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EDITORIAL

# Fanconi-Bickel syndrome as an example of marked allelic heterogeneity

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## Abstract

Renal tubular acidosis (RTA) encompasses many renal tubular disorders characterized by hyperchloremic metabolic acidosis with a normal anion gap. Untreated patients usually complain of growth failure, osteoporosis, rickets, nephrolithiasis and eventually renal insufficiency. Fanconi-Bickel syndrome (FBS) is an example of proximal RTA due to a single gene disorder; it is caused by defects in the facilitative glucose transporter 2 gene that codes for the glucose transporter protein 2 expressed in hepatocytes, pancreatic β-cells, enterocytes and renal tubular cells. It is a rare inherited disorder of carbohydrate metabolism manifested by huge hepatomegaly [hence it is classified as glycogen storage disease (GSD) type XI; GSD XI], severe hypophosphatemic rickets and failure to thrive due to proximal renal tubular dysfunction leading to glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting and hypophosphatemia. The disorder has been reported from all parts of Europe, Turkey, Israel, Arabian countries, Japan and North America. Many mutant alleles have been described, its exact frequency is unknown and there is no single mutation found more frequently than the others. The presence of consanguinity in affected families suggests an autosomal recessive pattern of inheritance. New cases of FBS have been recently reported in the Middle and Far East in collaboration with specialized centers. Two novel mutations have been discovered in two unrelated Egyptian families. The first was two bases deletion, guanine and adenine, (c.253_254delGA) causing a frameshift mutation (p. Glu85fs) and the second is mutation in exon6 in splicing acceptor site with intron5 (c.776-1G>C or IVS5-1G>A). Moreover, a new different mutation was described in a 3 year old Indian boy.



**Key words:** Proximal renal tubular acidosis; Fanconi-Bickel syndrome; *GLUT2* gene

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## INTRODUCTION

Renal tubular acidosis (RTA) defines many renal tubular disorders characterized by hyperchloremic metabolic acidosis with a normal anion gap. They represent chronic diseases with significant impact on the quality of life of the affected patients when left untreated, possibly leading to growth failure, osteoporosis, rickets, nephrolithiasis and eventually renal insufficiency[1-6]. These disorders may be primary genetic defects of tubular transport mechanisms[7] or secondary to systemic diseases or adverse drug reactions[8,9]. Defects in proximal bicarbonate reclamation or distal acid secretion give rise to the respective clinical syndromes of proximal or distal RTA[10-15]; proximal renal tubules are responsible for reabsorption of 80%-90% of the HCO3- filtered in glomeruli as well as generation of

"extra" HCO3- through the deamination of glutamine to glutamate, then forming α-ketoglutarate and eventually glucose[1,2,16-19]. Fanconi-Bickel syndrome (FBS) is a single gene disorder (OMIM 227810) caused by defects in the facilitative glucose transporter 2 (GLUT2 or SLC2A2) gene mapped on chromosome 3q26.1-26.3, that codes for the glucose transporter protein 2 expressed in hepatocytes, pancreatic β-cells, enterocytes and renal tubular cells[20-22]. FBS is a rare inherited disorder of carbohydrate metabolism; it is characterized by the association of huge hepatomegaly due to glycogen accumulation (hence it is classified as glycogen storage disease (GSD) type XI; GSD XI by Hug *et al*[23]), severe hypophosphatemic rickets and failure to thrive due to proximal renal tubular dysfunction. Proximal renal tubular dysfunction is documented by glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting and hypophosphatemia[24-28]. These findings are the characteristic laboratory evidence of the disease[29,30]. The disorder has been reported from all parts of Europe, Turkey, Israel, Arabian countries, Japan and North America. Many mutant alleles have been described, the exact frequency of the disease or each mutation is not known and there is no reported single mutation found more frequently than the others. The presence of consanguinity in most of the affected families suggests an autosomal recessive pattern of inheritance[21,22]. No specific therapy is available for FBS patients. Symptomatic treatment is directed towards a stabilization of glucose homeostasis and compensation for renal losses of various substances[22]. The overall prognosis seems to be favorable; several patients have been reported to have reached adulthood in a stable condition[21] and the first reports on fertility of female and male patients have recently been published[22,31,32]. Recently, two novel mutations have been discovered in two unrelated Egyptian families[33] and another different mutation in an Indian boy aged 3 years[34].

## DIAGNOSIS OF RENAL TUBULAR ACIDOSIS

RTA should be suspected in any patient with hyperchloremic metabolic acidosis and a normal anion gap (less than 12) after ruling out other causes of bicarbonate loss e.g., diarrhea. Thus, in a young infant with diarrhea and underlying RTA, diagnosis may be initially obscured. In such situations, RTA is further suspected if hyperchloremic metabolic acidosis shows delayed resolution[35,36]. However, acidosis with a high gap (more than 20) rules out RTA and suggests added anions, whether endogenous (lactic acidosis, inborn errors of metabolism) or exogenous (salicylates ingestion)[37].

Untreated children with RTA have nonspecific symptoms, such as failure to thrive[38], polydipsia, polyuria, anorexia, vomiting, constipation and restlessness[12]. There are also signs and symptoms which are more specific to some types of RTA. Metabolic bone disease is frequent in Fanconi syndrome secondary to excessive losses of phosphates and calcium, nephrocalcinosis and hypercalciuria are common in patients with distal RTA[39] and muscle weakness in hypokalemic patients[40].

Urinary pH may help to distinguish distal from proximal RTA; if less than 5.5, proximal RTA is possible, but if more than 6, distal RTA is more probable. Moreover, urinary anion gap [(urinary $Na^+$ and $K^+$) - urinary $Cl^-$] could add some confirmatory events in favor of distal RTA; a positive gap means a defect in ammoniogenesis which points to distal RTA[41-44].

**Table 1 Chromosomal mapping of some inherited forms of proximal renal tubular acidosis[49,69,70]**

| Inherited Fanconi syndromes | Gene | Mapping |
|---|---|---|
| Fanconi-Bickel syndrome | *SLC2A2* | Chromosome 3q26.1-26.3 |
| Autosomal recessive | *SLC4A4* | Chromosome 4q21 |
| Dent´s syndrome | *CLCN5* | Chromosome Xp11.22 |
| Cystinosis | *SLC3A1*, *SLC7A9* | Chromosome 2p21, Chromosome 19p13.1 |
| Tyrosinemia type 1 | *FAH* | Chromosome 15q23-q25 |
| Galactosemia | *GALT* | Chromosome 9p13 |
| Wilson´s disease | *ATP7B* | Chromosome 13q14.3-q21.1 |

## INHERITED FORMS OF PROXIMAL RTA

In recent years, remarkable progress has been made in the unraveling of the molecular pathogenesis of hereditary diseases caused by mutations in genes encoding transporters in renal tubules[45,46]. Proximal RTA is a heterogeneous group of disorders whose genes are dispersed in the human genome[47]. Fanconi syndrome, the most common prototype of proximal RTA[48], is part of a systemic disease, mostly autosomal recessive. Other forms of inherited proximal RTA (Table 1) show gene localization of some inherited forms of proximal RTA, including cystinosis, tyrosinemia, galactosemia, Fanconi-Bickel and many other syndromes[49].

FBS is a single gene disorder (OMIM 227810) caused by defects in the facilitative glucose transporter 2 (GLUT2 or SLC2A2) gene mapped on chromosome 3q26.1-26.3, that codes for the glucose transporter protein 2 expressed in hepatocytes, pancreatic β-cells, enterocytes and renal tubular cells[20,50,51]. Clinical diagnosis of FBS should be based on: (1) presence of consanguinity being an autosomal recessive disease[52]; (2) hepatomegaly with deranged carbohydrate metabolism (GSD type XI); (3) severe hypophosphatemic rickets, with its other clinical stigmata; and (4) proximal RTA e.g., glucosuria, phosphaturia, generalized aminoaciduria and bicarbonaturia.

## DISCUSSION

Santer *et al*[21] and Mueckler *et al*[53] considered GLUT2, the 524-amino acid isoform expressed in hepatocytes, pancreatic β cells and the basolateral membranes of intestinal and renal tubular epithelial cells, to be a candidate gene for the defect in FBS. They identified mutations in

the *GLUT2* gene in 3 families with FBS, including the patient originally described by Fanconi and Bickel[54]. These mutations represent the first detection of a congenital defect within a whole family of membrane proteins (facilitative glucose transporters). Sakamoto *et al*[20] studied 3 Japanese patients with FBS and found 4 novel mutations in the *GLUT2* gene, including a splice site mutation, a nonsense mutation and 2 missense mutations. Several family members who had a heterozygous missense mutation were shown to have glucosuria but a family member heterozygous for the nonsense mutation did not. It was speculated that mutant GLUT2 proteins may have a dominant-negative effect and that heterozygosity for a nonsense mutation may not lead to glucosuria because of selective and efficient degradation of the nonsense mRNA[55].

In the last decade, many mutations concerning *GLUT2* gene have been described in FBS patients. Later, Santer *et al*[22] reported a total of 109 cases from 88 families worldwide who had been diagnosed as FBS. They reported their results of mutation analysis in 49 patients from 39 families from Turkey, Europe, the Near East, North Africa and North America. Homozygosity or compound heterozygosity for *GLUT2* mutations was found in 49 patients among these cases and 23 novel mutations of the *GLUT2* gene were detected. These mutations were scattered over the whole coding sequence of the *GLUT2* gene and mutations were found in all exons. None of these mutations was particularly frequent, thus making the molecular diagnosis more laborious. It is interesting that most of the *GLUT2* mutations were private and confined to a single family. Of these patients, 12 were Turkish and all had a different mutation[55]. Since the first report of mutations in the *GLUT2* gene[56], more than 30 different mutations have been identified and most of the reported mutations are confined to a single family[55].

Some FBS patients did not have any detected mutations in the protein-coding region of the *GLUT2* gene[57,58]; this situation could be explained by the presence of heterozygous long-range deletions which are not detectable with the usually applied PCR-based method[58].

Recently, two new mutations were detected in two unrelated Egyptian families that presented with cases of FBS[33].

Selected examples of allelic variant of SLC2A2 (*GLUT2*) gene are tabulated (Table 2). The first one represents a mutation type causing non-insulin dependent diabetes mellitus and the other 14 types are responsible for FBS with different phenotypes.

The first allelic variant is for non-insulin dependent DM, SLC2A2 and VAL197ILE, reported with 2 amino acid substitutions in the human *GLUT2* gene. A thr110-to-ile substitution was present at equal frequency in diabetic and control populations, whereas a val197-to-ile substitution was discovered in a single allele of a patient with non-insulin dependent diabetes[57]. Mueckler *et al*[53] tested the effect of these amino acid changes on glucose transport activity by expression of the mutant proteins in Xenopus oocytes. The polymorphism at threonine-110 had no effect on the expression of GLUT protein or the uptake of 2-deoxyglucose. On the other hand, the highly conserved val197-to-ile amino acid change abolished transport activity of the GLUT2 transporter expressed in Xenopus oocytes. This was the first known dysfunctional mutation in a human facilitative glucose transporter protein. The presence of the mutation in a diabetic patient suggested that defects in *GLUT2* expression may be causally involved in the pathogenesis of non-insulin dependent diabetes mellitus[58]. Santer *et al*[22] stated that the patient reported by Tanizawa *et al*[57] was a woman of African American descent with gestational diabetes mellitus and that the mutation was heterozygous.

**Table 2 Allelic variants of *SLC2A2* gene; first allele causes non-IDDM and the other 14 variants cause fanconi-Bickel syndrome; in addition to the newly diagnosed Egyptian variants[33]**

| No. | Phenotype | Mutation | dbSNP |
|---|---|---|---|
| 1 | Non-IDDM | SLC2A2, VAL197ILE (22, 53, 56) | [rs121909741] |
| 2 | FBS | SLC2A2, 1-BP DEL-(21, 50) | |
| 3 | FBS | SLC2A2, ARG365TER (21, 22) | [rs121909742] |
| 4 | FBS | SLC2A2, ARG301TER (21, 22) | [rs121909743] |
| 5 | FBS | SLC2A2, PRO417LEU (62) | [rs121909744] |
| 6 | FBS | SLC2A2, TRP420TER (66) | [rs121909745] |
| 7 | FBS | SLC2A2, 1-BP DEL, 1363G (22) | |
| 8 | FBS | SLC2A2, 1405C-T (22) | |
| 9 | FBS | SLC2A2, 1-BP INS, 793C (22) | |
| 10 | FBS | SLC2A2, 1264G-A (22) | |
| 11 | FBS | SLC2A2, 469C-T (22) | |
| 12 | FBS | SLC2A2, VAL423GLU (20) | [rs28928874] |
| 13 | FBS | SLC2A2, IVS2, A-G, -2-(20) | |
| 14 | FBS | SLC2A2, GLN287TER (20) | [rs121909746] |
| 15 | FBS | SLC2A2, LEU389PRO (20) | [rs121909747] |

FBS: Fanconi-Bickel syndrome.

Three allelic variants, all of which are nonsense causing premature termination of protein synthesis[21]: (1) SLC2A2, 1-BP Del, in the two Turkish sibs with FBS described by Muller *et al*[59]. They were homozygous for a single-base deletion in a stretch of 4 thymine residues (positions 446 to 449) in exon 3 causing a frameshift with a premature TGA stop at codon 74 in the same exon, resulting in a truncated protein of 45 regular and 28 aberrant amino acids. This mutation had been found in four other patients, including those originally described by Fanconi *et al*[54]; (2) SLC2A2, ARG365TERin a Turkish boy with FBS who was homozygous for a C-to-T transition (CGA to TGA) at nucleotide 1405 in exon 8, causing a nonsense arg365-to-ter mutation (R365X); and (3) SLC2A2, ARG301TER, in the patient originally reported by Fanconi *et al*[54] and confirmed later[60]. A homozygous C-to-T transition (CGA to TGA) at nucleotide 1251 in exon 6 was described, causing a nonsense arg301-to-ter (R301X) mutation resulting in a truncated GLUT2 protein with only 6 of the 12 membrane-spanning segments[57]. The patient was found still alive at the age of 52 years, 140 cm tall but with persistent clinical and chemical features of FBS.

A homozygous missense mutation, SLC2A2, PRO-417LEU, was described in a large family with a high degree of consanguinity; it showed several affected individuals of both sexes, markedly reduced liver phosphorylase kinase activity was found in association with the characteristic clinical features and laboratory findings of FBS[61], thus suggesting that FBS is genetically heterogeneous and that there may be another subtype of PHK deficiency (possibly associated with a distinctive genotype) that gives rise to hepatorenal glycogenosis. Affected members of this family were shown to have a homozygous missense mutation (P417L) in *GLUT2* gene[62]. The affected proline residue is completely conserved in all mammalian glucose permease isoforms and even in bacterial sugar transporters and is believed to be critical for the passage of glucose through the permease. Homozygosity for this mutation was found in 7 affected individuals from different branches of that family. Recently, this mutation has been detected in a third Egyptian family (Al-Haggar, personal communication) but it is re-enumerated to exon 10 (not 9 as in the initial report) due to the changes of gene structure.

Five allelic variants were described by Santer *et al*[22], mostly missense mutations: (1) SLC2A2, 1-BP Del, 1363G, in two sibs of English ancestry with FBS[63] in whom the use of cornstarch provided a successful management, compound heterozygosity for 1363delG and 1405C-T substitution; (2) SLC2A2, 1405C-T, substitution of C>T at 1405; (3) SLC2A2, 1-BP Ins, 793C, in two sibs of Turkish-Assyrian ancestry who presented in infancy with failure to thrive because of intestinal malabsorption but without hepatomegaly[64], homozygous for a splice acceptor site 1-bp insertion, 793-4insC; (4) SLC2A2, 1264G-A, in a white American infant with FBS presented with renal hyperfiltration[65], compound heterozygosity for 1264G-A and 469C-T; and (5) SLC2A2, 469C-T, substitution of C>T at 496.

By 2000, five allelic variants had been described in Japanese. One nonsense mutation[66], a homozygous G-to-A transition at nucleotide 1159 in exon 9 was found and the four allelic variants published by Sakamoto *et al*[20]. They described three missense mutations and the fourth was frameshift: (1) SLC2A2, Val 423 Glu, patient was homozygous 1580T>A change; (2) SLC2A2, GLN287TER, in a Japanese patient diagnosed with FBS after hypergalactosemia was detected by neonatal screening, heterozygosity for two mutations 1171C>T change in exon 6 (resulting in a gln287-to-ter substitution), inherited from the father, and 1478T>C change in exon 8, resulting in a leu389-to-pro substitution, inherited from the mother. The father did not have glucosuria but the mother had glucosuria with a normal oral glucose tolerance test; (3) SLC2A2, LEU389PRO; and (4) SLC2A2, IVS2, A-G, -2, in a Japanese patient with FBS and mental retardation, a homozygous A-to-G substitution at position -2 of the splice acceptor site of intron 2 of the SLC2A2 gene causing skipping of exon 3 and resulting in a frameshift and creation of a premature termination codon. The principal investigator made the mutation analysis for the three Egyptian families, including the two new allelic variants.

Molecular analysis on three Japanese patients found four novel mutations: a splice-site mutation (IVS2-2A>G), a nonsense mutation (Q287X) and two missense mutations (L389P and V423E)[20]. Şimşek *et al*[67] found a novel mutation of the *GLUT2* gene in a Turkish patient; two bases were deleted with a homozygous pattern in exon 6 of the *GLUT2* gene (c.835_836delGA).

Recently, Al-Haggar *et al*[33] defined three different mutations in three Egyptian families with FBS, one mutation specific for each family. The first two mutations are novel: one in exon 3, two bases (GA) are deleted (c.253_254delGA causing a frameshift mutation p. Glu85fs), which presents with an early grave course despite adequate treatment, and the second novel mutation exists in exon 6 in the splicing acceptor site with intron5 (c.776-1G>C or IVS5-1G>A). The third mutation had previously been described in Arab families from Saudi Arabia[62]; a missense mutation C-to-T substitution at c.1250 (c.1250C>T) causing change of 417 codon (CCG) for proline to CTG for leucine (p. P417L). The last known mutation had been previously localized in exon 9; however, we re-enumerated it to exon 10 due to the fact that between exons 3-5, two exons (exon 4-a and exon 4-b) had been discovered[68]. In other words, discovery of new exons in a gene should make changes in exon re-numbering. This phenomenon is actually very frequent, especially in splicing mutations; about 15% of 11 000 splicing mutations when recently manually revisited at HGMD should have their exons re-numbered. This is because the structure of many genes has "changed" since the initial reports of mutations (Al-Haggar M, personal communication).

Generally speaking p. P417L mutation can be easily and unambiguously recognized irrespective of its exon number, especially for experts in this lesion, with no difficulty in locating it within *GLUT2* gene. However, re-numbering its location to exon 10 is highly recommended in subsequent publications, especially those submitted to journals not specialized in the genetics domain, in order to remove any confusion among young researchers.

In the three Egyptian families, the following findings are striking: (1) Consanguinity was positive in all families; (2) Three mutations (one specific for each family) were detected and the most severe form was the frameshift mutation (p. Glu85fs); (3) Two new mutations were found as well as the third known mutation; and (4) All affected cases were homozygous and all the heterozygous individuals were asymptomatic. These observations should yield the following conclusions: (1) FBS is an autosomal recessive disease; (2) Compound heterozygous is rare among Egyptian FBS patients; (3) Neither the new mutations nor the reported one are particularly more frequent; and (4) The third mutation (c.1250C>T) needs more attention in survey studies, especially if carried out in Arab patients, as it is re-enumerated.

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