
## 10th International Conference and Scientific Symposium

***October 4-9, 2023***

***Sheraton North Baltimore Hotel***

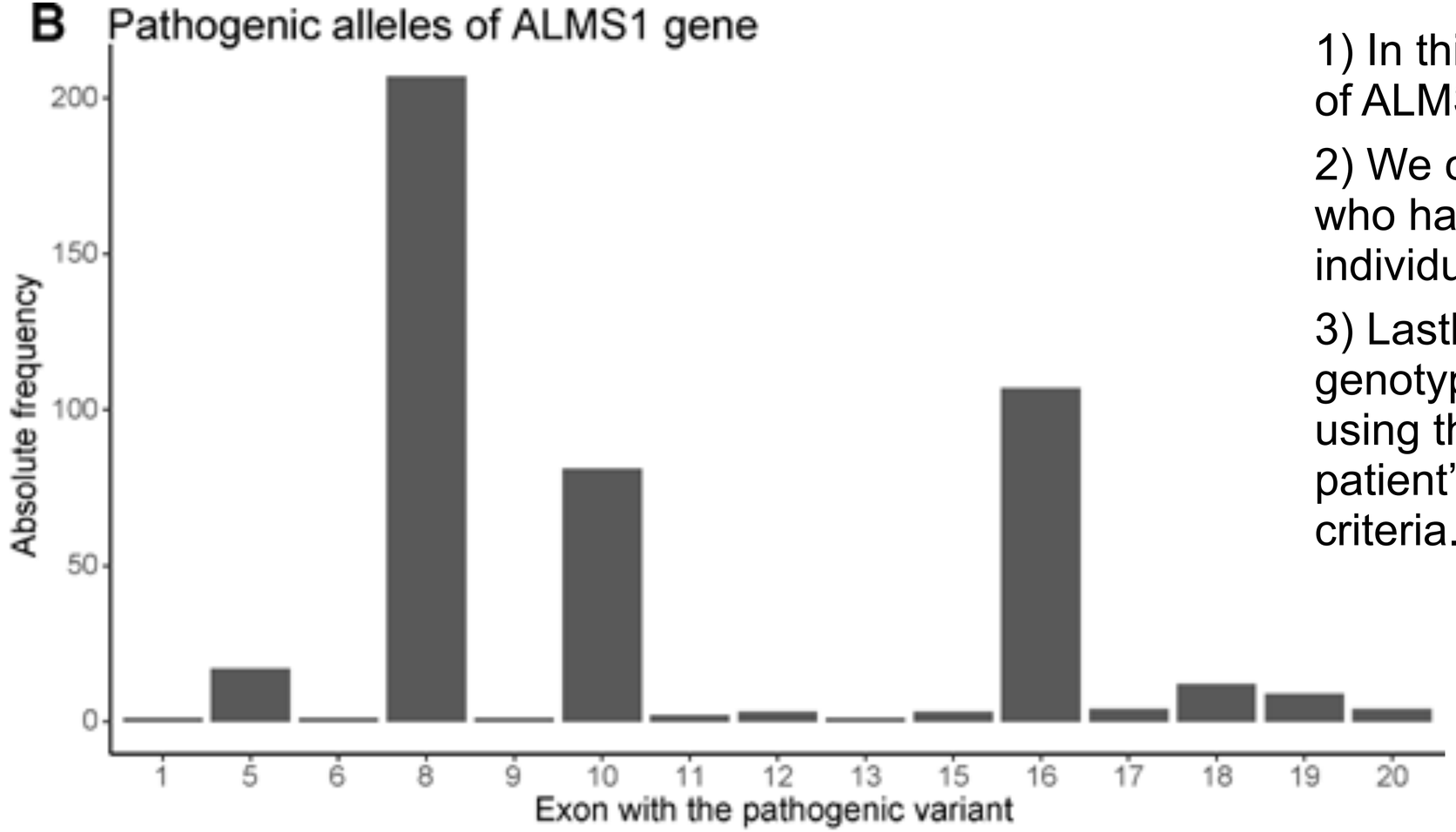
# Mild Phenotypes in Alstrom Syndrome

**Pietro Maffei, Padua University, Italy**

pietro.maffei@aopd.veneto.it, pietro.maffei@unipd.it


Endo-ERN
European Reference Network
on Rare Endocrine Conditions

# Genotype–phenotype associations in Alström syndrome: a systematic review and meta-analysis




1) In this study we collected all cases of ALMS published to date.

2) We created a database of patients who had a genetic diagnosis and an individualised clinical history.

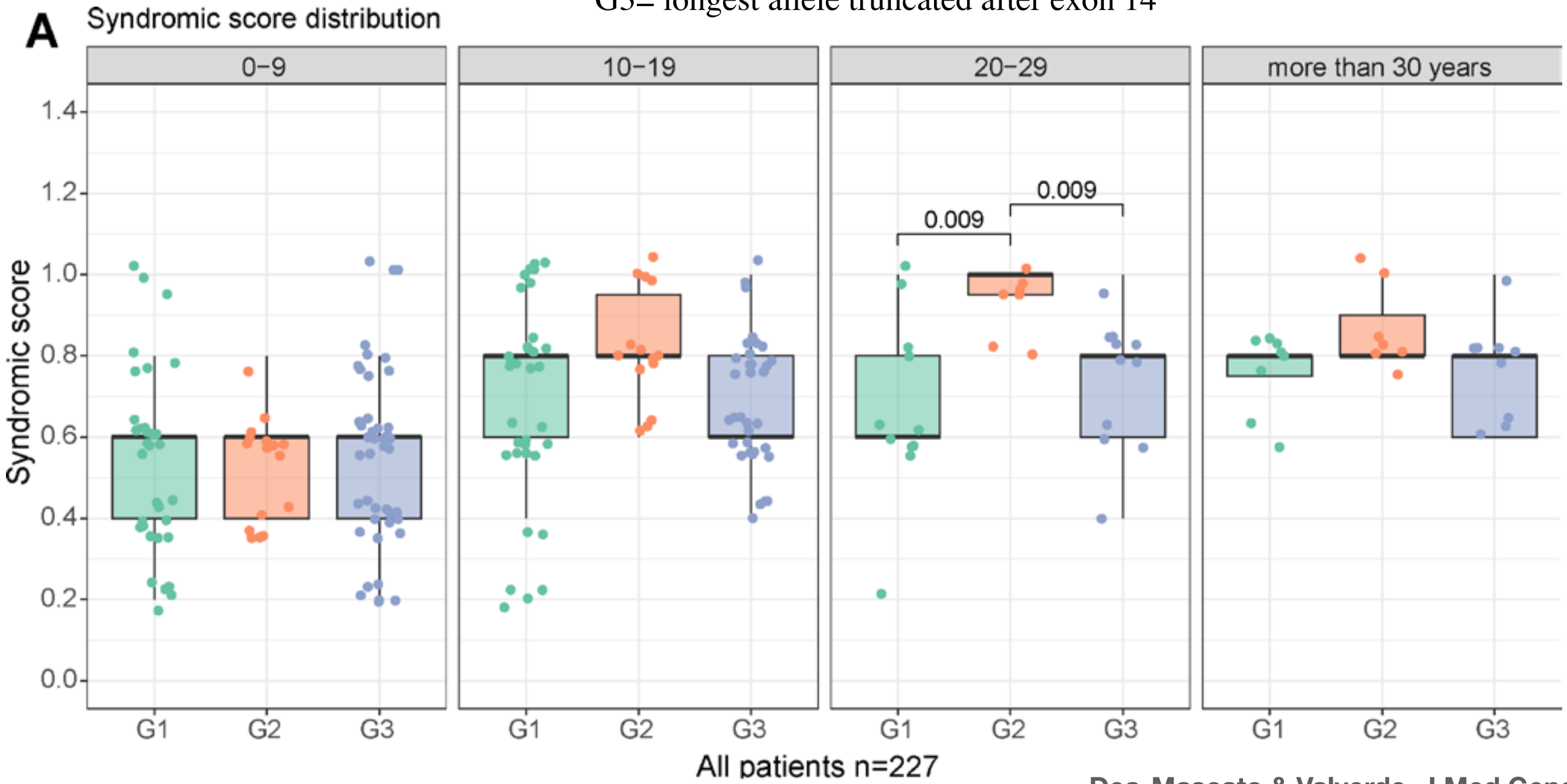
3) Lastly, we attempted to establish a genotype–phenotype correlation using the truncation site of the patient's longest allele as a grouping criteria.

Dea-Mascato & Valverde, J Med Genet 2023

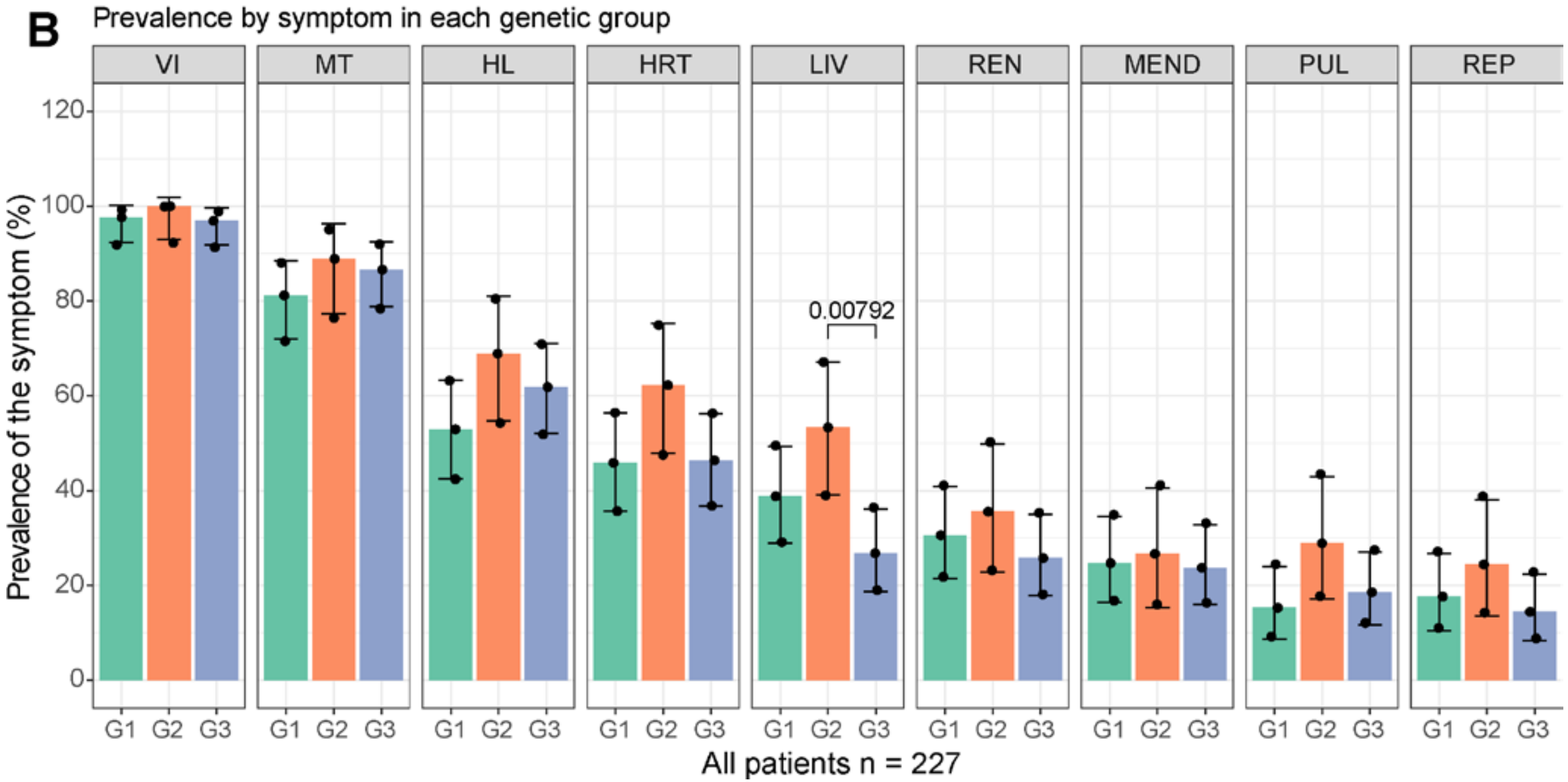
G1= longest allele truncated before exon 9

G2= longest allele truncated between exons 9 and 14

G3= longest allele truncated after exon 14




Dea-Mascato & Valverde, J Med Genet 2023




G1= longest allele truncated before exon 9

G2= longest allele truncated between exons 9 and 14

G3= longest allele truncated after exon 14

Dea-Mascato & Valverde, J Med Genet 2023

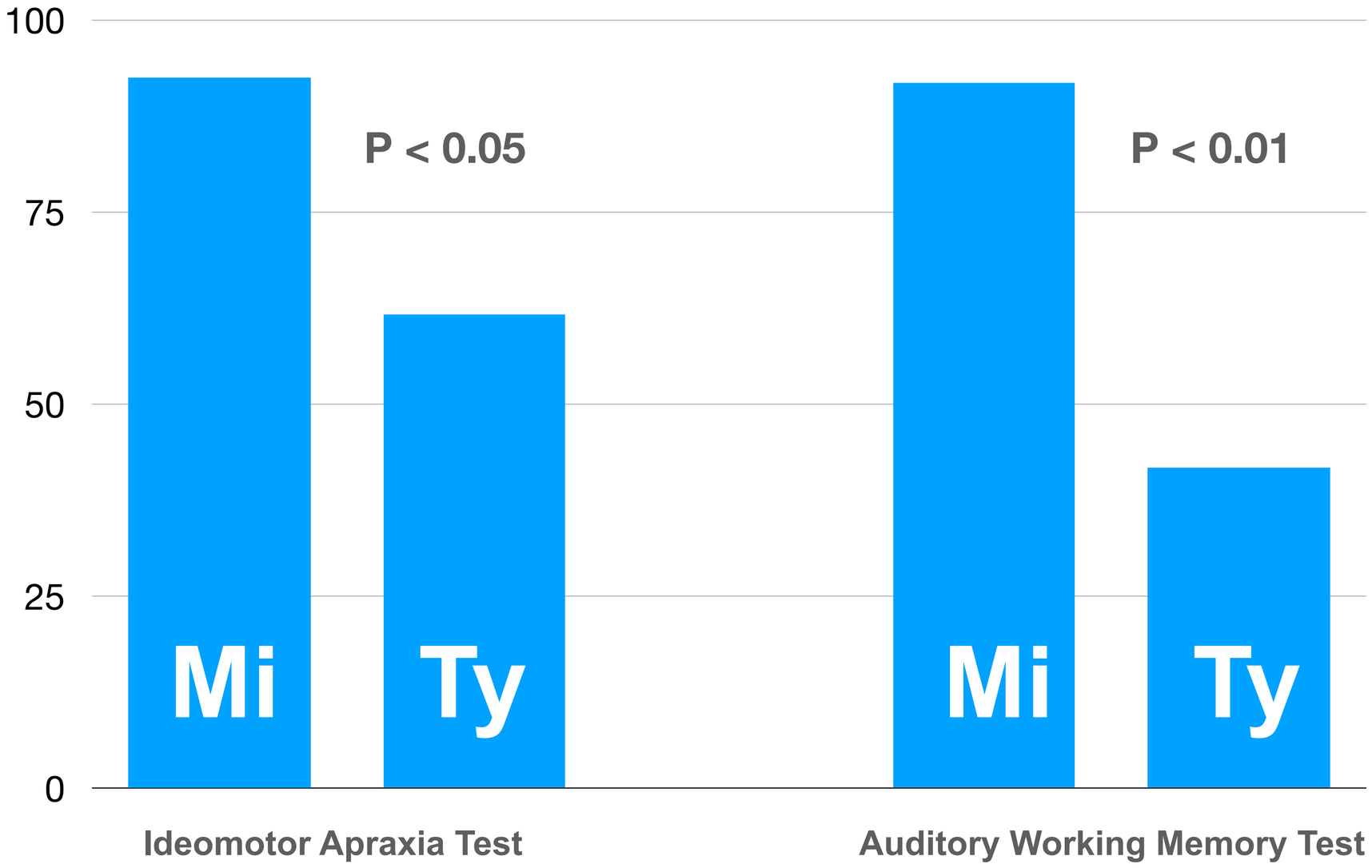
# Neurocognitive assessment and DNA sequencing expand the phenotype and genotype spectrum of Alström syndrome

We identified a subgroup of four patients with Alström syndrome with a “mild phenotype” featured by a:

1) **slow onset of visual impairment and photophobia**,
2) **normal hearing function or a mild hearing deficit which do not require hearing aids**,
3) **mild or any systemic complications**,
4) and **normal weight or underweight in childhood without hyperphagia**.

Dassie & Lorusso et al, Am J Med Genet 2021

# Neurocognitive assessment and DNA sequencing expand the phenotype and genotype spectrum of Alström syndrome

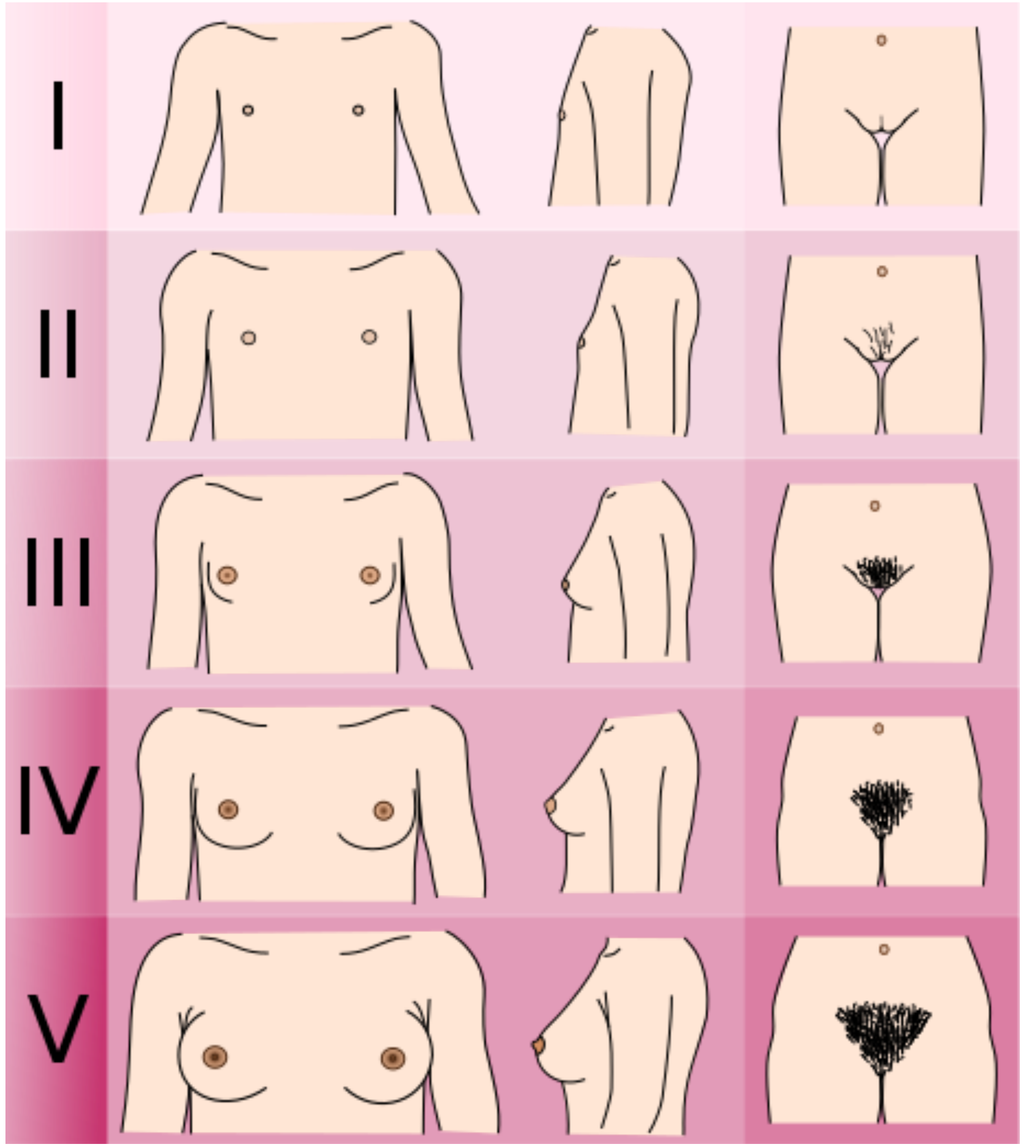



Dassie & Lorusso et al, Am J Med Genet 2021

Patient #7 is a 22-year-old female. She is the sister of patient #8. She reported **nystagmus in infancy**, **late onset visual impairment and cone-rod dystrophy**, no history of hyperphagia, or overweight in childhood. She showed normal metabolic profile (fasting glucose 4.9 mmol/L, Hba1c 34 mmol/mol, and insulin 5.3 mU/L), regular menses, normal breasts, normal long hair, no hyperlipemia, and no liver or renal impairment. The auditory test was normal. From a neurocognitive point of view, a normal verbal comprehension index was obtained on the WAIS and BF apraxia tests and scored low on the IDE apraxia tests.

Dassie & Lorusso et al, Am J Med Genet 2021

# Tanner scale for breast and pubic hair




Common findings in AS

Present Case

# Typical and mild gynecological phenotype of Alström syndrome

| Typical Phenotype | Mild Phenotype |
|---|---|
| Alopecia and hirsutism | Normal |
| Abnormal breast development | Normal |
| Ovary cysts | Normal |
| A/Oligomenorrhea | Normal |
| Hyperandrogenism | Mild increase in testosterone levels |

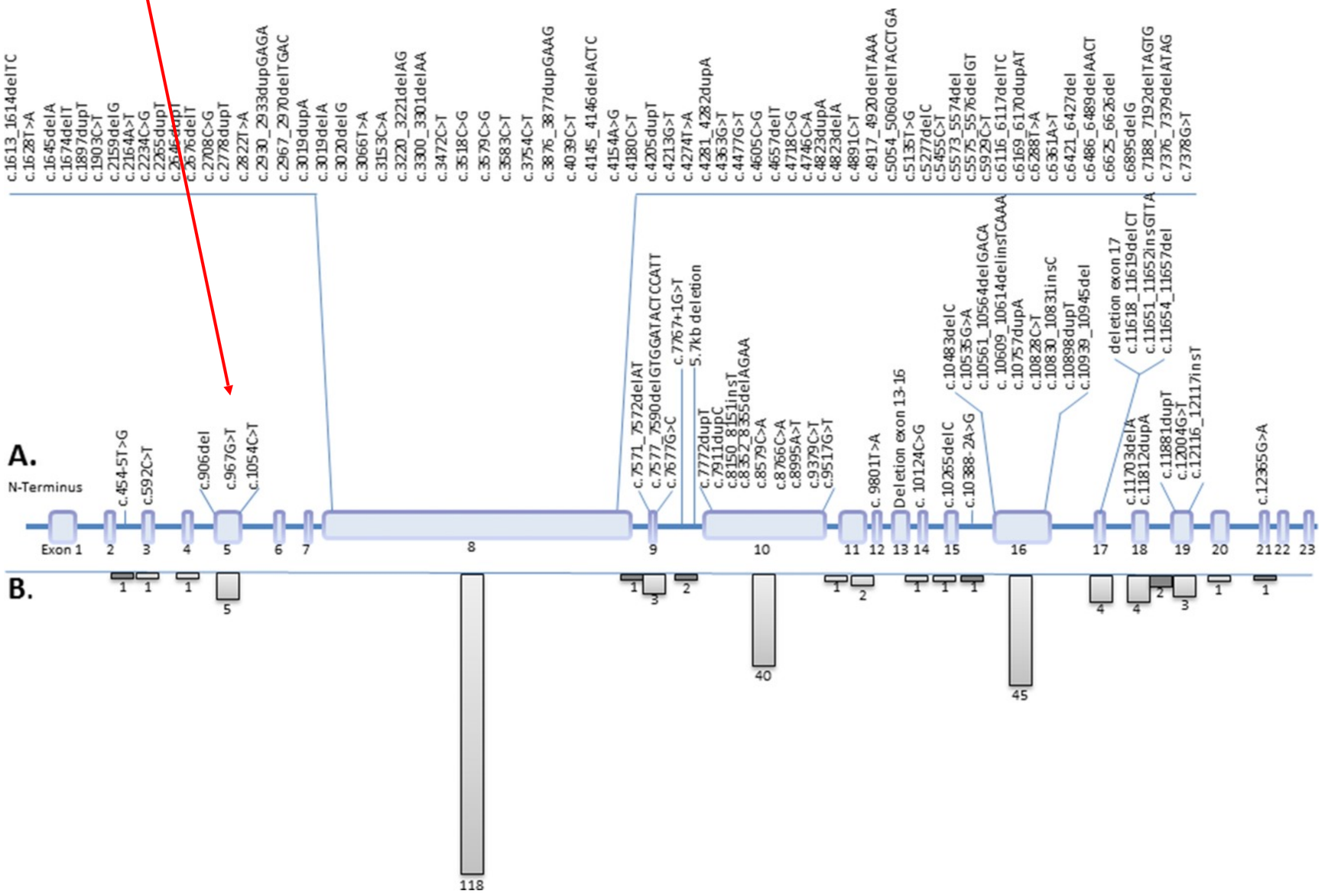
Marozio et al, Frontiers in Genetics 2022

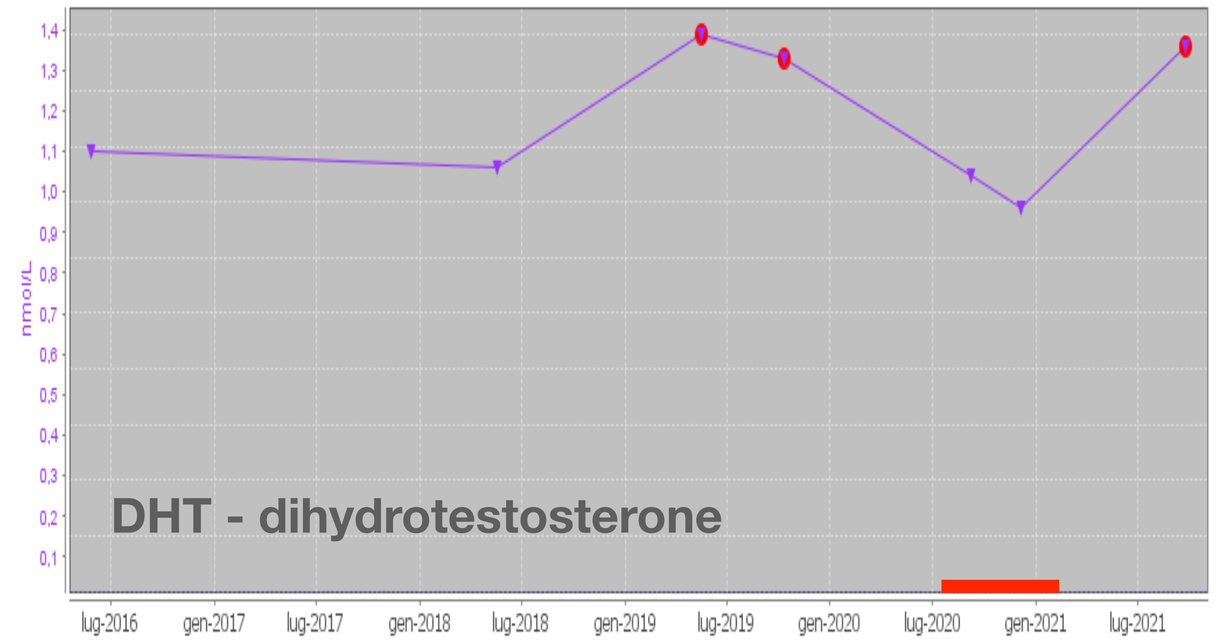
c.[1046G>A] + c.[1046G>A]

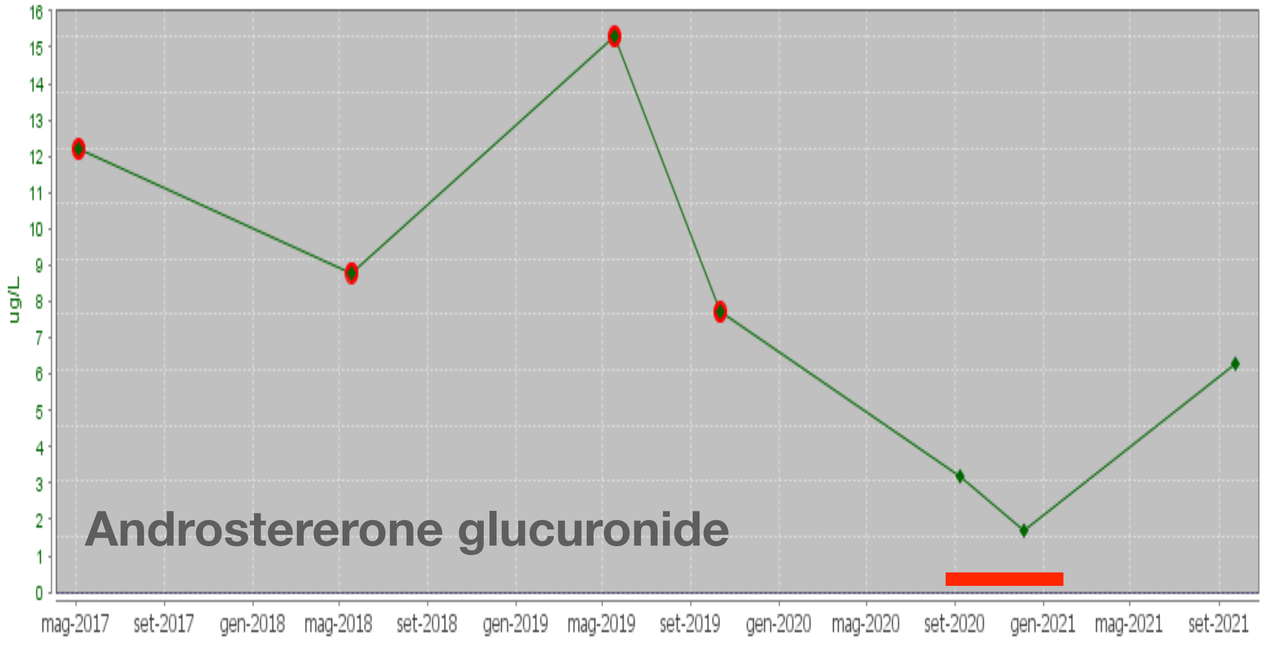
p.(Trp349*) + p.(Trp349*)

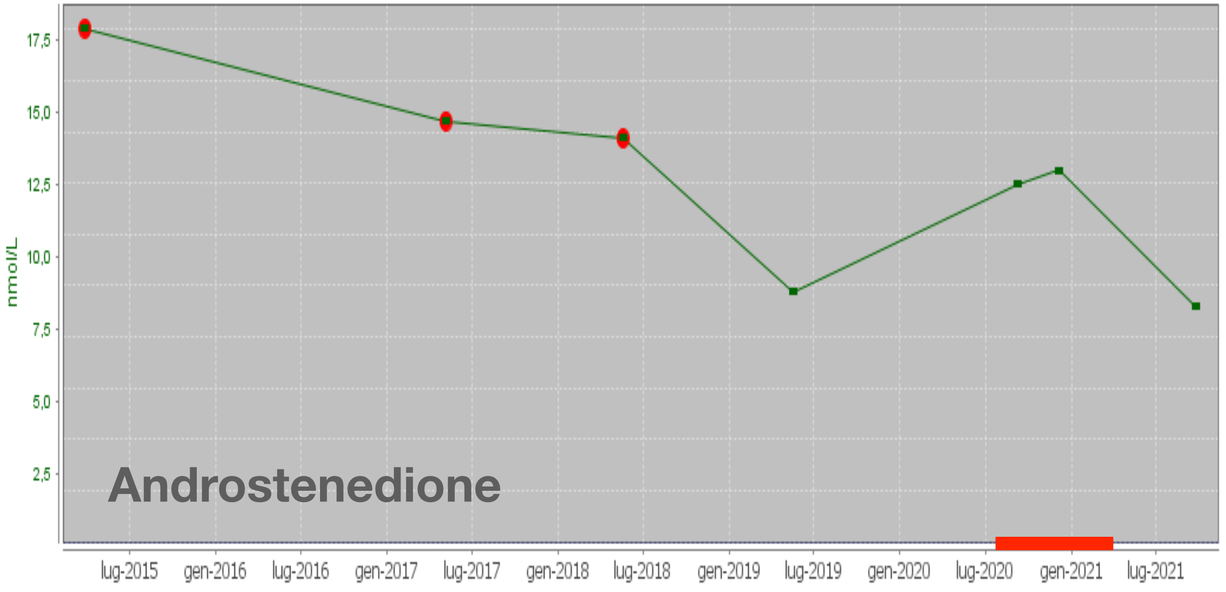
Non sense substitution

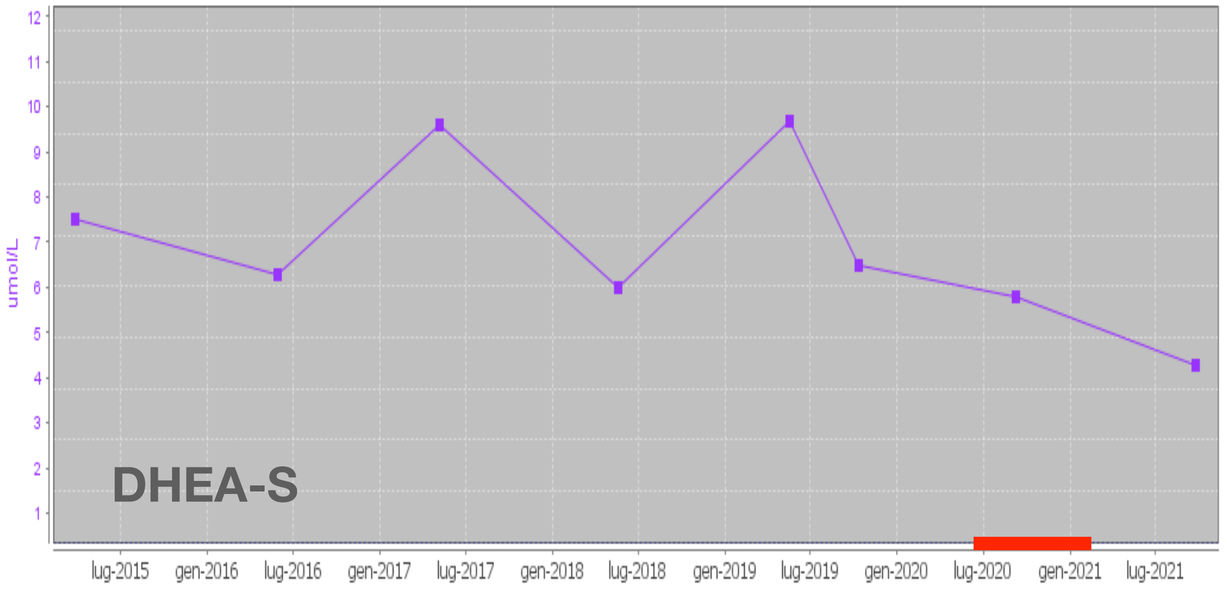
in Exon 5 of *ALMS1,* in homozygous state



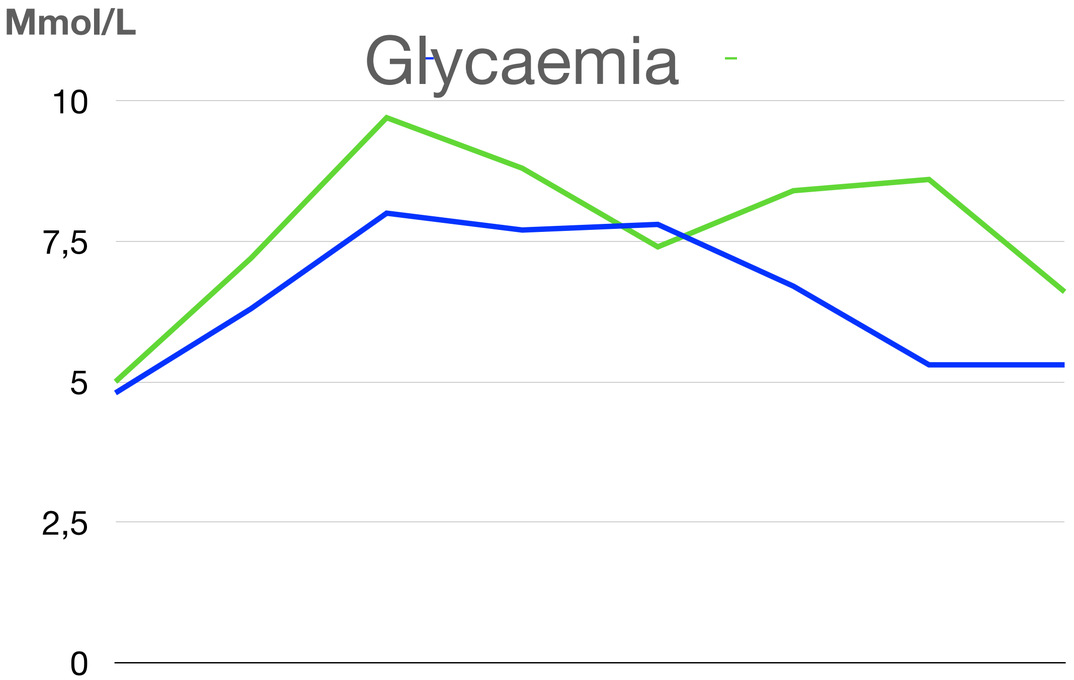

nmol/L
1,4
1,3
1,2
1,1
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
DHT - dihydrotestosterone
lug-2016
gen-2017
lug-2017
gen-2018
lug-2018
gen-2019
lug-2019
gen-2020
lug-2020
gen-2021
lug-2021

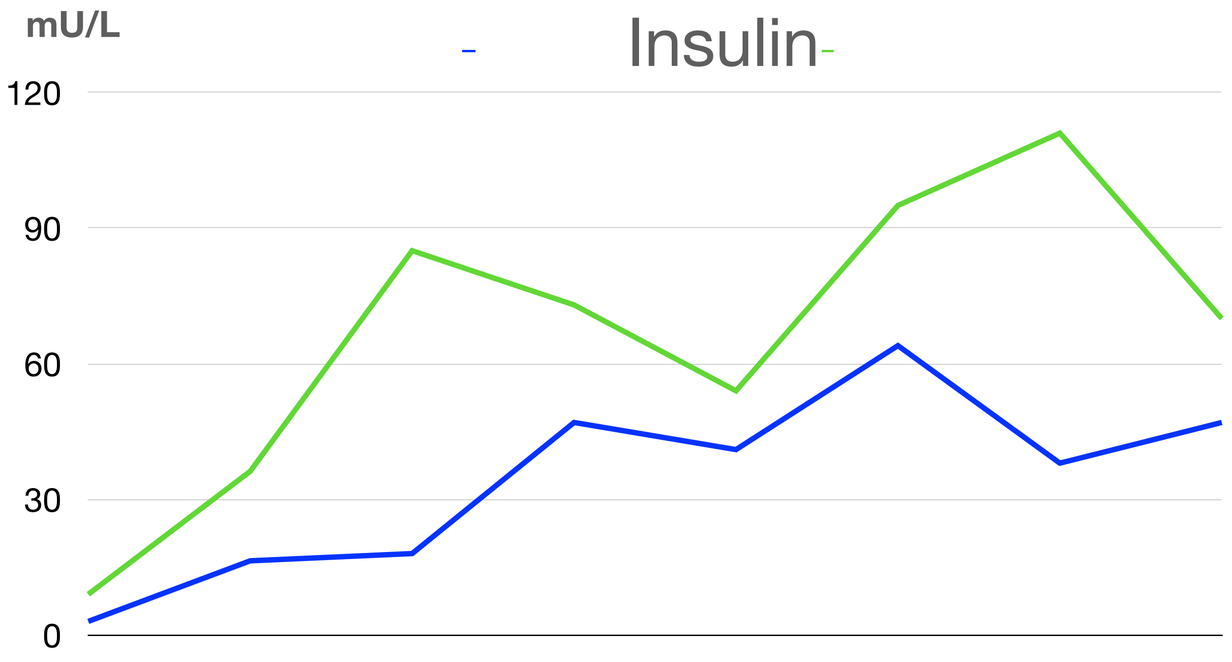

ug/L
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Androstererone glucuronide
mag-2017
set-2017
gen-2018
mag-2018
set-2018
gen-2019
mag-2019
set-2019
gen-2020
mag-2020
set-2020
gen-2021
mag-2021
set-2021

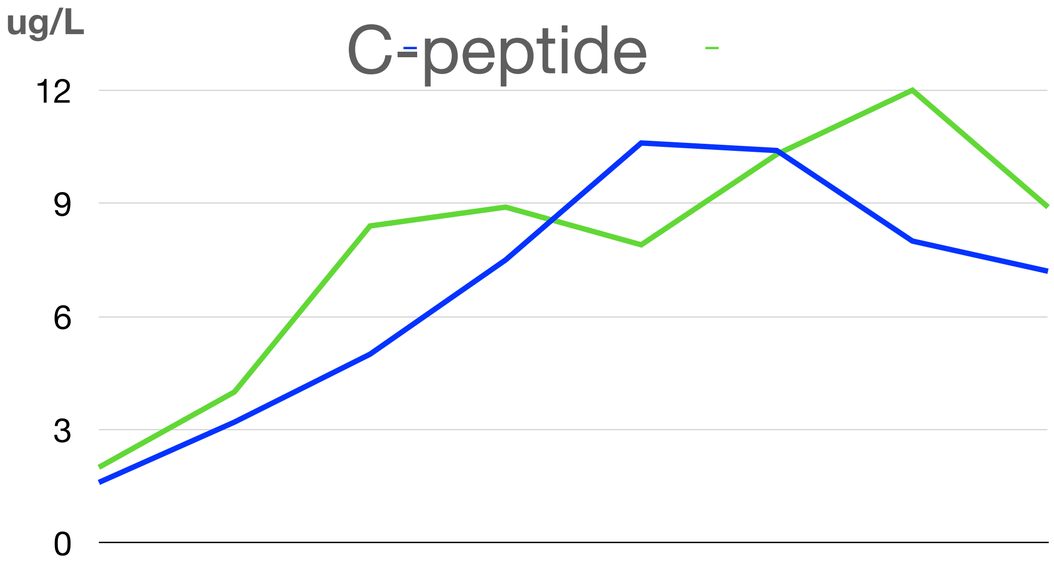

nmol/L
17,5
15,0
12,5
10,0
7,5
5,0
2,5
Androstenedione
lug-2015
gen-2016
lug-2016
gen-2017
lug-2017
gen-2018
lug-2018
gen-2019
lug-2019
gen-2020
lug-2020
gen-2021
lug-2021


umol/L
12
11
10
9
8
7
6
5
4
3
2
1
DHEA-S
lug-2015
gen-2016
lug-2016
gen-2017
lug-2017
gen-2018
lug-2018
gen-2019
lug-2019
gen-2020
lug-2020
gen-2021
lug-2021

# Oral Glucose Tolerance Test (OGTT)



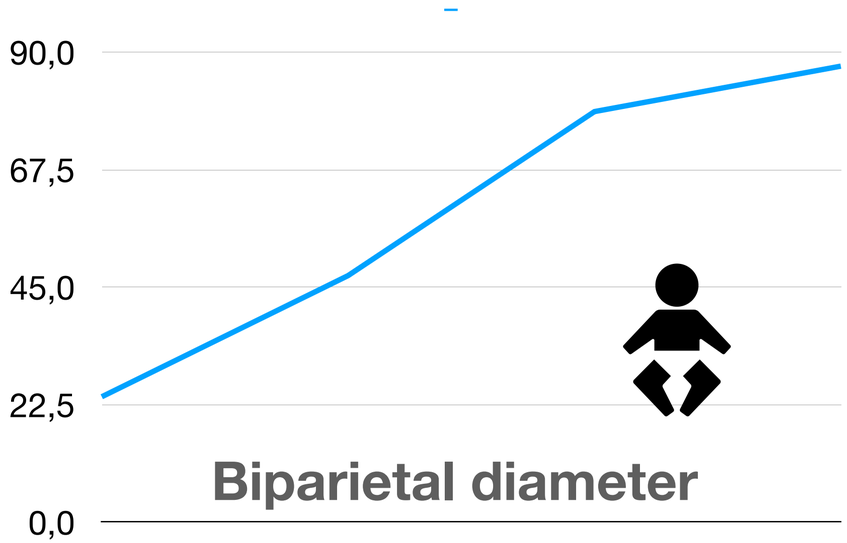




25-year-old

21-year-old

# January 12, 2021

# Regular fetal growth




## Biparietal diameter

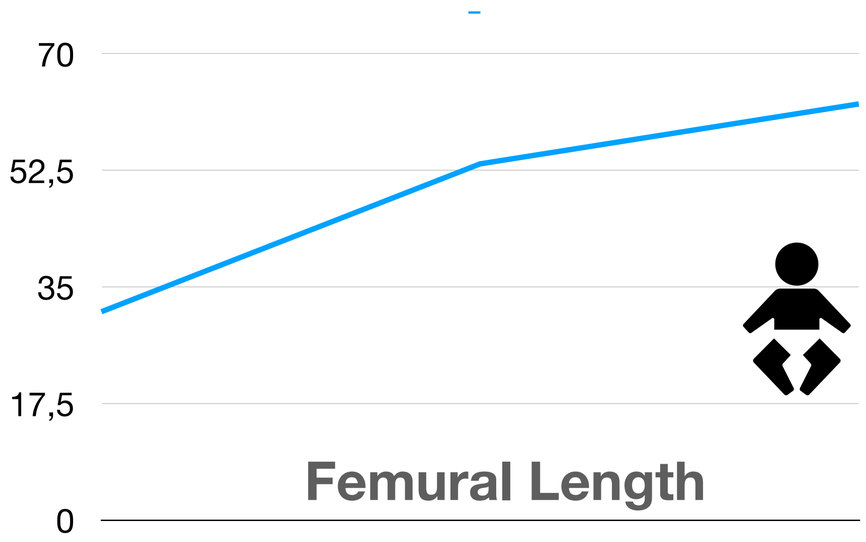
Sept 04, 2020 (10 wk +0)

Sept 18, 2020 (12 wk+0)

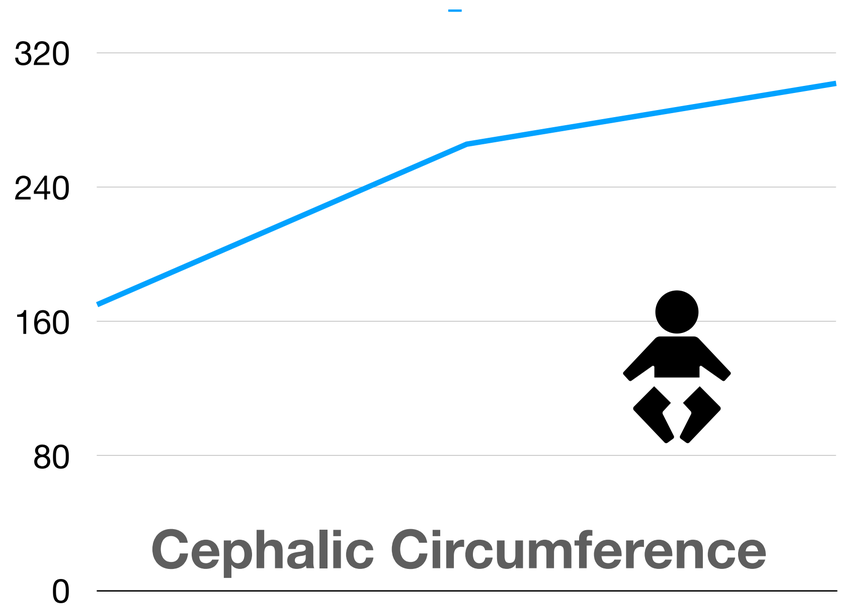
*Nov 10, 2020 (20 wk+4)*

*Jan 12, 2021 (29 wk+4)*

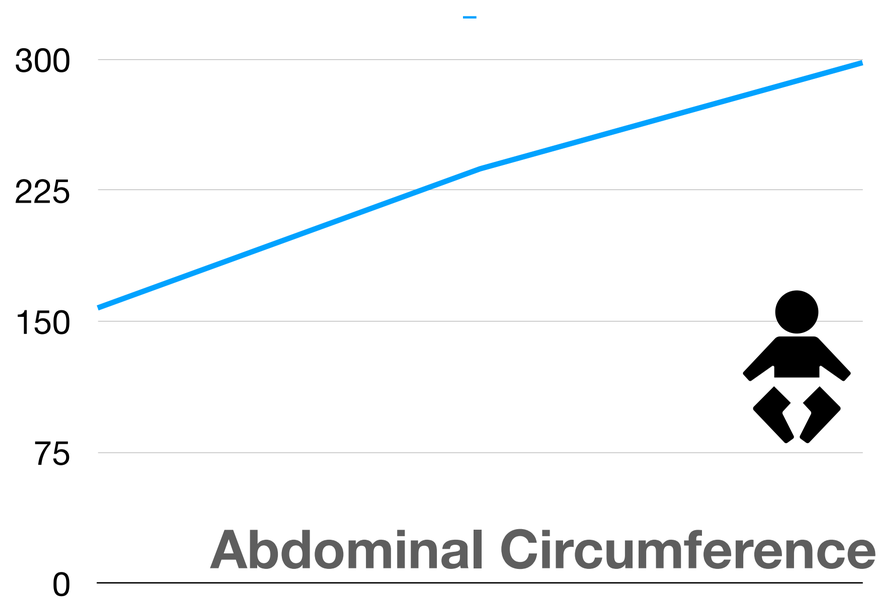
*Feb 14, 2021 (34 wk+2)*




## Femural Length




## Cephalic Circumference




## Abdominal Circumference

# Other US results along the pregnancy

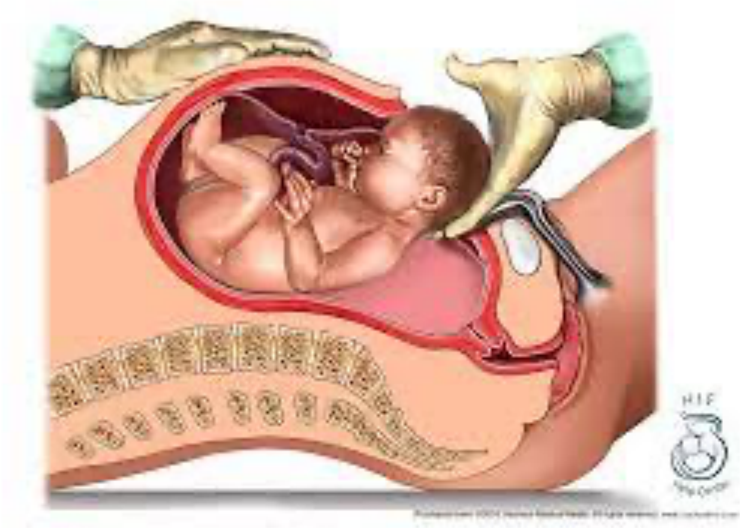
- **Heart activity**: regular
- **Fetal movement**: regular
- **Amniotic fluid volume**: normal
- **Fetal presentation**: cephalic
- **Placental position**: posterior
- **Biometric fetal growth:** regular (diameters or circumferences)
- **Doppler US of umblical artery**: regular (pulsatility index 0.87)
- **Any malformation of**: head-brain-face, spine, heart, major vessels, lungs, abdominal wall, stomach, kidney, bladder, bones

# Course of Pregnancy and Delivery

- **13 wk-26 wk**: monthly screening, regular clinical and lab results
- **26 wk**: dipstick proteinuria (not confirmed at 24h urine test)
- **34 wk**: hypertension and peripheral edema, cholestasis
- **34 wk**: hospitalization
  - Therapy:
    - Corticosteroids for respiratory distress syndrome prophylaxis
    - nifedipine 20 mg —> STOP (lack of efficacy)
    - alpha-methyldopa 500 mg + labetalol 100 mg
    - Ursodeoxycholic acid 450 mg

# Course of Pregnancy and Delivery

- **35 wk**: preeclampsia (hypertension not controlled by medications + protein in urine)
    - Urgent cesarean section (Feb 22, 2021):
        - male newborn,
        - 1950 g (121,875 oz)
        - APGAR score: 9 (at 1 and 9 minutes)
        - Placental pathology: 350 g (12,35 oz), small size, limited detachment marks, vascular obstruction, congested villi, single infarcted portion



# Postnatal…

- Hospital discharge after 6 days
- No lactation after delivery
- Resumption of regular menstrual cycle
- Therapy: ramipril 5 mg
- Regular growth of the new-born

| | | | | | |
|---|---|---|---|---|---|
| #17 | 8 | M | c.890_892delCTCinsA | 5 | p.(Ser 297*) |
| P | | | c.3425C>G | 8 | p.(Ser1142*) |

Patient #17 is an 8-year-old male, who reported only **nystagmus in infancy, cone-rod dystrophy**, a weight of 27.5 kg (SDS −0.97), height 131.5 cm (SDS −0.79), no cardiac, hepatic, or renal impairment.

During growth, the SDS for weight has been always negative on free diet.

He tested normal at auditory investigation.

He had normal glucose and lipid profile on free diet.

From a neurocognitive point of view, no developmental delay was found, and he resulted as having normal verbal comprehension on the index of the WISC-IV without IDE-BF apraxia.

Dassie & Lorusso et al, Am J Med Genet 2021

8-yr 8-yr 12-yr 23-yr

| | | | | | |
|---|---|---|---|---|---|
| #5 | 23 | M | c.1333C>T | 6 | p.(Gln445*) |
| A | | | c.4976T>A | 8 | p.(Leu1659*) |

Patient #5 is a 23-year-old male, with **retinal cone-rod dystrophy, a late onset visual impairment,**

**mild bilateral sensorineural hearing loss** that does not require hearing aids,

**hepatic steatosis, lumbar scoliosis, and kyphosis**.

He had no history of hyperphagia or obesity in childhood.

A normal metabolic profile (fasting glucose 4.2 mmol/L and insulin 10.2 mU/L), and mild hyperlipidemia (total cholesterol 3.60 mmol/L and triglycerides 1.54 mmol/L) on a free diet which includes fatty food and simple carbohydrates was reported.

The patient graduated from Law School before the term. From a neurocognitive point of view, the patient obtained a normal verbal comprehension index on the WAIS, a normal test score for IDE apraxia, and scored low on the BF apraxia tests.

Dassie & Lorusso et al, Am J Med Genet 2021

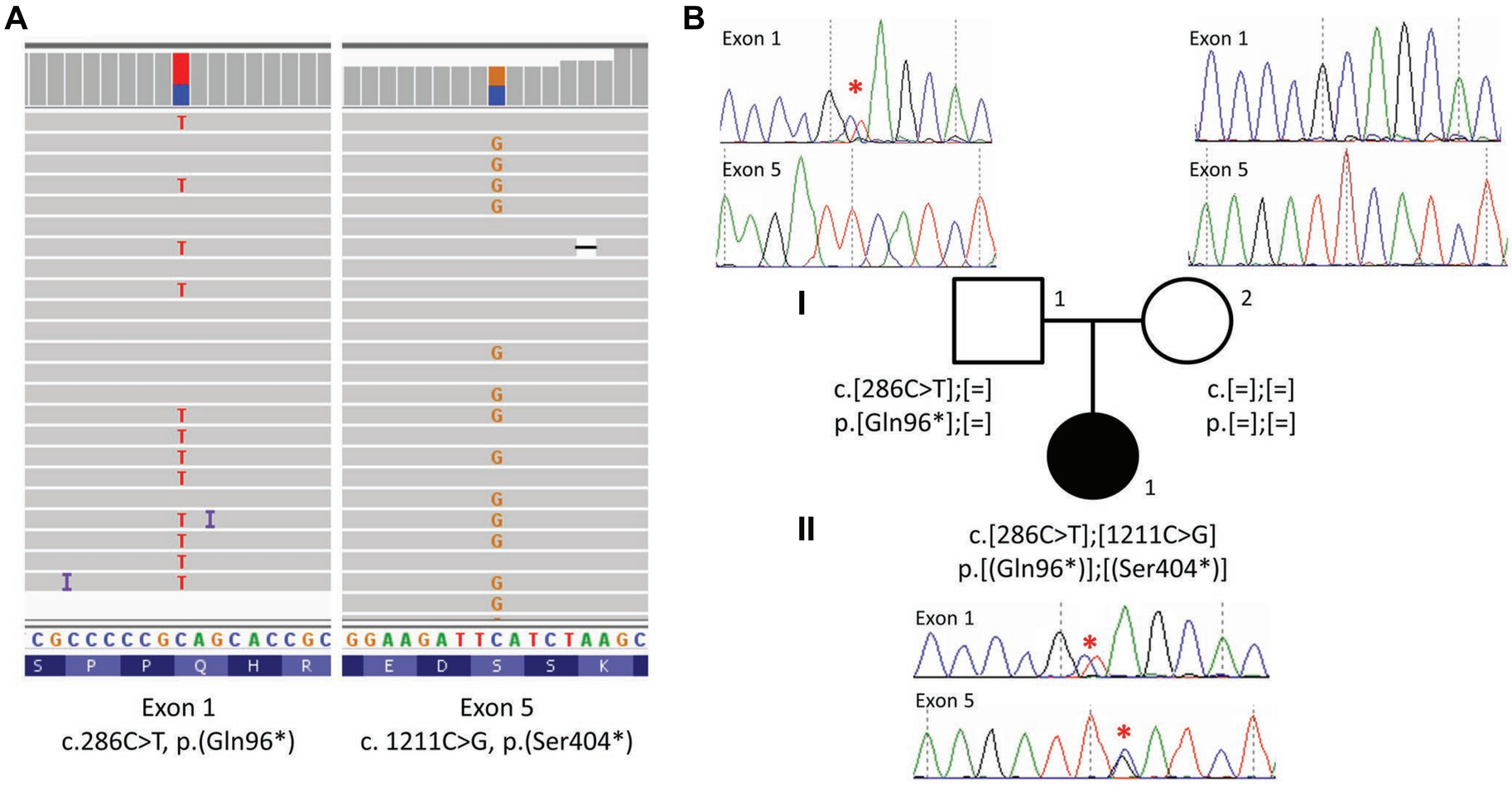
**Compound heterozygosis (exon 8):**

**c.1568dup (p.Ser524Lysfs*13)**
**c.2611_2614del (p.Phe8711lefs*10)**

**14-year-old**

**Medical History:**
- Phophofobia (early wks of life)
- Nystagmus 1 yr
- Cone-rod dystrophy
- Normal development milestones
- Sensorineural hypoacusia (11 yr)
- Mild dilative CMP (12 yr)
- Regular menses since age 12
- Psychological issues
- No obesity
- No metabolic abnormalities (lab test)
- No hormormonal issues (lab tests)

…14-year-old female who presented with a very mild and unusual retinal phenotype displaying exclusive cone dystrophy with complete preservation of rod function on serial electroretinograms (ERGs), a cardiomyopathy, and a slight, bilateral, and symmetric hearing loss….



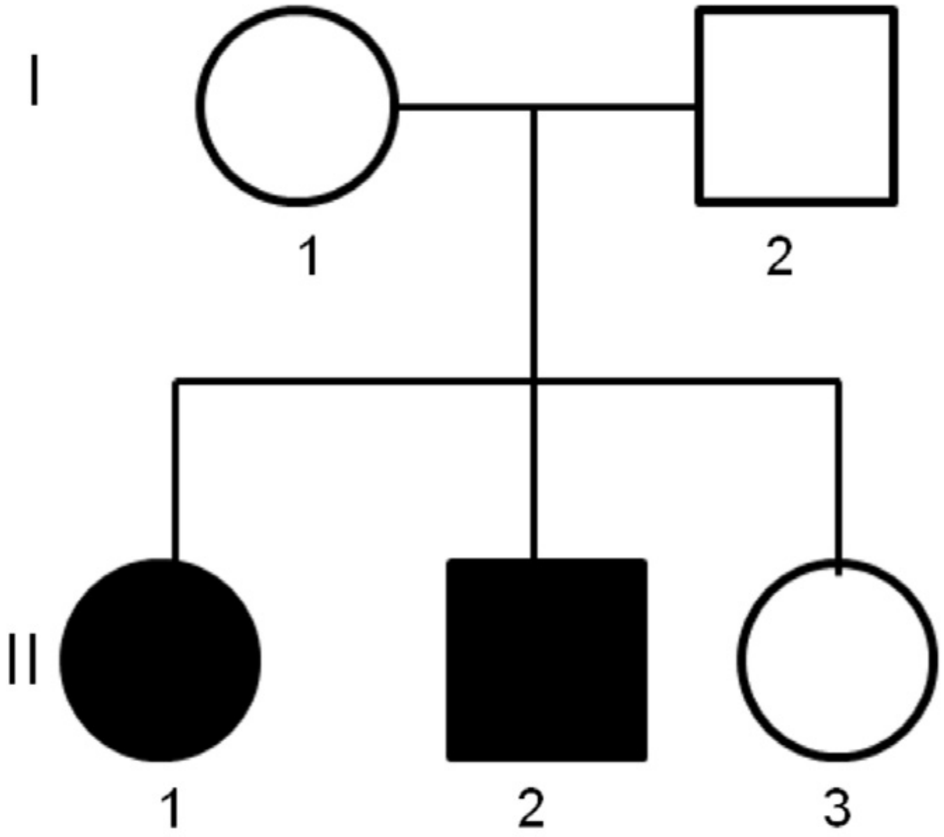

Mauring et al, Frontiers in Genetics 2020

| DEVELOPMENTAL MILESTONES | HEARING ASSESMENT (age 11) | ENDOCRINE PROFILE (age 13) | RENAL PROFILE and LIVER FUNCTION TESTS (age 13) | FBC (age 13) | CARDIAC ASSESSMENTS |
|---|---|---|---|---|---|
| Birth weight: 3270 g<br>Birth height: 50 cm<br>Gestation: 40 weeks<br><br>Independent walking: 14 months<br><br>Speech start: 12 months<br><br>No sleep disturbance<br><br>Normal intellect | Bilateral tympanic membrane dullness<br><br>Mild sensorineural hearing loss, predominantly in higher frequencies (2000-4000Hz)<br><br>No hearing aids | BMI: 22.6<br>Weight: 58.5kg<br>Height: 161 cm<br>Waist circumference: 72.5 cm<br><br>Lipid profile: normal<br><br>Pubertal stage: Tanner PIII, start age 11<br>Normal oestradiol, testosterone, LH/FSH ratios.<br>Prolactin: 228 mUI/l<br><br>Endocrine profile: normal<br><br>HBA1C: 5%<br>ACTH (ng/l): 55.7<br>Cortisol (ug/l): 128<br>TSH (mUI/l): 1.71<br>free T4 (ng/l): 11.2<br>free T3 (ng/l): 4.65<br>Leptin (ug/l): 31.8<br><br>OGTT: hyperinsulinism without glucose intolerance<br>Glucose T0 (g/l): 0.88<br>Insulin T0 (mUi/l): 20.7<br>Glucose T30 (g/l): 1.8<br>Insulin T30 (mUi/l): 188<br>Glucose T60 (g/l): 1.58<br>Insulin T60 (mUi/l): 180<br>Glucose T120 (g/l): 1.38<br>Insulin T120 (mUi/l): 120<br>HOMA: 0.8 (>3= insulin resistance) | Normal renal function<br><br>Urea and electrolytes:<br>$Na^+$ (mmol/l): 138<br>$K^+$ (mmol/l): 4.3<br>$Cl^-$ (mmol/l): 105<br>$Mg^{2+}$ (mmol/l): 0.83<br>Urea (mmol/l): 3.6<br>Creatinine (mmol/l): 44.2<br>Albumin (g/l): 42<br>Calcium (mmol/l): 2.34<br>Phosphate (mmol/l): 1.76<br>magnesium (mmol/l): 0.83<br>b2 microglublin (mg/l): 1.73<br>a1 microglobulin (mg/l): <5.4<br><br>Urinalysis:<br>Albumin/creatinine ratio (mg/mmol): 1.81<br>Diuresis (ml/24 hours): 700<br><br>Creatinine clearance (ml/min): 45<br>eGFR (ml/min/1.73$m^2$): 90<br>Normal LFTs | Normal | ECG: normal profile<br><br>Cardiac doppler US and MRI:<br>Discreet reduction of left ventricular systolic function.<br>LEV: 58 % MRI, 50% doppler estimates<br><br>Grade I systolic hypertension:<br>145/85 mmHg |

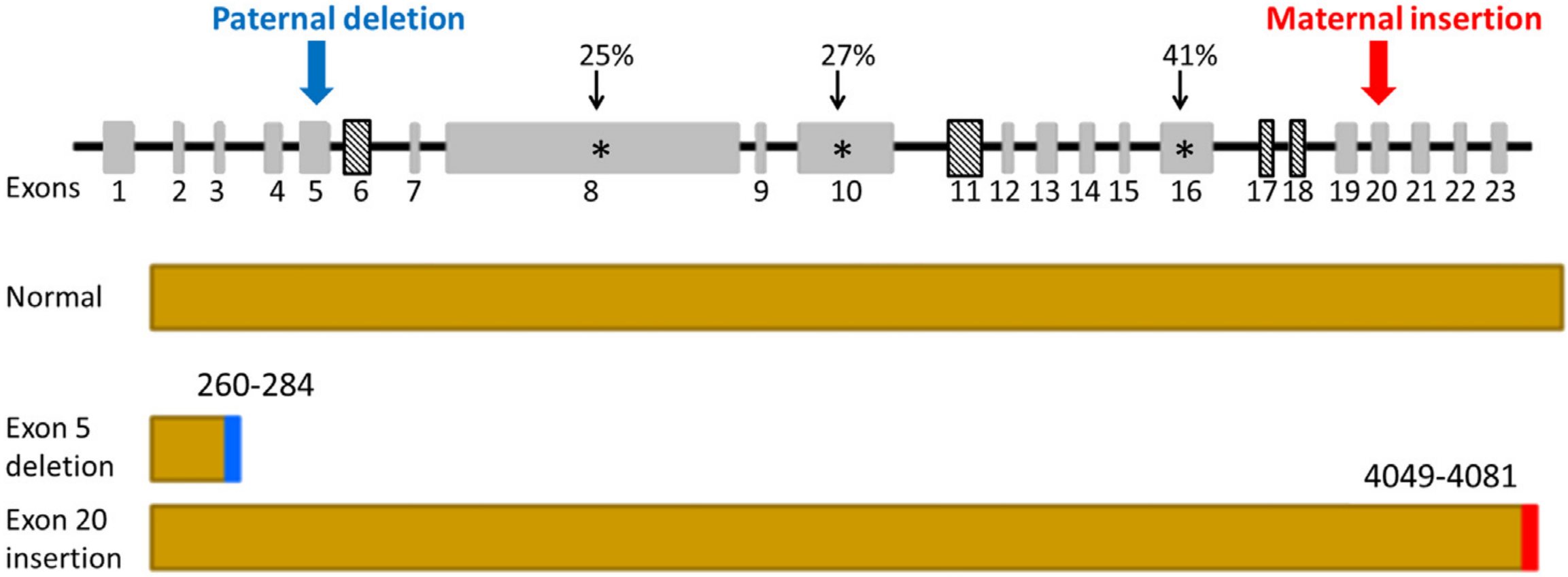
Mauring et al, Frontiers in Genetics 2020

We report on a pair of **Irish siblings (male and female)** with dilated cardiomyopathy (DCM) and cone-rod dystrophy born to non-consanguineous, phenotypically normal parents

To our knowledge, this is the first report of **AS without nystagmus, photophobia, obesity and hearing loss.**




Casey et a, European Journal of Medical Genetics 2014




Casey et a, European Journal of Medical Genetics 2014

Clinical investigations after molecular diagnosis of atypical Alströms.

| Test performed | Female II:1. Age 11 years | Male II:2. Age 9 years | Expected features in Alström syndrome |
|---|---|---|---|
| Current weight (kg) | 43.2 (90th ctl) | 31 (<90th ctl) | Childhood truncal obesity |
| Current height (cm) | 150.4 (90th ctl) | 137.4 (75–90th ctl) | Short stature (height <50th ctl) |
| Current head circumference (cm) | 52.2 (<50th ctl) | 54.1 (<98th ctl) | Normal |
| Current body mass index | 18 (<10th ctl) | 16.6 (<20th ctl) | Increased BMI (>95th ctl) |
| Alanine aminotransferase (<35 IU/L) | **54**, **76**, 25 | 22 | Elevated; indicative of liver dysfunction |
| Aspartate aminotransferase (<40 IU/L) | **50** | 23 | Elevated; indicative of liver dysfunction |
| Gamma glutamyl transferase (<25 IU/L) | **75**, **77**, **48** | 24, 19 | Elevated; indicative of liver dysfunction |
| Alkaline phosphatase (<300 IU/L) | 223, 265, 216 | 176, 207 | Elevated; indicative of liver dysfunction |
| Activated partial thromboplastin time (20.8–30.8) | **33.9, 32, 31.5** | **32.3, 32.5** | N/A (indicative of liver dysfunction) |
| Prothrombin time (9.6–11.8) | **12.1**, 11.8, **11.9** | **12.1, 11.9** | N/A (indicative of liver dysfunction) |
| Fasting lipid profile (cholesterol and triglycerides) | Normal | Normal | Elevated triglycerides and cholesterol |
| Renal function (sodium, creatinine, potassium, urea) | Normal | Normal | Elevated; indicative of renal dysfunction |

General paediatric reviews relevant to Alström Syndrome were undertaken following identification of the *ALMS1* variants. The normal ranges are reported in brackets in the left-hand column. Measurements outside of the normal range are shown in bold. Repeat tests were performed five weeks apart. Abbreviations: ctl; centile.

Casey et a, European Journal of Medical Genetics 2014

| | Twin A | Twin B |
|---|---|---|
| **3 wks** | DCM: no symptoms FE 50% | DCM: symptomatic; FE 30% —> 60% |
| **1-3 yr** | 25th centile weight | 5th centile weight |
| **19 m** | Nystagmus | Nystagmus |
| **5 yr** | Visual acuity 20/300 - cone dystrophy | Visual acuity 20/300 - cone dystrophy |
| **8 yr** | Visual acuity 20/400 - 20/200; normal rods | Visual acuity 20/400 - 20/200; normal rods<br>Mild elevation BG, BUN/creatinine, triglycerids |
| **11 yr** | Slight moderate hearing loss —> hearing aids at school recommended | Normal hearing tests |

**Mild phenotypes have several implications:**

- The atypical presentation suggests that the diagnostic criteria for AS may need to be broadened to include patients with a mild phenotype (isolated cone dystrophy; normal weight; body shape…)
- A thorough systemic evaluation is needed to avoid misdiagnosis. In view of the mild phenotype, the AS diagnosis could be initially questioned.
- The mild phenotype could spare the patient's fertility thus increasing the chances of pregnancy.
- Patients with missense variants could display a mild atypical retinal phenotype.
- At least three ALMS1 isoforms have been reported in mice with different tissue-specific expression and function. The type and location of ALMS1 variations could play a role in the phenotypic presentation of AS.


**Gabriella Milan, Sonia Leandri, Silvia Bettini, Roberto Vettor, Francesca Dassie, Francesca Favaretto**