כבד מוגדל ושומני....צריך בירור?

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כללית 100 שנה
הכי טובה למשפחה

20 שנות נוגולות

מרכז שניידר לרפואת ילדים בישראל
مركز شنايدر لطب الأطفال في إسرائيل
Schneider Children's Medical Center of Israel

רופאי הילדים בקהל שהיו בפרזנטציות האחרונות שלי...מתבקשים להתאפק בסבלנות ולא לזרוק את התשובה.

תודה

- 20 year old male presents with liver enlargement found incidentally following a motor vehicle accident.
- Patient informs that he was hospitalized at age 12 in the PICU for fulminant hepatitis A from which he recovered fully.
- No family history of liver disease.
- Distant relative who underwent a kidney transplant for unknown etiology.

Physical Examination on arrival

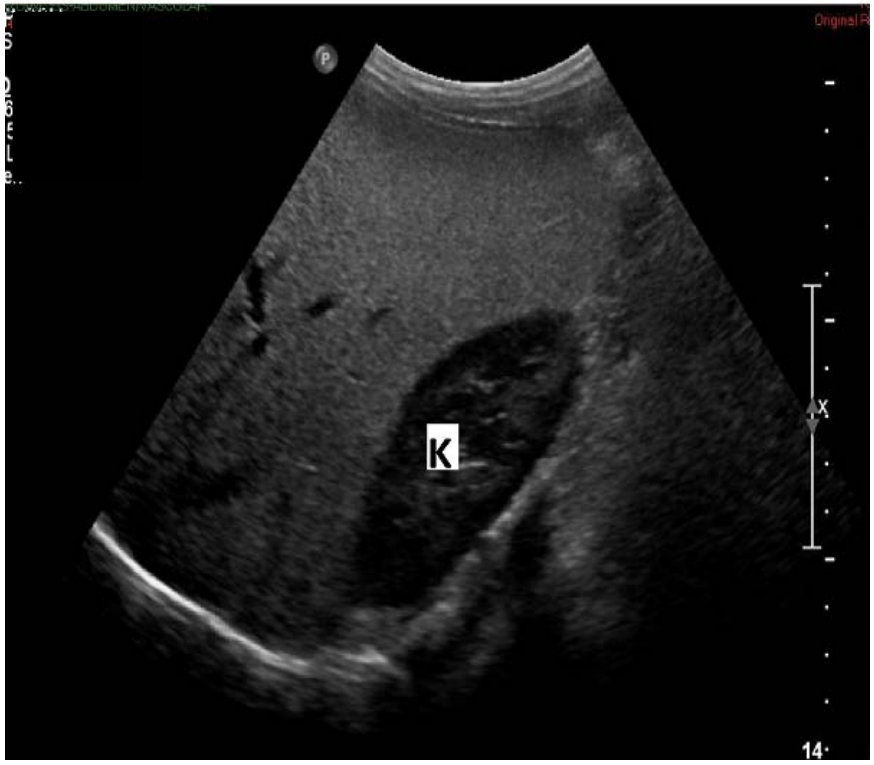
- Well built, healthy appearing.
- Ht. 160cm Wt. 58.5 kg (BMI 22.8).
- No abdominal pain or jaundice.
- Liver palpated 7cm below the costal margin, non-tender, firm consistency, no evidence of ascites.
- No addition relevant findings on examination.

- Initial Laboratory testing:
  - AST 57
  - ALT 78.8
  - LDH 344
  - ALKP 79
  - GGT 78
  - Albumin 5.4
  - Triglycerides 170
  - Cholesterol Tot 114
    HDL 35
  - Hgb 14.3
  - PLT 318
  - WBC 7.23
  - INR 0.94
  - PTT 32 sec
  - Fib 256

Similar values found on tests performed a year before

Imaging

- **Abdominal ultrasound - Enlarged, uniformly hyperechogenic liver. Compatible with Hepatosteatosis.**



- HBV/HCV serology negative
- HAV - IgG positive
- EBV/CMV IgG – positive , IgM negative
- HIV –neg
- Alpha-1-AT levels normal
- Copper / Ceruloplasmin – normal
- Anti-Smooth Muscle/ANA/anti-LKM – negative
- Sweat Test – normal
- Fasting Insulin and glucose - normal

PICU Chart Review

- **Review of Pediatric records showed:**
  - ✓ **As an infant (age 2 weeks) patient had an enlarged liver.**
  - ✓ **Fasting Hypertriglyceridemia up to 520mg/dl noted during the first two years of life which subsequently resolved.**
  - ✓ **Parents screened – normal liver function, normal lipids, normal ultrasound. Siblings healthy**
  - ✓ **Glycogen Storage disease type III and VI ruled out**

Two Years Later….

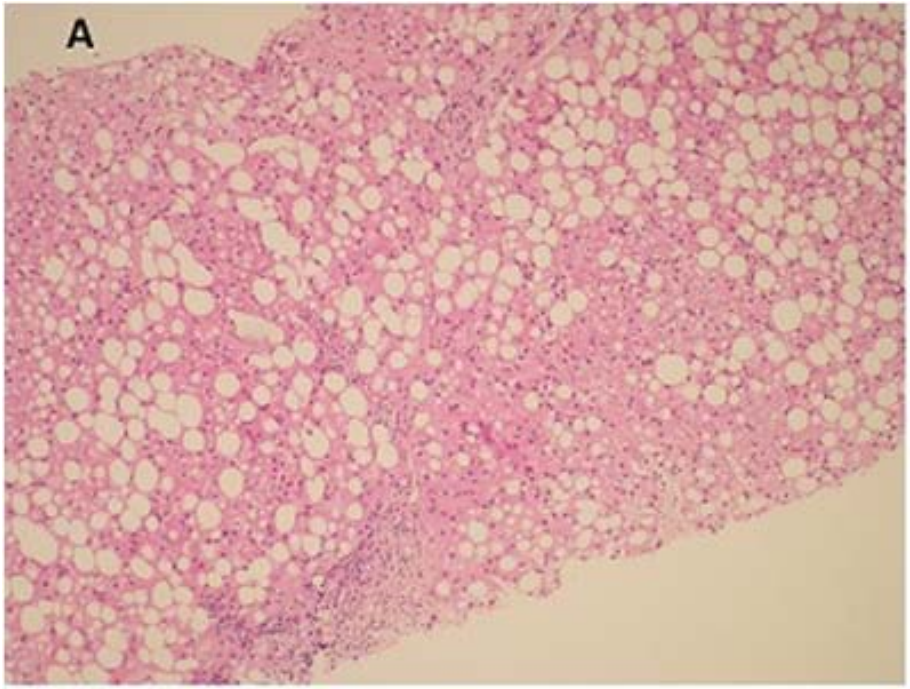
- A 6 month old female is seen for liver enlargement and elevated hepatocellular enzymes X2-3.
- Fasting Triglyceride levels – 1208mg/dl.
- Normal cholesterol.
- Normal synthetic function.

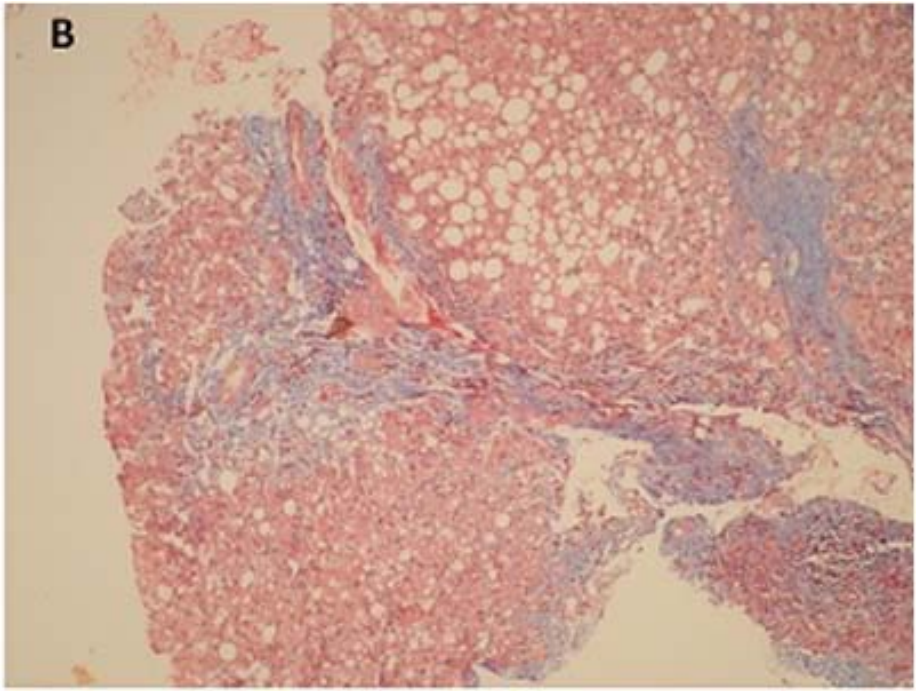
- She has an uncle…(you guessed correctly) who has an enlarged liver.

Negative work-up

- Similar work-up – negative
- Apolipoproteins
- Thyroid function
- Ferritin
- Alpha-fetoprotein
- Immunoglobulins
- Urinary organic acids – initially some dicarboxylic aciduria which resolved over time.
- Amino acids
- Lactate/Pyruvate
- Ammonia
- VLCFA
- Free fatty acids
- Acyl-carnitine profile

Biopsy at age 4





Hypertriglyceridemia

- Genetic causes of primary hypertriglyceridemia identified in <5%.

- Primary
  - ✓ With fasting chylomicronemia
    - Total LPL Deficiency
    - ApoC II Deficiency
  - ✓ Without fastingy chylomicronemia
    - Partial LPL Deficiency
    - Dysbetalipoproteinemia type III (remnant removal disease)
    - Collagen 18 Deficiency

Hypertriglyceridemia

Secondary

- ✓Obesity
- ✓Metabolic Syndrome
- ✓Diabetes Mellitus
- ✓Alchohol Consumption
- ✓Renal Disease
- ✓Medications

Hepatic Steatosis

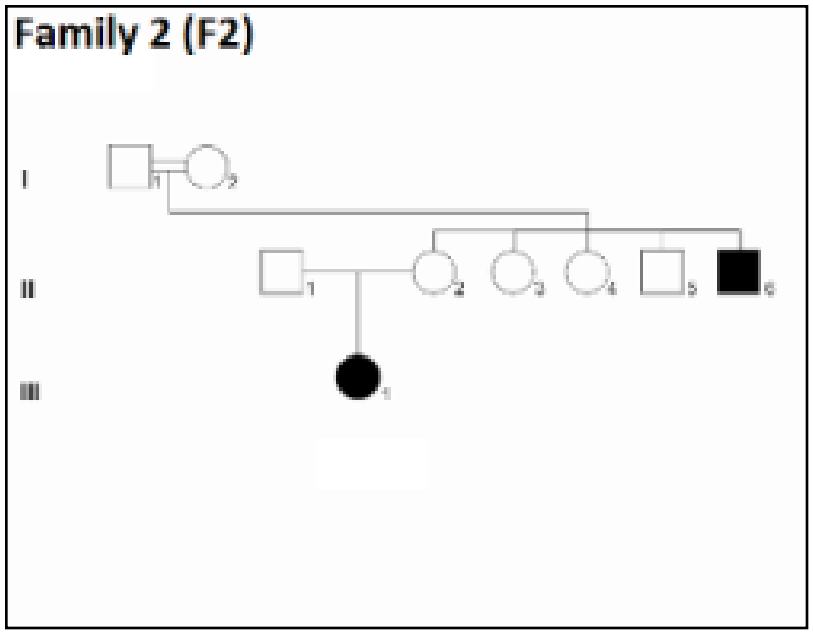
- Infectious – Hepatitis C
- Genetic/Metabolic – Wilson's disease, Galactosemia, Cystic Fibrosis
- Drug Induced – Valproic Acid, Amiodorone
- Nutritional – Obesity, Malnutrition, TPN
- Alchohol Abuse
- Multifactorial – **Metabolic Syndrome**
- Other

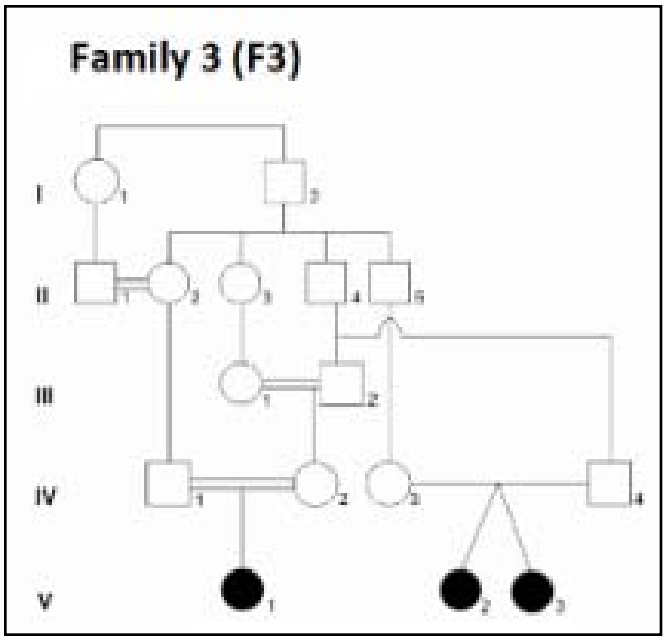
- Most conditions are readily diagnosed by adulthood.
- ~30% of patients with NAFLD are non-obese and DO NOT have evidence of metabolic syndrome or insulin resistance.
- The molecular mechanisms of NAFLD/NASH are poorly understood.

Glycerol-3-Phosphate Dehydrogenase 1 (*GPD1*) *Deficiency*

Identification of Patients

- 10 Patients from 4 families originating from a single village with a high degree of consanguinity.
- All presented between 1-9 months.
- Index case presented in 1989

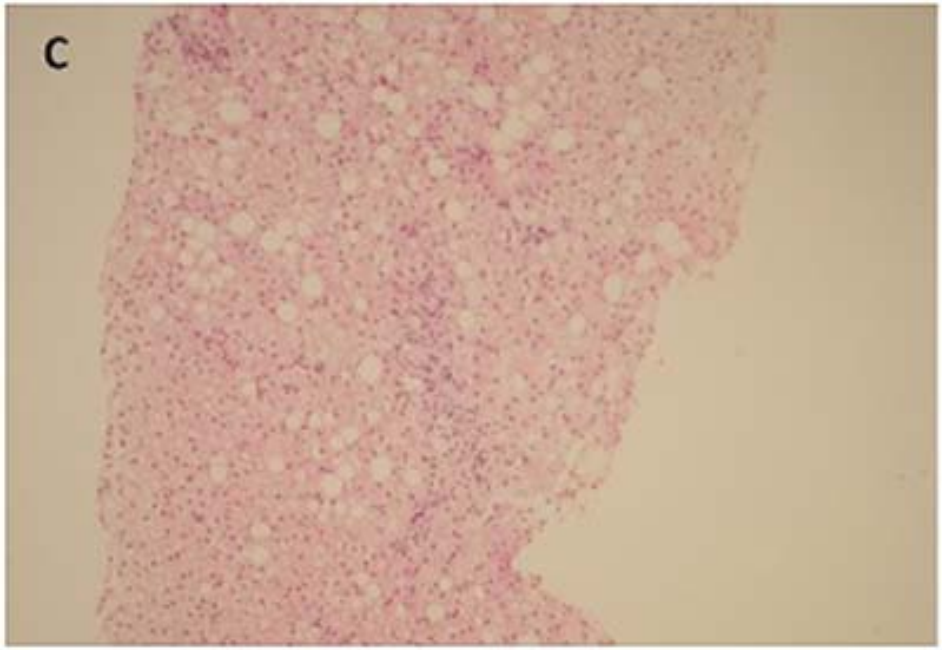


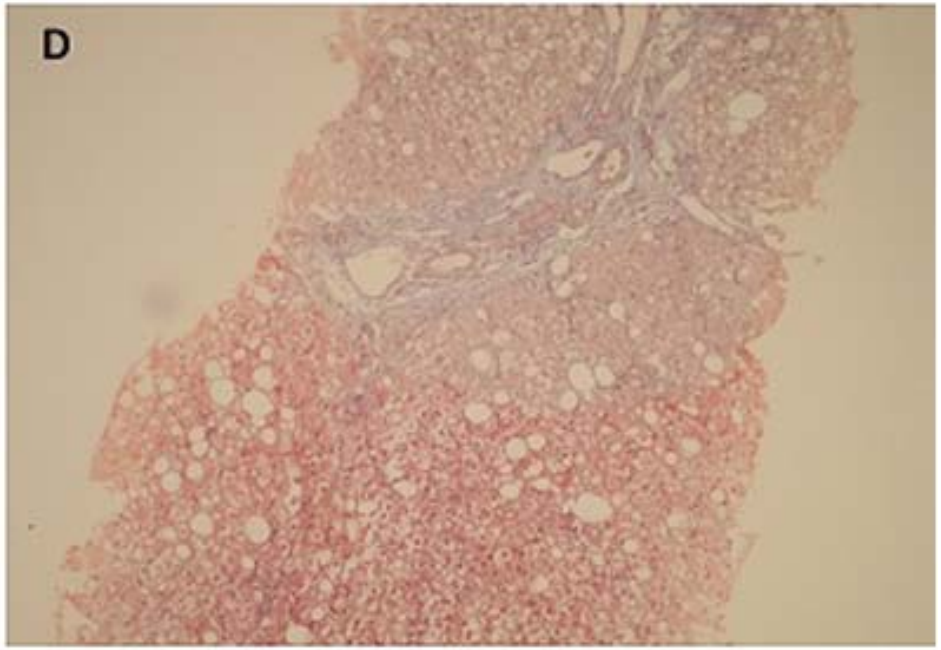


Clinical Signs and Symptoms

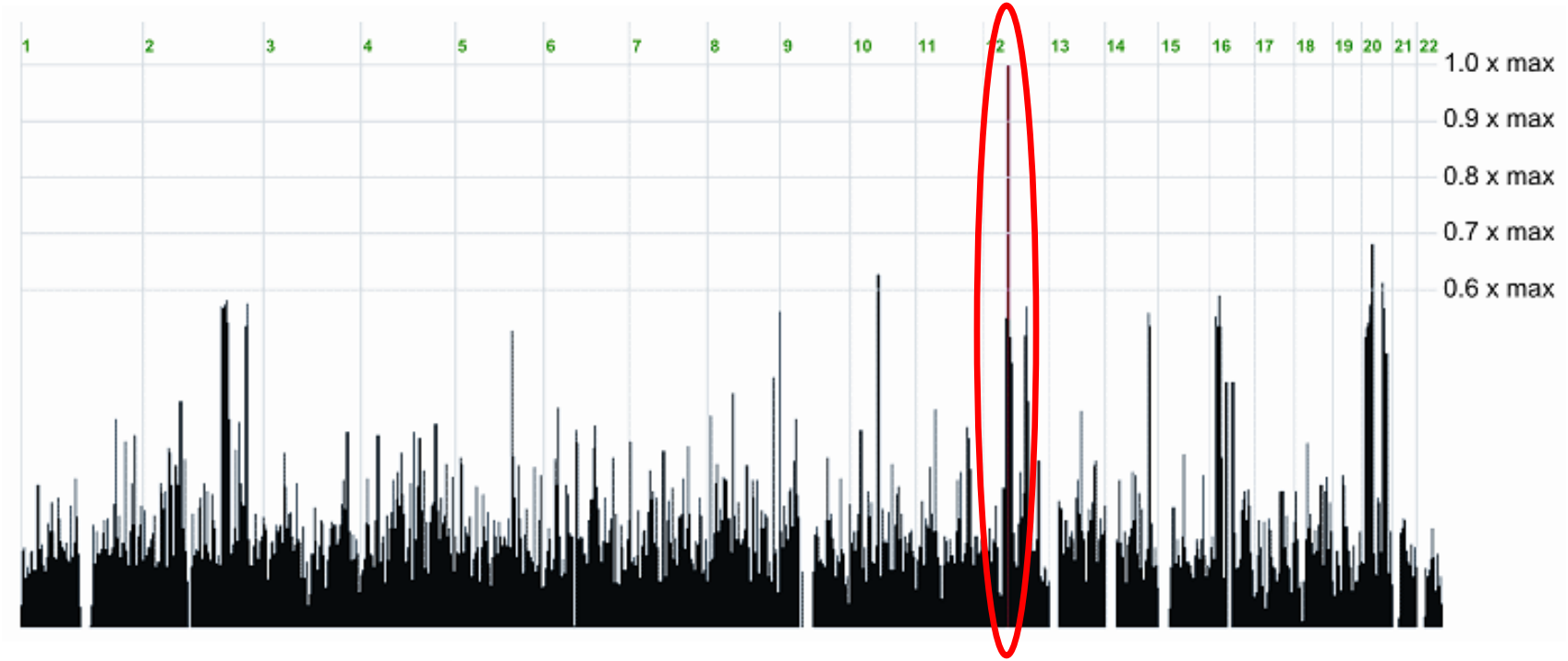
- Fasting Hypertriglyceridemia 10/10 258-6244mg/dl (2.9-70mmol/l)
- Moderate to Severe Hepatomegally 10/10
- Elevated Transaminases 10/10 ALT 51-230 U/l
- Asymptomatic 6/10
- Vomiting 3/10
- Splenomegally 3/10
- FTT 1/10
- Elevated Cholesterol 1/10 (420mg/dl)

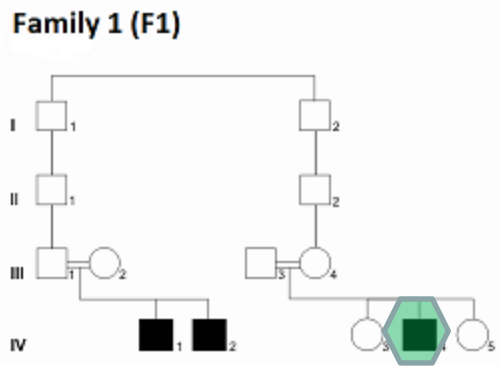
Biopsies

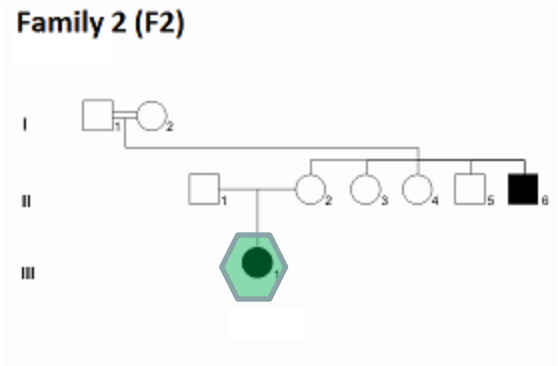




Homozygosity Mapping

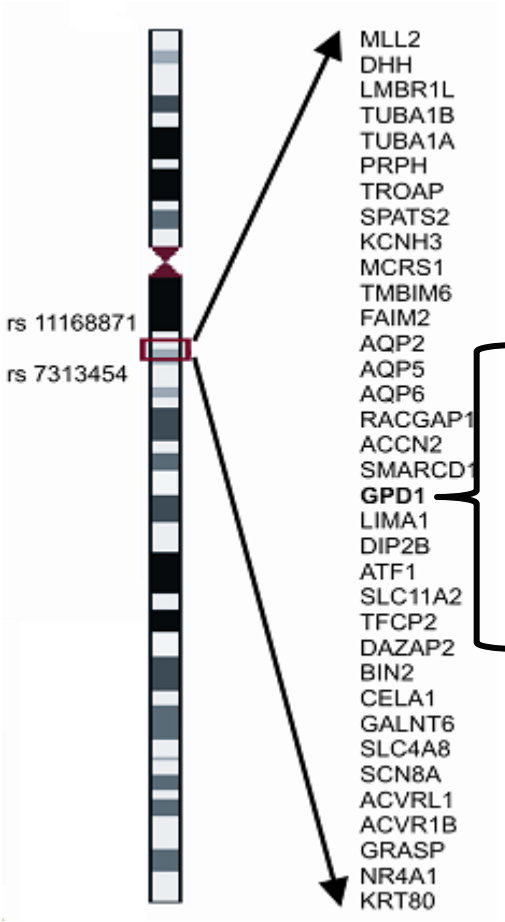


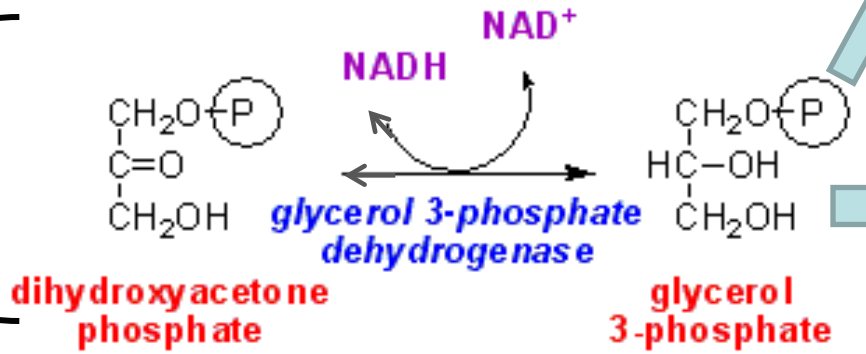




Candidate Gene Selection

Glycerol-3-Phosphate Dehydrogenase 1



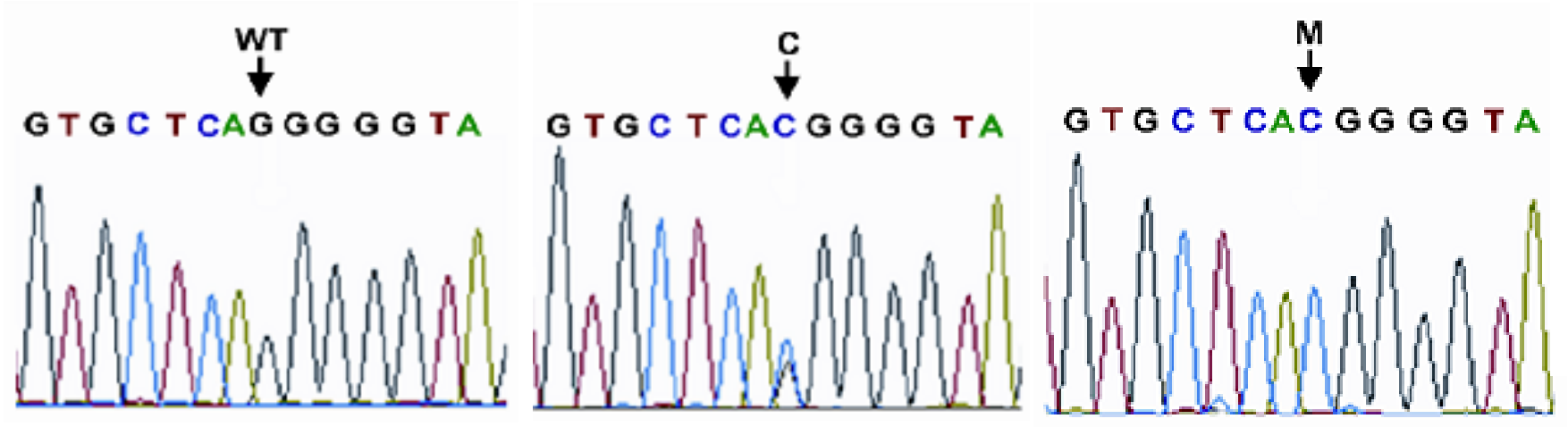


Triglyceride Formation

Gluconeogenesis

Respiratory Chain

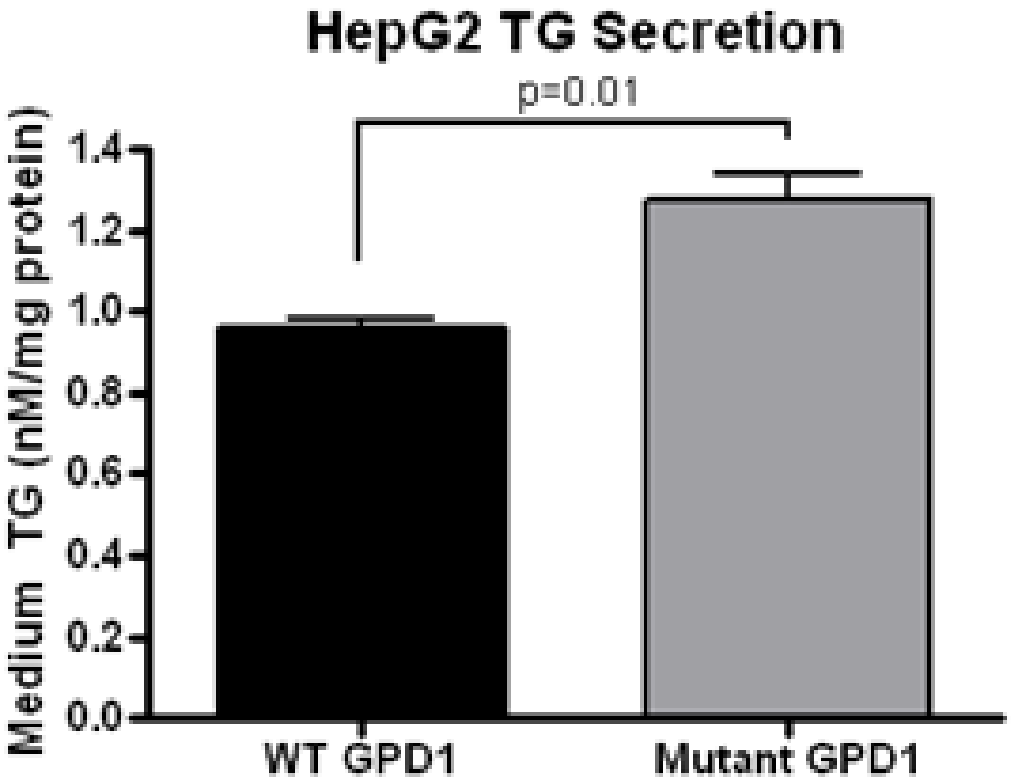
GPD1 Splice Site Mutation



Normal

Mutant

TG secretion



Summary

- We describe the first human disease associated with a mutation in glycerol-3-phosphate dehydrogenase 1.

- Clinical spectrum involves:
  - ✓ Transient infantile hypertriglyceridemia, hepatomegally, and elevated liver enzymes followed later in life with hepatic fibrosis and cirrhosis.

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Thank you

for your kind attention