Evaluating the Impact of the ABCG2 Q141K Polymorphism on Allopurinol Efficacy in Pediatric Patients with Hyperuricemia

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BACKGROUND

- The gene *ABCG2* encodes for the efflux transporter Breast Cancer Resistance Protein (BCRP), which helps excrete uric acid.
- In 2022, the Dutch Pharmacogenetics Working Group (DPWG) published a guideline recommending *ABCG2* genotype-guided dosing for allopurinol in the treatment of gout. This guideline focused on the loss-of-function *ABCG2 Q141K* variant (c.421C>A; rs2231142) on allopurinol efficacy.
- Allopurinol, a xanthine-oxidase inhibitor that prevents the formation of uric acid is also prescribed for the prevention and treatment of tumor lysis syndrome (TLS) in newly diagnosed patients with cancer.
- There is a gap in the literature for *ABCG2*-based allopurinol dosing in patients with an oncology diagnosis, making the applicability of the DPWG recommendations for hyperuricemia in conditions other than gout unclear.
- Allopurinol dosing differs based on the indication: For the prevention and treatment of TLS, the initial dose of allopurinol is 50–100 mg/m² every 8 hours. For gout, the initial dose is 5-10 mg/kg/day divided into 2-3 doses.
- Understanding the impact of the *ABCG2 Q141K* variant on allopurinol's efficacy for the prevention and treatment of TLS in pediatric oncology patients will help address the gap in literature and potentially guide clinical implementation practices.

OBJECTIVES

1) To determine the association between the *ABCG2 Q141K* polymorphism (rs2231142) and the effect of allopurinol on serum uric acid concentrations in pediatric oncology patients.
2) To determine whether the presence of the *ABCG2 Q141K* polymorphism is associated with higher dose requirements of allopurinol to treat or prevent hyperuricemia in pediatric oncology patients receiving chemotherapy.

METHODS

- This is a retrospective, single institution study evaluating pharmacogenomic test results and allopurinol efficacy between May 2011 and September 2024.
- Patients enrolled on the institution-wide pharmacogenomic testing protocol PG4KDS (www.stjude.org/pg4kds) were genotyped for *ABCG2*.
- Allopurinol efficacy was determined by assessing the change in serum uric acid at baseline to 48 hours after allopurinol therapy initiation. Allopurinol dose was also collected after 48 hours.
- Patients with one *Q141K* variant were categorized as ABCG2 decreased function, two variants were categorized as ABCG2 poor function, and those with no variants (WT; wild type) were categorized as ABCG2 normal function.
- Statistical analyses were conducted using R programming. Both major outcomes were computed using linear regression based on an additive genetic model. Baseline uric acid by phenotype was analyzed using the Kruskal-Wallis test.

METHODS

Figure 1 : Abbreviated Consort Diagram

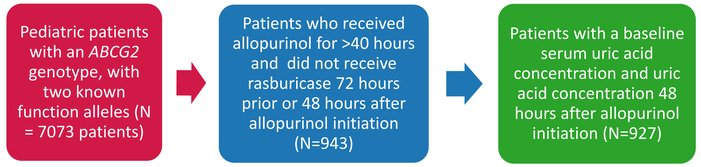


Table 1 : Serum Uric Acid Reference Range

Age	Reference Interval (mg/dL)
8 days – 9 years	1.8 – 5.1
10 – 19 years	Male: 2.3 – 8.5 Female: 3.0 – 5.9
> 19 years	Male: 3.5 – 8.5 Female: 2.5 – 7.5

RESULTS

Table 2: Patient Baseline Demographics (N=927)

Age, years (median, range)	7.0 (0.2-22.4)
Genomic Sex (%)	
Female	385 (41.5%)
Male	542 (58.5%)
Genomic Race (%)	
American Indian/Alaska Native	1 (0.1%)
Asian	24 (2.6%)
Black	179 (19.3%)
Other	31 (3.3%)
White	692 (74.6%)
Diagnosis (%)	
Brain Tumor	29 (3.1%)
Leukemia/Lymphoma	867 (93.5%)
Non-Malignant Hematology	5 (0.5%)
Solid Tumor	26 (2.8%)
Ethnicity (%)	
Hispanic	165 (17.8%)
Non-Hispanic	762 (82.2%)

RESULTS

Table 3: Patient Baseline Characteristics (N=927)

ABCG2 Phenotype (%)	
Normal Function	734 (79%)
Decreased Function	176 (19%)
Poor Function	17 (2%)
Median (range) Uric Acid at Baseline by ABCG2 Phenotype Group (p=0.37)	
ABCG2 Normal Function	3.8 mg/dL (0.1 – 13.9)
ABCG2 Decreased Function	4.3 mg/dL (0.1 – 10.2)
ABCG2 Poor Function	4.0 mg/dL (1.2 – 8.1)

Figure 2 : Median serum uric acid change by *ABCG2* diplotype from baseline (prior to starting allopurinol) to 48 hours after allopurinol initiation.

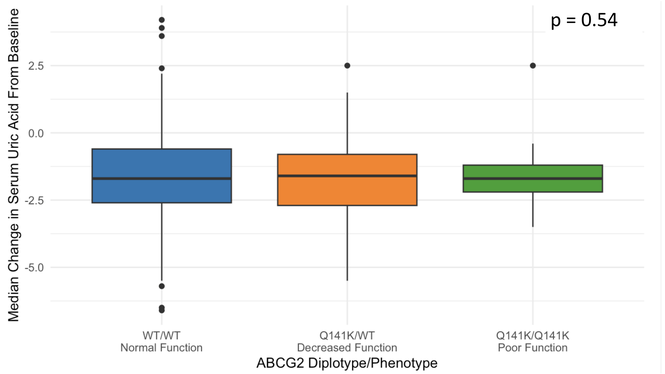
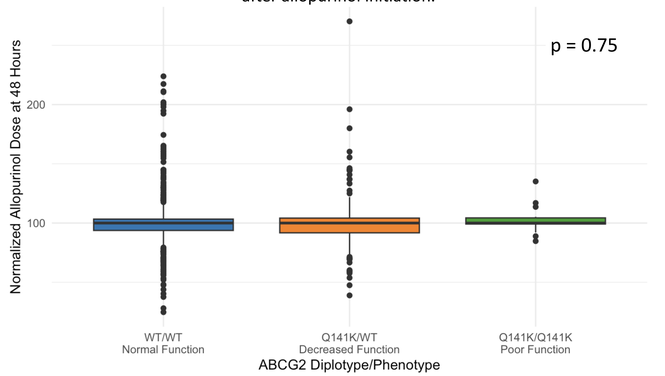


Figure 3: Median normalized allopurinol dose (mg/m²) by *ABCG2* diplotype 48 hours after allopurinol initiation.



CONCLUSIONS

- We observed no difference in change in serum uric acid from baseline to 48 hours among pediatric patients receiving allopurinol who were in the ABCG2 normal function, decreased function or poor function groups.
- We observed no difference in median allopurinol doses required to treat or prevent hyperuricemia in the first 48 hours of administration among ABCG2 phenotype groups.

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