

# Cancer Prone Disease Section

## Short Communication

### Glycogen storage disease type I (GSD I)

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#### Identity

##### Other names

von Gierke disease

##### Note

The disease comprises two sub-types: type Ia (glucose-6-phosphatase deficiency), type Ib (glucose-6-phosphate translocase deficiency).

##### Inheritance

Autosomal recessive. Incidence around 1/100 000 births.

#### Clinics

##### Note

Most of clinical manifestations are common to both sub-types of GSD I. Patients with type Ib have neutropenia.

##### Phenotype and clinics

Patients have poor tolerance to fasting (with hypoglycemia and hyperlactacidemia after 3 to 4 hours of fasting), marked hepatomegaly, full-cheeked round face, growth retardation (small stature and delayed puberty), generally improved by an appropriate diet, osteopenia and sometimes osteoporosis, enlarged kidneys and platelet dysfunctions leading to frequent epistaxis (Chen, 2000; Matern et al., 2002; Rake et al., 2002). In addition, in GSDIb, neutropenia and neutrophil dysfunction are responsible for tendency towards infections, relapsing aphthous gingivostomatitis, parodontitis, and enterocolitis. Late

complications are hepatic (adenomas with rare but possible transformation into hepatocarcinoma (Talente et al., 1994; Labrune et al., 1997; Franco et al., 2005; Reddy et al., 2007) and renal (glomerular hyperfiltration leading to proteinuria and sometimes to renal insufficiency, stones) (Talente et al., 1994; Rake et al., 2002; Scales et al., 2010) rare cases of pulmonary hypertension have been reported (Humbert et al., 2002).

##### Neoplastic risk

Hepatocellular adenomas are at risk of malignant transformation, even though this risk is weak. Patients with such adenomas must be regularly followed-up, with clinical, biological, and MRI evaluations.

Several studies have been performed to understand the physiopathology of adenomas development in GSD patients, and the transformation into hepatocellular carcinomas, but the precise mechanisms remain unknown (Kishnani et al., 2009).

##### Treatment

Diet is the basis of the treatment (Rake et al., 2002). It aims at avoiding hypoglycemia, combining, in infants, frequent meals and quite often nocturnal enteral feeding. Later, oral uncooked starch is introduced. Fructose and galactose intakes are restricted.

Many patients are given allopurinol (hyperuricemia frequently occurs), fibrates and/or statins (hypertriglyceridemia may have to be treated), converting enzyme inhibitors (should increased glomerular filtration rate and/or microalbuminuria be detected) (Melis et al., 2005).



CT: liver tomodensitometry showing an important heterogeneous tumor (white arrows) - MRI: liver MRI illustrating the same hepatic tumor.

G-CSF may be used in type Ib patients, to correct neutropenia.

Liver transplantation, performed on the basis of poor metabolic control and/or hepatocarcinoma, corrects hypoglycemia, but renal involvement may continue to progress and neutropenia is not always corrected in type Ib (Rake et al., 2002; Rake et al., 2002). Kidney transplantation can be performed in case of severe renal insufficiency.

Combined liver-kidney grafts have been performed in a few cases.

### **Prognosis**

Prognosis is usually good: late hepatic and renal

complications may occur, however, with adapted management, patients have almost normal life span.

## **Genes involved and proteins**

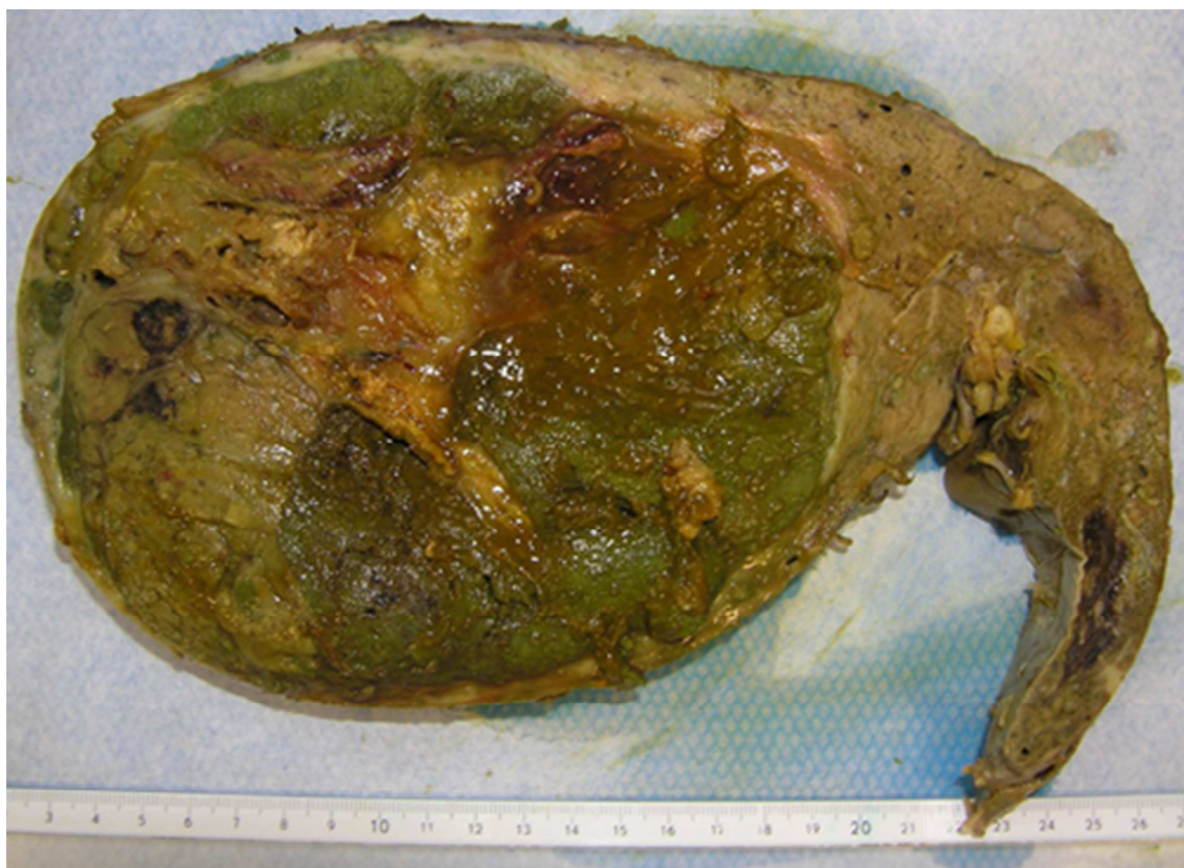
### **G6PC**

#### **Location**

17q21.31

#### **Note**

**GSD type Ia.** Not imprinted, maternally and paternally expressed.



Liver after hepatectomy: picture of the liver after liver transplantation, showing hepatocarcinoma.

#### DNA/RNA

##### Description

The human G6PC gene is 12,6 kb long and includes 5 coding exons (1071 bp for the coding region) (Lei et al., 1993).

#### Protein

##### Description

357 amino acids, trans-membrane protein.

##### Expression

The G6PC protein is constituted by 357 aminoacids and is expressed in liver, kidney and intestine. This protein is not expressed in neutrophils, explaining the absence of neutropenia in GSD type Ia.

#### Localisation

The protein is located in the endoplasmic reticulum membrane with its catalytic site on the internal side.

#### Function

G6PC hydrolyses glucose-6-phosphate to glucose in the endoplasmic reticulum. The enzyme forms with the glucose-6-phosphate transporter (SLC37A4) the complex responsible for glucose production and homeostatic regulation of blood glucose levels.

#### Mutations

##### Somatic

The G6PC mutations are responsible for the glycogen

storage disease type Ia (Von Gierke disease). More than 90 mutations have been described affecting the whole coding sequence (Matern et al., 2002; Shieh et al., 2002; Chou and Mansfield, 2008).

#### SLC37A4

##### Location

11q23.3

##### Note

**GSD type Ib.** Not imprinted, maternally and paternally expressed.

#### DNA/RNA

##### Description

The human SLC37A4 gene is 6,4 kb long and includes 9 coding exons (3870 bp for the coding region, exon 7bis being exclusively expressed in neutrophils (Hiraiwa et al., 1999; Veiga-da-Cunha et al., 1999).

#### Protein

##### Description

1290 amino acids, trans-membrane protein.

##### Expression

The SLC37A4 protein is constituted of 1290 aminoacids and is co-expressed with G6PC gene in liver, kidney and intestine, and with G6PC3 in neutrophils (probably required for normal neutrophil function).



**Localisation**

The protein is located in the endoplasmic reticulum membrane.

**Function**

SLC37A4 transfers glucose-6-phosphate from cytoplasm to internal endoplasmic reticulum. This activity associated with glucose-6-phosphatase activity (G6PC or G6PC3) regulates glucose production from glycogenolysis and gluconeogenesis (Van Schaftingen and Gerin, 2002).

**Mutations****Somatic**

The SLC37A4 mutations are responsible for the glycogen storage disease type Ib (Von Gierke disease). More than 80 mutations have been described affecting the whole coding sequence (Veiga-da-Cunha et al., 1999).

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