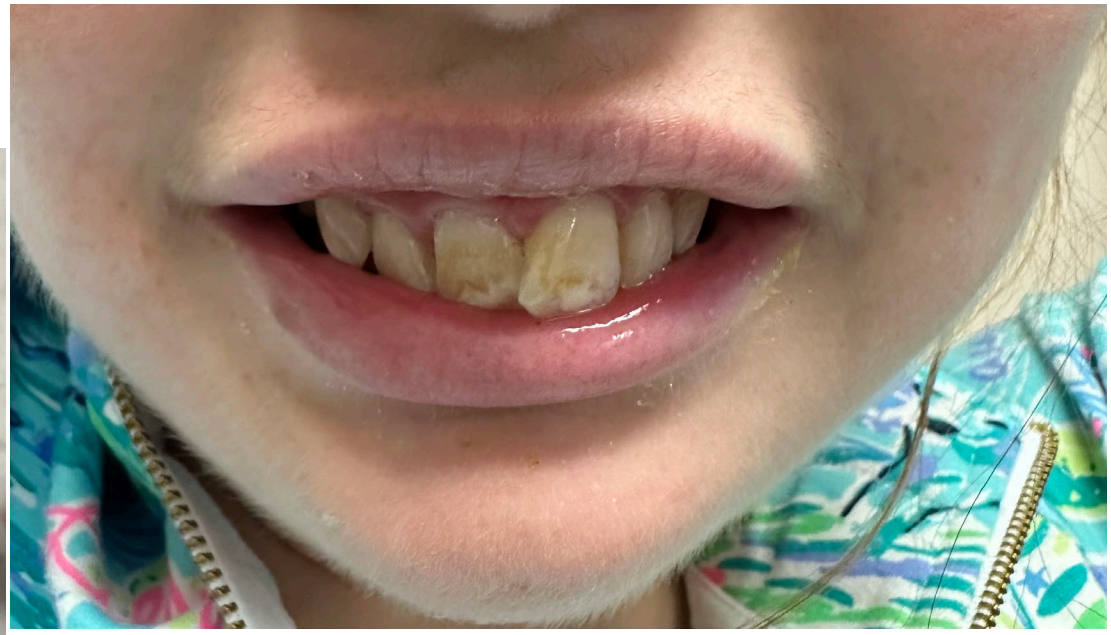
✓ broad forehead
✓ square-shaped face with broad chin
✓ flat mid face
✓ deep set eyes with long palpebral fissures
✓ full eyebrows or unibrow
✓ hirsutism (excessive hair)
✓ flat nasal bridge with bulbous tip
✓ wide mouth
✓ thin upper lip
✓ a few ear anomalies
✓ hand and foot anomalies

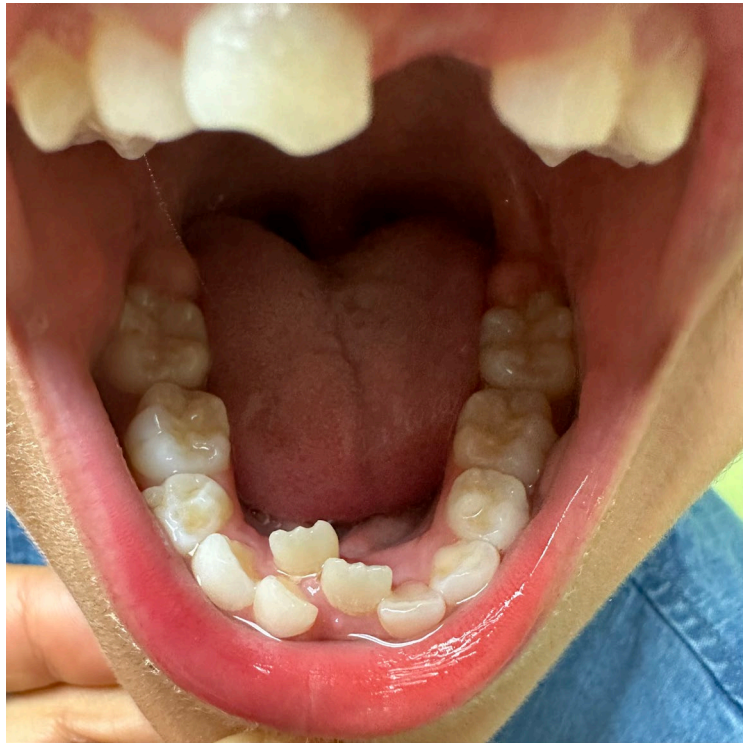
Figure 4. Facial features of patients with DESSH syndrome.


1A
2A
3A
1B
2B
3B

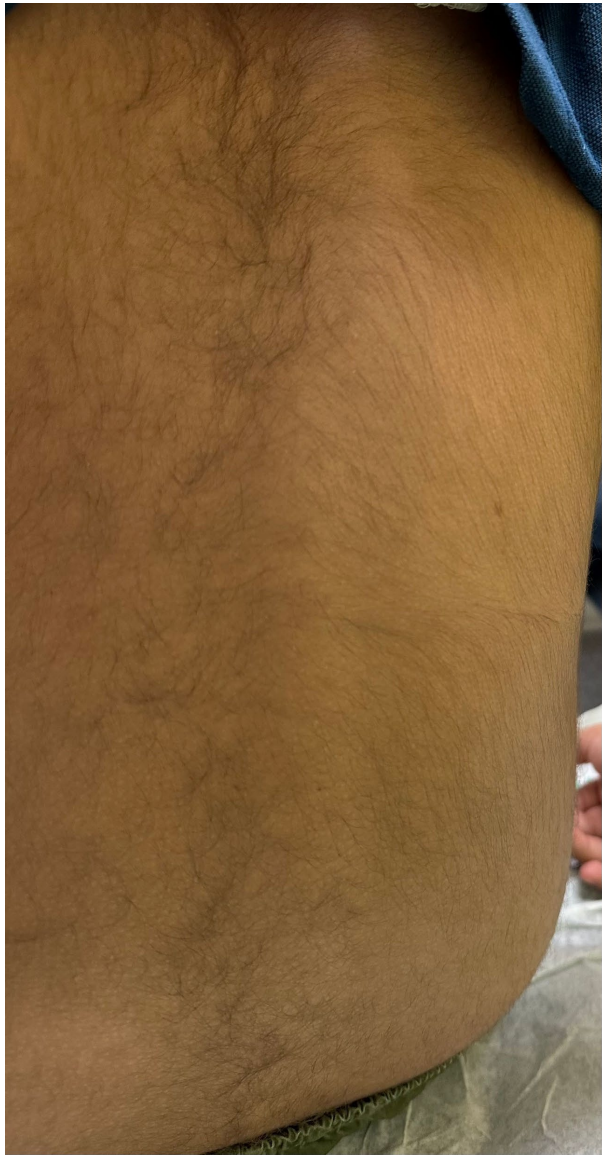


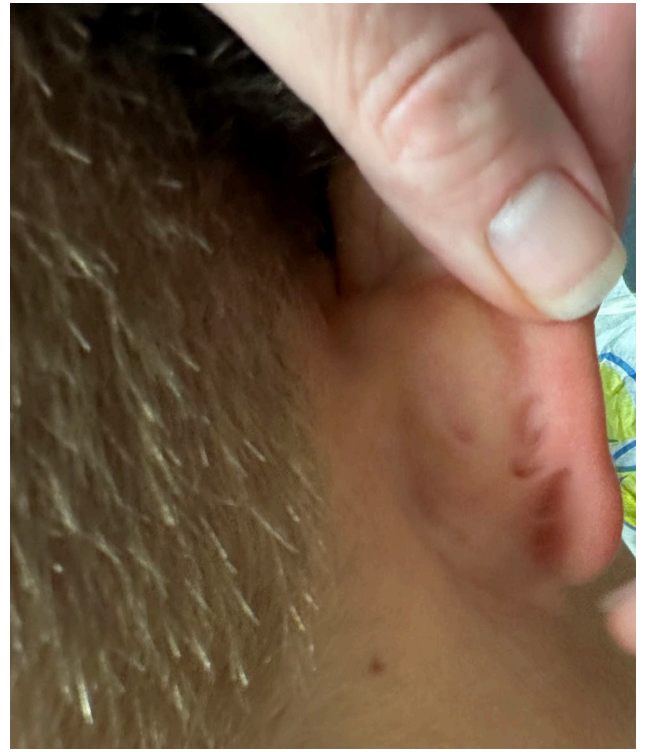




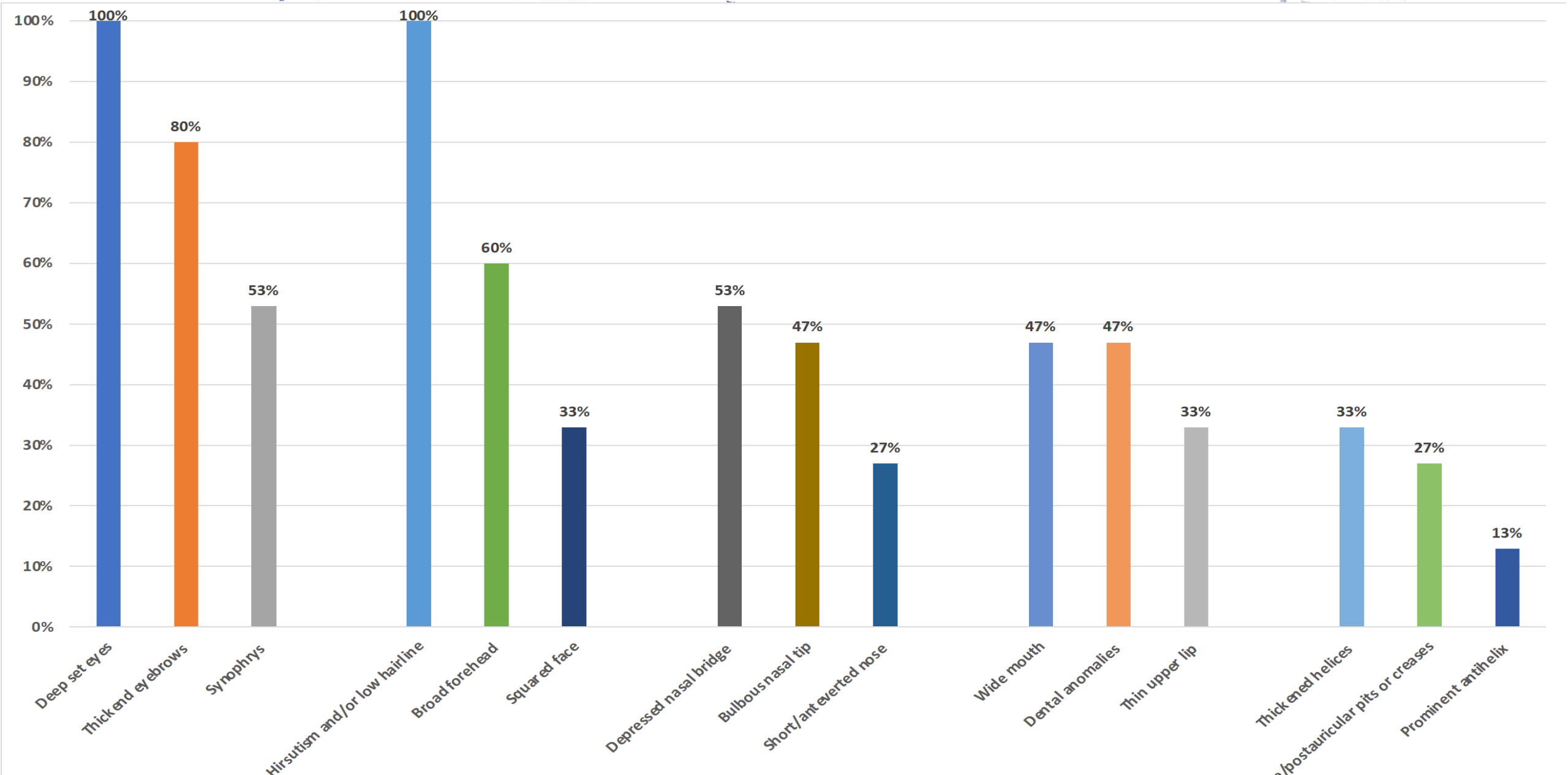


Hallux valgus deformity; nail abnormalities



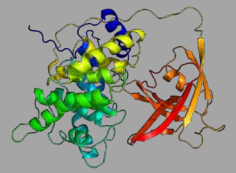


Frequency of dysmorphic facial features in DESSH patients



Etiology of DESSH Syndrome

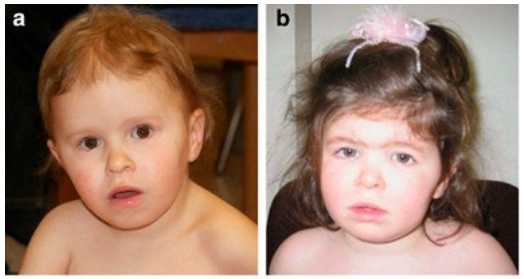
Individuals with DESSH syndrome carry genetic variants in the WW domain containing adaptor coiled coil (WAC) gene



The great majority of patients have point genetic alterations (=pathogenic variants=mutations) that disrupt the function of the product of the WAC gene

There are individuals who have a missing piece (deletion) on the short arm of chromosome 10 at 10p12p11 and who exhibit similar manifestations (more severe with large deletions)

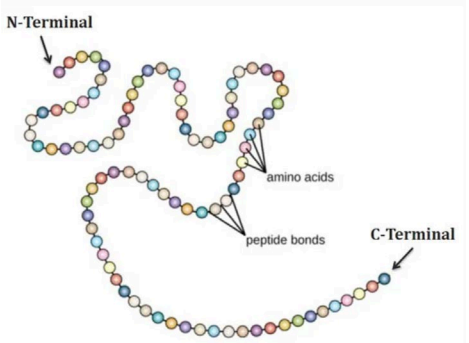
10p Deletions

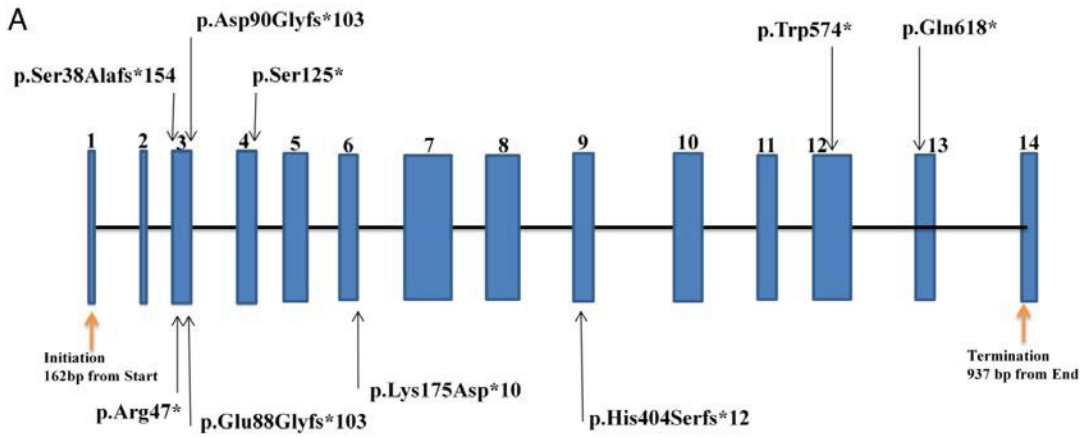


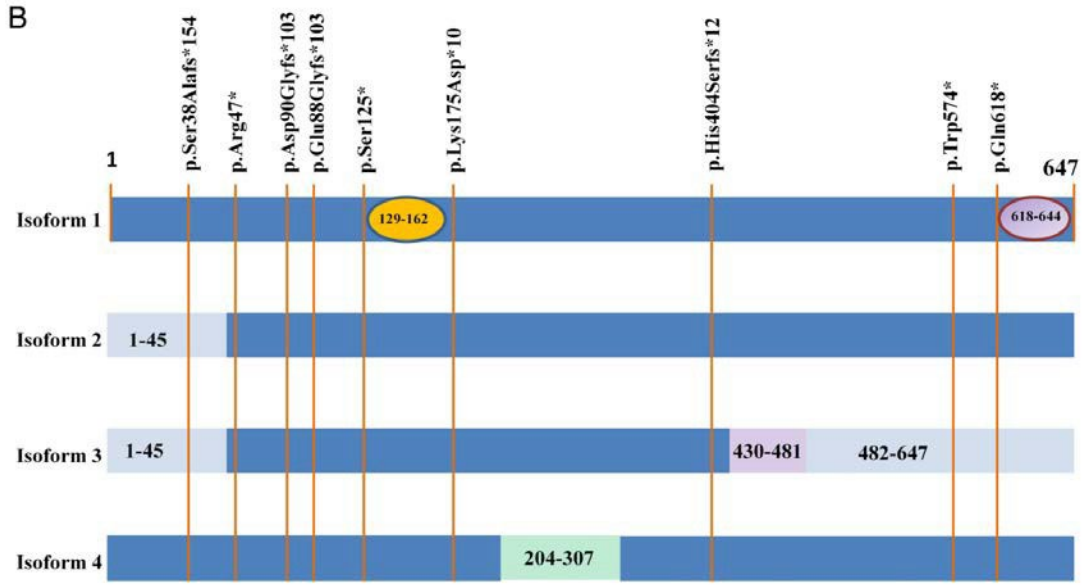
- Individuals with 10p11.23 deletions encompassing WAC have been reported
- 0.7-10.6 Mb deletions
- Developmental delay, dysmorphic features, hyperactivity, and congenital heart defects.
- Their facial features included synophrys, thick eyebrows, short neck, deep set eyes, bulbous nose, full cheeks
- Lack of one copy of WAC is responsible for most of the phenotypic features associated with deletions encompassing 10p11.23

Genotype-Phenotype Correlation

- Severity of ID and other clinical findings vary between patients:
  - Type of mutation
  - Patients with C-terminal mutations are less severely affected as compared to patients with N-terminal mutations
  - The position of the mutation may affect different isoforms
  - Other genetic factors (modifiers)




A
p.Asp90Glyfs*103
p.Ser38Alafs*154
p.Ser125*
p.Trp574*
p.Gln618*
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Initiation
162bp from Start
p.Arg47*
p.Glu88Glyfs*103
p.Lys175Asp*10
p.His404Serfs*12
Termination
937 bp from End


B
N
C
1
p.Ser38Alafs*154
p.Arg47*
p.Asp90Glyfs*103
p.Glu88Glyfs*103
p.Ser125*
p.Lys175Asp*10
p.His404Serfs*12
p.Trp574*
p.Gln618*
647
Isoform 1
129-162
618-644
Isoform 2
1-45
Isoform 3
1-45
430-481
482-647
Isoform 4
204-307

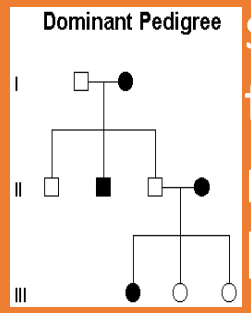
DESSH Syndrome - Inheritance

Most cases of DESSH syndrome are not inherited. Affected individuals typically have no history of the disorder in their family

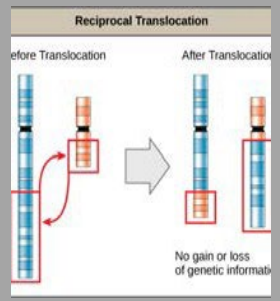
The genetic changes in the WAC gene are random events during the formation of reproductive cells (eggs & sperms)

4-5 familial recurrences due to a presumed germline mosaicism (parents have negative testing)

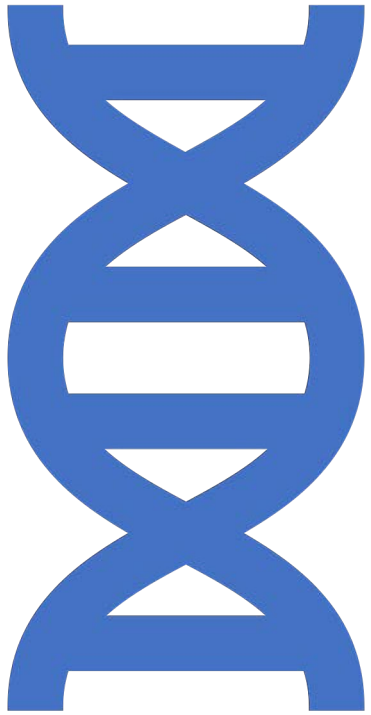
DESSH Syndrome - Inheritance



Recent data suggest that DESSH syndrome can run in families and therefore testing parents is recommended (especially with family history of mild ID/DD) for genetic counseling purposes



10p12p11 deletion are not inherited but can be related to unusual chromosomal rearrangements. It is recommended to test parents to rule out balanced chromosomal rearrangements in parents or



Who Names Newly Discovered Disorders?

- In the world of genetics, OMIM (Online Inheritance in Man) often does

- OMIM (www.omim.org) is a comprehensive, authoritative collection of human genes and genetic phenotypes that is freely available and updated daily

- Conditions can be called after gene names: WAC-related disorder. Potential limitations: 1) one gene can cause a number of diseases; 2) less convenient for families; 3) gene names & association can change from time to time

616708

DESANTO-SHINAWI SYNDROME; DESSH

Alternative titles; symbols

DEVELOPMENTAL DELAY, BEHAVIORAL ABNORMALITIES, FACIAL DYSMORPHISM, AND OCULAR ABNORMALITIES

Other entities represented in this entry:

CHROMOSOME 10p12-p11 DELETION SYNDROME, INCLUDED

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
10p12.1	Desanto-Shinawi syndrome	616708	AD	3	WAC	615049

Clinical Synopsis | PheneGene Graphics

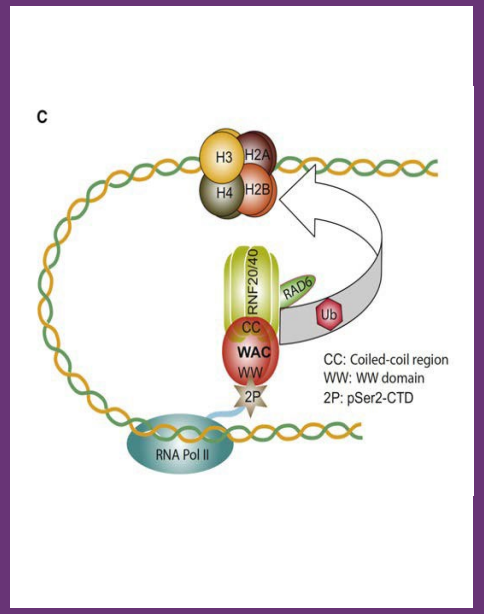
WAC Functions

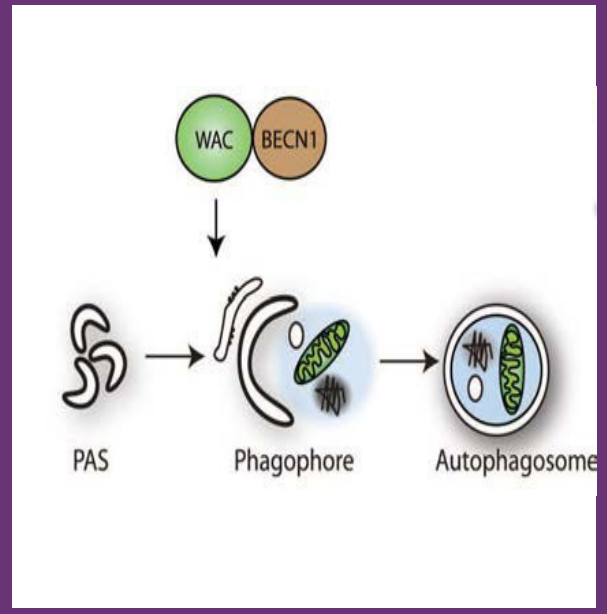
- The WAC gene provides instructions for making a protein called WW domain-containing adapter protein with coiled-coil

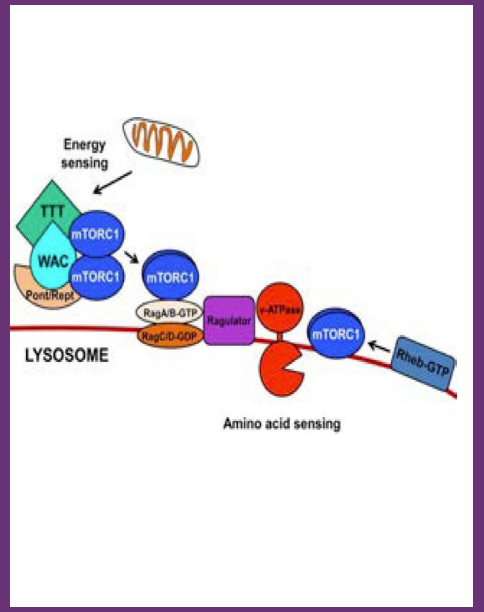
- The protein is composed of 647 amino acids and mainly located in the nucleus but also found in Golgi (helps process and package proteins and lipid)
- Expressed in all adult and fetal tissues but highest expression is found in the cerebellum

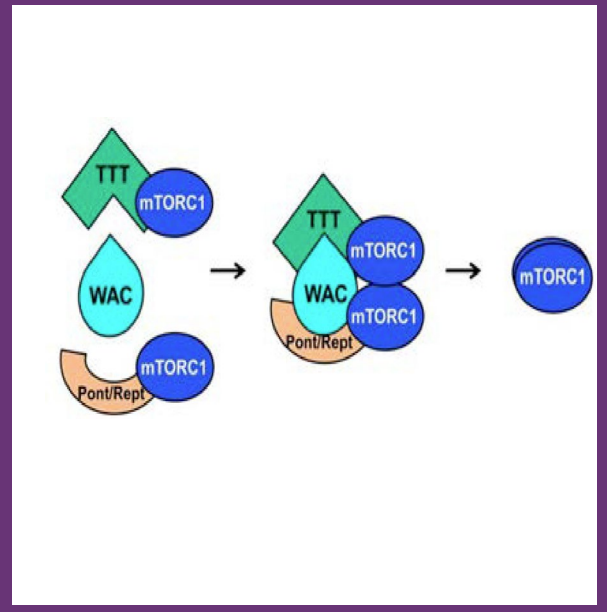
WAC Functions

- Involved in multiple cell processes:
  - Transcription elongation regulation through promoting monoubiquination of histone H2B at Lys12
  - Cell-cycle checkpoint activation in response to DNA damage
  - Autophagosome formation (autophagy: transferring cytoplasmic components in autophagosomes to lysosomes for degradation)
  - Golgi biogenesis
  - Regulation of mTOR pathway (important for the regulation of growth & metabolism in response to environmental cues such as nutrient and energy availability









What is Next?

1

Study larger cohorts of individuals with DESSH syndrome is needed to understand the full spectrum of manifestations and the possible relationship between mutation type and extent/severity of clinical findings

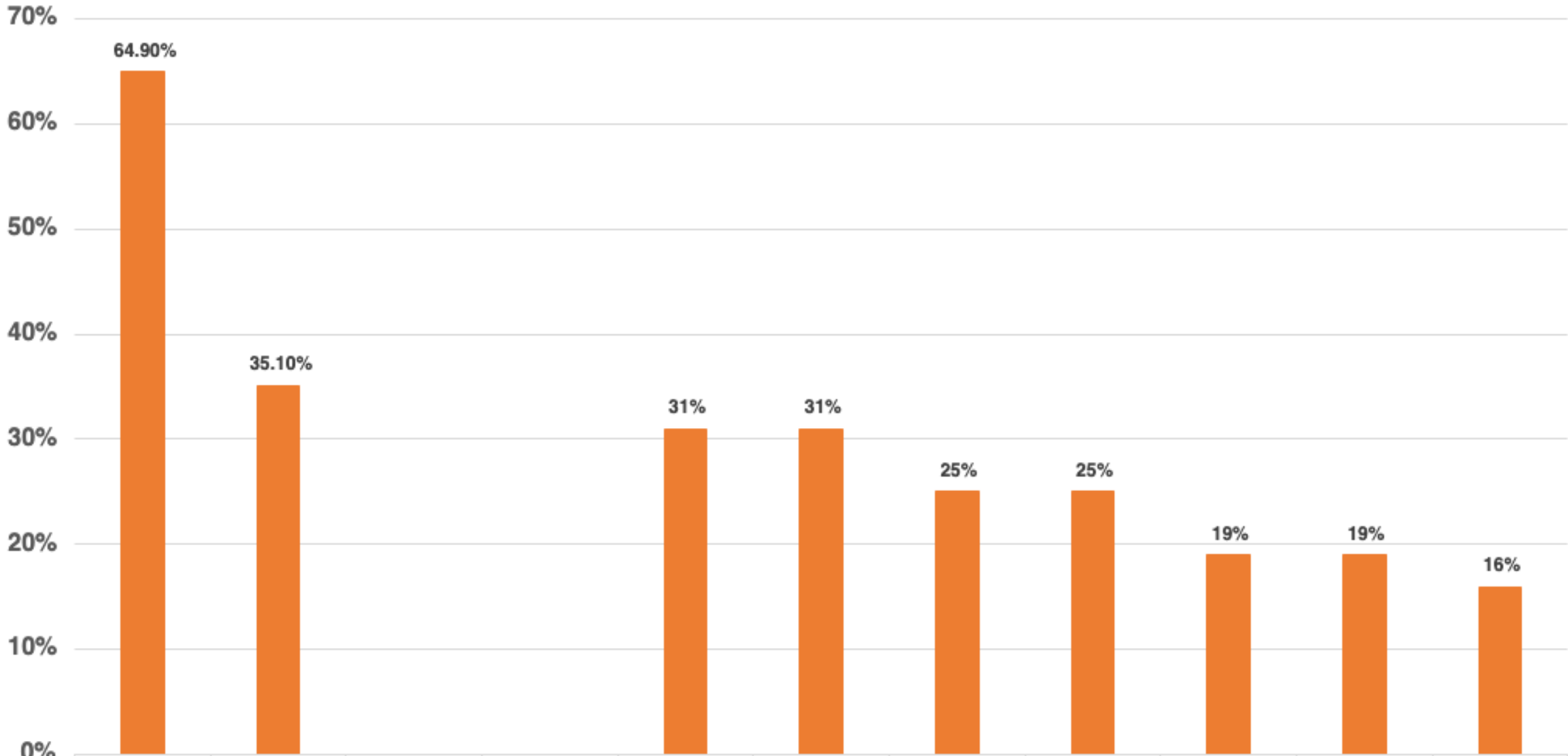
2

Study individuals longitudinally and adult individuals to understand the natural history of this condition focusing on signs or symptoms of developmental regression or neurodegeneration or development of new symptoms

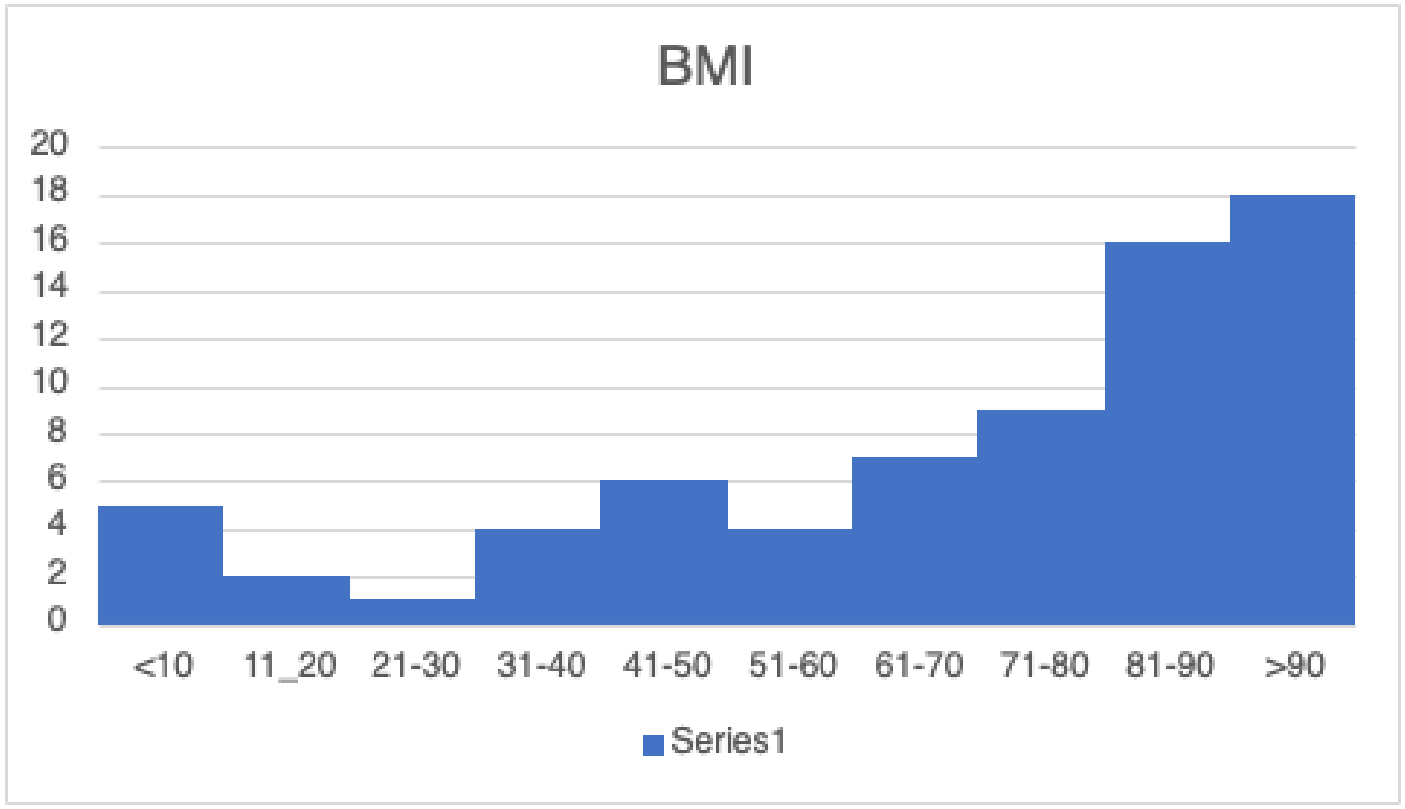
3

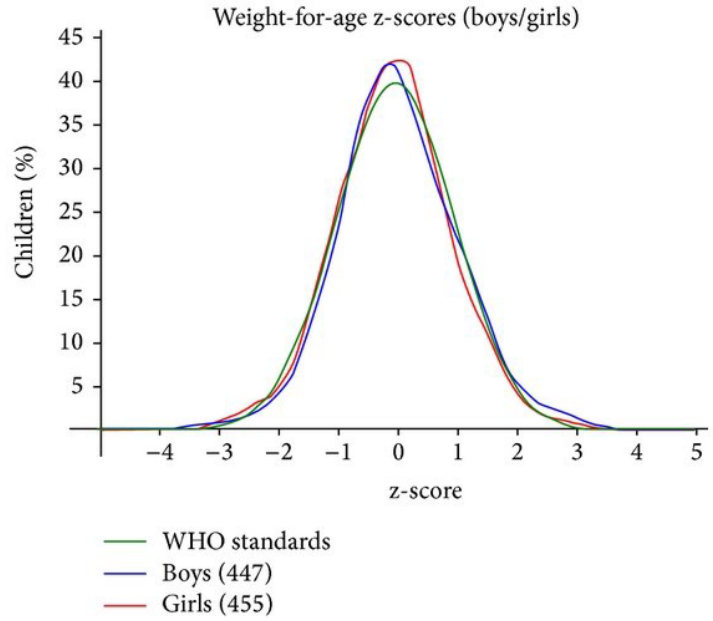
- Study the effect of early therapeutic interventions on ameliorating the neurobehavioral abnormalities
- Medical interventions
- Gene therapy

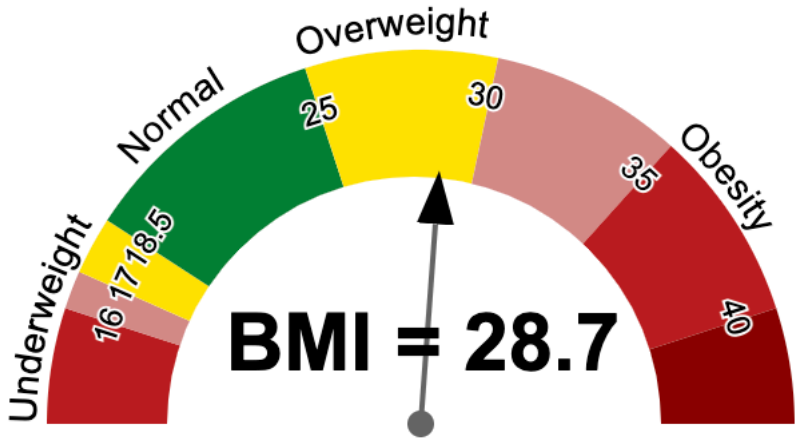
Medications



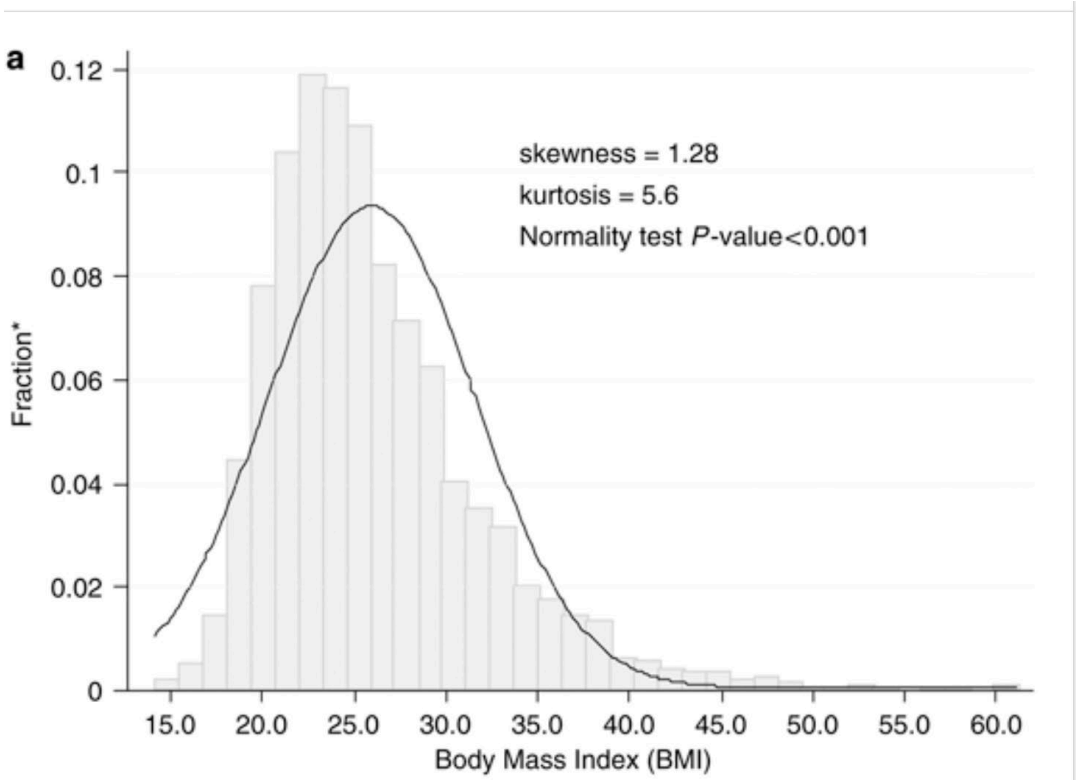
	Yes	No			Laxatives	Allergy/asthma	Stimulants	Anti-epileptic	Sleep	Antidepressent/anti psychotic	Acid reducing
Series1	64.90%	35.10%			31%	31%	25%	25%	19%	19%	16%



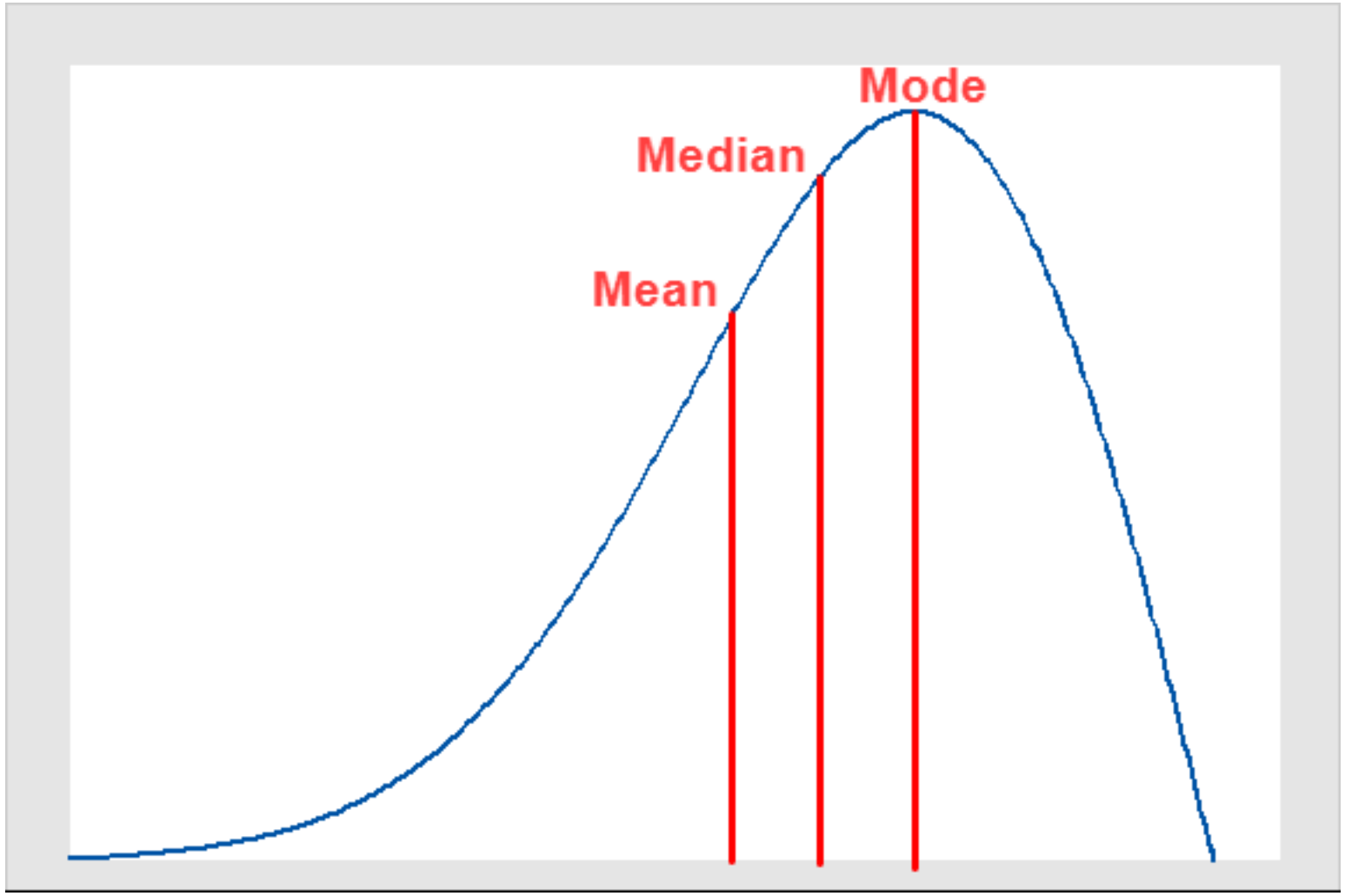




BMI=weight (kg)/height^2(m)



Left skewed distribution



Because the mean underestimates the most frequently occurring values, the median is a more robust statistic

What is Next?

Research the functions of WAC and the pathophysiology of DESSH syndrome in model organisms and *in vitro* systems

Utilization of available resources and opportunities in science to advance efforts toward the long-term goal to find cure for DESSH syndrome

Support families' efforts including WWW.DESSH.ORG to increase awareness and fundraising

The future of the DESSH syndrome Clinic

DESSH Clinic

- A multidisciplinary setting is a successful model for evaluating and managing the complex needs of patients with DESSH syndrome
- The evaluation of large number of patients with a rare condition will pave the way for medical professionals to develop expertise in this condition
- The collection of biospecimens will provide a platform to establish a large repository that can serve researchers interested in this condition
- This pilot experience highlights the value of collaborating with family support groups and provides guidance for future DESSH clinic planning

Acknowledgements

- DESSH Foundation
  Caitlin Piccirillo, Susan Ford
- Patients and their families
- Division of Genetic and Genomic Medicine
  Dr. Patricia Dickson, Dr. Jennifer Heeley, Dr. Nate Jensen, Katherine Sisco, NP, Kimberly Turner, Dana Kiley, Michelle Oliva, Yolonda Phillips, Sharice Yates
- Pediatric Neurology
  Dr. Judith Weisenberg, Dr. Amanda Clorfeine, Dr. Siefaddeen Sharayah, Dr. Nicholas DeKorver
- Pediatric Ophthalmology
  Dr. Margaret Reynolds
- Psychology Services
  Dr. Girresch-Ward
- IDDRC
  Anna Abbacchi, Virginia Lanzotti
- PCRU team