

A homozygous *SLC5A2* mutation: A natural protection against diabetes?

Gyan Ramsingh, Michael Brugts, Ad Dees

ABSTRACT

Introduction: Familial renal glucosuria (FRG) is the result of a mutation in the *SLC5A2* gene, which codes for the sodium/glucose cotransporter 2 (SGLT2). The main task of this transporter lies in the proximal tubular reabsorption of filtered glucose. **Case Report:** In this case report, a healthy 35-year-old male of Moroccan descent was diagnosed with a homozygous *SLC5A2* mutation after presentation with glucosuria without showing any other symptoms. The patient showed renal glucosuria while having normal serum glucose levels. **Conclusion:** The present case highlights the possible importance in performing additional DNA analysis in patients with renal glucosuria without any other symptoms. This in turn will aid in deciding what intervention to apply for patient and possibly their relatives.

Keywords: Diabetes mellitus, Familial renal glucosuria, Mutations, Renal glucosuria, SGLT2, *SLC5A2*

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INTRODUCTION

Familial renal glucosuria is characterized by a persistent glucosuria in the presence of a normal serum glucose concentration, a normal glucose tolerance test in regard to serum glucose concentration with normal serum levels of insulin and the absence of any other impairment of tubular function [1]. It is caused by a homozygous, compound heterozygous, or heterozygous mutation in the *SLC5A2* gene on chromosome 16p11 [2]. This mutation is due to an autosomal recessive inheritance pattern [3]. Usually, this is caused by missense or nonsense mutations, but other types of mutations have been described, such as splicing mutations and small deletions [4]. To date, over 50 different *SLC5A2* gene mutations are reported, the majority of these mutations are restricted to a single individual or family [5]. *SLC5A2* mutations are responsible for the vast majority of FRG cases [6]. The estimated prevalence of FRG is approximately 1/20,000 [7]. This mutation leads to persistent glucosuria but unaltered serum glucose concentration and kidney function is not impaired [8]. Familial renal glucosuria is a benign hereditary condition that does not pose serious clinical or physical consequences to patients with the mutation [8].

The *SLC5A2* gene codes for the SGLT2 protein. The main task of this transporter lies in the proximal tubular reabsorption of filtered glucose with high efficiency (around 90%) [3, 8]. Figure 1 illustrates this process [9].

Some recent antidiabetic medications target SGLT2, functionally mimicking the *SLC5A2* gene mutation: the SGLT2 inhibitors, such as canagliflozin, dapagliflozin, and empagliflozin. Sodium/glucose cotransporter 2 inhibitors block proximal tubular glucose reabsorption. Therefore, the mechanism behind this therapy is that it decreases blood glucose by increasing urinary glucose excretion. This leads to glucosuria.

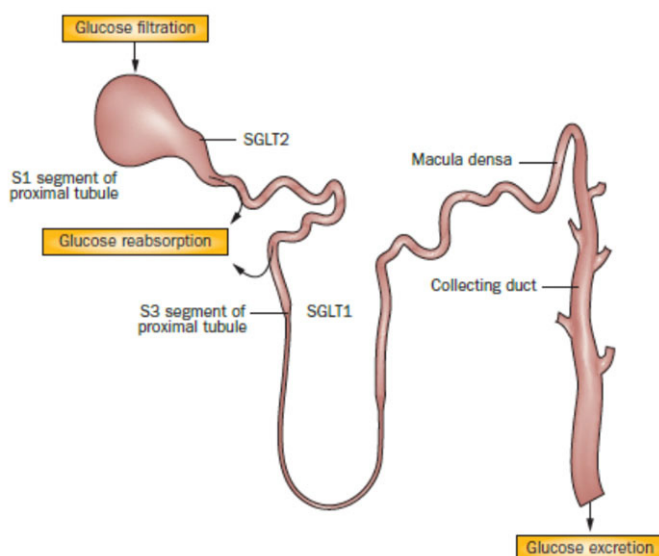


Figure 1: Schematic representation of the distribution of sodium–glucose cotransporters along an unrolled nephron. The macula densa is normally juxtaposed to the vascular pole of the glomerulus. Abbreviations: SGLT1, sodium–glucose cotransporter 1; SGLT2, sodium–glucose cotransporter 2. This figure is obtained from the article of Ferrannini et al. and is used in this case report with explicit approval of the author [9].

It is attractive to theorize about a possible protection against diabetes in this specific population. However, as far as we know studies lack in this area and because of this, it would be interesting to investigate whether this mutation gives a natural protection against diabetes.

CASE REPORT

A 35-year-old male was admitted to the outpatient clinic because of intermittent pain in the flanks during urination and persisting high glucose in the urine without an elevated serum glucose. His medical history was unremarkable, except for mild upper gastrointestinal (GI) complaints. His family history was not entirely clear, except for his mother who has diabetes mellitus type 2 and father who died of prostate cancer. Because of the unclear family history, possible consanguinity could not be established. Physical examination revealed no abnormalities; normal vital signs were noted. He had no recurrent thrush. His weight was 82 kg and body mass index (BMI) was 25.3 kg/m². Laboratory results showed serum glucose 5.9 mmol/L (reference 4.0–7.8), the erythrocyte sedimentation rate was 2/first hour (reference <15), where arterial blood gas results, kidney, and liver enzyme tests were within reference. The HbA1c level was within range. Urine analysis demonstrated high glucose (4+), while pH 5 (n 5–8) and otherwise normal results. Endoscopy of the upper GI tract and abdominal ultrasound did not show any abnormalities. A diagnosis of glucosuria was made and genetic testing was started.

With the help of DNA sequence analysis (the Sanger method), a homozygous missense mutation in the *SLC5A2* gene was found [c.1102C>T p.(Arg368Trp)].

With this information, a differential diagnosis can be made. However, isolated renal glucosuria with normal serum glucose levels does not have an extensive differential diagnosis. Because our patient did not have any symptoms, except for intermittent pain in the flanks, chronic diseases such as Wilson’s disease or hyperthyroidism where there can be glucosuria with normal serum glucose levels, did not seem likely. For this reason, and because he did not have any symptoms, there was no treatment given. This patient remained, however, under control and would be investigated if he has any symptoms.

Table 1 shows a short overview of diagnoses possibly associated with renal glucosuria.

DISCUSSION

In this article we report a case of a homozygous *SLC5A2* which was diagnosed with the help of DNA sequencing analysis. In this case, the patient presented with renal glucosuria, without any other clinical significant symptoms. Patients with FRG usually do not show symptoms and glucosuria is found incidentally. Glucosuria in nondiabetic patients is usually associated with tubular diseases or acute pyelonephritis (Table 1).

An interesting part about this case is that this patient is from Morocco. In the Netherlands, people from Moroccan descent are two to three times more likely to be diagnosed with diabetes mellitus type 2, in comparison to the native population. This may imply that this patient (and maybe other family members of this patient) has a natural protection against diabetes. Though stated earlier, studies in this area lack as far as we know. It would be interesting to investigate whether this mutation is really a natural prevention of diabetes or cardiovascular risk. To our knowledge, this is the first described case of a Moroccan patient with this mutation.

Table 1: Classification of diseases associated with glucosuria

| With elevated serum glucose levels | With normal serum glucose levels |
|------------------------------------|----------------------------------|
| Diabetes mellitus | Fanconi syndrome |
| Liver cirrhosis | Cystinosis |
| | Wilson’s disease |
| | Tyrosinemia |
| | Lowe syndrome |
| | Acute pyelonephritis |
| | Hyperthyroidism |

Based on mutations like this, medication has been developed: the so-called SGLT2 inhibitors. This new class of drugs displays promising properties. In diabetes treatment they seem to be equally effective as regular therapy, for instance metformin or insulin. Recent data also suggest that SGLT2 inhibitors are able to reduce the risk of cardiovascular morbidity and mortality in type 2 diabetes patients at high cardiovascular risk [10–13].

However, some serious adverse events have been described when using these medications, such as hypotension, infections in the genitourinary tract, acute kidney injury, and metabolic acidosis have been described [14–16]. With this in mind, the interesting part about this case is that this patient has had his renal tract exposed to glucosuria for decades and yet, there does not seem to be damage to his renal tract. Thus, there seems to be a discrepancy between the long-term effects of SGLT2 inhibitors and an SGLT2 mutation and further longitudinal studies are required to establish the long-term risks of these SGLT2 inhibitors. Furthermore, it would be interesting to investigate the differences between having a mutation of this kind and using these types of medication for a longer period of time.

Unfortunately, we did not have the opportunity yet to analyze other family members. Therefore we could not determine the mutational pattern or from where this patient had inherited this mutation, assuming it is not a de novo mutation. The patient was unaware of consanguinity in the family.

CONCLUSION

In conclusion, it is useful to keep FRG in mind when a patient presents himself or herself with unexplained renal glucosuria without any other symptoms. In addition to this, DNA testing (*SLC5A2* gene testing in particular) should be considered in these cases as this could be beneficial in deciding the clinical measures for this patient, and possibly his/her family.

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Author Contributions

Gyan Ramsingh – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved

Michael Brugts – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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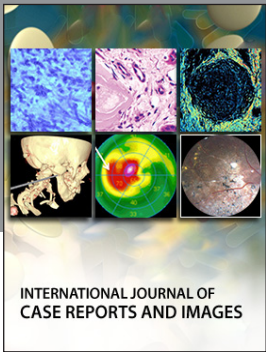
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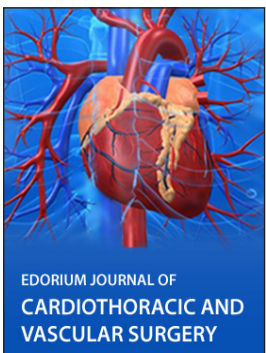


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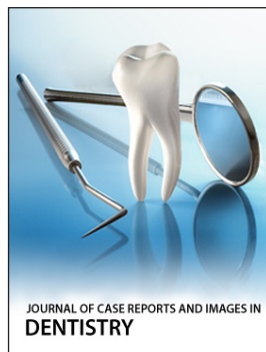
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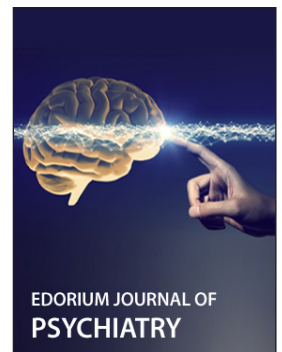
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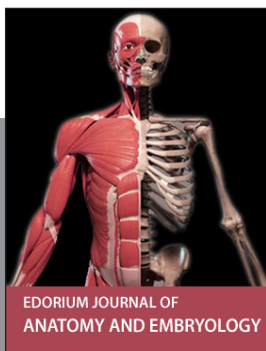
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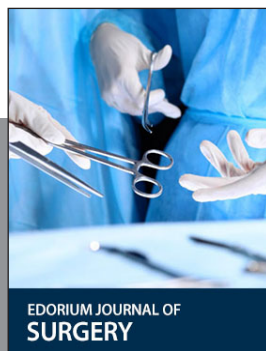
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