Alström Syndrome: Clinical Overview for Families

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Alström Clinic at GBMC

- Started in 2013
- Robin and Jan Marshall from Alström Syndrome International, Clair Francomano from Greater Baltimore Medical Center
- Formed by Otolaryngology and Cochlear Implant Centers of Excellence and Harvey Institute for Human Genetics
- Recruited participation from Alex Levin, Wills Eye Hospital and Meral Gunay-Aygun, Johns Hopkins Hospital and NIH
- Over time recruited specialists from GBMC, JHH and UMMC

Set-up of Clinic

- Attendees recruited through ASI
- 6-8 families per clinic
- Biannual clinic: have alternated pediatric (early – late childhood) with adolescent/young adult or older adult
- Affected individual(s) in family and at least one family member attend
- Follow-ups only if room

https://www.youtube.com/watch?v=UJ6GmaZVFkU&list=RDUJ6GmaZVFkU&start_radio=1&t=0

Format of Clinic

- Held over 2 days (Friday-Saturday)
- Families stay in local hotel, van transport
- First day: Otolaryngology, Audiology, (Speech Pathology), Hoover Low Vision, Hepatology, and Pediatric Ophthalmology
- Second day: Genetics, Genetic Counseling, Endocrinology, Cardiology, Gastroenterology, (Gynecology), Nephrology, Behavioral Psychology
- Records ahead of time
- Medical history summarized, physical exams performed and summary letter sent to PCP and family

Demographics

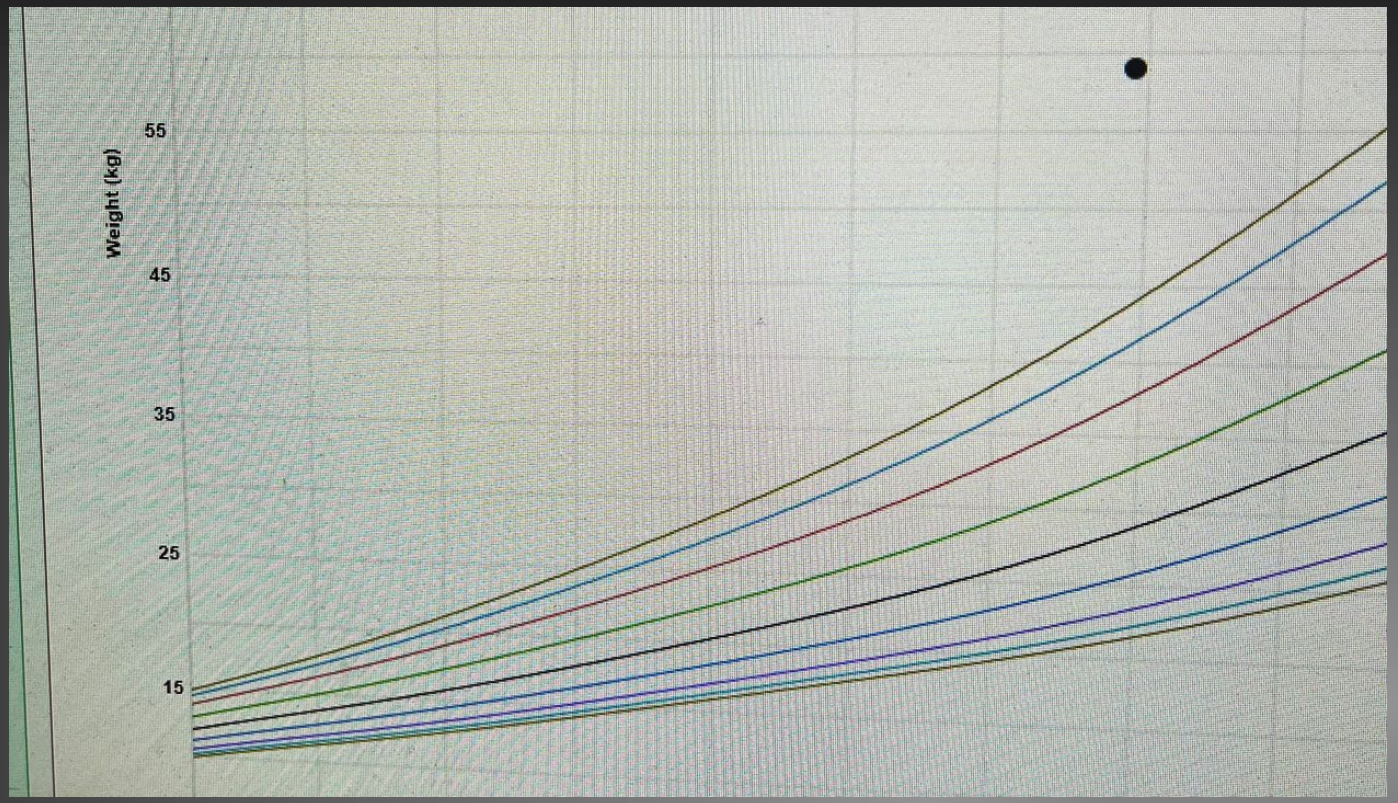
- 65 total individuals with Alström syndrome to date
- Sex: 36 males, 29 females, 1.24:1
- Age:
  - Age range 15 months – 45 years, born 1975 – 2021
  - Average age 15.9 years (formerly 24.2, 17.1 years)
  - 44 individuals <18 years (68%), 21 individuals ≥18 years (32%)
- Location:
  - 77% from United States (eg CA 9, FL 5, KY 4)
  - Other countries: Canada 9%, Brazil, Belgium, Poland, Greece, Netherlands, Turkey, India, Malaysia
- Follow-ups: 9 (14%)
- Deaths: 4 (6%) over 10 **years**

Diagnosis

- Diagnosis made
  - Ages of diagnosis: 4 months – 32 years
  - Average age of diagnosis 8.4 years
  - For ≥ 18 yo, average age 14 years
  - For < 18 yo, average age 5.3 years
- Diagnosis made by different specialties:
  - Ophthalmology 44%
  - Genetics 37%
  - Endocrinology 7%
  - Dermatology, Cardiology, Neurology 2% each
  - Diagnosed by mother 5% (not counting siblings)

Physical Exam: Growth

- Height
  - Mostly normal
  - 8% above 97th percentile
  - 8% below 3rd percentile
- Obesity
  - Truncal
  - 46% above 97th percentile
- Head circumference
  - Normal to macrocephaly
  - 25% $\geq$ 98th percentile
  - 1 pt below 2nd percentile



Physical Exam: Characteristic Facial Features

- Oval facies 55/65 (85%)
- Prominent supraorbital ridge 71%
- Epicanthal folds 83%
- Deep-set eyes 75%
- Thickened ear helices 68%
- Full cheeks 60%
- Small mouth 80%
- Small chin 49%
- Exaggerated chin crease 69%

Frontal Facial Features, Younger

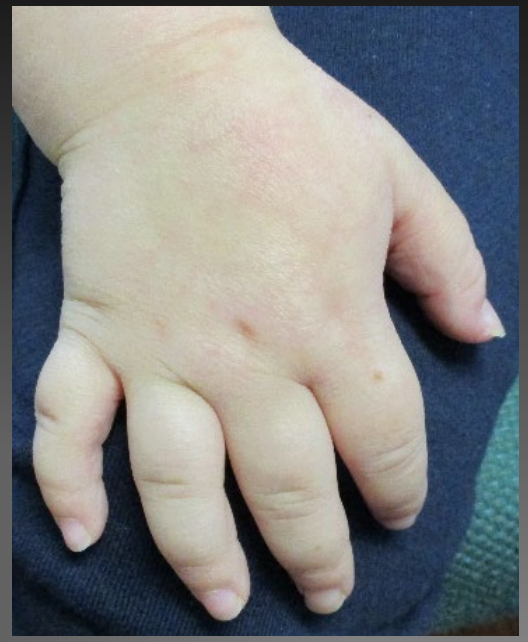
- Very similar, recognizable phenotype
- Note oval face 89%
- Deep-set eyes 89%
- See epicanthal folds 89%, thick nares, full lips, well-defined cupid's bow

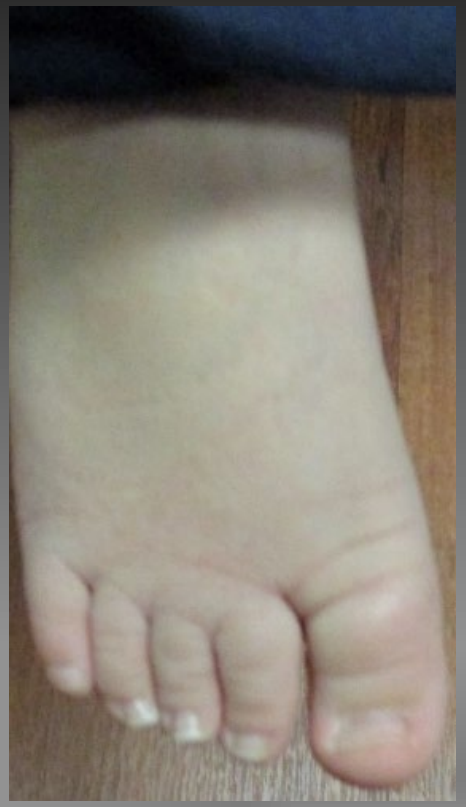
Side Facial Features

- Long ears, often simple
- Thickened lobes
- Chins often forward

Physical Exam: Extremity Findings

- Broad hands 74%
- Tapered fingers 90%
- Broad first phalanges
- 5th finger clinodactyly 41%
- Short hands and feet 25%
- Broad feet 85%
- Flat feet 65%
- Large/broad great toes 92%
- Convex toenails 77%



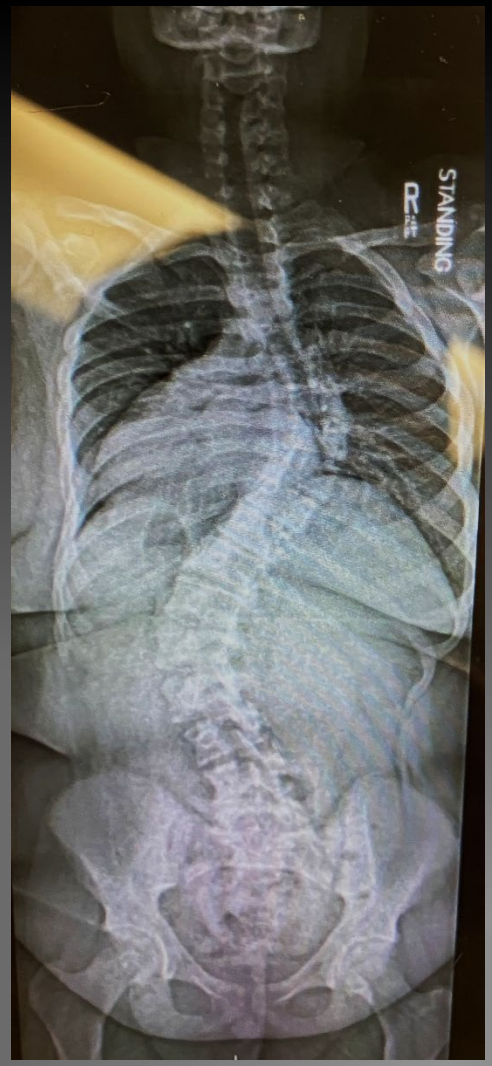


Orthopedic Complications

- Limited movement joints (elbow, fingers)
- Flat feet 65%

- Scoliosis 19% - can be severe
- Kyphosis 6%
- Leg length discrepancy – can be due to scoliosis

- Lymphedema – upper limbs, breast, feet
- Edema secondary to cardiac/renal causes

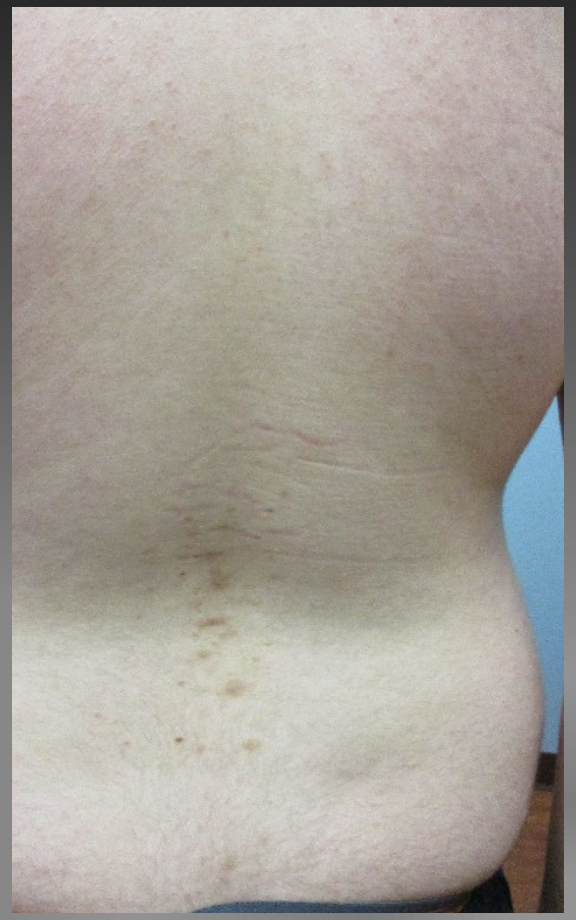


Orthopedic Management

- Monitor movement of joints and obtain physical therapy if any limitation
- Discuss need for orthotics for shoes with physical therapy if flat feet present
- Consider pediatric orthopedic evaluation if any major concern including scoliosis, hip problem
- Leg length discrepancy – try lift in shoes
- Management for lymphedema by specialist

Skin Findings

- Acanthosis nigricans – related to diabetes
- Acrochordons (small skin growths)
- Stretch marks
- Thinning hair



Skin Findings Management

- Acanthosis nigricans – once the diabetes is under control, this will resolve; need to follow HgbA1c
- Acrochordons (small skin growths) – followed by dermatology
- Stretch marks – no treatment
- Thinning hair – a sign of liver disease involvement and estrogen resistance

Eye Findings

- Cone-rod retinal dystrophy 100%
- Nystagmus 72%, onset in infancy but resolves
- Cataracts 20%
- Other rarer complications
- Previous diagnosis of achromatopsia common
- Management: vision services, Braille, orientation and mobility, cane, dog

Otolaryngology Findings

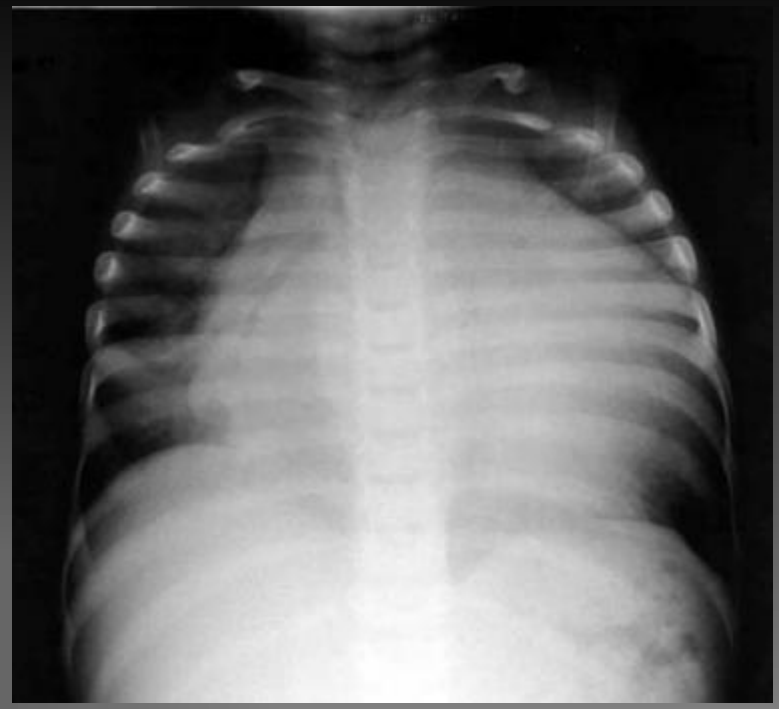
- Hearing loss 60% of total group
- Sensorineural hearing loss or mixed
  87% usually bilateral
- Conductive hearing loss 9%
- Recurrent ear infections when younger

Otolaryngology Management

- Hearing loss – follow up with Audiology
- Sensorineural hearing loss - consider hearing aids and/or cochlear implant
- Conductive hearing loss – consider myringotomy and ear tube placement
- Cochlear implants 3 – 5 yo, 40 yo x2

Cardiovascular System Findings

- Cardiomyopathy 20/65 (31%) - most infantile onset but can recur in adulthood
  - Congestive heart failure 8%
  - LVH 8%
  - Enlarged heart 9%
  - 2 patients had had cardiac arrest
- Ejection fraction - usually normal but low at times
- Hypertension 18%
- Hyperlipidemia 32%
  - Elevated triglycerides
  - Elevated cholesterol



https://emedicine.medscape.com/article/895187-overview

Cardiovascular Management

- Cardiomyopathy – cardiology management
- Continue to have regular echocardiograms
- Hypertension – often on one medication
- Hyperlipidemia – treat with medications but needs to be followed

Endocrine System Findings

- Type 2 diabetes 34%
  - ≥ 18 years 12/22 (55%)
  - < 18 years 10/22 (45%)
  - Elevated HgbA1c when not in good control
- Hypothyroidism 12%
- Growth hormone deficiency 6%

Endocrine System Findings

- Type 2 diabetes -
  - Often insulin is used
  - Also metformin, or both
  - Follow HgbA1c to assess good control
  - Prevention is the most important!! Diet and exercise seem to work well
- Hypothyroidism – treated with thyroid hormone
- Growth hormone deficiency – treated with growth hormone injection if needed

Gastrointestinal System Findings

- Liver involvement 44%
  - Fatty liver 19/65 (29%)
  - Liver fibrosis / enlargement 15%
  - Hepatocellular carcinoma – 2 pts (3%)
- Pancreatitis 8%
- Esophageal varices 6%
- Gastroesophageal reflux 6%
- Gastroparesis – constipation common
- Feeding tube needed when younger

Gastrointestinal System Management

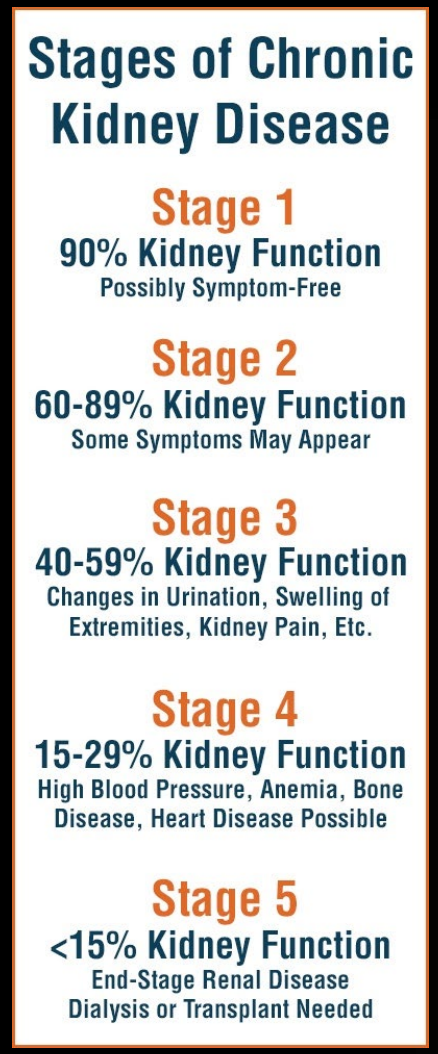
- Fatty liver and liver fibrosis - can be followed by Fibroscan but ***
- Pancreatitis – need to be aware of the risks and check enzymes if present with abdominal pain
- Gastroesophageal reflux – managed by medications
- Constipation – treated with Miralax

Reproductive System Findings

- Early puberty 5%, delayed puberty 3%
- Males:
  - Hypogonadism 17/36 males (47%)
    - Low testosterone
    - Short penis / Small testes
  - Genital anomalies – hypospadias, cryptorchidism
  - Gynecomastia 5/36 males (14%)
- Females:
  - Ovarian cysts 3%
  - Menstrual problems
    - Irregular / abnormal menses 8/29 females (28%)
    - PCOS 12%

Reproductive System Management

- Followed by pediatric endocrinology for pubertal changes with hormone assessed and treated if indicated
- Males:
  - Testosterone treatment – injection or patch
  - Genital anomalies – surgery indicated
  - Gynecomastia – often resolves, occasional surgery
- Females:
  - Menstrual problems – consider estrogen treatment if not active liver problem
  - Need to follow liver functions if elevated
  - Check liver functions once if starting estrogen



Renal Findings

- Chronic kidney disease 11/65 (17%)
  - Stages 2-5
  - Several individuals on dialysis
- Hydronephrosis 9%
- Urinary retention 11%
- Nephrocalcinosis, renal stones

https://www.anapolweiss.com/the-stages-of-chronic-kidney-disease/`

Neurologic Findings

- Depressed deep tendon reflexes 53%
- Sleep apnea
  - Obstructive 11%
  - Central rare
- Sleep dysfunction 8%
- Seizures - rare
- Hypotonia – rare
- Brain MRI - typically normal

Neurologic Management

- Monitor neurologic exam
- Obstructive sleep apnea - adenoidectomy if indicated
- Sleep dysfunction - can try melatonin, good sleep hygiene
- Seizures - if present, might need medications
- Hypotonia - treatment is physical therapy

Development in Alström Syndrome

- Majority developmentally normal – 15% delayed overall (compared to 22% initially)
- Early milestones
  - 22% had delayed walking (after 19 months)
  - 22% had delayed speech (after 20 months)
  - 33% had delayed toileting (over 4 years)
- Degrees: 4 with master's, 4 with bachelor's, 3 with associate's, 10 taking college classes/in college, 3 graduated high school
- Occupation: most students, 4 working, 2 volunteer jobs, 1 artist, 3 toddlers, 2 not working

Development Management

- Early intervention therapy – managed by the counties in each state
- Important to access therapy if indicated
  - Physical therapy – for gross motor
  - Occupational therapy – for fine motor, oral motor, sensory integration
  - Speech therapy – for feeding and speech/language
- Follow development through pediatric visits
- Developmental evaluation if any concern or delays

Behavioral/Psychiatric Issues

- Depression 15%
- Anxiety 14%
- ADD/ADHD 9%
- Autism spectrum disorder 7/65 (11%)
- Chronic pain – risk for narcotic abuse
- Socially
  - Almost all enjoy being social but some feel socially isolated
  - Dependent on family members to transport them to events/outings
  - Eager to gather with similarly affected friends

Behavioral/Psychiatric Management

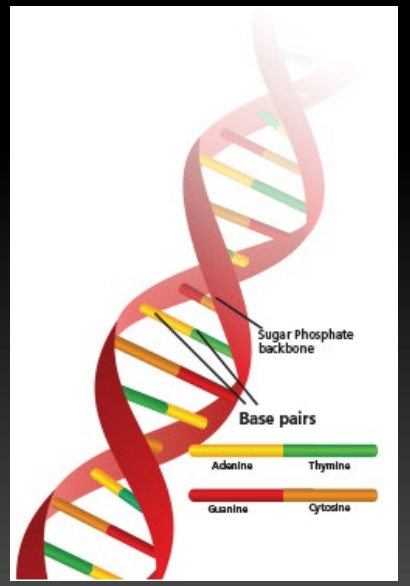
- Be seen by child psychiatry or psychiatry if any concern about depression and if need for medication for anxiety
- Behavioral psychology to help diagnose autism spectrum disorder, ADHD
- Therapy/counseling very helpful
- Chronic pain management – mindfulness, coping therapy, not narcotics or medications!
- Socially – try and identify activities that the individual enjoys and make an effort to help it happen
- Younger children – distract when behaviors are not good and reward when behaviors are improved

Gene: *ALMS1*

- Homozygous or compound heterozygous variants in *ALMS1* lead to loss of function of protein
- This causes systemic fibrosis which lead to Alstrom syndrome
- Regulates non-motile ciliary assembly and/or function but not a “ciliopathy disorder”
- Functions in:
  - Cell cycle
  - Cilia signaling pathways
  - Apoptosis
  - Axonal development and migration
  - Intracellular trafficking
- No reported genotype-phenotype correlation

Catlin et al., 2012

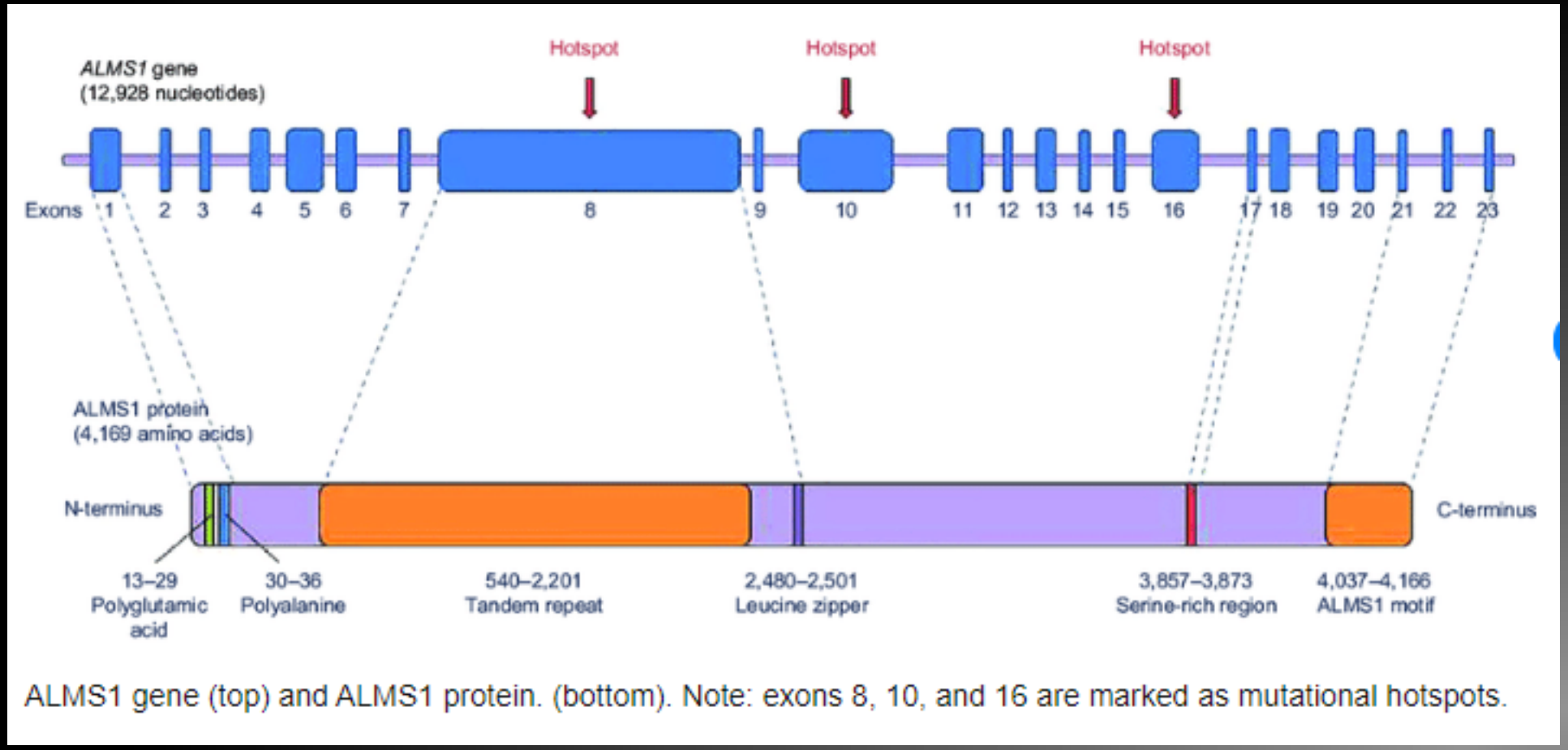
Our Molecular Results



- All but 1 appear to be loss of function mutations
- 86% molecular confirmation
  - 1 pt - unable to confirm variants
  - 1 pt – only able to find 1 parental variant
- 6/28 (12%) homozygous
  - 3/6 from consanguineous families
  - 1 adopted – could be consanguineous
- 2 pts with same 2 variants
- 6 recurrent mutations not counting siblings
  - c.4156dupA (3 pts, one UPD)
  - c.6305C>A (3 pts), c. 6304C>T (1 pt)
  - c.10539_10557ins(n)19 (2 pts)
  - c.10775delC (4 pts, 1 homozygous) – previously reported recurrent variant
  - c.11313_11316delTAGA (5 pts including sibs), c.11316_11319delAGAG (1 pt) – first previously reported recurrent variant
  - c.11416C>T (4 pts including sibs)

https://medlineplus.gov/magazine/issues/summer13/articles/summer13pg11-12.html

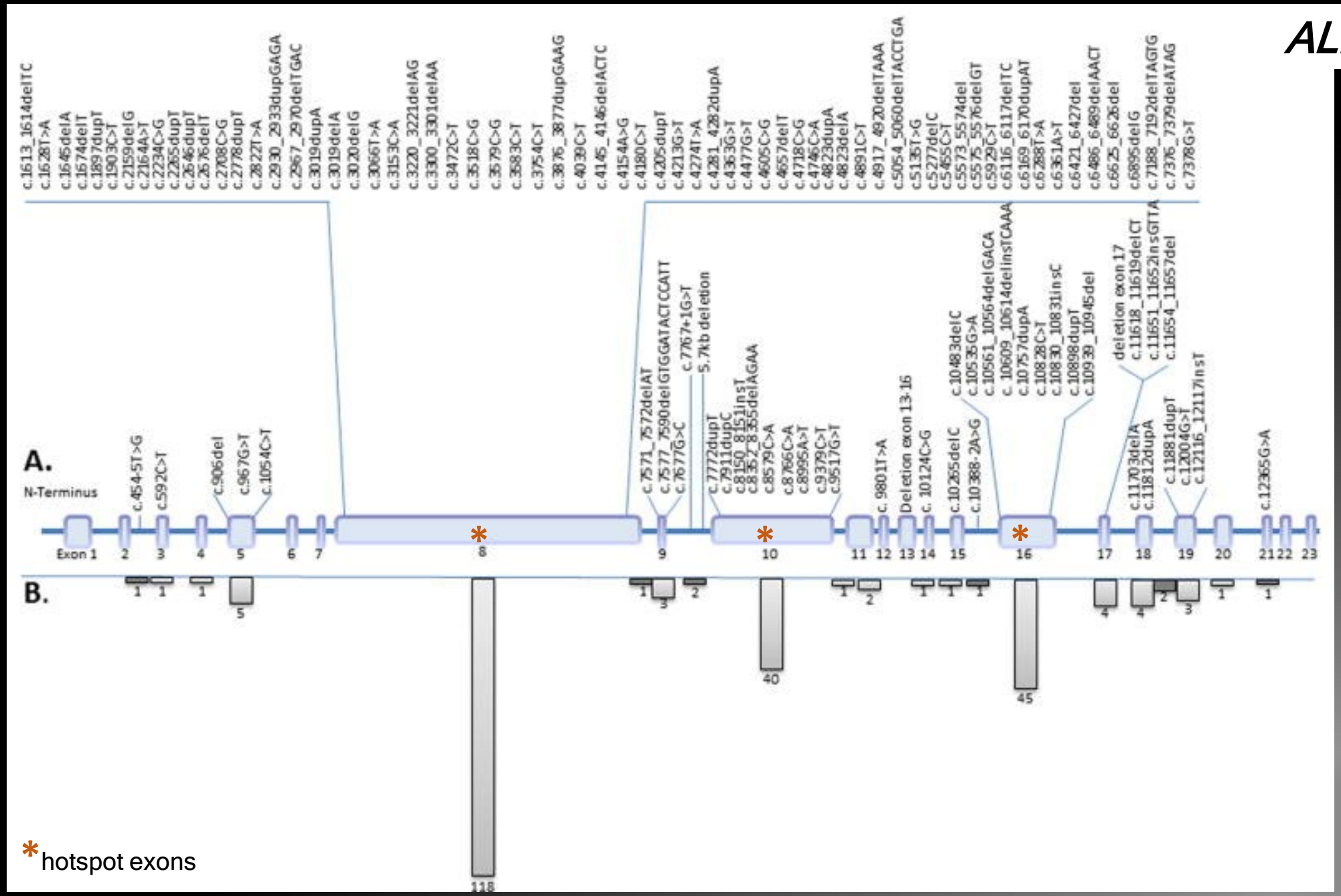
ALMS1 Gene



ALMS1 gene (top) and ALMS1 protein. (bottom). Note: exons 8, 10, and 16 are marked as mutational hotspots.

Alvarez-Satta M., et al., Appl Clin Genet 2015;8:171-9

ALMS1 Gene



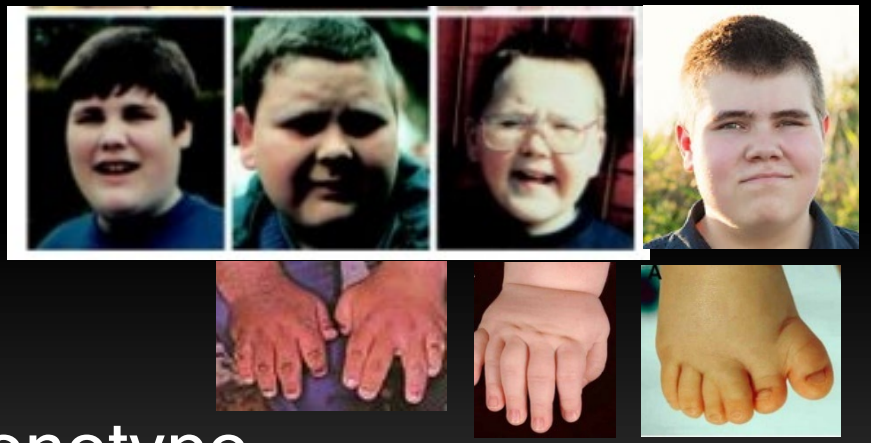
Marshall, JD, et al, Hum Mut, 2015 Jul; 36: 660–668

Summary

- Normal height, 25% macrocephaly, 46% obese
- Facial features typical
- Broad hands, feet, also typical
- 100% retinal cone-rod dystrophy
- 60% hearing loss
- 31% cardiomyopathy + 8% CHF
- 34% type II diabetes
- 44% liver involvement
- 26% severe kidney involvement
- 25% behavioral problems
- Mostly normal developmentally - 15% delayed and 11% with autism spectrum
- 86% have an *ALMS1* variant detectable

Conclusions

Bardet-Biedl syndrome



- AS with variable presentations, recognizable phenotype
- Several non-motile ciliopathy disorders (Alström syndrome and Bardet-Biedl syndrome) have similar dysmorphic facial features/structural findings, previously unreported; may aid in earlier diagnosis
- No exact genotype-phenotype correlations
- Alstrom syndrome multidisciplinary clinic is helpful medically and also socially for behavior and mental health
- This type of longitudinal study with a diverse cohort should continue to prove useful clinically as well as help clarify the ultimate role and function of the *ALMS1* protein

We thank the individuals
with Alstrom syndrome
and their families
and all who help with
the Clinic!

Thanks to all of the Healthcare Providers in AS Clinic at GBMC

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