The Impact of rs505802 for *SLC22A12* on Oxipurinol and Uric Acid Disposition in Hmong Patients on Allopurinol from the Genetics Of HyperUricemia Therapy in Hmong (**GOUT-H**) Study

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Introduction

- Hyperuricemia (HU), elevated serum uric acid (SUA), is the strongest predictor of gout, which is strongly associated with hypertension, type 2 diabetes (T2DM), obesity and metabolic syndrome[1]
- The risks for HU or gout are modulated by genetic[2] and non-genetic factors[3]
- The Hmong, a unique Asian population of 64,000[4] in Minnesota, have a 2-5 fold increased risk of gout, gout comorbidities and a higher prevalence of HU and gout risk alleles compared to non-Hmong[5,6]
- Compared to non-Hmong, the Hmong have a higher prevalence of the HU risk allele (C>T; rs505802) within the URAT1 gene *SLC22A12*[7]
- The URAT1 transporter modulates oxipurinol pharmacokinetics (PK) which is the active metabolite of allopurinol commonly used to treat gout
- **Hypothesis:** rs505802 in *SLC22A12* affects the disposition of oxipurinol and allopurinol response
- **Study Aims:** Quantify the impact of rs505802 on the PK and pharmacodynamics (PD) of oxipurinol
- **Significance:** Elucidating factors which contribute to the variability in response to allopurinol may inform optimal drug/dose selection for managing Hmong patients with gout

Methods

- **Design:** Prospective genetic-guided, open-label clinical trial (clinicaltrial.gov, NCT02371421)
- **Subjects:** Hmong participants, ≥ 18 years old with gout or SUA ≥ 6mg/dL or documented use of urate lowering therapies (ULT) and eCrCl >30ml/min (Table 1)
- After a baseline visit (V0 or V1), participants underwent 7days washout of ULT, if applicable (Fig.1)
- Participants took 7 days of allopurinol 100mg twice daily followed by 7 days of 150mg twice daily (Fig.1)
- Serum oxipurinol measurements at 0, 2, 4 and 6 hours were used to determine oxipurinol $AUC_{0\text{-}6hr}$
- Genotyping conducted using qPCR for screening and sequenom iPlex design for final analyses
- SUA pre (V2) and post (V3) allopurinol were compared using paired t-test with $p<0.05$ for significance and one-way ANOVA for multiple comparison (ΔSUA ,oxipurinol $AUC_{0\text{-}6hr}$,C_{min}) across genotypes
- Stepwise regression was used to identify significant predictors for absolute SUA change

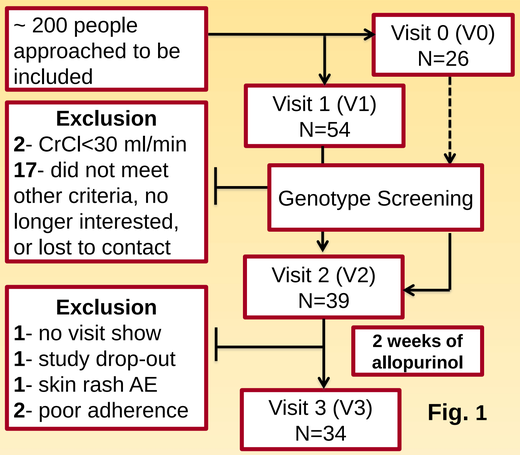

Fig. 1

Table 1. Participant Characteristics at Baseline

Characteristics (N=34)	Mean (SD)	Range
Age (years)	44 (12.7)	24 - 67
BMI (kg/m²)	32.5 (5.4)	21.6 - 46.9
Waist Circumference (inches)	40.6 (5.1)	29.0 - 50.8
Systolic BP (mm Hg)	141 (17)	114 - 182
Diastolic BP (mm Hg)	91 (12)	69 - 121
SUA (mg/dL)	9.3 (1.5)	5.8 - 12.8
Glucose (mg/dL)	145 (99)	67- 464
eCrCl (ml/min)	74 (26)	39 - 148

Results

- 80 screened (V0+V1). 36 completed the study. 2 were dropped from PD analyses due to poor medication adherence rate (<79% by tablet count). 1 was dropped from PK analysis for unreliable dose timing
- Prevalence of self-reported T2DM and hypertension were 21% and 41%, respectively
- Allopurinol reduced SUA from 9.3 to 5.8 mg/dL ($p<0.001$) (Fig.2)
- Oxipurinol $AUC_{0\text{-}6hr}$ and C_{min}were associated with rs505802 C>T and eCrCl (Fig.4-5) ($p<0.001$) with > 2-fold difference between the CC and TT genotypes (Table 2)
- Mean (SD) oxipurinol levels were 12.6 (6.2) mg/L at 0hr and 14.0 (5.8) mg/L at 6hr
- Absolute SUA reduction association with rs505802 was not significant (p=0.29) (Table 3)

Table 2 . Summary of Oxipurinol Pharmacokinetics by Genotype

SLC22A12 (rs505802) Genotype	Oxipurinol $AUC_{0\text{-}6hr}$ (mg*hr/L) Mean ± (SD)	Range	95% CI	P-value
CC (n=14) (ref)	105.2 (38.1)	53.1-176.6	83.2 to 127.2	
CT (n=14)	77.5 (23.9)	43.3-118.2	63.7 to 91.3	0.041
TT (n=5)	49.7 (10.5)	39.9-65.6	36.6 to 62.8	0.002
	Oxipurinol $C_{min\ 0hr}$ (mg/L)			
CC (n=14) (ref)	15.7 (6.7)	5.8-28.0	11.8 to 19.6	
CT (n=14)	11.0 (3.9)	4.3-17.5	8.7 to 13.3	0.046
TT (n=5)	6.9 (1.7)	5.2-9.4	4.8 to 9.0	0.005

Table 3. Absolute Change in SUA by Genotype

SLC22A12 (rs505502C>T)	Count	Mean ± (SD) SUA Reduction
CC	14	4.21 (1.6)
CT	14	3.94 (1.2)
TT	5	3.04 (1.0)

Table 4. Stepwise Multiple Linear Regression Summary*

Independent Variable	Beta Coefficient	P-value	R^2	Adjusted R^2
V2 SUA 6h (mg/dL)	-0.327	0.008	0.69	0.65
Oxipurinol $AUC_{0\text{-}6hr}$ (mg*hr/L)	-0.0375	<0.001		
V3 eCrCl (mL/min)	-0.0195	0.016		
SLC22A12 (rs505802 **C**>T)	0.565	0.036		

*Dependent Variable: SUA 6hr(V3-V2)

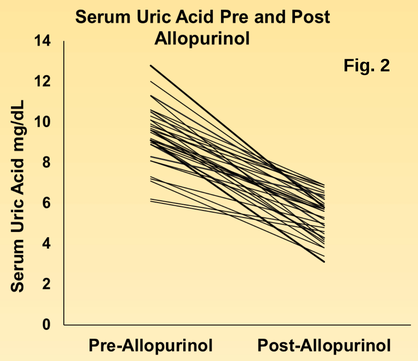

Fig. 2

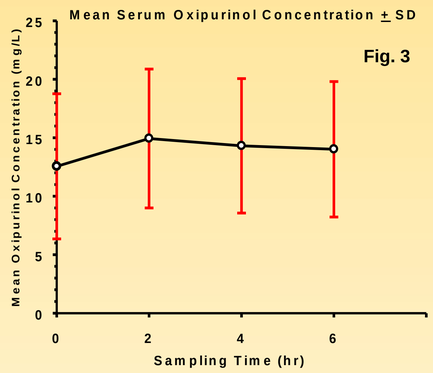

Fig. 3

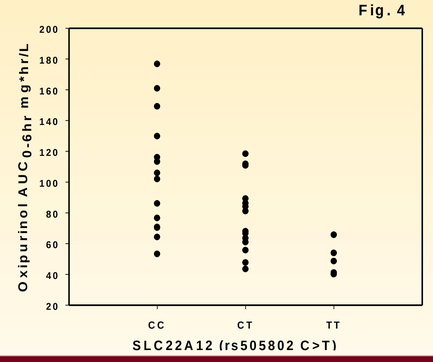

Fig. 4

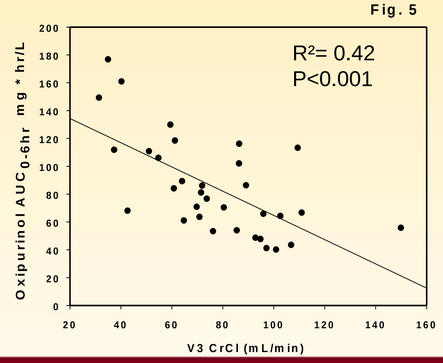

Fig. 5

Conclusions

- rs505802 C>T in *SLC22A12* significantly contributes to the absolute change in SUA with baseline SUA, eCrCl and oxipurinol $AUC_{0\text{-}6hr}$ in the base model
- Oxipurinol $AUC_{0\text{-}6hr}$ and C_{min} were significantly higher in the CC relative to CT or TT genotype for rs505802
- Allopurinol effectively reduced SUA in Hmong adults with a mean (SD) [range] reduction of 41% (± 11%) [23-66%]. Most participants (71%, 24/34) achieved SUA target <6 mg/dL

Interpretations

- Allopurinol effectively reduces SUA in the majority of Hmong participants *albeit* with marked inter-subject variability which, in part, can be attributed to the effect of rs505802 C>T on oxipurinol PK
- Our model, including rs505802, can explain 65% of the variability in absolute change in SUA (Table 4)
- Oxipurinol levels at 6hr indicate that 67% of Hmong achieve sub-therapeutic (<15.2mg/L)[8] oxipurinol concentrations in part due to genetics

Future Directions

- Comparative efficacy studies of ULT considering prospective pharmacogenomics-based drug selection with a focus on patient-centered outcomes

Disclosure

All authors have declared no conflict of interests

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