

A novel heterozygous mutation in the SLC5A2 gene causing mild failure to thrive and subclinical hypoglycemia in a 2-year old girl

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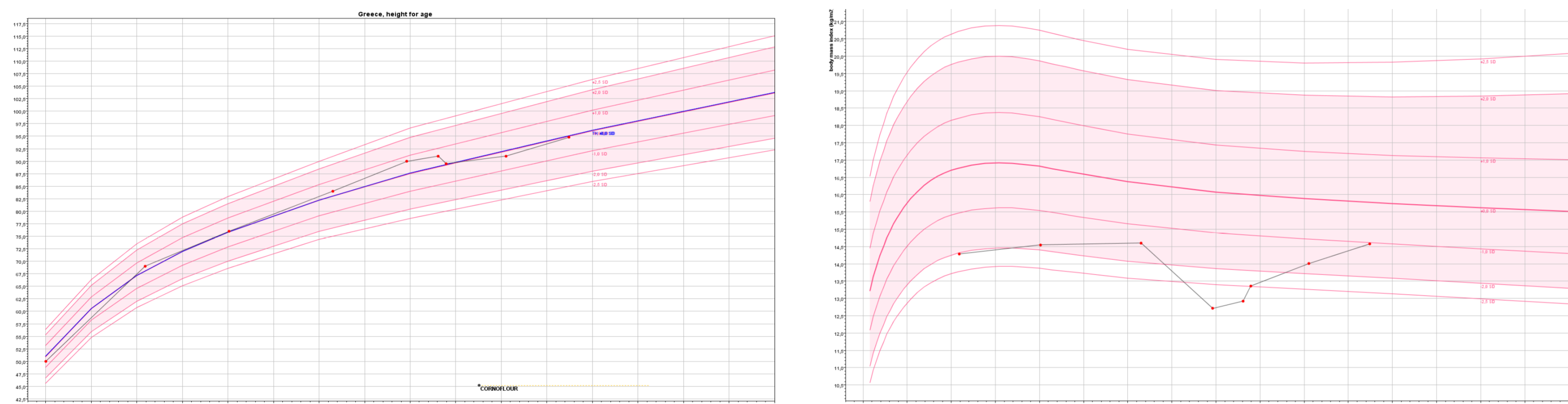
No disclosures

Patient

A 2-year old girl was referred due to glucosuria 1874 mg/dl. Her medical and familial history was normal.

- Fasting blood sugar: 71 mg/dl
- HbA1c 4.8%

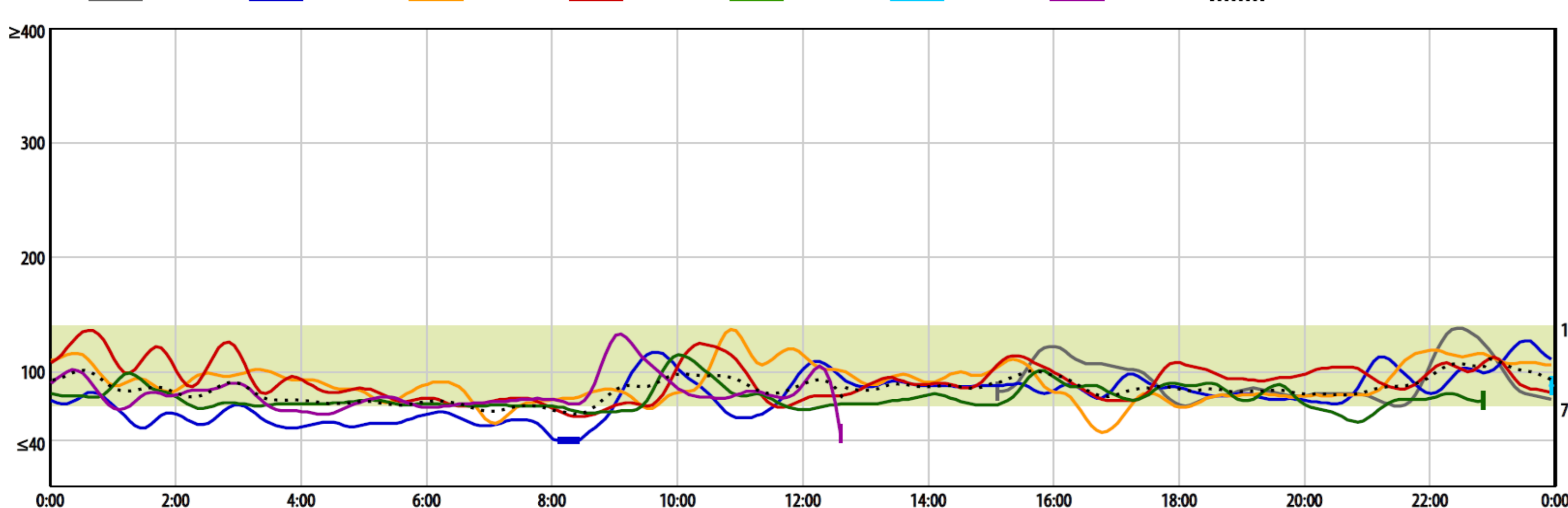
Examination of her growth charts revealed poor weight gain since 15 months of age.



We used Medronic iPro2 continuous glucose monitoring to identify hypoglycemic episodes, for 6 days:

- 14% of the time was < 70 mg/dl
- Lowest 40 mg/dl
- Estimated HbA1c 4,6%

Πεμ 9 Αυγ Παρ 10 Αυγ Σαβ 11 Αυγ Κυρ 12 Αυγ Δευ 13 Αυγ Τρι 14 Αυγ Τετ 15 Αυγ Μέσος όρος

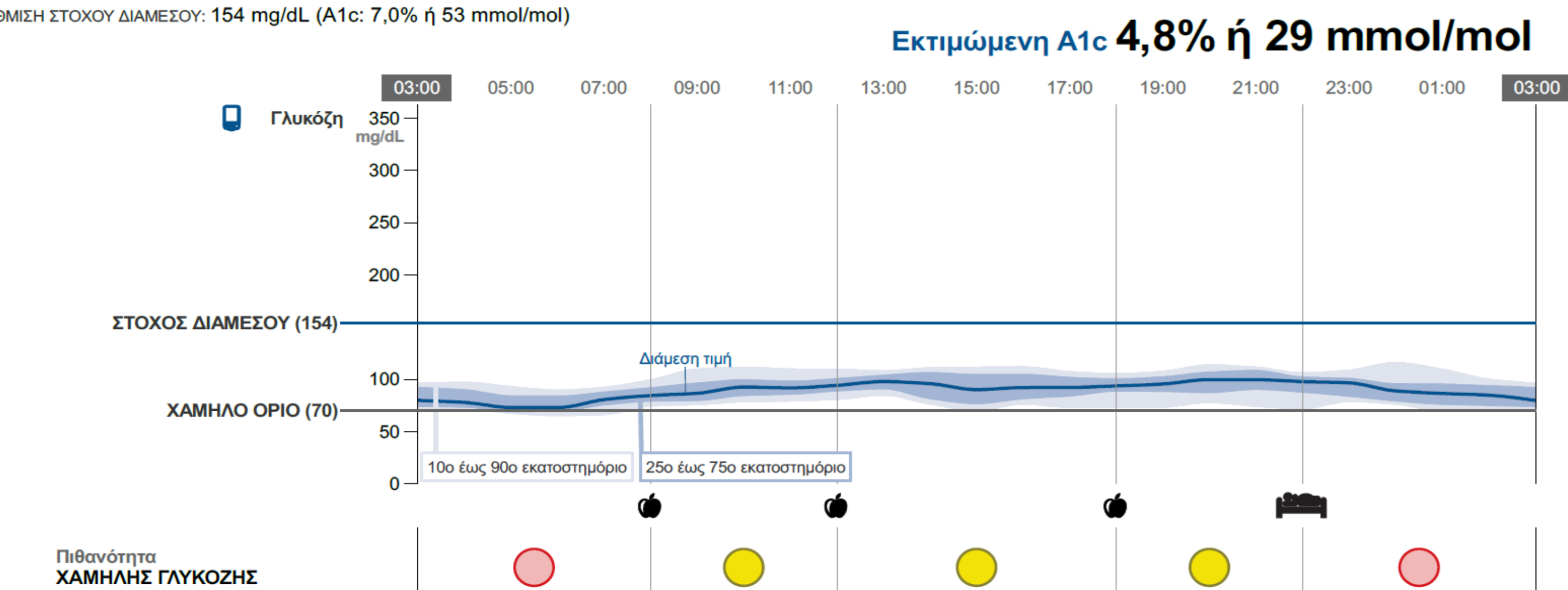


Treatment

We started the child on cornflower 1 g/Kg, with her milk at bedtime and advised for frequent feedings every 3-4 hours during the day.

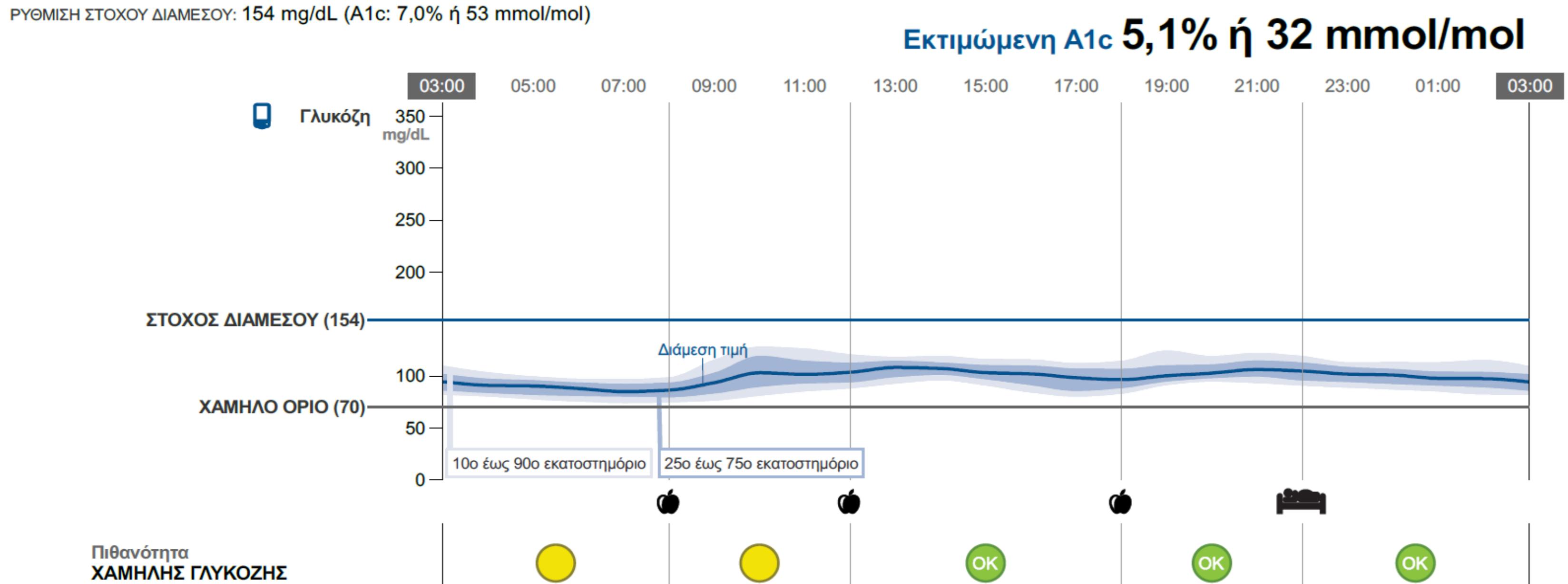
There was significant improvement in weight gain and within 6 months the BMI normalized completely.

ΠΥΘΜΙΣΗ ΣΤΟΧΟΥ ΔΙΑΜΕΣΟΥ: 154 mg/dL (A1c: 7,0% ή 53 mmol/mol)



We used Flash technology (FreeStyle Libre) to record patient's progress and adjust cornflower dose to 1.5 g/Kg after the first 14-day report (shown above). Subsequent scans showed elimination of all hypoglycemic excursions (shown below).

ΠΥΘΜΙΣΗ ΣΤΟΧΟΥ ΔΙΑΜΕΣΟΥ: 154 mg/dL (A1c: 7,0% ή 53 mmol/mol)



6 months after treatment initiation, in Libre record (14 days duration):

- 1% of the time was < 70 mg/dl
 - Lowest 69 mg/dl
 - Estimated HbA1c 5,1%
- And laboratory tests were:
- Fasting blood sugar: 80 mg/dl
 - HbA1c 4,8%
 - Glucose in urine sample 1835 mg/dl

Methods

We decided to sequence the **SLC5A2 gene**, as most probable genetic cause. Genomic DNA extracted from peripheral blood.

- The sample was analyzed using the SeqCap EZ HyperCAP Library (Roche), followed by next generation sequencing (IlluminaNovaSeq 6000). The bioinformatics analysis has been performed using software packages (bcftfastq version 2.20, Isaac Aligner version 4, GATK "Genome Analysis Toolkit" version 4, Samtools version 1.9 and Bedtools version 2).
- Data analysis and interpretation were done based on patient's clinical information and filtered for a requested gene panel.
- Variants with a minor allele frequency greater than or equal to 1% were not evaluated.
- Variants in genes lacking evidence of clinical significance and variants in genes unrelated to the patient's characteristic were not evaluated, unless present in genes assessed for medically actionable secondary findings, in accordance with ACMG recommendations.

Results

- Variant **c.1021+1G>A** in heterozygous state is identified in exon 8 in **SLC5A2 gene**; this variation causes the elimination of canonical splice site.
- This gene encodes a member of the sodium glucose cotransporter family which are sodium-dependent glucose transport proteins. **The encoded protein is the major cotransporter involved in glucose reabsorption in the kidney.** Mutations in this gene are associated with renal glucosuria.
- This variant has not a resident no frequency data are reported (gnomAD, dbSNP, ExAC).
- The variant is not reported in scientific literature and in ClinVar.

Mother was also carrier but with no glucosuria.

Discussion

- **Familiar Renal Glucosuria (FRG) is an isolated disorder of glucose transport** in the proximal tubule with normal glucose metabolism
- The **prevalence of FRG is about 0.29%** in the general Caucasian population
- **FRG is classified into three types (A, B and O) according to urinary glucose levels.** Severe FRG (glucosuria ≥ 10 g/1.73 m²/24 h), termed type O FRG, is a rare subtype. Patients with type A FRG are characterized by a low renal threshold for glucose and low maximum tubular glucose reabsorption. Those with type B have a low threshold but normal maximum tubular glucose reabsorption.
- **In most of the affected individuals, the condition causes no apparent symptoms** (apart from polyuria, enuresis and a mild delay in growth, which are reported in some patients with type O FRG)
- **However, our patient had subclinical hypoglycemia and mild failure to thrive, along with reported irritability that resolved after treatment (the latter was expressed by the parents 3 months after treatment initiation).**
- **FRG may be inherited in an autosomal recessive or autosomal dominant pattern.** However, studies have demonstrated that the inheritance of FRG may best be described as co-dominant with reduced penetrance

Conclusions

- **Heterozygous mutations in the SLC5A2 gene may cause subclinical hypoglycemia and mild failure to thrive in early infancy.**
- **Given the mother's state, this novel mutation may be behaving as dominant in early infancy, or there may be an imprinting mechanism involved.**
- **Early detection and treatment of this rare disorder may prevent neurological sequelae of undetected hypoglycemia while restoring weight gain and height velocity.**

