Rối loạn dự trữ Glycogen type IX

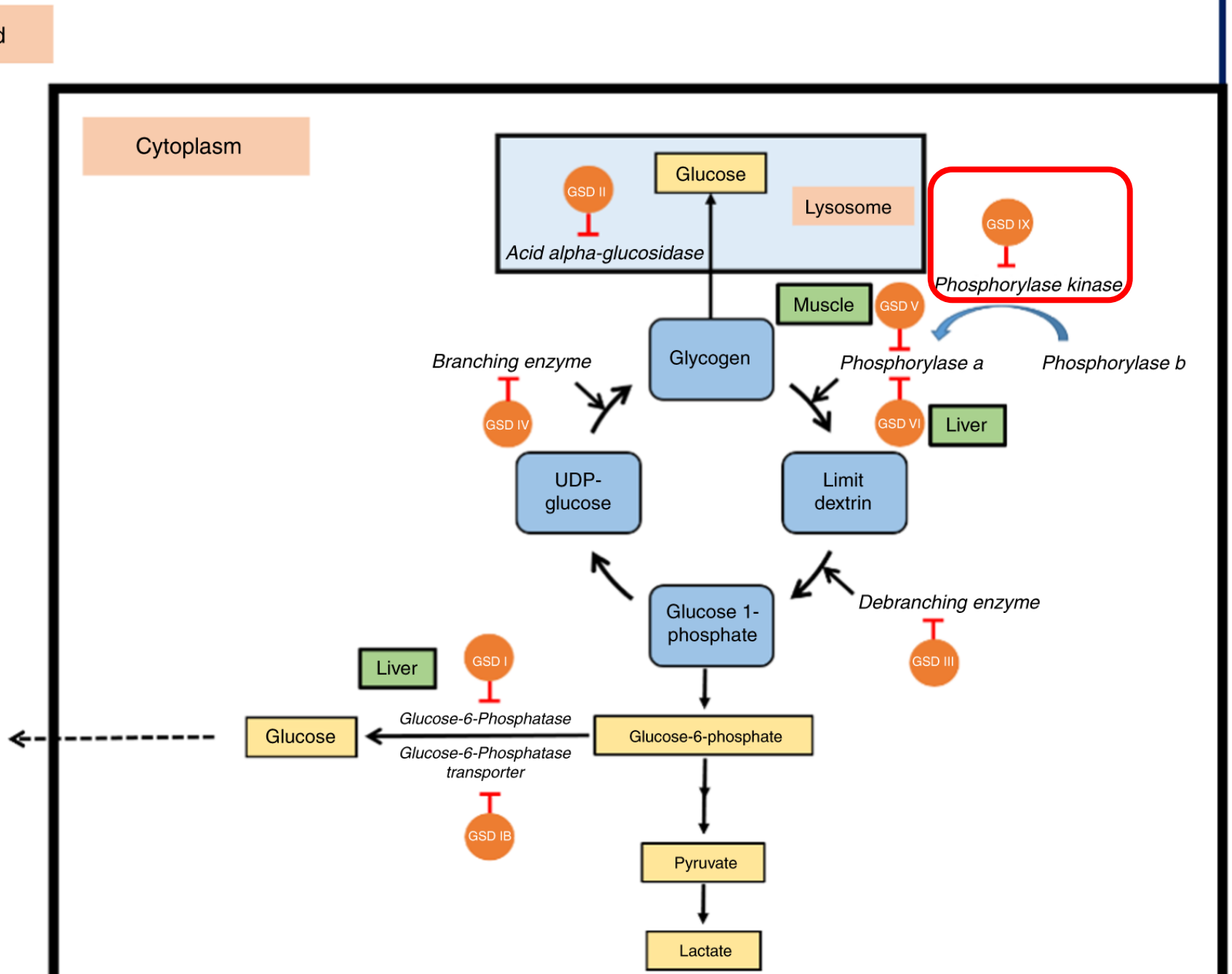
BS. Đỗ Phước Huy.

Nội dung

- Bệnh dự trữ glycogen.
- Ca bệnh lâm sàng.
- Tiếp cận từ lâm sàng đến di truyền.

Bệnh dự trữ glycogen

- Là một nhóm bệnh lý rối loạn chuyển hoá di truyền hiếm.
- Nguyên nhân: bất thường một hay nhiều enzyme tham gia quá trình sinh tổng hợp glycogen.
- Hệ quả: Biến đổi từ nhẹ (có thể sống được) -> nặng (chết trong giai đoạn sơ sinh)
- Có 15 phân nhóm nhỏ (khoảng 15 gen liên quan).



Kishnani, P.S., Goldstein, J., Austin, S.L. *et al.* Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* **21,** 772–789 (2019).

Rối loạn dự trữ glycogen type IX

Affected Populations

The autosomal recessive forms of glycogen storage disease IX affect males and females in equal numbers. The X-linked forms primarily affect males, although females can have symptoms, such as enlargement of the liver and, more rarely, females can have symptoms similar to those seen in males. GSD-IX types A, B and C are estimated to affect 1 in 100,000 individuals in the general population. These disorders account for approximately 25% of all glycogen storage disorders making GSD-IX one of the most common forms of these disorders. Because some affected individuals go undiagnosed or misdiagnosed, it is difficult to determine the true frequency of GSD-IX in the general population. GSD-IXd is extremely rare and its prevalence is unknown.

Glycogen Storage Disease Type IXa

GSD-IXa is the most common subtype of GSD IX, and is caused by the deficiency of phosphorylase kinase in the liver. It accounts for approximately 75% of affected individuals and is also known as X-linked liver glycogenesis or PHKA2-related phosphorylase kinase deficiency. Affected individuals often develop an enlarged liver (hepatomegaly), low blood glucose levels (hypoglycemia) and high levels of blood ketones during fasting, and growth delays. Some children have delays in

Genomic Locations for PHKA2 Gene

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chrX:18,892,298-18,984,114 (GRCh38/hg38) *chrX:18,910,416-19,002,716* (GRCh37/hg19)

Size: 91,817 bases *Orientation:* Minus strand *Size:* 92,301 bases *Orientation:* Minus strand

Genomic View for PHKA2 Gene

Genes around PHKA2 on UCSC Golden Path with GeneCards custom track

Cytogenetic band: Xp22.13 by HGNC Xp22.13 by Entrez Gene Xp22.13 by Ensembl

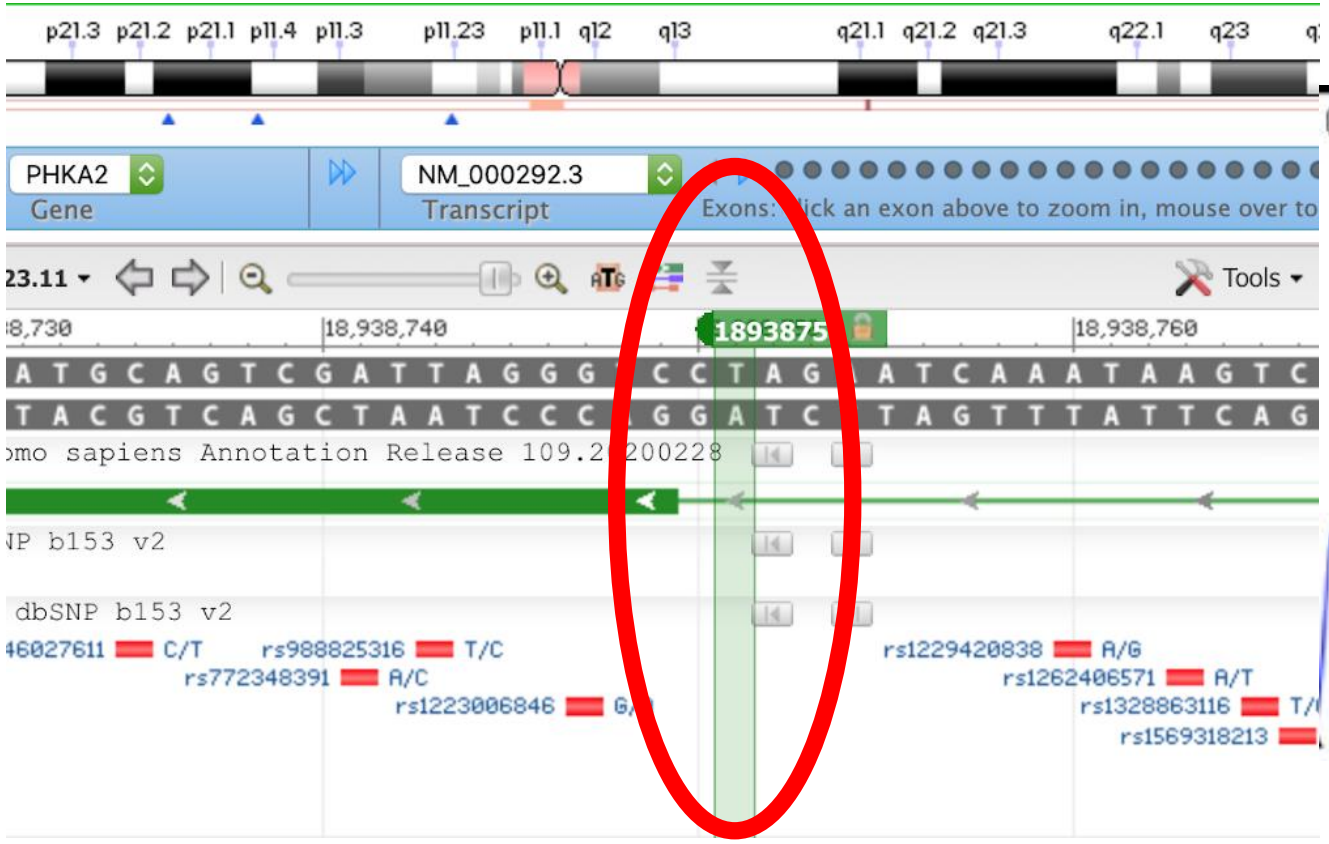
PHKA2 Gene in genomic location: bands according to Ensembl, locations according to GeneLoc (and/or Entrez Gene and/or Ensembl if different)

33 exons và 1235 amino acid

Ca lâm sàng

- Bệnh nhi Nam, 8 tháng tuổi, NV vì gan to và tăng men gan.
- Siêu âm gan to (11 cm),
- Xét nghiệm khác:
  - Glycemia: 5.5mmol/L
  - AST/ALT: 108/231 U/L (8 tháng), 1137/851 (15 tháng).
  - LDH: 654 U/L

Ca lâm sàng



Trình tự vùng chuyển tiếp exon 10 trên gen *PHKA2*. Đột biến tại vị trí 18938751 trên NST (chrX: 18938751 theo GRCh38) chưa được báo cáo trên database SNP (dbSNP) và trên Clinvar

Kết quả giải trình tự theo phương pháp Sanger khẳng định có sự thay đổi T thành A tại vị trí gióng cột chrX:18938751. Hệ quả tạo đột biến hemizygous NM_000292.3 (*PHKA2*):c.919-2T>A.

Cách tiếp cận trên lâm sàng

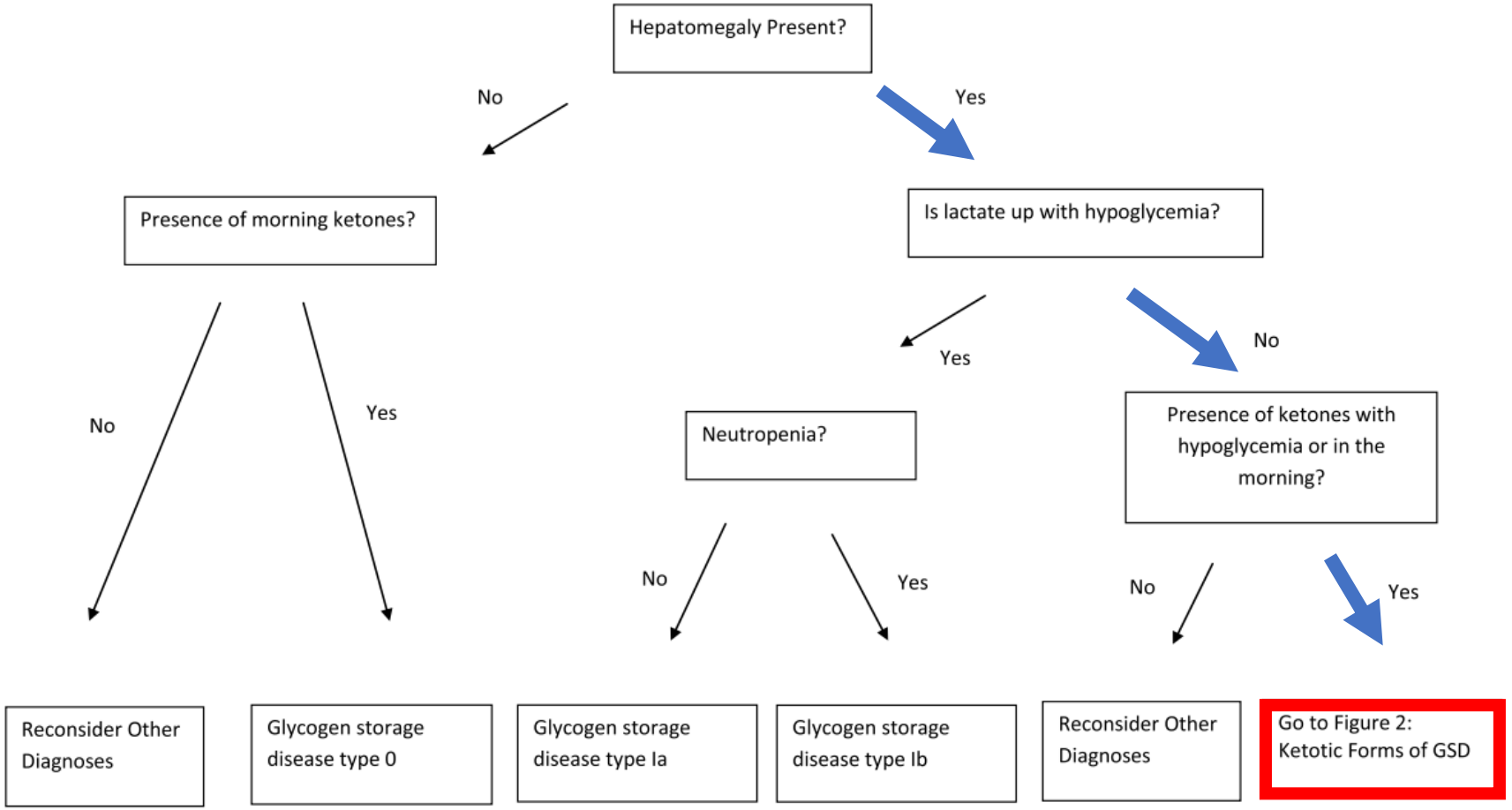


Fig. 1. Suspected glycogen storage disease.

Cách tiếp cận trên xét nghiệm di truyền

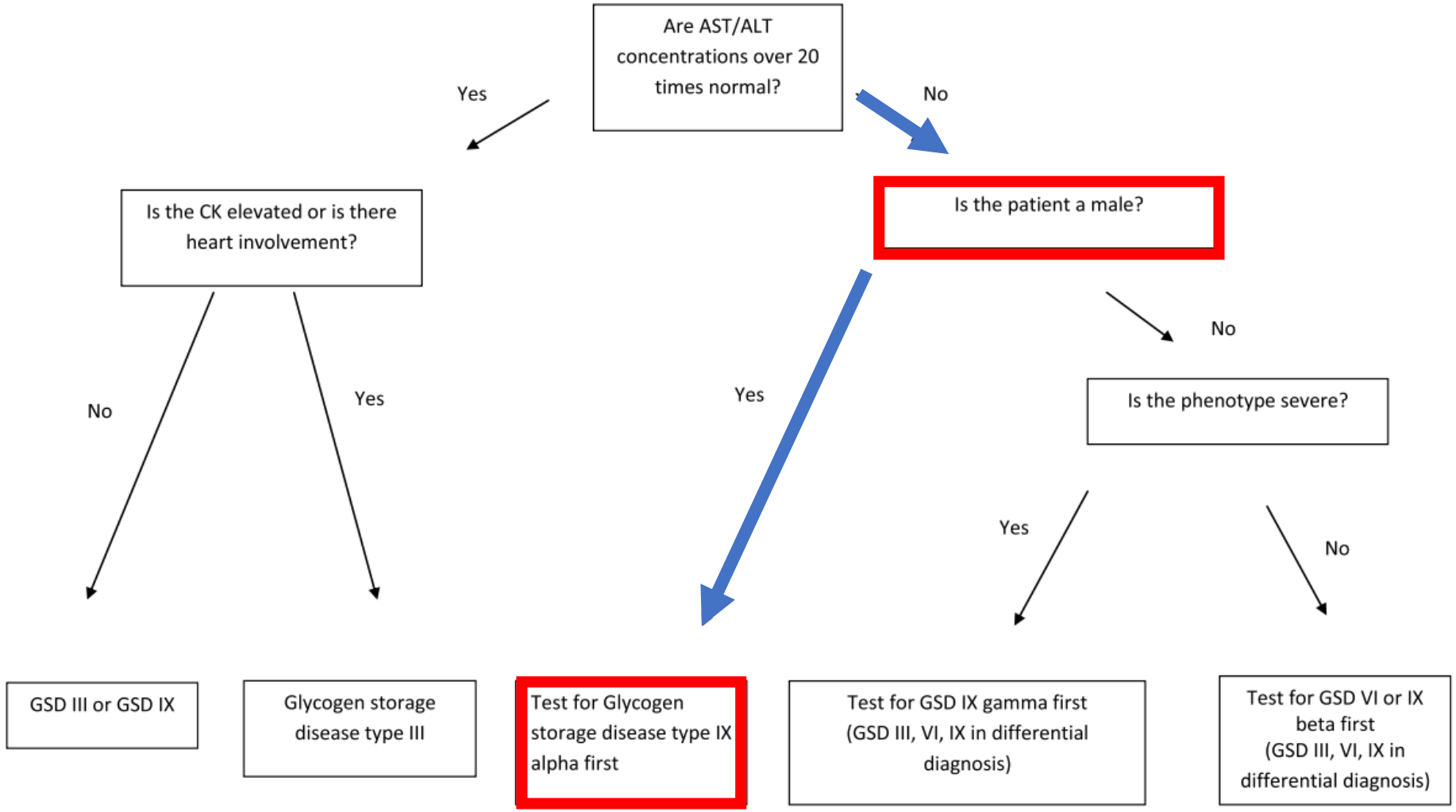


Fig. 2. Ketotic forms of GSD.

Xét nghiệm gen trong bệnh lý GSD IXa

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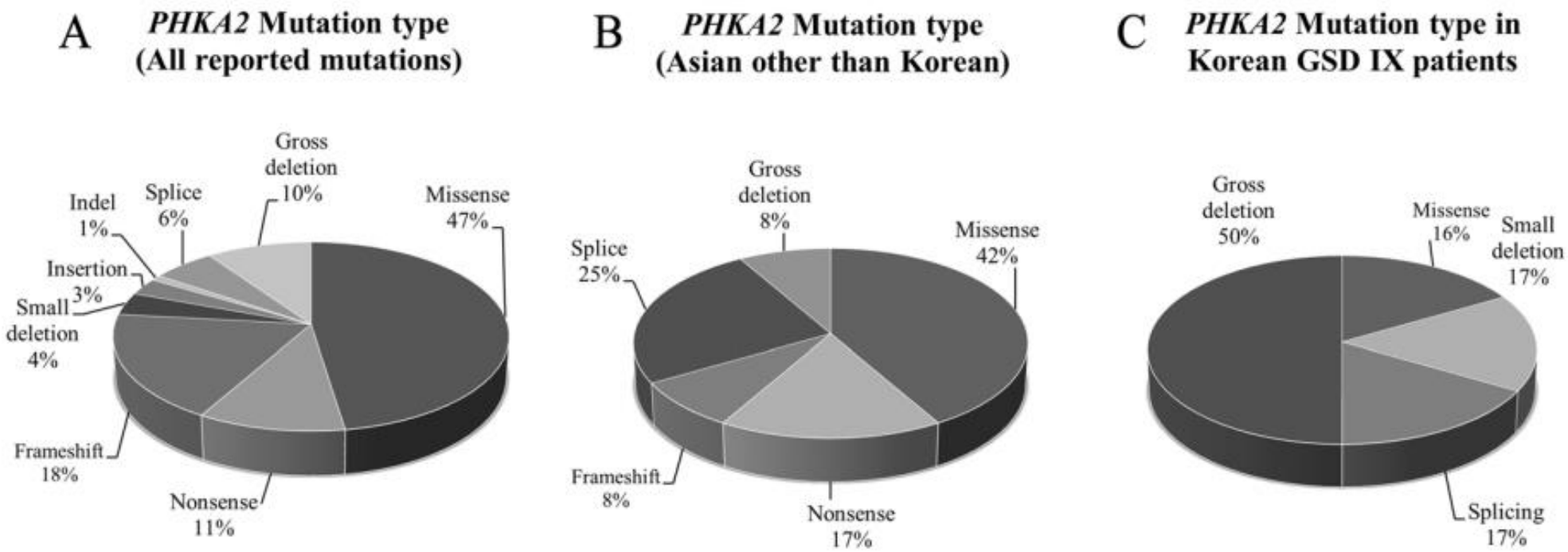
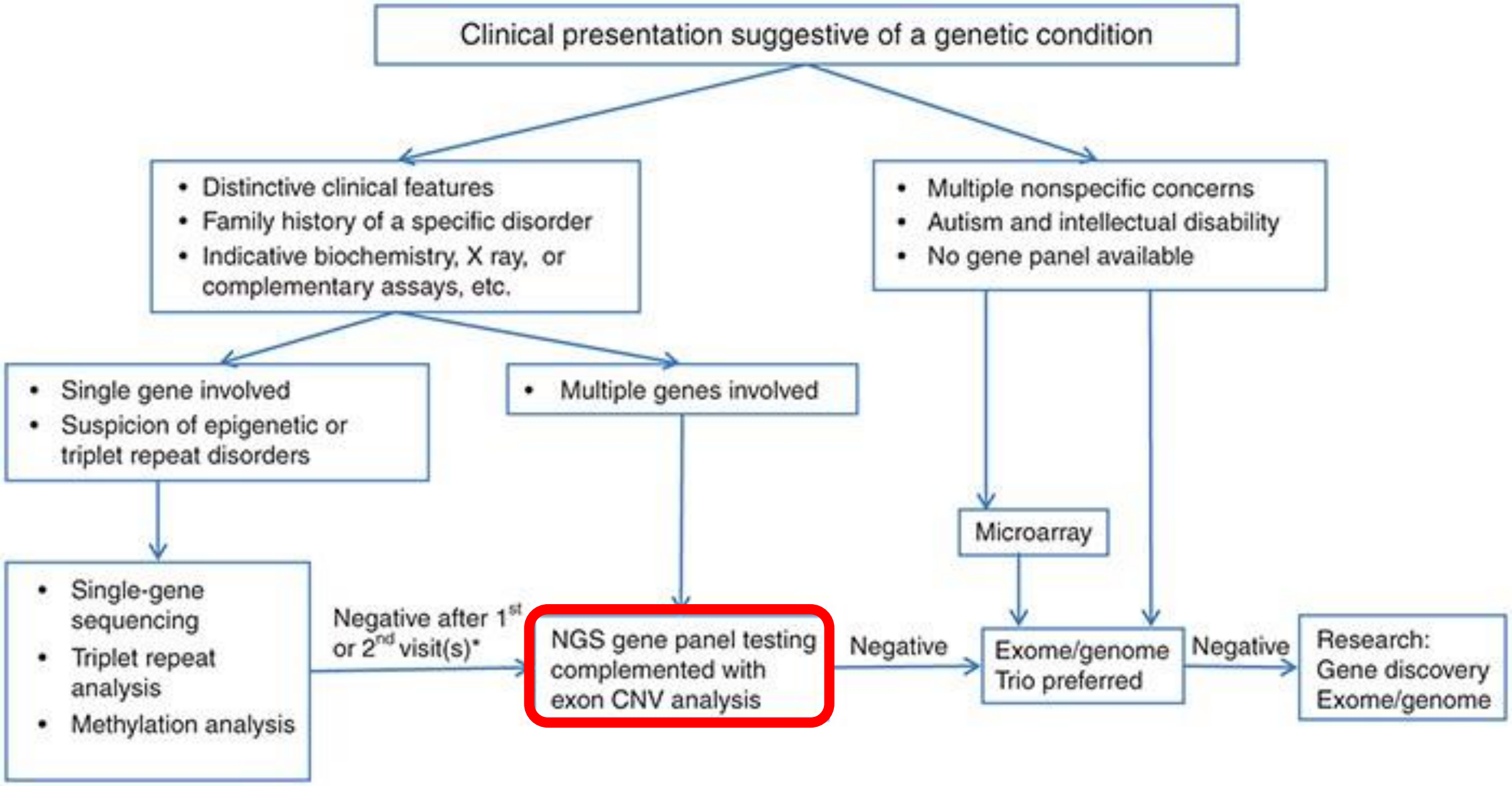
33 exons và 1235 amino acid => SANGER rất tốn chi phí



Choi, Rihwa et al. “PHKA2 mutation spectrum in Korean patients with glycogen storage disease type IX: prevalence of deletion mutations.” *BMC medical genetics* vol. 17 33. 21 Apr. 2016,



Xue, Y., Ankala, A., Wilcox, W. *et al.* Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. *Genet Med* **17,** 444–451 (2015).

Tiếp cận di truyền trong thời đại Exome Sequencing

Assay type	Sanger sequencing	NGS-based gene panels[5]	**Exome sequencing[2,3,4]**	Genome sequencing[1]
Detection rates	3 – 5 %	5 – 10%	~20 - 40%	~34 – 60%

[1]Glissen et al. Genome sequencing identifies major causes of severe intellectual disability. Nature 2014; 511:344-7.
[2]Yang et al. Clinical whole-exome sequencing for the diagnosis of Mendelian disorders. N Engl J Med 2013; 365:1502-11
[3]Wright et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet 2015; 385:1305-14
[4]https://www.nextgxdx.com/order-guides/exomes-sequencing
[5]https://www.genomeweb.com/sequencing/hereditary-cancer-panels-increase-dx-yield-vus-rate-high-clinical-guidelines-mis

Kết luận

- GSD IX: bệnh lý di truyền hiếm. Tiên lượng tốt (trong nhóm GSD) nếu kiểm soát dinh dưỡng đúng cách.
- Cần có cách tiếp cận hợp lý về lâm sàng và di truyền.
- Tư vấn di truyền là cần thiết trong mọi trường hợp thực hiện xét nghiệm di truyền.

XIN CHÂN THÀNH CẢM ƠN