Gout and Hyperuricemia

Review

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WD40-repeat proteins and gout

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Purpose: Despite progress in understanding the genetics of hyperuricemia, many unanswered questions still remain about the genetic factors besides hyperuricemia that determine the development of gout. WD40-repeat (WDR) proteins are implicated in a variety of biologic functions including signal transduction, transcription regulation, apoptosis and etc. Whether this family is involved in the development of gout warrants further investigation**.**
Findings: Genetic variation in WDR1 was initially found to be associated with gout in the Han Chinese population in northern China. WDR77 is a novel androgen receptor cofactor that plays an important role in enhancing androgen receptor (AR) transcriptional activity in prostate cancer, which was prevalent in gout. Ubiquitin specific peptidase 12 (Usp12)/ Usp1-associated factor 1 (Uaf-1)/WDR20 complex plays a critical role in AR regulation. WDFY4 are associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and could potentially be involved in gouty arthritis.
Conclusion: WDR proteins family consists of 277 proteins. What we know is very limited at present. In the future, studies about WDR proteins may provide a novel understanding for the mechanisms of gout.

Key words: Gout; WD40-repeat proteins; WDR

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Introduction

Gout is a global health burden [1], and is currently known as the “king” of diseases due to its association with diabetes mellitus (DM) [2,3], chronic kidney disease (CKD) [4], cardiovascular diseases [5] and malignancies [6]. Gout has been known to have familial links suggesting a hereditary component to these traits.

Genetics of gout

Genetic factors have been recognized as an important element for gout susceptibility. Initially, single gene variants have been reported, such as hypoxanthine phosphoribosyltransferase (HPRT) mutation [7,8], or other single nucleotide polymorphisms (SNPs), such as tumor necrosis factor-α (TNF-α) polymorphism [9].

GWAS

In this decade, more than 17 genome-wide association study (GWAS) have revealed several genetic variants for gout or hyperuricemia, such as ATP binding cassette subfamily G member 2 (ABCG2), solute carrier family 2 member 9 (SLC2A9) [10], as well as cGMP-dependent type II (CGKII) [11].

According to the combined data from individuals of European ancestry within the Global Urate Genetics Consortium (GUGC), 28 genome-wide significant loci in association with serum urate concentrations have been identified. In 2016, according to the report by Matuso et al. [12], the total variance explained by the seven SNPs was estimated to be 9.0% and by the three SNPs of *SLC2A9* and *ABCG2* being 6.9%. Therefore, further investigations to discover new genetic variants are needed [13].

WD40-repeat proteins

WD40-repeat (WDR) proteins, an ancient regulatory-protein family, are implicated in a variety of functions including signal transduction, transcription regulation, cell cycle, apoptosis and autophagy. According to the initial analysis of the human genome WDRs contain 277 proteins. Recently, WDR proteins have been noted to play a role in various kinds of diseases [14,15]. Whether WDR family is involved in the susceptibility of gout warrants further study.

WD40 repeat protein 1 (WDR1)

In 2016, Liu et al. reported that genetic variation in WDR1 was associated with gout risk in the Han Chinese population at Xianyang City [16]. They identified the minor alleles of rs3756230 to be negatively associated with gout. In contrast, the minor allele of rs12498927 was positively associated with gout risk. Moreover, they revealed that the "A/A" genotype of rs12498927 was associated with increased risk of gout under either codominant or recessive models.

Previously, Kato et al. [17] reported that WDR1 (also known as Aip1) plays an important role in directional cell migration by restricting the stimulus-induced membrane protrusion to one direction via promoting cofilin activity.

Since WDR1 is localized to the core structure of macrophage podosomes [18], we propose that macrophages carrying mutated WDR1 might present with aberrant migration, which contribute to the risk of gout. However, this hypothesis has yet to be studied.

In addition, Kile et al. [19] have generated an allelic series for WDR1 and report that reductions in WDR1 function produce a dramatic phenotype gradient. In mice, loss of function at the WDR1 locus can cause autoinflammatory disease.

Taken together, of the role of WDR1 in gout is very worthy of further studies in different ethnic population.

WDR19

Previously, we conducted a study using data from national outpatients records in Taiwan to analyze the incidence of cancers in patients with gout and revealed that prostate cancer has a much higher incidence than controls [6]. Lin et al. firstly revealed that WDR19 is expressed in normal and neoplastic prostate epithelium and is regulated by androgenic hormones [20]. Furthermore, using microarrays and real-time quantitative PCR, they revealed that WDR19 mRNA expression was increased in prostate cancer compared with controls [21].

WDR20

Androgen receptor (AR) is known to be a key transcriptional regulator in prostate cancer. McClurg et al. proved that ubiquitin specific peptidase 12 (Usp12)/Usp1-associated factor 1 (Uaf-1)/WDR20 complex plays a key role in AR stability and activity. Moreover, expression of WDR20 and Uaf-1 is higher in prostate cancer tissue as compared to benign controls [22]. In brief, their findings suggest the Usp12/Uaf-1/WDR20 complex plays a critical role in AR regulation and the progression of prostate cancer.

WDR77 (p44)

Based upon a series of studies, a novel AR cofactor, WDR77 (also known as p44), was identified to play an important role in enhancing AR transcriptional activity in not only prostate gland but also prostate cancer [23-25]. Therefore, the WDR77-AR signaling pathway may play a role in gout, especially for the subgroup with concomitant prostate cancer.

WDFY4

WDFY family member 4 (WDFY4) is a huge protein with unknown function but is predominantly expressed in primary and secondary immune tissues. A nonsynonymous SNP in this gene was found to be highly associated with systemic lupus erythematosus (SLE) susceptibility, based upon a genome-wide association study in a Hong Kong Chinese population and following replication in three other cohorts from Mainland China and a cohort from Thailand [26].

Zhao et al. examined the mRNA expression of WDFY4 in patients with SLE. WDFY4 mRNA was found to be significantly downregulated in SLE patients as compared with controls. Using electrophoretic mobility shift and supershift assays, they revealed that Yinyang1 (YY1) binds to rs877819 with lower affinity to the A allele as compared to G allele. Therefore, they concluded the rs877819 inWDFY4 might be a functional site associated with SLE [27].

In addition, Zhang et al. reported that WDFY4 rs7097397 A/G may be associated with rheumatoid arthritis (RA). Both SLE and RA are models of chronic arthritis caused by both innate and adaptive immune

dysregulation. Whether other SNPs in this gene is related with gout, another model of arthritis predominantly caused by innate immune dysregulation, might be worthy of study [28].

Perspective of WDR

In this review we have described recent findings that WDR proteins could be related with gout (Table 1). Indeed, what we know is very limited, just like "looking at the sky through a bamboo tube". In summary, studies about WDR proteins could provide a novel approach to the mechanisms of gout.

Table 1. Recent findings that WD40 repeat (WDR) proteins could be related with gout.

Gene	SNP	Disease association or function	Year	Authors	References
WDR1	rs12498927	Gout	2016	Liu et al.	[16]
WDR19		Prostate cancer	2003	Lin et al.	[20]
WDR20		AR* regulation	2015	McClurg et al.	[22]
WDR77 (p44)		AR* cofactor	2004	Zhou et al.	[24]
WDR77 (p44)		Prostate cancer	2008	Peng et al.	[25]
WDFY4		SLE	2010	Yang et al.	[26]
WDFY4	rs877819	SLE	2012	Zhao et al.	[27]
WDFY4	rs7097397	RA	2014	Zhang et al.	[28]

*AR denoting androgen receptor.

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