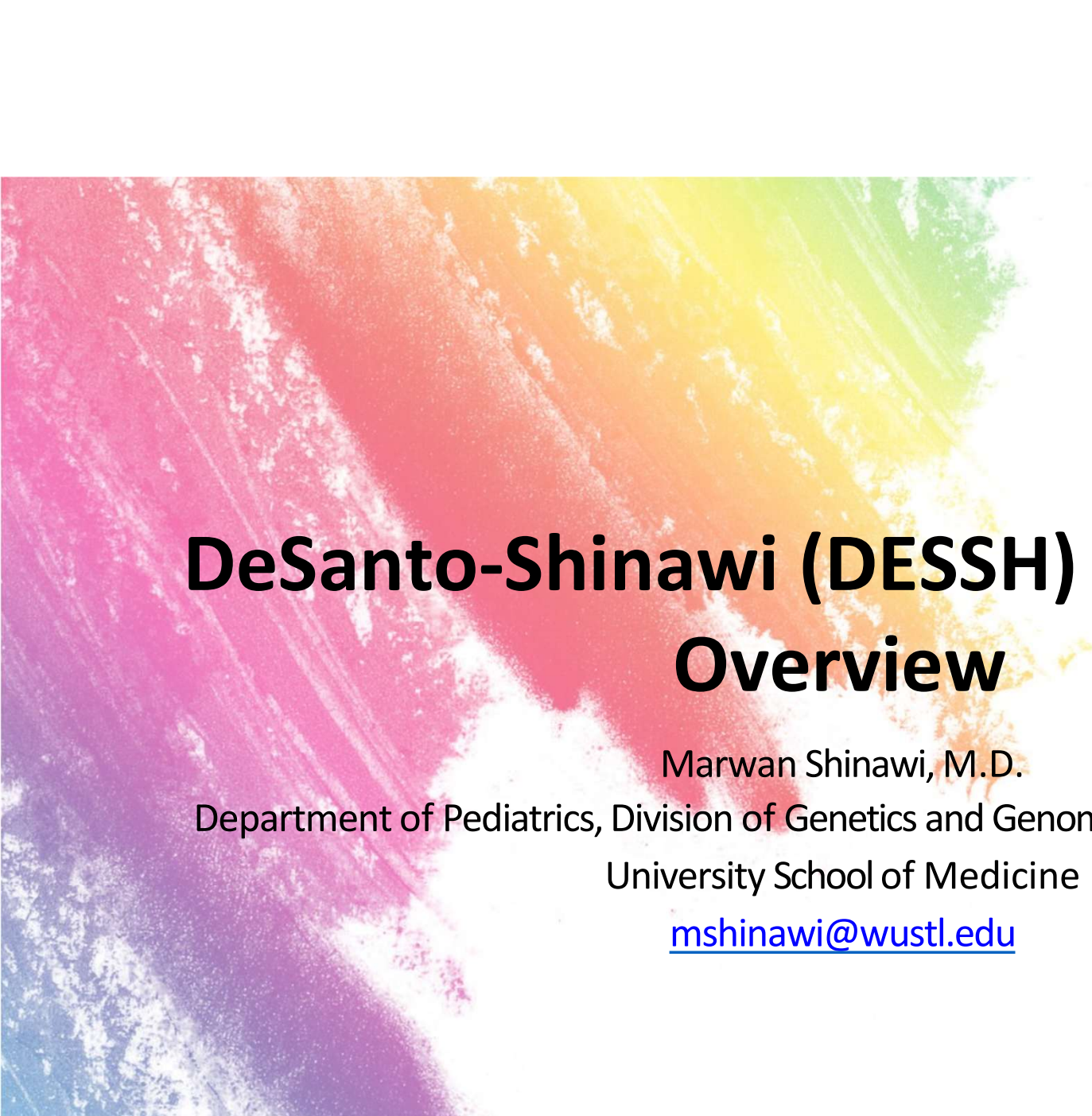




DeSanto-Shinawi (DESSH) Syndrome- Overview

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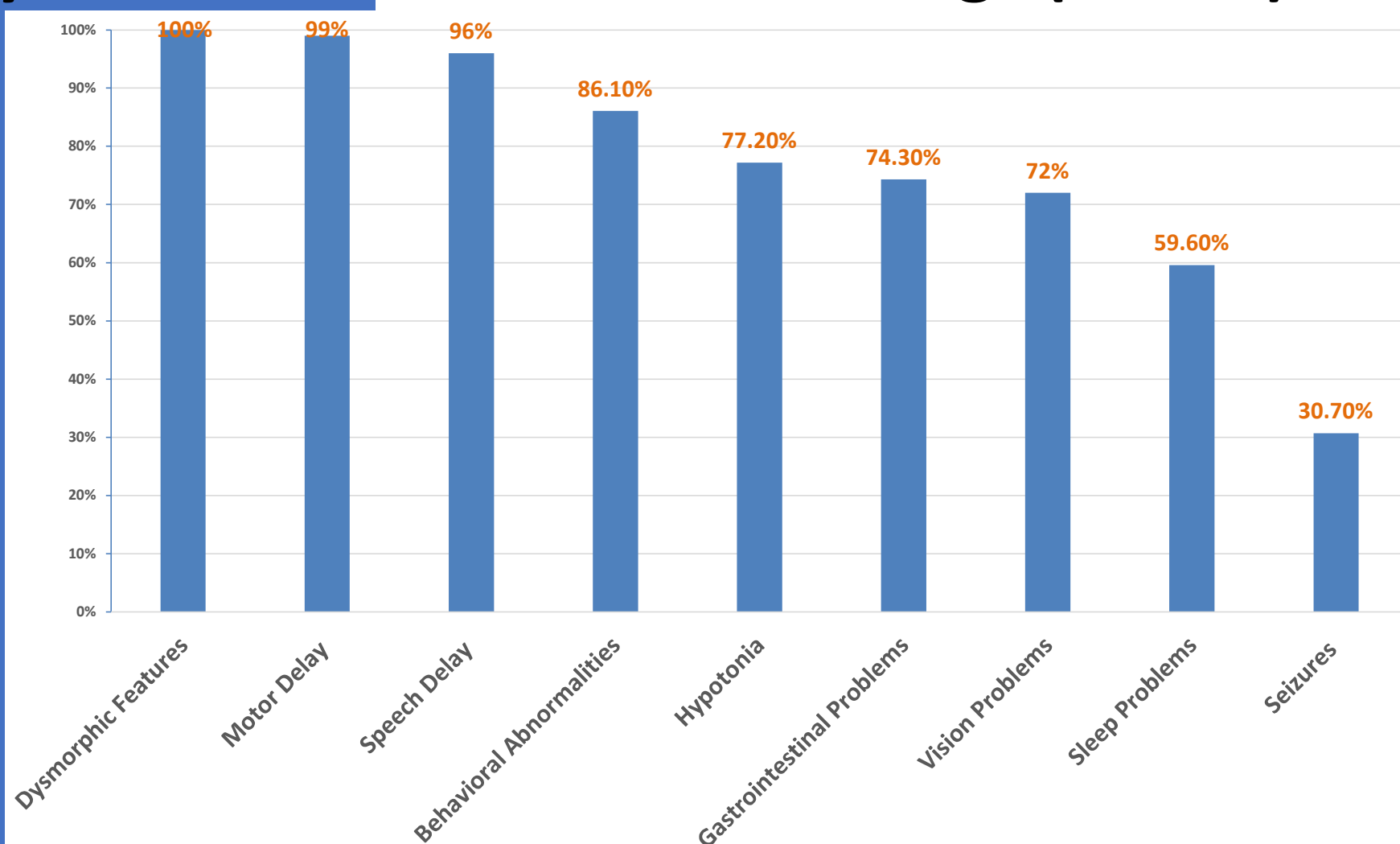
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Background

- 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 problems**
 - **Distinctive facial differences**

DESSH Syndrome: Main Clinical Findings (n=101)



Prevalence of DESSH syndrome

The prevalence of DESH syndrome is unknown

~50 individuals with this disorder have been described in the medical literature

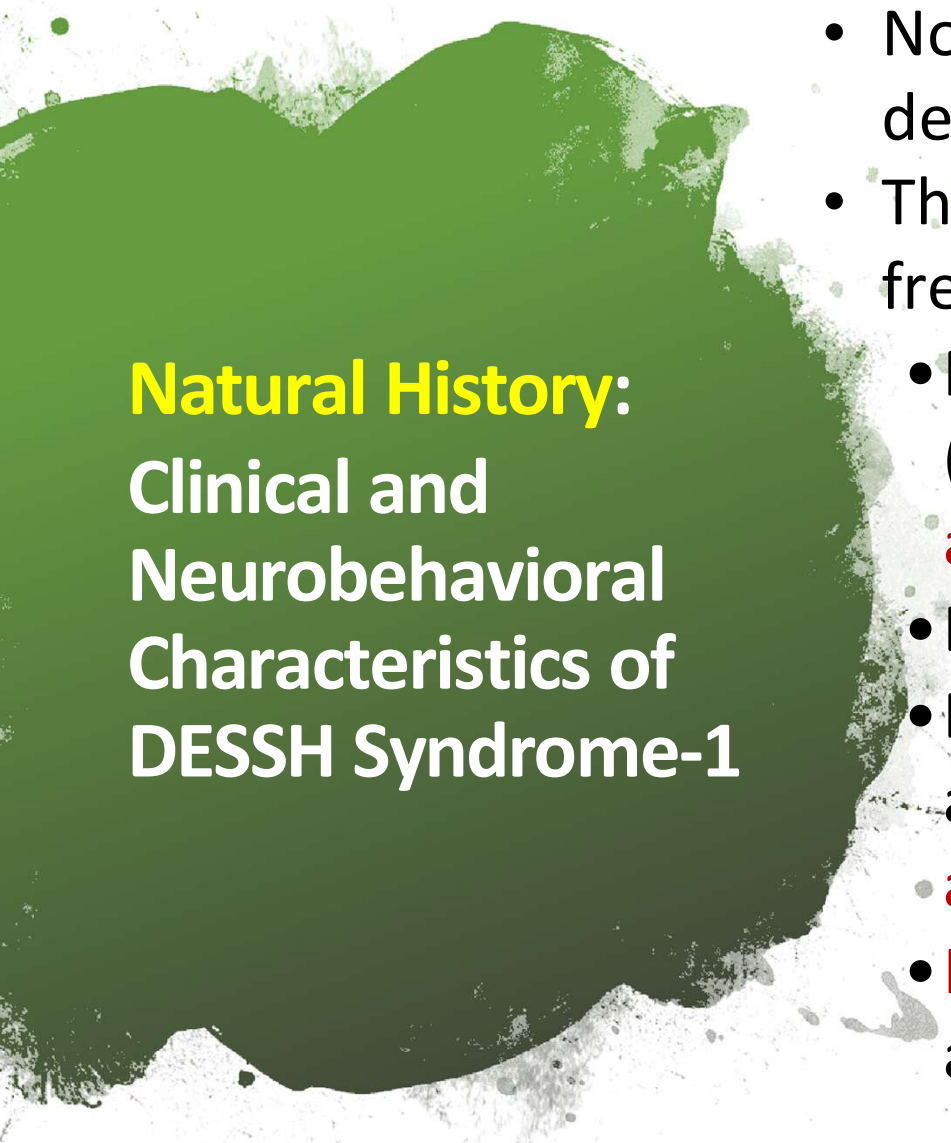
However, there are many individuals (total ≈ 120) who are being studied & characterized. Worldwide: ~200-250

We anticipate many more to be identified through exome, whole genome, and (ID/autism) panel sequencing

Large Cohort of individuals w/DESSH syndrome (n=101)

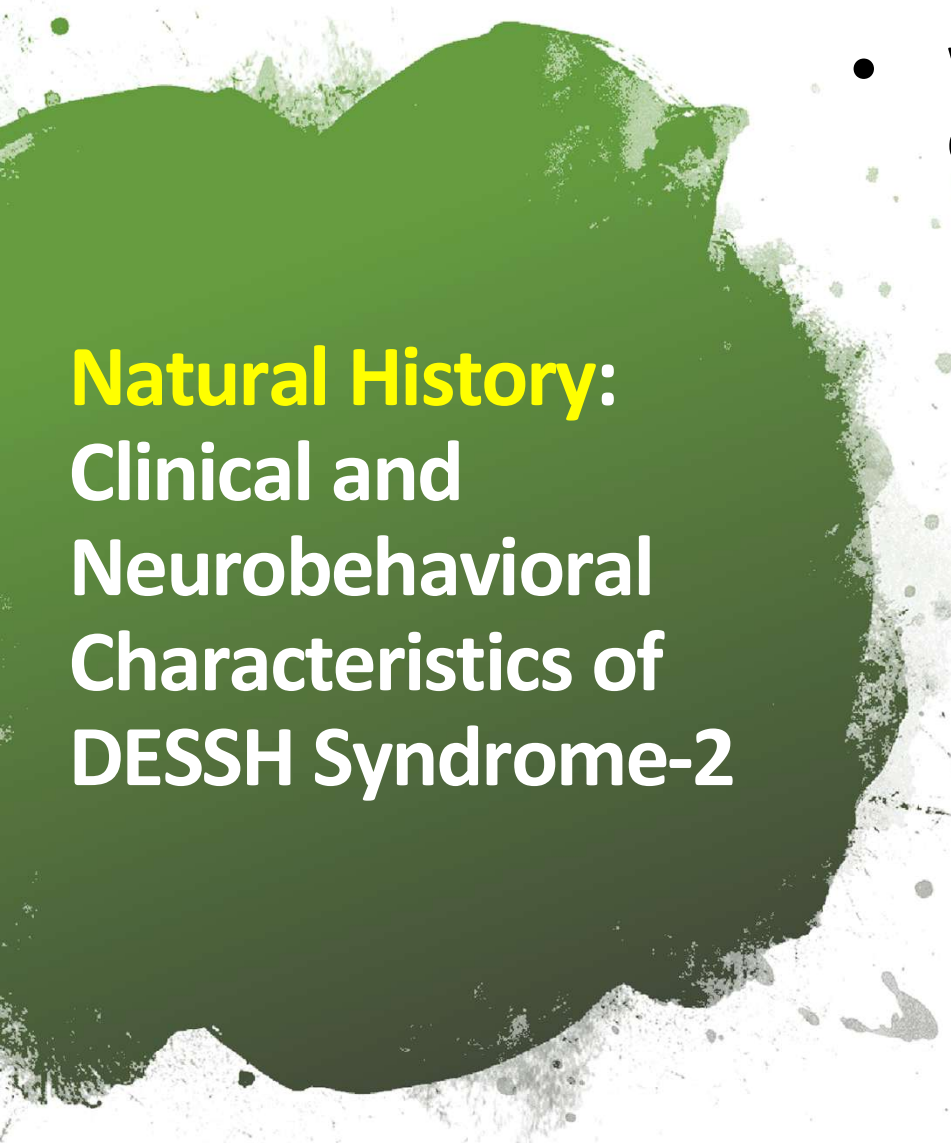


- 101 patients (44 females and 57 males)
- 90 w/ point mutations and 11 w/ deletions
- Current Age, Median (IQR): 12.3 (8, 17.1) (31mo-44yo).
- Age at diagnosis (year), Median (IQR): 6 (3, 12)
- Method of diagnosis:
 - Exome sequencing- 81
 - Chromosomal microarray analysis (CMA)- 7
 - ID/autism panels-6
 - Whole genome sequencing-4
 - Targeted-3



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

- No increased rate of pregnancy and delivery complications
- The **newborn** and **infancy** periods are frequently characterized by:
 - Nonspecific feeding and GI problems (e.g. **constipation, feeding difficulties and acid reflux**)
 - Decrease muscle tone (**hypotonia**)
 - Eye abnormalities, such as **strabismus** and refractive errors (**nearsightedness, astigmatism**)
 - **Recurrent respiratory infections** can also occur (w/or w/out immune def.)



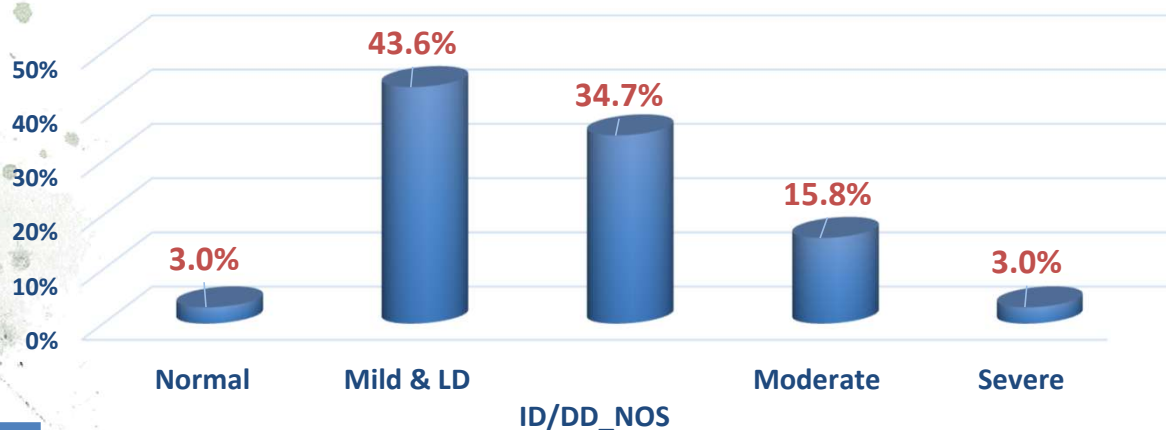
Natural History: Clinical and Neurobehavioral Characteristics of DESSH Syndrome-2

- When **children** get older, developmental delay and neurobehavioral difficulties become more apparent:
 - **Gross motor delay** is very common; independent walking usually starts around 22.3 ± 5.4 mo
 - Difficulty with **fine motor** tasks are also common
 - **Language acquisition** is delayed in almost all individuals (single words 24 mo and sentences 3-4 yo)
 - Potty training is typically delayed (3-8 yo)

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

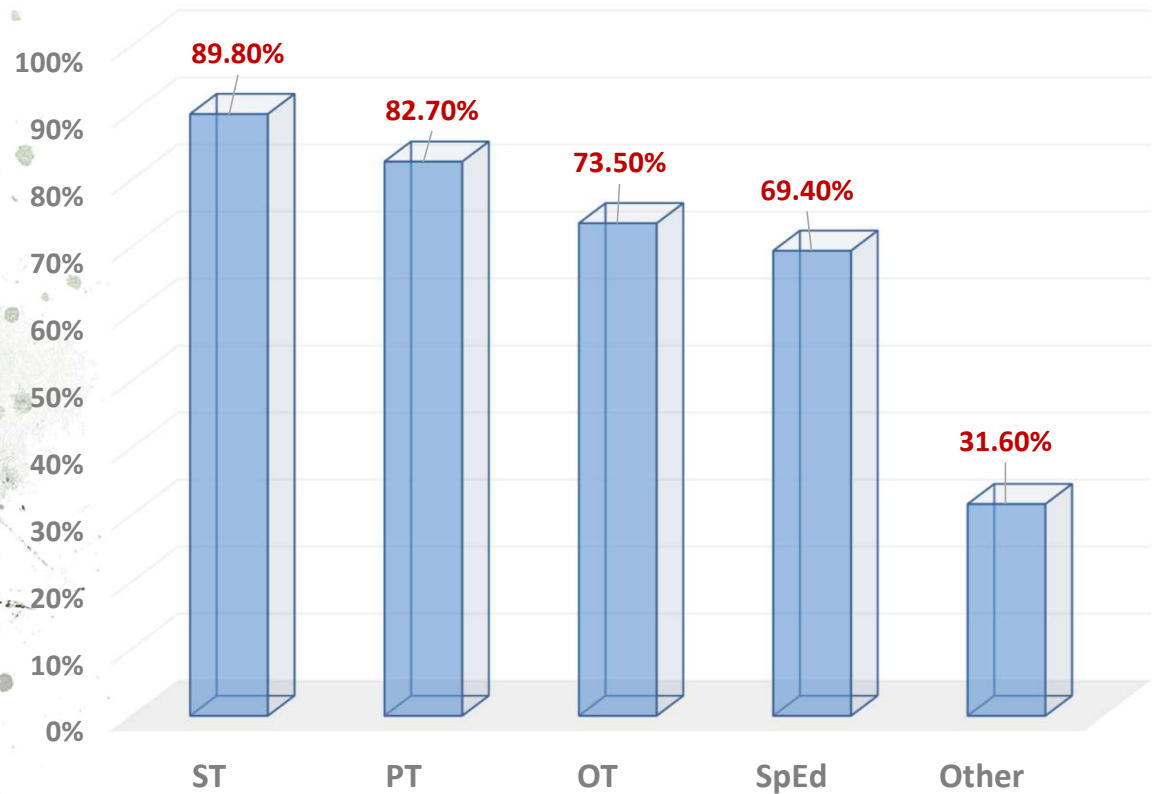
- Cognitive disabilities are mostly **mild to moderate**
- Most patients with formal cognitive testing display mild ID (mean 62.5 ± 14.3 ; n=42)

Severity of DD/ID (n=101)



IQ range		ID severity	
50–69		Mild	
35–51		Moderate	
20–35		Severe	
<20		Profound	

Type of Therapeutic Interventions



Behavioral abnormalities and/or mental illness are prominent component of DESSH :

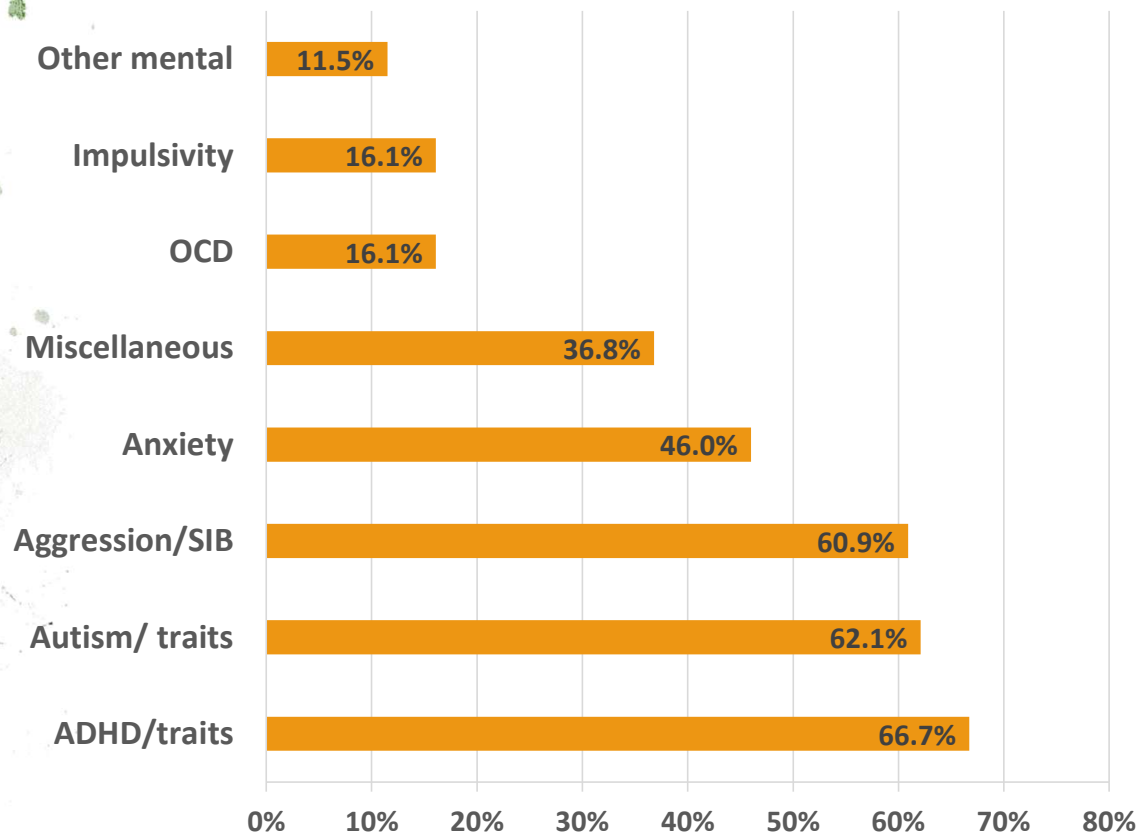
Clinical and Neurobehavioral Characteristics of DESSH Syndrome-4: Behavioral Problems



- Inconsolable crying in infancy (colicky , fussy baby)
- Attention deficits and/or hyperactivity
- Autism/autistic features
- Aggressive behaviors (including SIB)
- OCD, Impulsivity and stubbornness
- Anxiety
- Sleep problems (60%) (falling asleep, awakening, night terror, restless leg, sleep apnea)
- High tolerance to pain and temperature

Clinical and Neurobehavioral Characteristics of DESSH Syndrome-5: Behavioral Problems

Prevalence of behavioral problems in 101 individuals with DESSH syndrome:



Neurological Findings



$\frac{3}{4}$ of patients exhibit hypotonia (delayed motor skills)



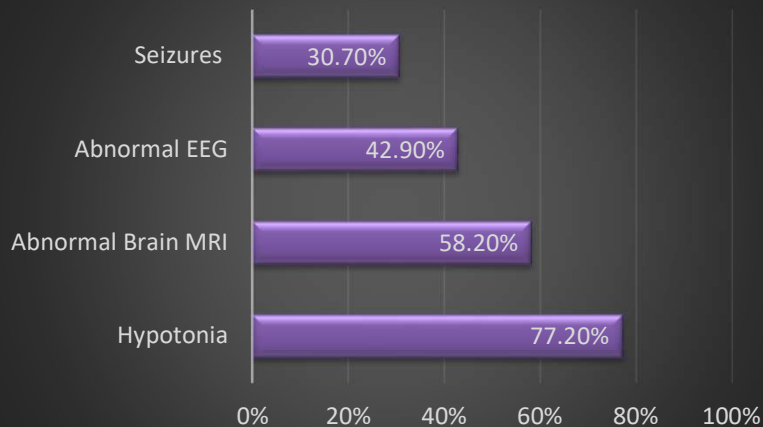
- Seizures (~31%): different types (can be in sleep). Age of onset: 2 mo-15 yo.
- Possibly correlate w/more severe developmental and cognitive outcome?
- Abn. EEG ~42.9% (EEG can be normal w/ Sz)



Brain neuroimaging may reveal nonspecific abnormalities [58.2%]: white matter abnormalities, ventriculomegaly , corpus callosum abnormalities)



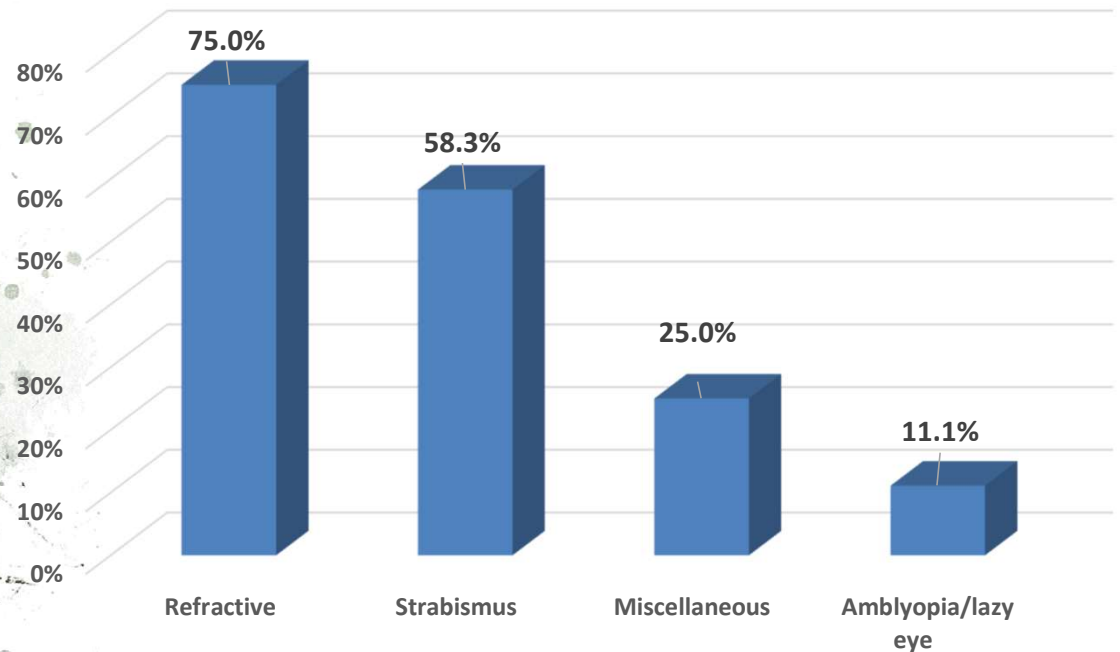
13/18 patients w/ abn. EEG had abnormal bMRI-
-> higher seizure risk w/ abn. bMRI findings?



Ophthalmological Findings in DESSH Syndrome

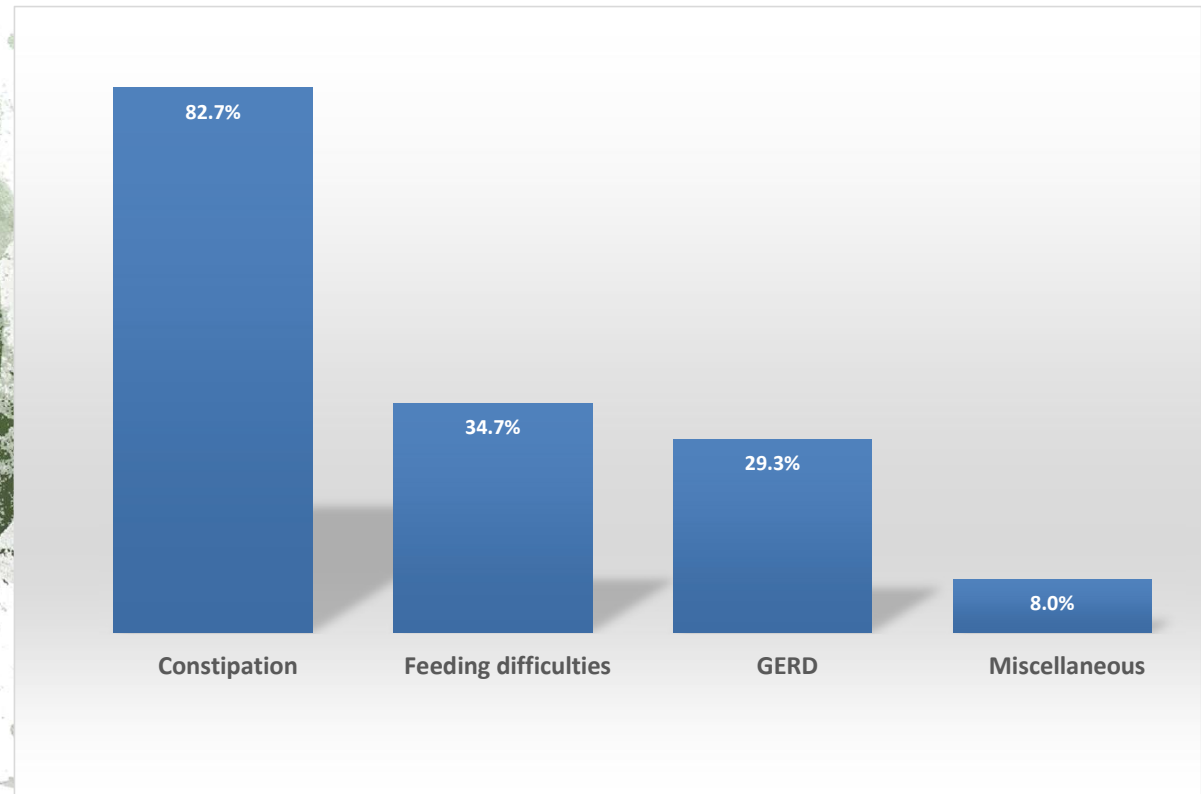


➤ 72% of individuals with DESSH syndrome have eye abnormalities

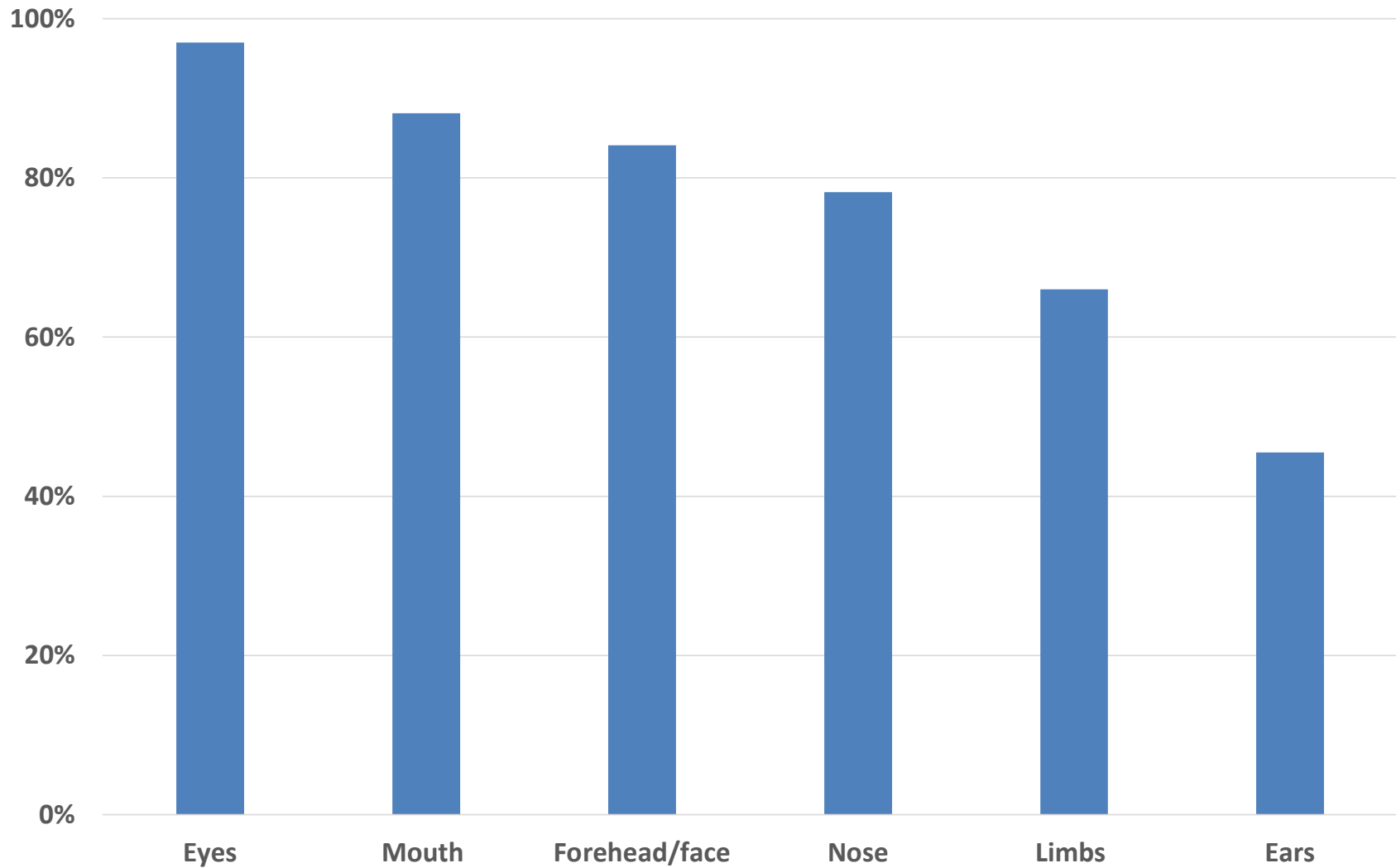


GI Findings in DESSH Syndrome

- 74.3% of individuals with DESSH syndrome have GI abnormalities



Frequency of dysmorphic facial features in DESSH patients





Facial Differences in DESSH Syndrome

- Many but not all individuals with DESH syndrome exhibit recognizable facial features
- Common findings include:
 - ✓ deep set eyes
 - ✓ thick/broad eyebrows or unibrow
 - ✓ wide mouth
 - ✓ abnormal dental morphology
 - ✓ thin upper lip
 - ✓ broad/prominent forehead
 - ✓ square-shaped face
 - ✓ Depressed/wide nasal bridge w/bulbous tip
 - ✓ Ear anomalies: pits, creases, folding
 - ✓ hirsutism (excessive hair)
 - ✓ hand and foot anomalies (short digits, nail anomalies)

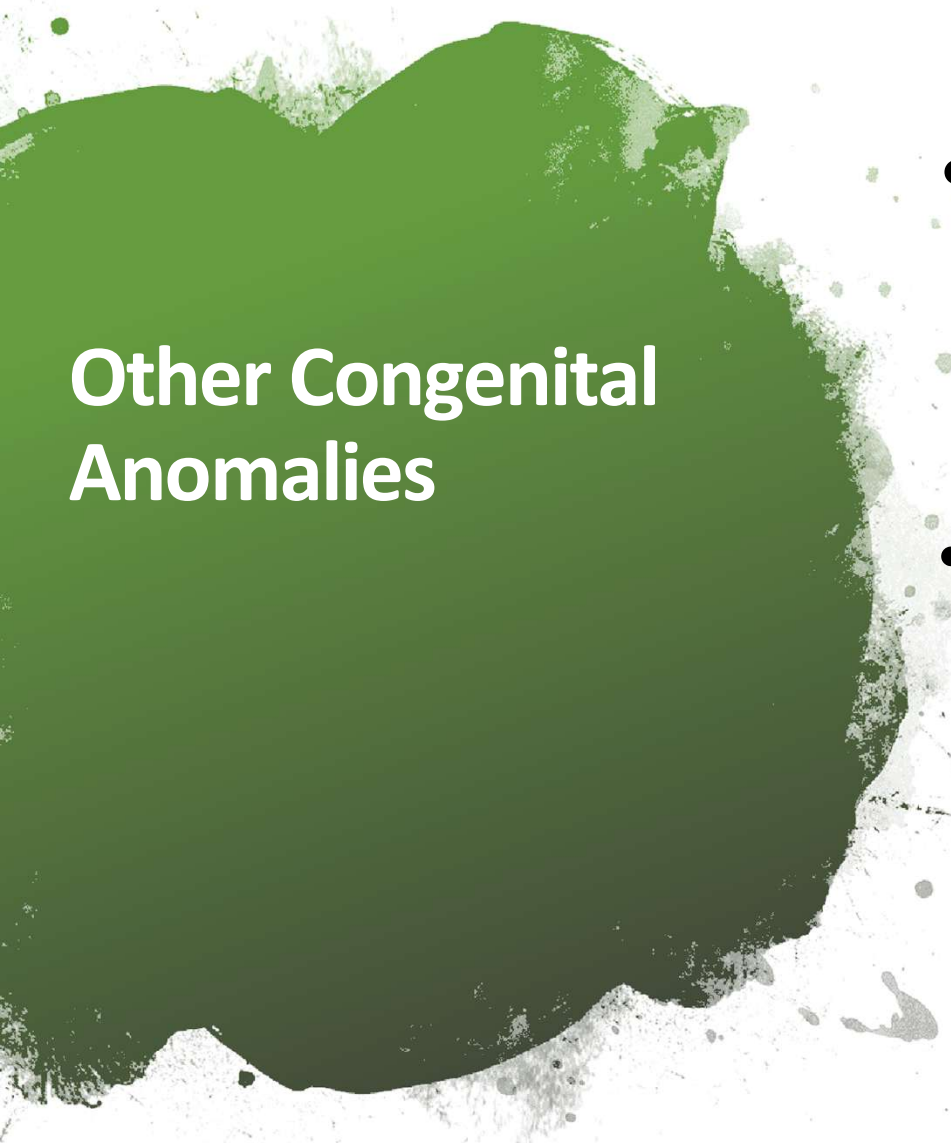


Figure 4. Facial features of patients with DESSH syndrome.



Hallux valgus deformity; nail abnormalities



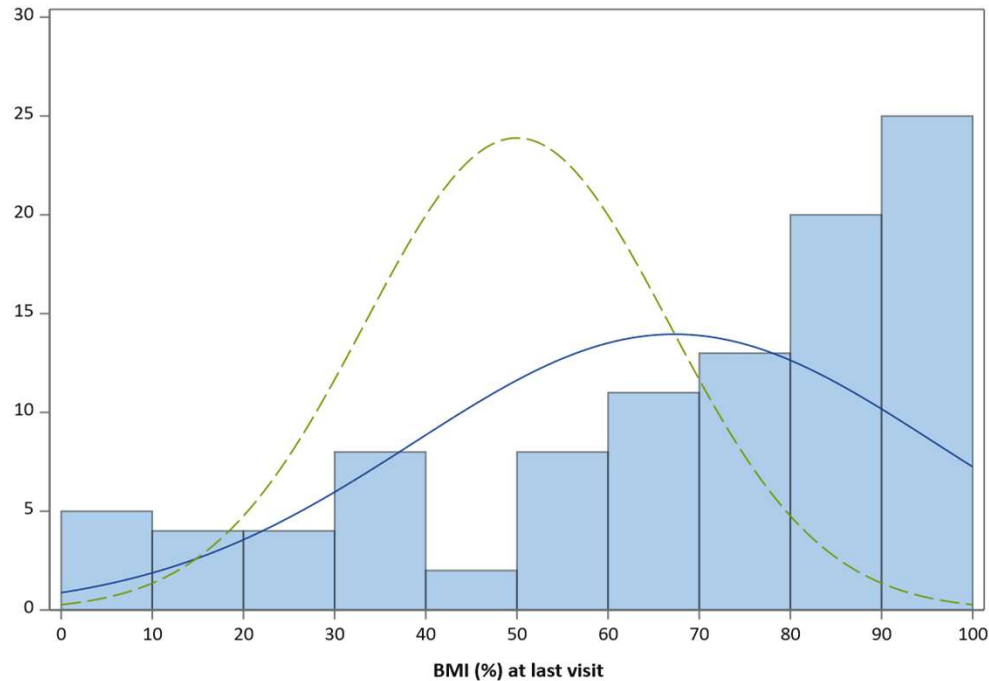


Other Congenital Anomalies

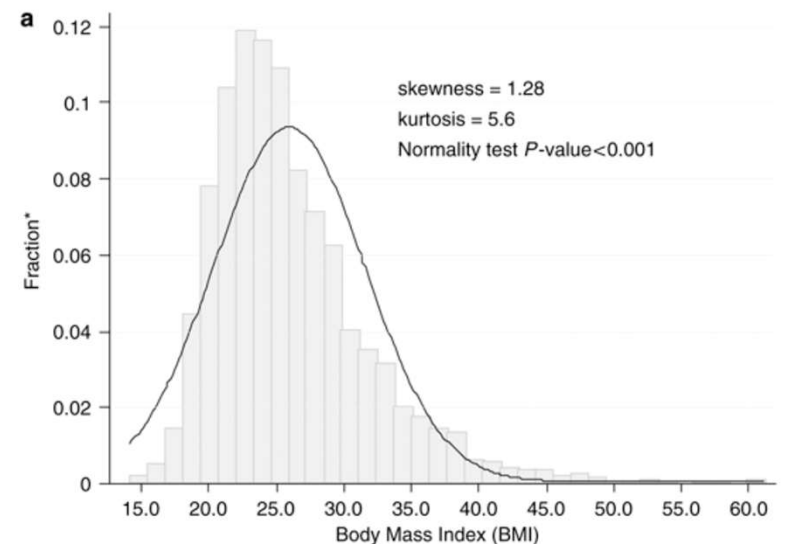
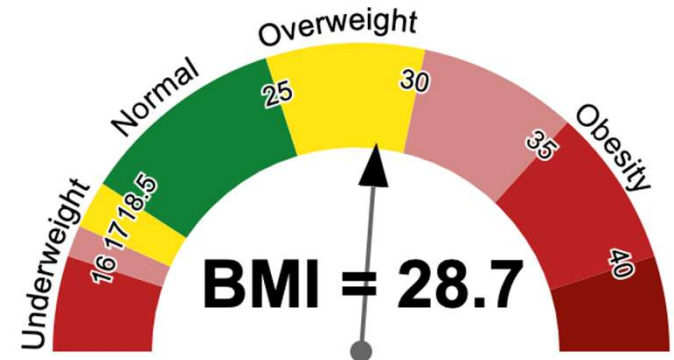
- Renal ultrasound (n=51): 27.5% had nonspecific kidney abnormalities (hydronephrosis)
- Cardiac echo (n=46): 1/2 had cardiac abnormalities (VSD, PDA, PFO)

BMI Among Individuals w/ DESSH syndrome

25% of individuals have BMI ≥ 90

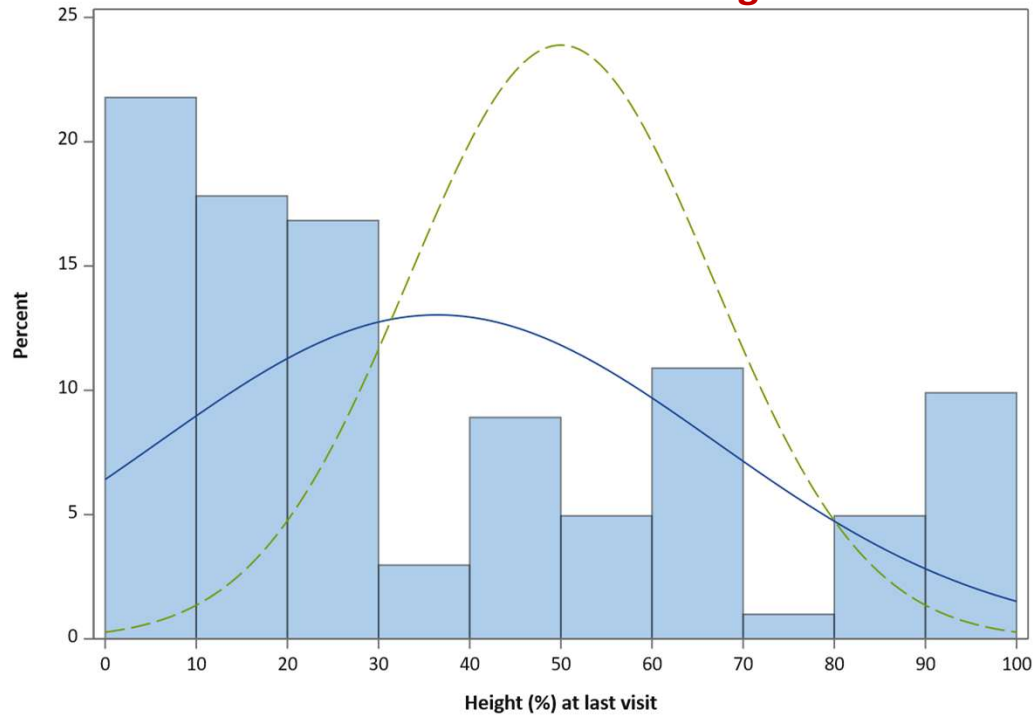


$BMI = \text{weight (kg)} / \text{height}^2(\text{m})$

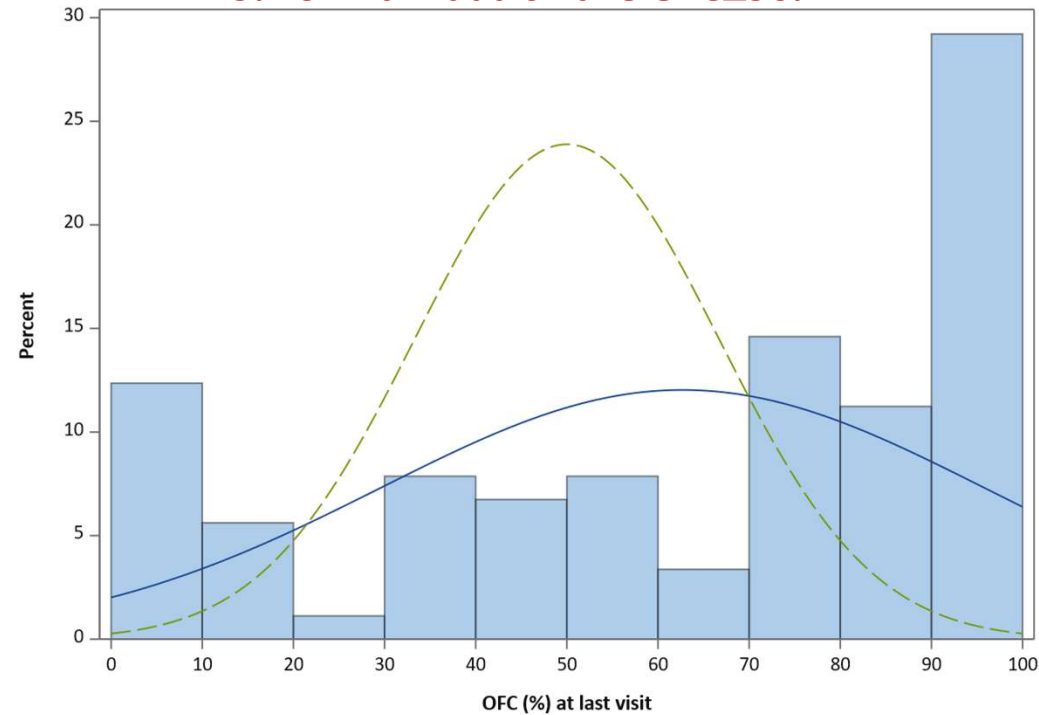


Height and Head Size in DESSH syndrome

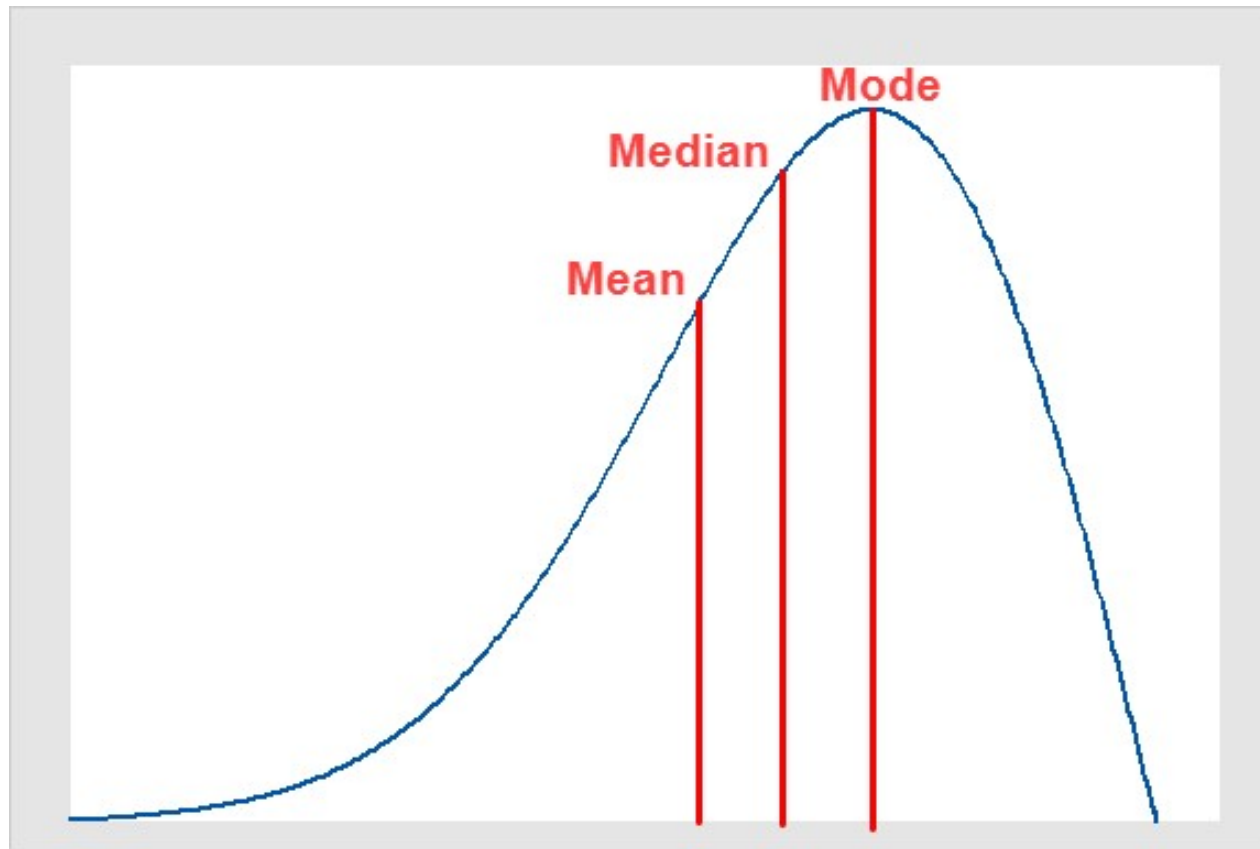
~24% of individuals have height $\leq 10\%$



29% of individuals have OFC $\geq 90\%$

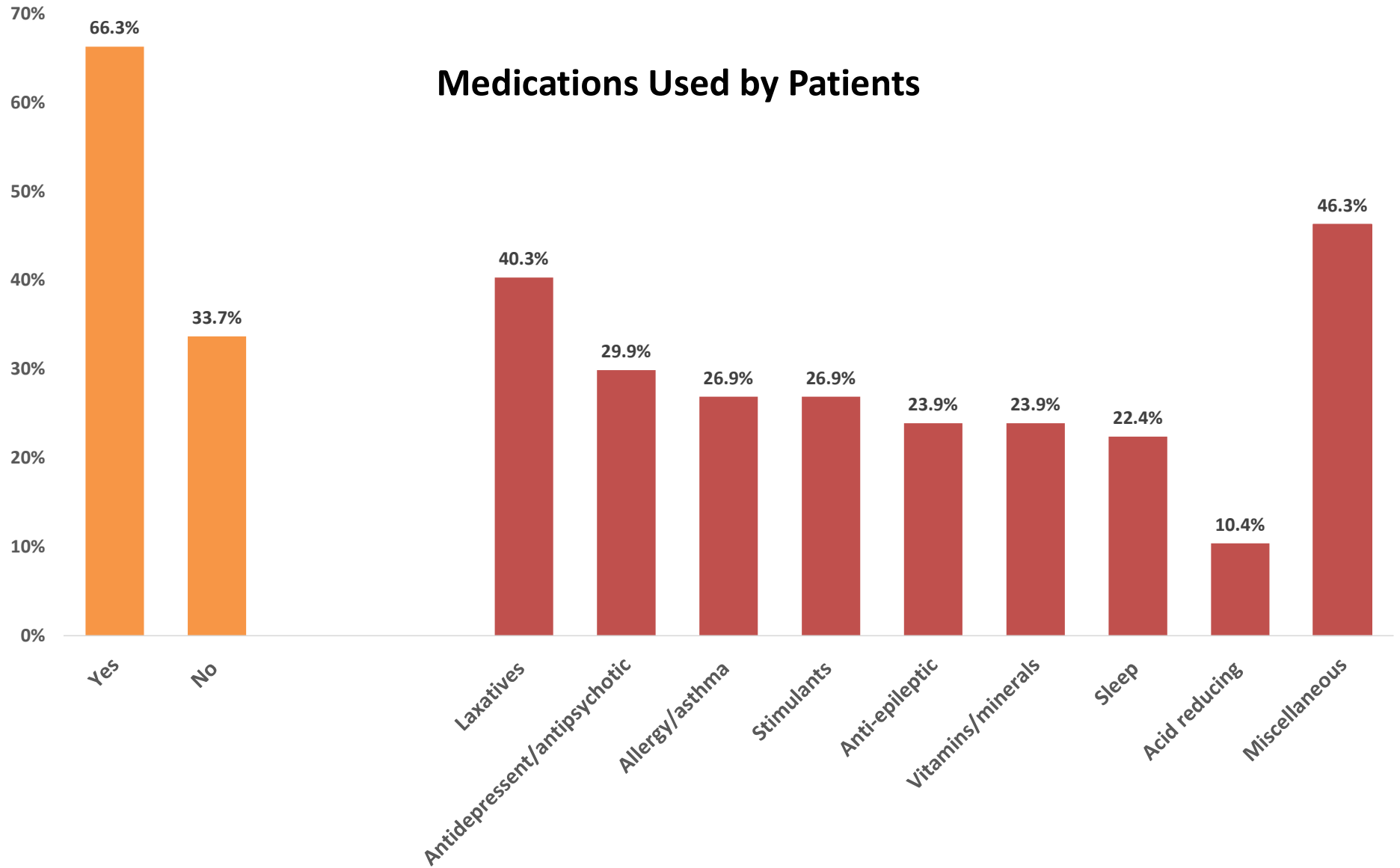


Left skewed distribution



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

Medications Used by Patients

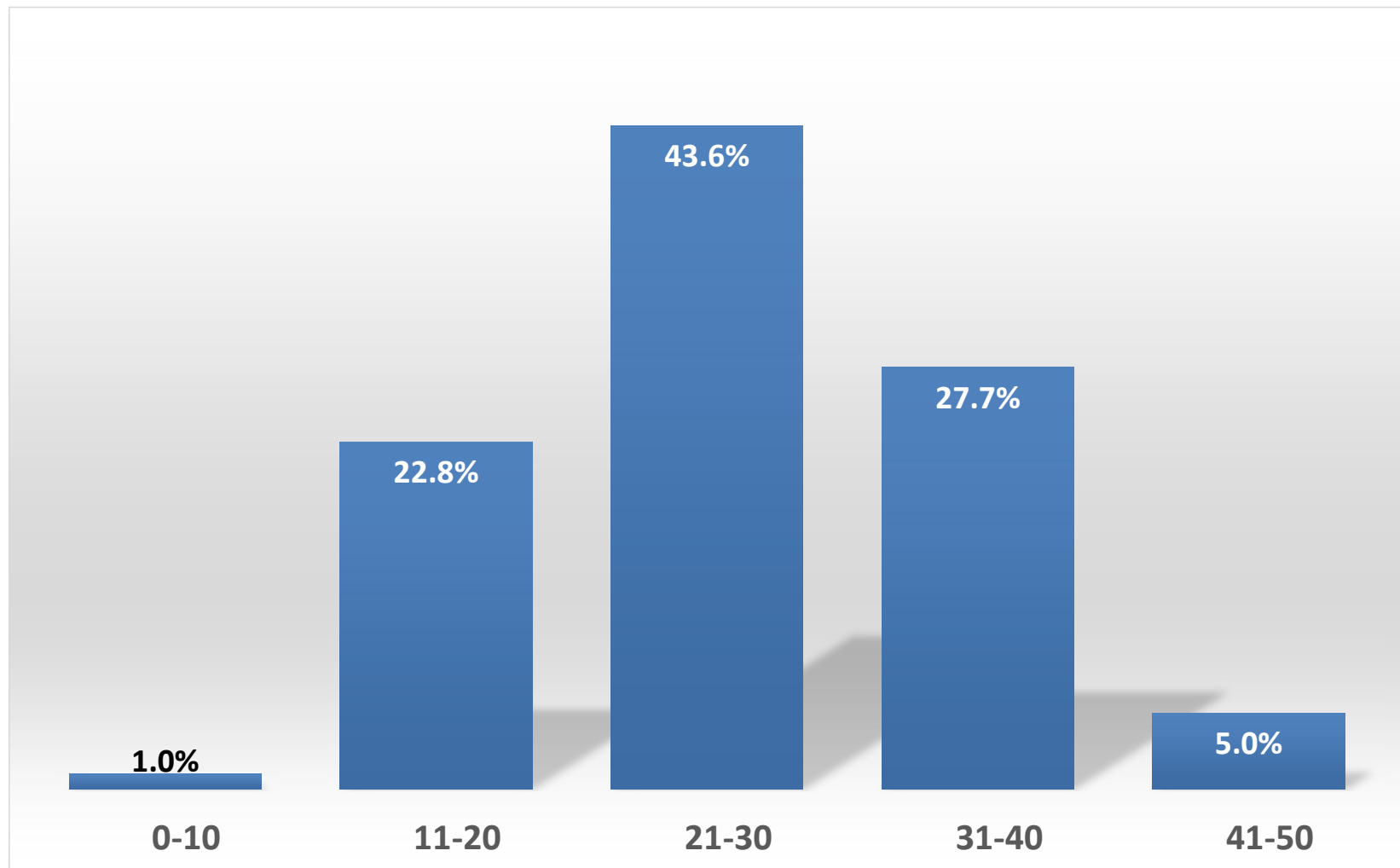


DESSH Syndrome Severity Scale

Item	Criteria	Score
# of any behavioral problems	0 >3	0-4
Seizure	Yes , No	0, 4
Hypotonia	Yes, No	0, 2
# of dysmorphic features	≤5 - ≥15	0-4
Abnormal brain MRI	Yes, No	0,4
Abnormal EEG	Yes, No	0,4
Age of walking	<15 mo - >30	0-4
Age of first word	<15 mo - >30	0-4
Any sleep abnormality	Yes, No	0, 4
Any vision abnormality	Yes, No	0, 4
Any GI abnormality	Yes, No	0, 4
Degree of DD/ID	Normal - severe	0-4
# of therapies	0 >3	0-4

Total Score: 0-50

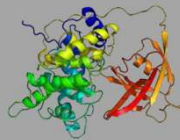
DESSH Syndrome Severity Scale (n=101)



Etiology of DESSH Syndrome



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

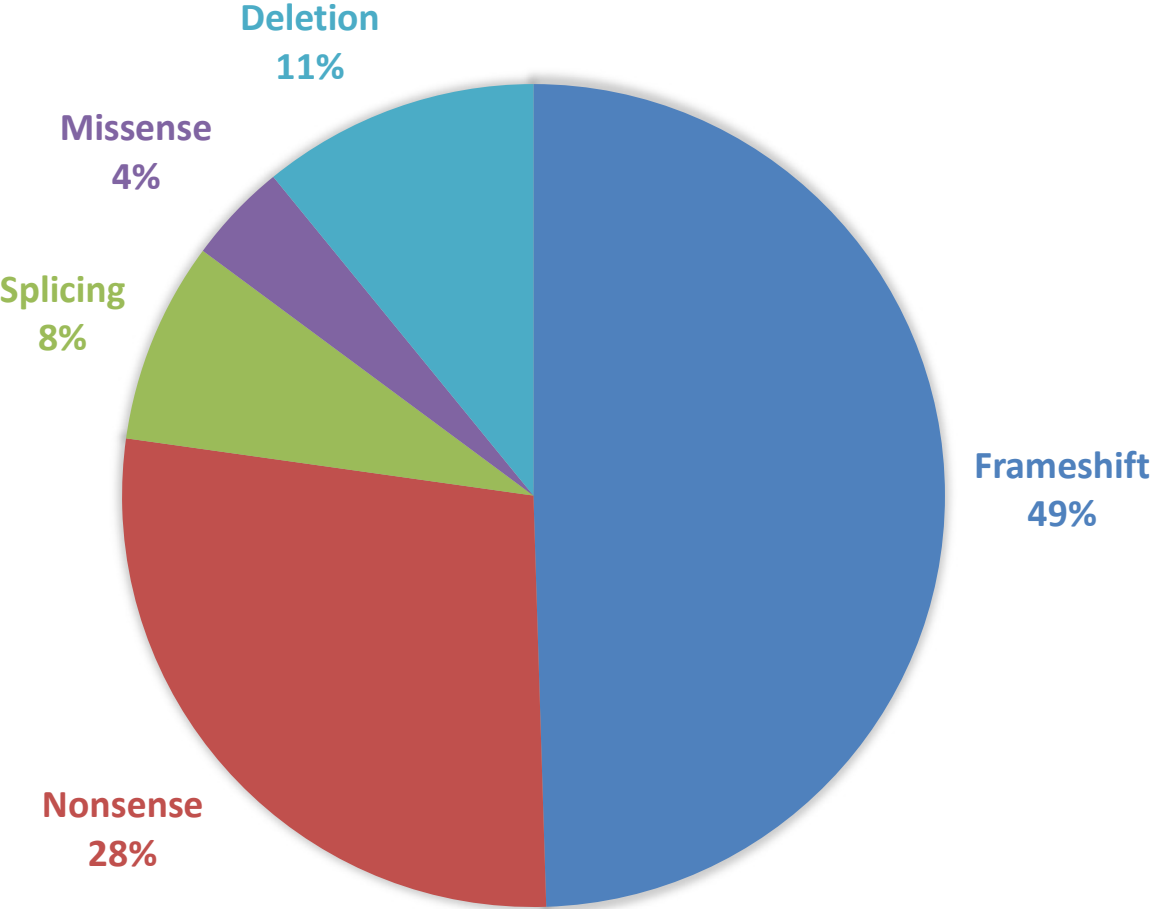


The great majority of patients have point genetic alterations (=pathogenic variants=mutations) that disrupt the function of the product of the WAC gene



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

FREQUENCY OF VARIANT TYPES AMONG INDIVIDUALS IN THE COHORT (N=101)



Mutation	Recurrence
55 variants	1
p.Arg47* , p.Arg85Serfs*2, p.Glu88Glyfs*10 3, p.Leu419Aspfs* 15, .Arg513* , p.Arg622*	2
p.Gly92Alafs*2, p. Arg550*	3
p.Arg151*	6

10p Deletions

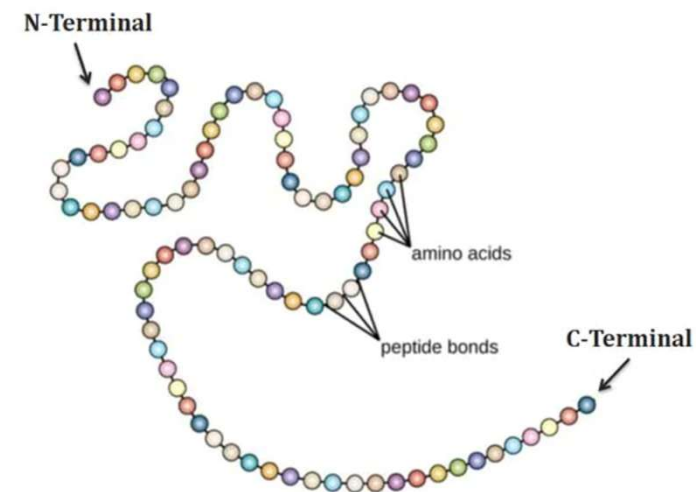


- Individuals with 10p11.23 deletions encompassing WAC have been reported
- 0.7-10.6 Mb deletions
- Developmental delay, dysmorphic features, hyperactivity, and congenital heart defects.
- Their facial features included synophrys, thick eyebrows, short neck, deep set eyes, bulbous nose, full cheeks
-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

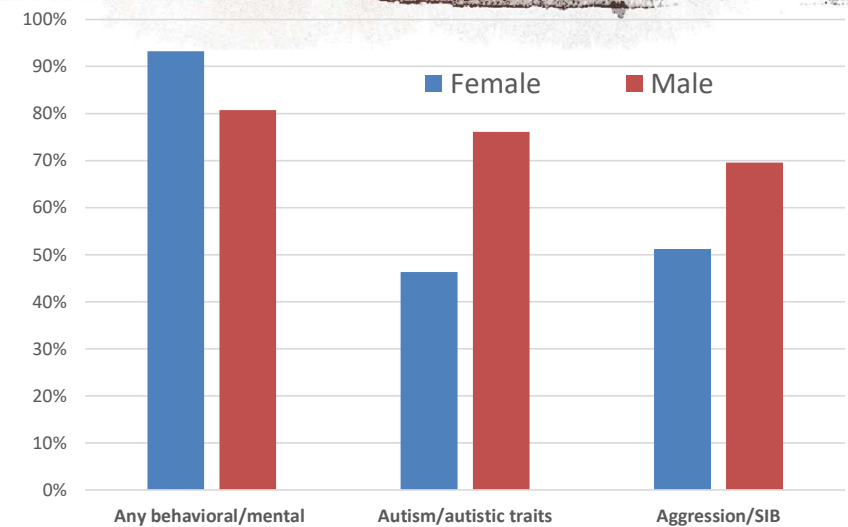
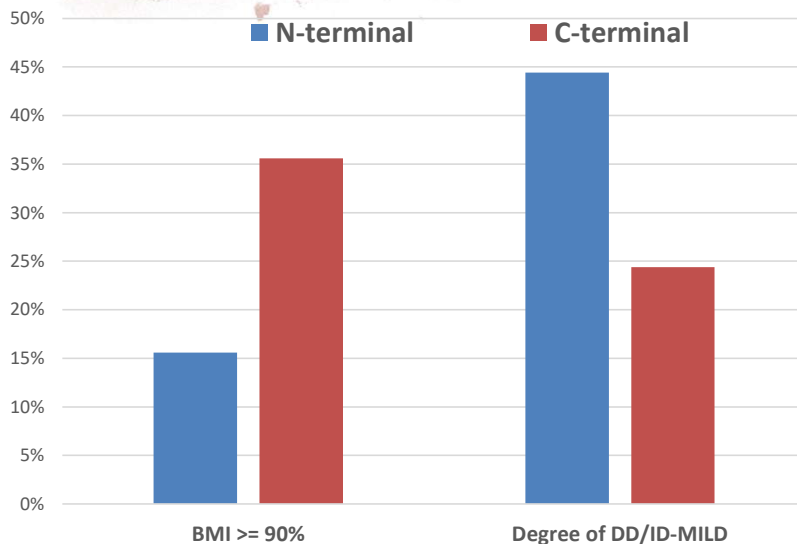
Genotype-Phenotype Correlation

- Severity of ID and other clinical findings vary between patients:

- Type of mutation
- Location of the mutations in the protein
- Other genetic factors (modifiers)
- Demographics (gender)



Genotype-Phenotype Correlation



- All 5 deletion individuals who had echocardiography had abnormal results **100%** (95% CI, 25.7%–54.3%) as compared to **39%** (95% CI, 25.7%–54.3%) in the remainder of the group.

DESSH Syndrome - Inheritance



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

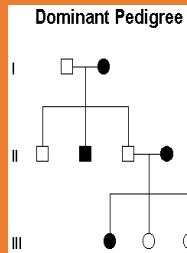


The genetic changes in the WAC gene are random events during the formation of reproductive cells (eggs & sperms)

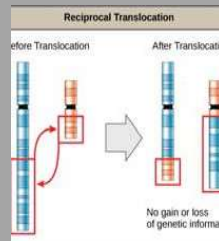


3 familial recurrences due to a presumed germline mosaicism (parents have negative testing)

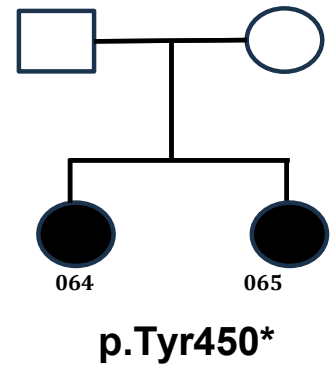
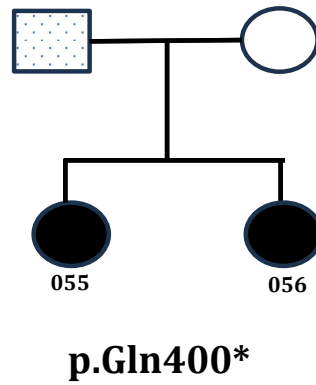
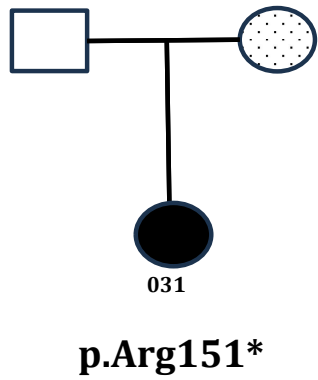
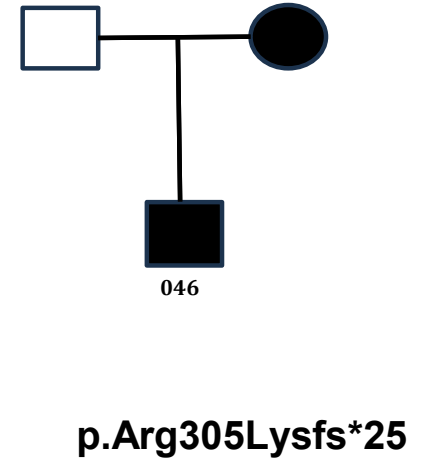
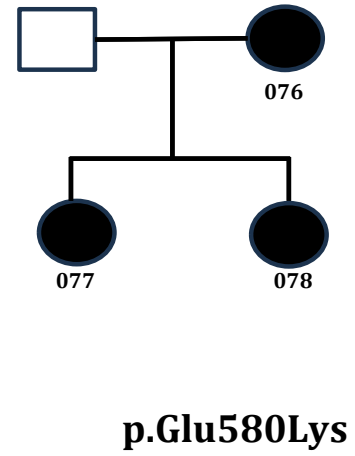
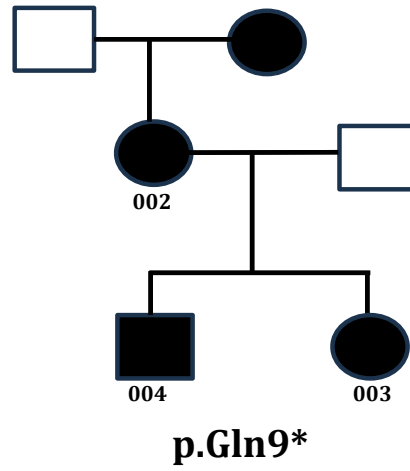
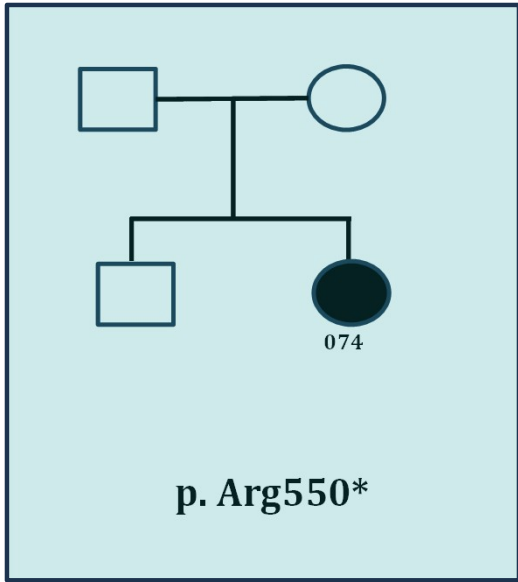
DESSH Syndrome - Inheritance



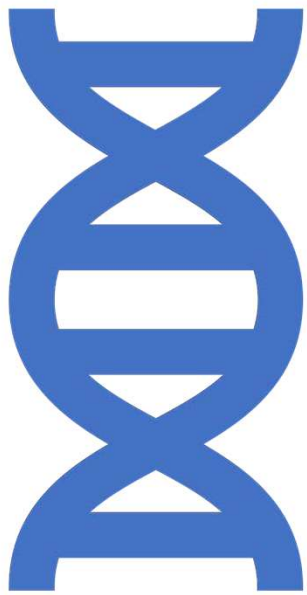
Recent data suggest that DESSH syndrome can run in families and therefore testing parents is recommended (especially with family history of mild ID/DD) for genetic counseling purposes



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 mosaicism



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



What is Next?

1

Study larger cohorts of individuals with DESSH syndrome is needed to understand the **full spectrum** of manifestations and the possible genotype phenotype correlation

2

Study individuals longitudinally and adult individuals to understand the **natural history** of this condition
Study the burden of the disease from caregivers' standpoint

3

- Study animal models and the function of WAC protein
- Study the effect of early therapies and medical treatment on outcomes
- Gene therapy

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



Maintain the DESSH syndrome Clinic

DESSH Clinic

- A **multidisciplinary setting** is a successful model for evaluating and managing the complex needs of patients
- The evaluation of large number of patients with a rare condition will pave the way for medical **professionals to develop expertise** in this condition
- **Natural history study (2025-2028)**
- **The collection of biospecimens** will provide a platform to establish a large repository that can serve researchers interested in this condition
- It highlights the value of collaboration between **academia** and **family support groups**

Acknowledgements

➤ DESSH Foundation

Board of the DESSH Foundation

➤ Patients and their families

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