

## 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<sup>1</sup> The risks for HU or gout are modulated by genetic<sup>2</sup> and non-genetic factors<sup>3</sup> The Hmong, a unique Asian population of 64,000<sup>4</sup> 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<sup>5,6</sup> Compared to non-Hmong, the Hmong have a higher prevalence of the HU risk allele (C>T; rs505802) within the URAT1 gene SLC22A12<sup>7</sup>

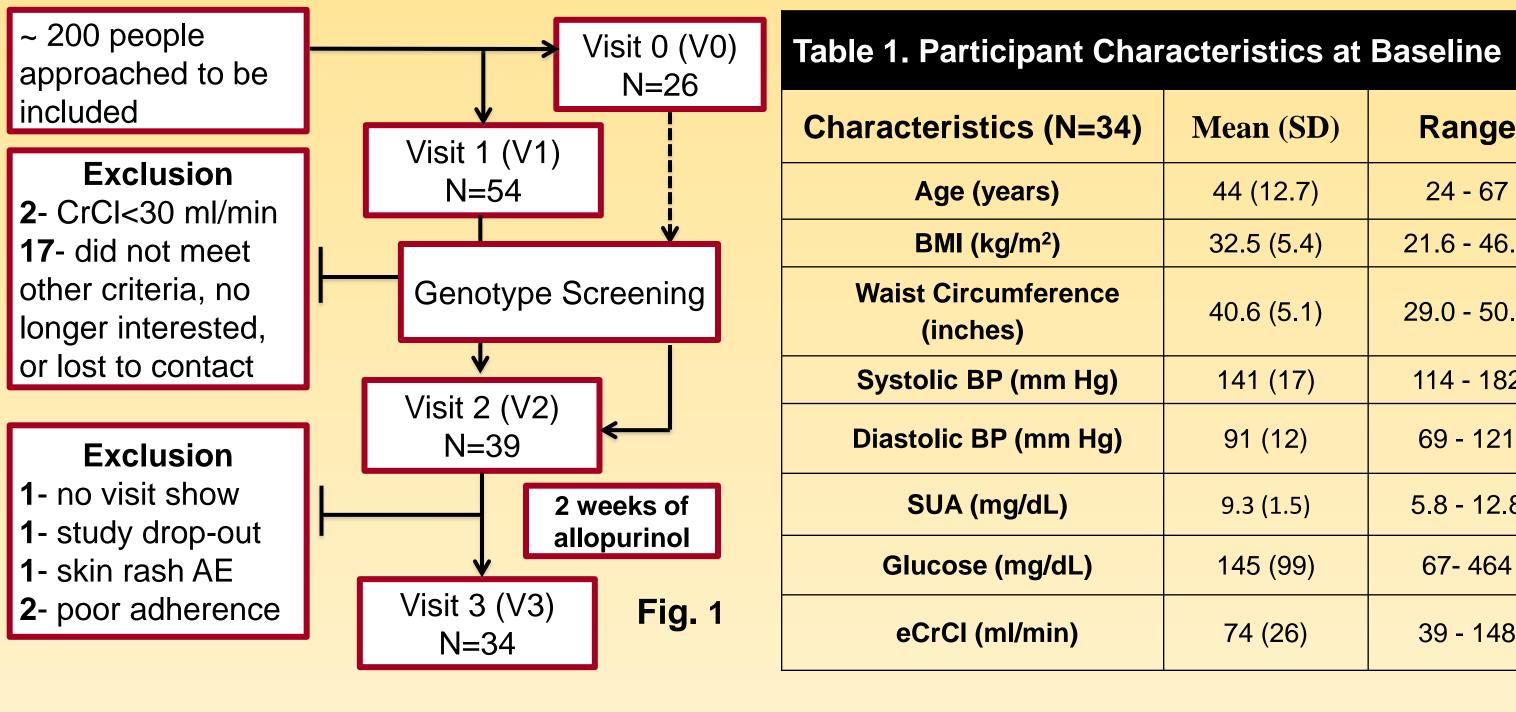
The URAT1 transporter modulates oxipurinol pharmacokinetics (PK) which is the active metabolite of allopurinol commonly used to treat gout

**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) **<u>Subjects</u>**: Hmong participants,  $\geq$  18 years old with gout or SUA  $\geq$  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)  $\Box$ Serum oxipurinol measurements at 0, 2, 4 and 6 hours were used to determine oxipurinol AUC<sub>0-6hr</sub> 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 ( $\Delta$ SUA ,oxipurinol AUC<sub>0-6hr</sub>, C<sub>min</sub>) across genotypes Stepwise regression was used to identify significant predictors for absolute SUA change



### Results

| 80 screened (V0+V1). 36 completed the study. 2 were dropped fron                       |
|--|
| poor medication adherence rate (<79% by tablet count). 1 was drop                      |
| for unreliable dose timing   |
| Prevalence of self-reported T2DM and hypertension were 21% and                         |
| Allopurinol reduced SUA from 9.3 to 5.8 mg/dL (p<0.001) (Fig.2)                        |
| Oxipurinol AUC <sub>0-6hr</sub> and $C_{min}$ were associated with rs505802 C>T and eC |
| 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) m               |
| Absolute SUA reduction association with rs505802 was not significant (p                |
|  |

The Impact of rs505802 for SLC22A12 on Oxipurinol and Uric Acid Disposition in Hmong Patients on Allopurinol from the <u>Genetics</u> <u>Of HyperUricemia</u> <u>Therapy in Hmong</u> (GOUT-H) Study Youssef M. Roman, Pharm.D.<sup>1</sup>, Kathleen A. Culhane-Pera, M.D.,M.A.<sup>2</sup>, Shoua Yang, B.S.<sup>2</sup>, John Yang, B.S.<sup>2</sup>, Muaj C. Lo, M.D.<sup>2</sup>, Robert J. Straka, Pharm.D.<sup>1</sup> <sup>1</sup>Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN,<sup>2</sup> West Side Community Health Services, St. Paul, MN

| Mean (SD)  | Range       |
|------------|-------------|
| 44 (12.7)  | 24 - 67     |
| 32.5 (5.4) | 21.6 - 46.9 |
| 40.6 (5.1) | 29.0 - 50.8 |
| 141 (17)   | 114 - 182   |
| 91 (12)    | 69 - 121    |
| 9.3 (1.5)  | 5.8 - 12.8  |
| 145 (99)   | 67- 464     |
| 74 (26)    | 39 - 148    |

om PD analyses due to opped from PK analysis

d 41%, respectively

CrCl (Fig.4-5) (p<0.001)

mg/L at 6hr p=0.29) (Table 3)

|   | Table 2 . Summary of Ox                                    | kipurinol Pharn  |  |                               |                             | Conclusions  |
|---|--|------------------|--|-------------------------------|-----------------------------|--|
|   | SLC22A12 (rs505802)  |                  |  | AUC <sub>0-6hr</sub> (mg*hr/l |                             | □rs505802 C>T in SLC22A12 significantly of   |
|   | Genotype   | Mean ± (SD       | <u> </u>   | 95% CI                        | P-value                     | to the absolute change in SUA with baseline  |
|   | CC (n=14) (ref)  | 105.2 (38.1)     | 53.1-176.6   | 83.2 to 127.2                 |                             | eCrCl and oxipurinol AUC <sub>0-6hr</sub> in the base me   |
|   | CT (n=14)  | 77.5 (23.9)      | 43.3-118.2   | 63.7 to 91.3                  |                             | Oxipurinol AUC <sub>0-6hr</sub> and C <sub>min</sub> were signification  |
|   | TT (n=5)   | 49.7 (10.5)      | 39.9-65.6  | 36.6 to 62.8                  | 0.002                       | in the CC relative to CT or TT genotype for r  |
|   |  |                  |  | C <sub>min Ohr</sub> (mg/L)   |                             | Allopurinol effectively reduced SUA in Hm  |
|   | CC (n=14) (ref)  | 15.7 (6.7)       | 5.8-28.0   | 11.8 to 19.6                  |                             | with a mean (SD) [range] reduction of 41%  |
|   | CT (n=14)  | 11.0 (3.9)       | 4.3-17.5   | 8.7 to 13.3<br>4.8 to 9.0     | 0.046                       | [23-66%]. Most participants (71%, 24/34) ac  |
|   | TT (n=5)   | 6.9 (1.7)        | 5.2-9.4  | 4.0 10 9.0                    | 0.005                       | SUA target <6 mg/dL  |
|   | Table 3. Absolute Chang                                    | e in SUA by Ge   | enotype  |                               |                             |  |
|   | SLC22A12 (rs505502   | 2C>T)            | Count  | Mean <u>+</u> (SD) S          | SUA Reduction               |  |
|   | CC   |                  | 14   | 4.21                          | (1.6)                       | Allopurinol effectively reduces SUA in the<br>Hmong participants albeit with marked inter-   |
|   | СТ   |                  | 14   | 3.94                          |                             | variability which, in part, can be attributed to   |
|   | TT   |                  | 5  | 3.04                          |                             | of rs505802 C>T on oxipurinol PK   |
|   |  |                  | <b>J</b>   | 0.04                          | (1.0)                       | □Our model, including rs505802, can expla  |
|   | Table 4. Stepwise Multip                                   |                  |  |                               |                             | the variability in absolute change in SUA (Ta  |
|   | Independent Variable                                       | Beta Coeffi      | cient P-v  | value R <sup>2</sup>          | Adjusted R <sup>2</sup>     | Oxipurinol levels at 6hr indicate that 67%   |
|   | V2 SUA 6h (mg/dL)  | -0.327           | 0.   | 800                           |                             | achieve sub-therapeutic (<15.2mg/L) <sup>8</sup> oxipu   |
|   | Oxipurinol AUC <sub>0-6hr</sub> (mg*hr/                    | /L) -0.0375      | 5 <0   | .0010.69                      | 0.65                        | concentrations in part due to genetics   |
|   | V3 eCrCl (mL/min)  | -0.0195          | <b>5</b> 0.  | 0.08                          | 0.05                        | Euture Directions  |
|   | SLC22A12 (rs505802 C>                                      | T) 0.565         | 0.   | 036                           |                             | <b>Future Directions</b>   |
|   |  |                  |  |                               |                             | prospective pharmacogenomics-based drug  |
|   | *Dependent Variable: SUA                                   | 4 6hr(V3-V2)     |  |                               |                             | with a focus on patient-centered outcomes  |
|   | Serum Uric Acid Pre  |                  | 25 <b>1</b> Me   | an Serum Oxipurino            | I Concentration <u>+</u> SD |  |
|   | 14 Allopurinol   |                  | g/L)   |                               | Fig. 3                      | Dicelecture  |
| _ | 12   | Fig. 2           | <u>ب</u><br>20   | Тт                            | T                           | Disclosure<br>All authors have declared no conflict of inte  |
| _ | Tp/fu  |                  | ratio  |                               |                             |  |
| _ |  |                  | ມີ<br>ອີງ 15   |                               |                             | Acknowledgments  |
|   | Acid<br>8  |                  | Con  |                               |                             | Hmong Gout Research Board, West Side Community Health  |
|   | Uric A   |                  | 0 10   |                               |                             | U of M, Office of Community Engagement of the Clinical and<br>Science Institute, 2014 Collaborative Pilot Grants CTSI No. 225  |
| _ | □  | AN .             | n di   |                               |                             | Research reported in this publication was supported by the N   |
|   | 2  |                  | ŏ 5 ;  |                               |                             | for Advancing Translational Sciences of the National Institutes of Number UL1TR000114. The content is solely the responsibility  |
|   | <b>S</b> 2   |                  | . Be   |                               |                             | and does not necessarily represent the official views of the NIH<br>ASCPT Trainee Travel Award   |
|   | 0 Pre-Allopurinol  | Post-Allopurinol | 0  | 2 4                           |                             |  |
|   | Fie-Alloputition   | r ost-Anopulnioi |  | Sampling Tir                  | me (hr)                     | References   |
|   | 200 -  | Fig. 4           | ↓<br>  |                               | Fig. 5                      | <b>1.</b> Edwards NL. The role of hyperuricemia and gout in kidney and cardio<br><i>Cleveland Clinic Journal of Medicine.</i> Jul 2008;75 Suppl 5:S13-16.  |
|   |  |                  | المعاد | •                             | R <sup>2</sup> = 0.42       | 2. Kottgen A, Albrecht E, et al. Genome-Wide Association Analyses Ider<br>Associated with Serum Urate Concentrations. Nat Genet. 2013;45(2):14   |
|   | ⊆ 100<br>⊈<br>*<br>Ø 160 -                                 |                  | ے<br>* 160 -   | •                             | P<0.001                     | <b>3.</b> Hyon K. Choi M. A Prescription for Lifestyle Change in Patients with I Gout. <i>Current Opinion in Rheumatology.</i> 2010.   |
|   | E •  |                  | 50<br>E 140 -  | •                             |                             | 4. Pfeifer ME, et al Hmong Population and Demographic Trends in the 2  |
|   |  |                  | ц<br>ц<br>ц<br>ц   | • • •                         | •                           | 2010 American Community Survey. <i>Hmong Studies Journal.</i> 2012;13(2)<br><b>5.</b> Portis AJ., et al. "High prevalence of gouty arthritis among the Hmong Misses to "Authritic Open & December 2010, 20(40), 4000, 4004 |
|   | $\begin{array}{c} 3 & 120 \\ 0 & 3 \\ 2 & 100 \end{array}$ |                  | ່ <sub>100</sub> -<br>ບ  |                               |                             | <ul> <li>Minnesota." Arthritis Care &amp; Research 2010; 62(10):1386-1391.</li> <li>6. Portis AJ., et al. "Rapid Communication: Stone Disease in the Hmong</li> </ul>  |
|   |  |                  | N 80 − V 80 −  |                               | •••                         | Initial Description of a High-Risk Population." <i>Journal of Endourology</i> 20<br><b>7.</b> Roman YM, Culhane-Pera KA, Menk J, Straka RJ. Assessment of Ge   |
|   |  | •                |  | • • • •                       |                             | Polymorphisms Associated with Hyperuricemia or Gout in the Hmong. <i>Medicine</i> . 2016;13(5):429-440.  |
|   |  | •                | <b>1</b> 40 -<br><b>1 4</b> 0 -<br><b>1 4</b> 0 -<br><b>1 4</b> 0 -<br><b>1 1 1 1 1 1 1 1 1 1</b>  |                               |                             | <ul> <li>8. Stamp LK, Barclay ML, O'Donnell JL, Zhang M, et al. Relationship be<br/>Urate and Plasma Oxypurinol in the Management of Gout: Determination</li> </ul>  |
|   | O 20   |                  |  |                               |                             | Plasma Oxypurinol Concentration to Achieve a Target Serum Urate Lev  |
|   | СС СТ  | тт<br>05802 C>T) | 20   | 40 60 80<br>V3CrCl(m          | 100 120 140 160             | Ther. 2011;90(3):392-398.  |
|   |  |                  |  |                               |                             |  |

|   |                                      |   | , , , , , , , , , , , , , , , , , | ,                     |                           |   |
|---|--------------------------------------|---|-----------------------------------|-----------------------|---------------------------|---|
|   | 2. Summary of Oxi                    | purinol Pharm                             | -                                 |                       |                           | Conclusions   |
| SLC   | 22A12 (rs505802)                     | Oxipurinol AUC <sub>0-6hr</sub> (mg*hr/L) |                                   |                       |                           | □rs505802 C>T in SLC22A12 significantly of  |
|   | Genotype                             | Mean $\pm$ (SD)                           |                                   | 95% CI                | P-value                   | to the absolute change in SUA with baseline   |
| C   | C (n=14) (ref)                       | 105.2 (38.1)                              | 53.1-176.6                        | 83.2 to 127.2         |                           | eCrCI and oxipurinol AUC <sub>0-6hr</sub> in the base mo  |
|   | CT (n=14)                            | 77.5 (23.9)                               | 43.3-118.2                        | 63.7 to 91.3          | 0.041                     | Oxipurinol AUC <sub>0-6hr</sub> and C <sub>min</sub> were signification   |
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|   | TT (n=5)                             | 6.9 (1.7)                                 | 5.2-9.4                           | 4.8 to 9.0            | 0.005                     | SUA target <6 mg/dL   |
| Table 3   | 3. Absolute Change                   | e in SUA by Ge                            | notype                            |                       |                           |   |
| SL  | .C22A12 (rs5055020                   | C>T) C                                    | ount                              | Mean <u>+</u> (SD) SI | UA Reduction              | Interpretations   |
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|   | ependent Variable                    | Beta Coeffic                              |                                   |                       | Adjusted R <sup>2</sup>   | the variability in absolute change in SUA (Ta   |
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|   | ,                                    |   |                                   |                       |                           | concentrations in part due to genetics  |
|   | rinol AUC <sub>0-6hr</sub> (mg*hr/L  |   | <0.0                              | — 0.69                | 0.65                      | concentrations in part due to genetios  |
|   | 3 eCrCl (mL/min)                     | -0.0195                                   | 0.01                              |                       |                           | Future Directions   |
| SLC22   | 2A12 (rs505802 <b>C</b> >T           | ) 0.565                                   | 0.03                              | 36                    |                           | Comparative efficacy studies of ULT const   |
| *Dener  | ndent Variable: SUA                  | 6hr(\/3_\/2)                              |                                   |                       |                           | prospective pharmacogenomics-based drug   |
| Deper   |                                      |   |                                   |                       |                           | with a focus on patient-centered outcomes   |
| 4.4   | Serum Uric Acid Pre a<br>Allopurinol | and Post                                  | 25 Mear                           | n Serum Oxipurinol    | Concentration <u>+</u> SD |   |
| 14  | Anopurnor                            | Fig. 2                                    | n g/L                             |                       | Fig. 3                    | Disclosure  |
| 12  |                                      | 9. –                                      | <u> </u>                          | Тт                    | Т                         | All authors have declared no conflict of inte   |
| 10<br>lp/g  |                                      |   | tratio                            |                       |                           |   |
| ů,  |                                      | •   | <sup>น</sup> ี้ 15                |                       |                           | Acknowledgments   |
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| 9 c   |                                      |   |                                   | 1 1                   |                           | U of M, Office of Community Engagement of the Clinical and<br>Science Institute, 2014 Collaborative Pilot Grants CTSI No. 225   |
| ⊃<br>ε 4  |                                      | I.  | cip u r                           |                       |                           | Research reported in this publication was supported by the N for Advancing Translational Sciences of the National Institutes o |
| Serul<br>5  |                                      |   | ô5<br>⊆                           |                       |                           | Number UL1TR000114. The content is solely the responsibility  |
| <u>ہ</u> ک  |                                      |   | - B                               |                       |                           | and does not necessarily represent the official views of the NIH<br>ASCPT Trainee Travel Award  |
| 0   | Pre-Allopurinol                      | Post-Allopurinol                          | _ 0+0                             | 2 4                   | 6                         |   |
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| ב 180 -<br>ק<br>8 160 -                             | •                                    |   | ت<br>• 160 -                      | •                     | P<0.001                   | <b>3.</b> Hyon K. Choi M. A Prescription for Lifestyle Change in Patients with F Gout. <i>Current Opinion in Rheumatology.</i> 2010.  |
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| x ip u  | • •                                  |   |                                   |                       |                           | 8. Stamp LK, Barclay ML, O'Donnell JL, Zhang M, et al. Relationship be  |
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| 20  | сс ст                                | тт  | 20                                | 40 60 80              | 100 120 140 160           | Ther. 2011;90(3):392-398.   |
|   | SLC22A12 (rs505                      | 802 C>T)                                  |                                   | V3 CrCl (ml           | L/min)                    |   |

| ٦ | Table 2 . Summary of Ox                 | kipurinol Pharma | acokinetics b                     | y Genotype                               |                                       | Conclusions  |
|---|---|------------------|-----------------------------------|--|---------------------------------------|--|
|   | SLC22A12 (rs505802)                     |                  |                                   | □rs505802 C>T in SLC22A12 significantly  |                                       |  |
|   | Genotype                                | Mean ± (SD)      | Range                             | VUC <sub>0-6hr</sub> (mg*hr/L)<br>95% CI | P-value                               | to the absolute change in SUA with baseline  |
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| I | SLC22A12 (rs505502                      | 2C>T) C          | ount                              | Mean <u>+</u> (SD) SU                    | A Reduction                           | Interpretations  |
| ╡ | СС                                      |                  | 14                                | 4.21 (1                                  | 6)                                    | Allopurinol effectively reduces SUA in the   |
| I | СТ                                      |                  | 14                                | 3.94 (1                                  | ,                                     | Hmong participants <i>albeit</i> with marked inter-  |
| I |   |                  |                                   | <b>X</b>                                 | ,                                     | variability which, in part, can be attributed to of rs505802 C>T on oxipurinol PK  |
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| I | V3 eCrCl (mL/min)                       | -0.0195          | 0.0                               | 0.69<br>I6                               | 0.65                                  |  |
| I | SLC22A12 (rs505802 <b>C</b> >           |                  | 0.03                              |  |                                       | Future Directions  |
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|   | *Dependent Variable: SUA                | A 6hr(V3-V2)     |                                   |  |                                       | prospective pharmacogenomics-based drug  |
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|   | 14 Allopurinol                          |                  |                                   | n Serum Oxipurinol C                     | concentration $\pm$ SD                |  |
|   | 12                                      | Fig. 2           | бш)                               | <b>-</b>                                 | Fig. 3                                | Disclosure   |
|   |   |                  |                                   | I  | T                                     | All authors have declared no conflict of inte  |
|   | Jp/6u                                   |                  |                                   |  |                                       |  |
|   | kcid n                                  |                  |                                   |  | <b></b>                               | Acknowledgments  |
|   |   |                  | ບັ<br>⊽10 •                       |  |                                       | <ul> <li>Hmong Gout Research Board, West Side Community Health</li> <li>U of M, Office of Community Engagement of the Clinical and</li> </ul>  |
|   | O Lic                                   |                  | i i                               | - I                                      | 1                                     | Science Institute, 2014 Collaborative Pilot Grants CTSI No. 225<br>Research reported in this publication was supported by the N  |
|   | E 4                                     |                  | $\stackrel{\underline{\alpha}}{}$ |  |                                       | for Advancing Translational Sciences of the National Institutes of   |
| - | Ser 2                                   |                  | 0<br>0                            |  |                                       | Number UL1TR000114. The content is solely the responsibility and does not necessarily represent the official views of the NIH  |
| _ | 0                                       |                  |                                   |  | ,                                     | ASCPT Trainee Travel Award   |
|   | Pre-Allopurinol                         | Post-Allopurinol | 0                                 | 2<br>Sompling Time                       | 6                                     | References   |
|   |   | Fig.4            |                                   | Sampling Time                            | Fig. 5                                | 1. Edwards NL. The role of hyperuricemia and gout in kidney and cardio   |
|   | 200                                     |                  |                                   |  |                                       | <ul> <li><i>Cleveland Clinic Journal of Medicine.</i> Jul 2008;75 Suppl 5:S13-16.</li> <li><b>2.</b> Kottgen A, Albrecht E, et al. Genome-Wide Association Analyses Ider</li> </ul>  |
| ٦ | ר_ 180 -<br>ב<br>ג                      |                  | ב 180 -<br>ב                      |  | R <sup>2</sup> = 0.42<br>P<0.001      | Associated with Serum Urate Concentrations. <i>Nat Genet.</i> 2013;45(2):14<br><b>3.</b> Hyon K. Choi M. A Prescription for Lifestyle Change in Patients with H  |
| I | ο <sub>160</sub> - •<br>Ε •             |                  | * 160 -<br>50 •<br>E 140 -        | •  | 1 <0.001                              | Gout. <i>Current Opinion in Rheumatology.</i> 2010.<br><b>4.</b> Pfeifer ME, et al Hmong Population and Demographic Trends in the 2  |
| I | <u>ר</u> 140 -<br>ני 140 -<br>ני 140 -  |                  |                                   | •  |                                       | 2010 American Community Survey. Hmong Studies Journal. 2012;13(2)  |
|   | 0 120 -<br>U                            |                  | 0 100 -                           |  | •                                     | <ul> <li>5. Portis AJ., et al. "High prevalence of gouty arthritis among the Hmong Minnesota." Arthritis Care &amp; Research 2010; 62(10):1386-1391.</li> <li>6. Dertis A.L. et al. "Denid Communication: Stand Disease in the Umana"</li> </ul> |
|   | → 100 - <b>×</b>                        |                  |                                   | • • •                                    |                                       | 6. Portis AJ., et al. "Rapid Communication: Stone Disease in the Hmong<br>Initial Description of a High-Risk Population." <i>Journal of Endourology</i> 20   |
|   |   |                  |                                   |  | • •                                   | 7. Roman YM, Culhane-Pera KA, Menk J, Straka RJ. Assessment of Ge<br>Polymorphisms Associated with Hyperuricemia or Gout in the Hmong. F   |
|   | L 60 -<br>C •                           | •                | 1.<br>                            |  | ••                                    | <ul> <li>Medicine. 2016;13(5):429-440.</li> <li>8. Stamp LK, Barclay ML, O'Donnell JL, Zhang M, et al. Relationship be</li> </ul>  |
|   | × 40 -<br>O                             | •                | <u>d</u><br>× 20 -                |  |                                       | Urate and Plasma Oxypurinol in the Management of Gout: Determination   |
|   | 20 L CC CT                              | тт               | 0                                 | 40 60 80 10                              | , , , , , , , , , , , , , , , , , , , | Plasma Oxypurinol Concentration to Achieve a Target Serum Urate Lev <i>Ther.</i> 2011;90(3):392-398.   |
|   |   | 05802 C>T)       |                                   | V3 CrCl (m L/                            |                                       |  |

|   |                                     | ·                |                   | •                           |                           |   |
|---|-------------------------------------|------------------|-------------------|-----------------------------|---------------------------|---|
| Table 2. Summary of Oxipurinol Pharmacokinetics by Genotype         SLC22A12 (rs505802)       Oxipurinol AUC <sub>0-6hr</sub> (mg*hr/L) |                                     |                  |                   |                             |                           | Conclusions   |
|   | 22A12 (rs505802)<br>Genotype        | Mean ± (SD)      |                   | 95% CI                      | P-value                   | □ □rs505802 C>T in SLC22A12 significantly of  |
|   | CC (n=14) (ref)                     | 105.2(38.1)      | 53.1-176.6        | 83.2 to 127.2               | r-value                   | to the absolute change in SUA with baseline   |
|   | CT (n=14)                           | 77.5 (23.9)      | 43.3-118.2        | 63.7 to 91.3                | 0.041                     | eCrCl and oxipurinol AUC <sub>0-6hr</sub> in the base me  |
|   | TT (n=5)                            | 49.7 (10.5)      | 39.9-65.6         | 36.6 to 62.8                | 0.002                     | Oxipurinol AUC <sub>0-6hr</sub> and C <sub>min</sub> were signification in the CC relative to CT or TT genotype for r   |
|   | <u> </u>                            |                  |                   | S <sub>min Ohr</sub> (mg/L) |                           | Allopurinol effectively reduced SUA in Hm   |
| C   | CC (n=14) (ref)                     | 15.7 (6.7)       | 5.8-28.0          | 11.8 to 19.6                |                           | with a mean (SD) [range] reduction of 41% (   |
|   | CT (n=14)                           | 11.0 (3.9)       | 4.3-17.5          | 8.7 to 13.3                 | 0.046                     | [23-66%]. Most participants (71%, 24/34) ac   |
|   | TT (n=5)                            | 6.9 (1.7)        | 5.2-9.4           | 4.8 to 9.0                  | 0.005                     | SUA target <6 mg/dL   |
| Table   | 3. Absolute Change                  | e in SUA by Ge   | notype            |                             |                           |   |
|   | _C22A12 (rs5055020                  |                  | Count             | Mean + (SD) SL              | JA Reduction              | Interpretations   |
|   | ,<br>CC                             | ,                | 14                | _ ( )                       |                           | Allopurinol effectively reduces SUA in the  |
|   |                                     |                  |                   | 4.21 (1                     | •                         | Hmong participants <i>albeit</i> with marked inter-   |
|   | CT                                  |                  | 14                | 3.94 (1                     | ,                         | variability which, in part, can be attributed to  |
|   | TT                                  |                  | 5                 | 3.04 (1                     | 1.0)                      | of rs505802 C>T on oxipurinol PK  |
| Table 4   | 4. Stepwise Multiple                | e Linear Regre   | ssion Summa       | ry*                         |                           | the variability in absolute change in SUA (Ta   |
| Ind   | ependent Variable                   | Beta Coeffic     | ient P-va         | lue R <sup>2</sup>          | Adjusted R <sup>2</sup>   | Oxipurinol levels at 6hr indicate that 67%  |
| V2  | 2 SUA 6h (mg/dL)                    | -0.327           | 0.00              | )8                          |                           | achieve sub-therapeutic (<15.2mg/L) <sup>8</sup> oxipu  |
| Oxipu   | rinol AUC <sub>0-6hr</sub> (mg*hr/L | .) -0.0375       | <0.0              |                             |                           | concentrations in part due to genetics  |
| V:  | 3 eCrCl (mL/min)                    | -0.0195          | 0.01              | 0.69                        | 0.65                      |   |
| SLC22   | 2A12 (rs505802 <b>C</b> >T          | ) 0.565          | 0.03              | 36                          |                           | <b>Future Directions</b>  |
|   |                                     |                  |                   |                             |                           | prospective pharmacogenomics-based drug   |
| *Depei  | ndent Variable: SUA                 | 6hr(V3-V2)       |                   |                             |                           | with a focus on patient-centered outcomes   |
|   | Serum Uric Acid Pre                 | and Post         | 25 J Mear         | n Serum Oxipurinol (        | Concentration <u>+</u> SD |   |
| 14  | Allopurinol                         | Fig. 2           | 1 g /L )          |                             | Fig. 3                    | Disclosure  |
| 12  |                                     | 1 ig. 2          |                   | Тт                          | T                         | All authors have declared no conflict of inte   |
| 10<br>Jp/Gm   |                                     |                  | tratio            |                             |                           |   |
| id m<br>8   |                                     | A.               | u 15              |                             | o                         | Acknowledgments   |
| Acid  |                                     |                  |                   |                             |                           | <ul> <li>Hmong Gout Research Board, West Side Community Health</li> <li>U of M, Office of Community Engagement of the Clinical and</li> </ul>   |
| Jric<br>9   |                                     |                  | 0 1 0<br>         | 1 1                         | 1                         | Science Institute, 2014 Collaborative Pilot Grants CTSI No. 225   |
| ц<br>Ц  |                                     |                  | n di x            |                             |                           | Research reported in this publication was supported by the N<br>for Advancing Translational Sciences of the National Institutes of  |
| Seri  |                                     | •                |                   |                             |                           | Number UL1TR000114. The content is solely the responsibility<br>and does not necessarily represent the official views of the NIH  |
| 0   |                                     |                  | _ <sup>©</sup> 0  |                             |                           | ASCPT Trainee Travel Award  |
| Ŭ   | Pre-Allopurinol                     | Post-Allopurinol | 0                 | 2 4                         | 6                         | Defenences  |
|   |                                     | Fig.4            |                   | Sampling Time               | e (hr)<br>Fig. 5          | <b>References</b> 1. Edwards NL. The role of hyperuricemia and gout in kidney and cardid  |
| <sup>200</sup> T  |                                     | F 19. 4          | 200               |                             |                           | Cleveland Clinic Journal of Medicine. Jul 2008;75 Suppl 5:S13-16.<br>2. Kottgen A, Albrecht E, et al. Genome-Wide Association Analyses Ider   |
| ך<br>180 -<br>4   | •                                   |                  | 180 -<br>4        | ,                           | $R^2 = 0.42$              | Associated with Serum Urate Concentrations. <i>Nat Genet.</i> 2013;45(2):14<br><b>3.</b> Hyon K. Choi M. A Prescription for Lifestyle Change in Patients with H   |
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| ւ 140 -<br>Կ  | •                                   |                  | E 140             | •                           |                           | 2010 American Community Survey. Hmong Studies Journal. 2012;13(2)   |
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| ⊃ <sub>100</sub> -<br>⊄   | *                                   |                  | O N 80 -          | • • •                       |                           | 6. Portis AJ., et al. "Rapid Communication: Stone Disease in the Hmong<br>Initial Description of a High-Risk Population." <i>Journal of Endourology</i> 20  |
| n - 80 -  |                                     | •                | 0 60 -<br>L       |                             | •                         | <b>7.</b> Roman YM, Culhane-Pera KA, Menk J, Straka RJ. Assessment of Ge Polymorphisms Associated with Hyperuricemia or Gout in the Hmong. <i>F</i>   |
| n d -   | • •                                 |                  | n 40 -            |                             |                           | <ul> <li>Medicine. 2016;13(5):429-440.</li> <li>8. Stamp LK, Barclay ML, O'Donnell JL, Zhang M, et al. Relationship be</li> </ul>   |
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| 20 -  | СС СТ                               | тт               | 0 <del> </del> 20 | 40 60 80 1                  | 00 120 140 160            | Ther. 2011;90(3):392-398.   |
|   | SLC22A12 (rs505                     | 5802 C>T)        |                   | V3 CrCl (m L                | /min)                     |   |

