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An X chromosome-wide meta-analysis based on Japanese cohorts revealed that non-autosomal variations are associated with serum urate

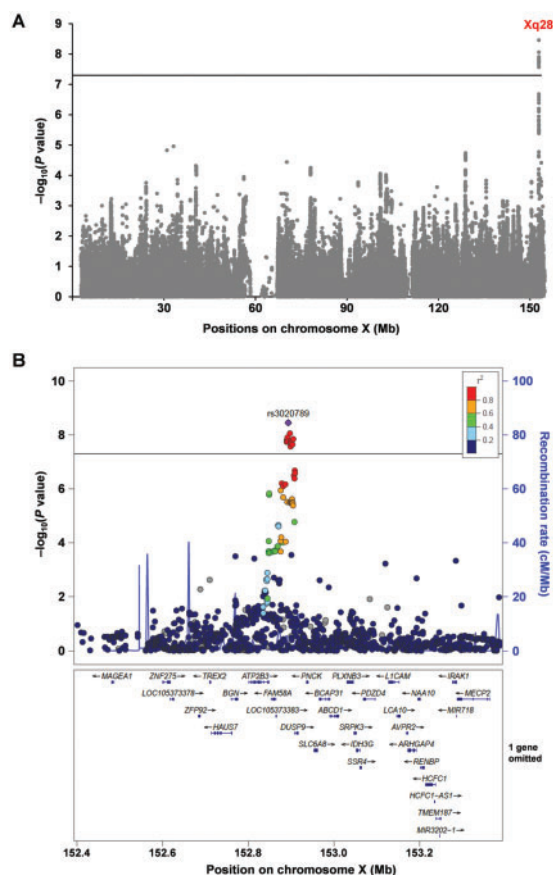
Rheumatology key message

- An XWAS revealed that variations in the X chromosome influence serum urate levels.

DEAR EDITOR, we have recently identified 36 genomic loci influencing serum urate (SU) levels via a genome-wide meta-analysis using 121,745 Japanese individuals [1]; however, non-autosomal data have hitherto been excluded in genome-wide association study (GWAS) quality-control procedures. The same limitation was applied to a trans-ancestry GWAS of SU in 457,690 individuals, the largest currently published genetic study on SU [2]. Other previous GWASs [3] have focussed exclusively on the associations between genetic variants in the autosomes and SU. The largely unknown role of the X chromosome in SU levels, in spite of it constituting ~5% of the human nuclear genome, prompted us to conduct an X chromosome-wide meta-analysis. We herein report our results, which reveal a novel locus that influences SU. Our findings may provide insights into gender differences in the homeostasis of urate, the circulating form of uric acid.

To investigate the contribution of genetic variations in the X chromosome to SU levels, we conducted an X chromosome-wide meta-analysis for SU using enlarged data sets encompassing 142,121 Japanese subjects based on three Japanese cohorts: the Japan Multi-institutional Collaborative Cohort Study, the Kita-Nagoya Genomic Epidemiology Study and the BioBank Japan Project. Details of these cohorts and analysis methods are described in the [Supplementary Methods](#), available at *Rheumatology* online. Via our meta-analysis for SU, we successfully identified 12 single nucleotide polymorphisms (SNPs) at the Xq28 locus that satisfied a genome-wide significance threshold of $\alpha = 5.0 \times 10^{-8}$ (Fig. 1A, [supplementary Table S1](#), available at *Rheumatology* online). Strong linkage disequilibrium among these 12 SNPs was observed in the Japanese population. We first identified a novel non-autosomal locus that is associated with SU. A regional association plot for this locus is shown in Fig. 1B, where the lead SNP (rs3020789) with the lowest *P*-value was in an intergenic region between *LOC105373383* and *dual specificity phosphatase 9 (DUSP9)*. The results of sex-stratified analyses with the lead SNP both in each cohort and the meta-analysis are summarized in [supplementary Table S2](#), available at *Rheumatology*

Fig. 1 An X chromosome-wide meta-analysis revealed genetic loci influencing serum urate levels in humans



(A) Manhattan plot of the meta-analysis that combines males and females. Supplementary results for males and females alone are shown in [supplementary Fig S1A and B](#), available at *Rheumatology* online, respectively. (B) Regional association plot for the Xq28 locus identified in the meta-analysis. The vertical axis indicates the $-\log_{10}(P\text{-value})$ for the assessment of the association of each SNP with serum urate (SU) levels. The colours indicate the linkage disequilibrium (r^2) between each lead SNP and neighbouring SNPs based on female subjects of the JPT population (Japanese in Tokyo) in the 1000 Genomes Project Phase 3 (<https://www.internationalgenome.org/home>). Horizontal lines represent the genome-wide significance threshold ($\alpha = 5 \times 10^{-8}$). The regional plot was drawn using LocusZoom (<http://locuszoom.org/>).

online. In the meta-analysis, the rs3020789 showed a genome-wide significant association and a nominally significant association for the male group ($\beta = -0.020$; $P = 2.12 \times 10^{-8}$) and female group ($\beta = -0.012$; $P = 0.024$).

To enhance understanding of the functional annotation of the newly identified locus (Xq28) in the context of SU, we then performed further analyses using publicly available data in the Genotype-Tissue Expression database (GTEx). We found that among the 12 SNPs associated with SU at the locus, 10 SNPs harbour variants that

affect the expression of at least one gene in more than one tissue in humans (supplementary Table S3, available at *Rheumatology* online). Based on the results of expression quantitative trait loci (eQTL) analysis, these SNPs were associated with the expression levels of their near genes [*DUSP9*, family with sequence similarity 58 member A (*FAM58A*, also known as *cyclin Q-CCNQ*), *biglycan* (*BGN*) or/and *SRSF protein kinase 3* (*SRPK3*)]. Interestingly, with *DUSP9*, significant associations were confirmed in many tissues, including subcutaneous adipose tissue, ovary and testis. These results support the contention that *DUSP9* is the most plausible gene for the effects of the identified non-autosomal variations on SU levels.

Given the well-characterized role of *DUSP9* as a cytosolic mitogen-activated protein kinase phosphatase (MKP) that regulates intracellular signalling pathways [4], *DUSP9* is not likely to be directly involved in SU regulation via the metabolism or transport of urate. Of note, the rs5945326 near *DUSP9* has reportedly been identified as a type 2 diabetes susceptibility locus [5]. Its risk allele (rs5945326-A) was associated with SU-lowering in this study. *DUSP9* is expressed in insulin-sensitive tissues and the kidney (a dominant tissue for urate elimination) [6]. Thus, besides its protective effect against the development of insulin resistance [4], *DUSP9* may influence renal functions via a different mechanism. Although our eQTL analysis found little effect of the identified SNPs on *DUSP9* levels in the kidney (possibly due to a lack of information on the kidney in GTEx), finding out how, with or without inter-organ communication, *DUSP9* might be involved in renal urate handling is likely to be significant and merits further study.

In this study we provide genetic evidence showing the SU-influencing effects of non-autosomal variants. Interestingly, for the lead SNP, its effect allele (rs3020789-T) frequencies in various populations range from 0.480 to 0.805 (supplementary Table S4, available at *Rheumatology* online). Whether a similar association can be found in other populations, as in this study on a Japanese population, should therefore be addressed. Considering that this association was been uncovered in a previous study that consisted of a GWAS for 58 quantitative traits including SU using autosomal and X chromosome variants [7], and the fact that knowledge of sex chromosomes lags behind that of autosomal chromosomes in population genetics research [8], our findings may contribute to a better understanding of the genetic factors that might be associated with gender differences in SU levels, and open a path to elucidating the physiological regulatory mechanisms of SU in humans.

Ethics statement

Data and sample collection for the cohorts participating in the present study were approved by the respective research ethics committees (National Defense Medical

College; Osaka University; Nagoya University; RIKEN; Jichi Medical University). All studies were performed according to the guidelines of the declaration of Helsinki. All participants had provided their written informed consent.

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Collaborators: Members of the Japan Uric Acid Genomics Consortium (Japan Urate) are: Kimiyoshi Ichida, Tappei Takada, Seiko Shimizu, Kenji Takeuchi, Kiyonori Kuriki, Sadao Suzuki, Yoshikuni Kita, Ritei Uehara, Kokichi Arisawa, Hiroaki Ikezaki, Keitaro Tanaka, Ken Yamamoto, Tomoko S. Kato, Tatsuaki Matsubara, Yuka Aoki, Takahiro Nakamura, Hiroshi Nakashima and Masashi Tsunoda.

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Data availability statement

Data are available upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Masahiro Nakatochi¹, Yu Toyoda², Masahiro Kanai^{3,4}, Akiyoshi Nakayama⁵, Yusuke Kawamura², Asahi Hishida⁵, Haruo Mikami⁶, Keitaro Matsuo^{7,8}, Toshiro Takezaki⁹, Yukihide Momozawa¹⁰, The Biobank Japan Project¹¹, Yoichiro Kamatani¹², Sahoko Ichihara¹³, Nariyoshi Shinomiya², Mitsuhiro Yokota¹⁴, Kenji Wakai⁴, Yukinori Okada^{3,15,16} and Hirotaka Matsuo²; for the Japan Uric Acid Genomics Consortium (Japan Urate)

¹Public Health Informatics Unit, Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, ²Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Tokorozawa, ³Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan, ⁴Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA, ⁵Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, ⁶Cancer Prevention Center, Chiba Cancer Center Research Institute, Chiba, ⁷Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, ⁸Department of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, ⁹Department of International Island and Community Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, ¹⁰Laboratory for Genotyping Development, RIKEN Center for Integrative Medical Sciences, Yokohama, ¹¹Institute of Medical Science, ¹²Laboratory of Complex Trait Genomics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, ¹³Department of Environmental and Preventive Medicine, Jichi Medical University School of Medicine, Shimotsuke, ¹⁴Kurume University School of Medicine, Kurume, ¹⁵Laboratory of Statistical Immunology, Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita and ¹⁶Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Suita, Japan

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Correspondence to: Hirotaka Matsuo, Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan. E-mail: hmatsuo.ndmc@gmail.com
Masahiro Nakatochi and Yu Toyoda contributed equally to this study.

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New prescribing recommendations bring an opportunity to focus on better reproductive health for women with rheumatic disease

Rheumatology key message

- Prescribing recommendations for women treated with potentially teratogenic medications are an opportunity to deliver better reproductive health for women with rheumatic disease.

DEAR EDITOR, It is approaching 2 years since the UK Medicines and Healthcare products Regulatory Agency (MHRA) published a drug safety update with pregnancy prevention guidance for women treated with drugs with potential teratogenic effects, which has relevance for patients and prescribers in rheumatology in the UK [1]. There are several medicines in routine rheumatology practice with teratogenic potential (including mycophenolate mofetil, leflunomide, methotrexate and cyclophosphamide) and unplanned pregnancies still occur in women treated with these medications.

The guidance is focused on drugs with *potentially* teratogenic effects but does not specify medications for which they apply, and signposts the UK Teratology Information Service (UKTIS) in identifying such drugs. However, teratogenicity is not binary, and UKTIS often recommend a balanced risk assessment about using medications in pregnancy—a nuance which is not reflected in this guidance.

Certain teratogenic medications (such as sodium valproate and retinoids) have a formal pregnancy prevention