No association between *wolframin* gene H611R polymorphism and mood disorders: Evidence from 2570 subjects

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Background: In the past few decades, a number of studies have investigated the association of the *wolframin* (*WFS1*) gene H611R polymorphism with mood disorders, but the findings are not always consistent. Aims: The objective of the present study is to assess the association between *WFS1* gene H611R polymorphism and mood disorders by using a meta-analysis. Methods: A comprehensive literature search of PubMed, Excerpta Medica Database, Elsevier Science Direct and China National Knowledge Infrastructure databases was conducted to identify relevant articles, with the last report up to April 15, 2014. Pooled odds ratio (OR) with 95% confidence interval (CI) was estimated. Results: Seven studies including 1318 cases and 1252 controls were selected from potentially relevant articles. This meta-analysis showed that there was no significant association between *WFS1* gene H611R polymorphism and mood disorders (R vs. H: OR/H11005 0.93, 95% CI/H11005 0.82 – 1.05, P/H11005 0.22; HR vs. HH: OR/H11005 0.98, 95% CI/H11005 0.82 – 1.17, P = 0.80; RR vs. HH + HR: OR = 0.84, 95% CI = 0.67 – 1.04, P = 0.11; RR vs. HH: OR = 0.86, 95% CI = 0.67 – 1.10, P = 0.24; HR vs. HH: OR = 1.03, 95% CI = 0.78 – 1.36, P = 0.83). In subgroup analyses by ethnicity, we did not detect any significant association of this polymorphism with mood disorders in Caucasian and Asian populations (P > 0.05). In subgroup analyses by types of mood disorders, we also did not detect any significant association of this polymorphism with bipolar disorder or major depressive disorder (P > 0.05). Conclusions: The results of this meta-analysis suggest that there is no association between *WFS1* gene H611R polymorphism and mood disorders.

Meta-analysis, Mood disorders, Polymorphism, *WFS1*.

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Mood disorders, mainly including major depressive disorder (MDD) and bipolar disorder (BD), are serious psychiatric diseases, often causing disability, significant functional impairment and are sometimes life-threatening (1, 2). Mood disorders are a serious problem for public health, and epidemiological studies indicate that about 21% of the population are affected by mood disorders during their life time (2, 3). The accumulating evidence provides strong support for genetic factors in the pathogenesis of these diseases (4). Wolfram syndrome (WS), autosomal recessive disorder, is caused by a mutation in the gene encoding wolframin (*WFS1*) on the short arm of chromosome 4 (4p16.1) (5, 6). Patients with WS may develop psychiatric manifestations such as depression, psychosis, aggression and impulsivity (7). Meanwhile, there are high rate of psychiatric hospitalization and suicide in non-symptomatic carriers of WS (8). Thus, the *WFS1* gene may be a good candidate for genetic studies on mood disorders.

The *WFS1* gene cDNA is 3688 base pairs in length, and is composed of eight exons that encode for an 890 amino-acid glycoprotein. A large number of polymorphisms in this gene have been found (9, 10). Several *WFS1* gene polymorphisms have been shown to be significantly associated with diabetes mellitus and this gene has also been implicated in psychiatric diseases (11). Of these polymorphisms, the H611R polymorphism is located in exon 8 of *WFS1* gene, and represents an A/G polymorphism at locus 611, resulting in an amino acid substitution (histidine to arginine) in the wolframin protein. Recently, the H611R polymorphism has attracted widespread attention, and a number of studies have been conducted to assess the association between it and mood disorders risk (12–18). Some studies...
showed that this polymorphism may play an important role in the genetic predisposition for mood disorders (12, 13), but other studies did not detect the association (14–18). These studies had relatively small sample sizes (cases: ranging from 30 to 320; controls: ranging from 61 to 314), and their statistical powers could be very limited for efficient assessment of the association. Integration of these studies may provide improved statistical power to detect the significance.

In the present study, we have electronic searched all genetic association studies published in the field of mood disorders and WFS1 gene polymorphisms, and performed a meta-analysis to summarize the effect size of WFS1 gene H611R polymorphism associated with susceptibility of mood disorders.

Methods

Search strategy and selection criteria
The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was used in this meta-analysis (19). (Supplementary Table 1 – Please find this material with the following direct link to the article: http://www.informaworld.com/[10.3109/08039488.2014.936503.) We searched PubMed, Excerpta Medica Database (EMBASE), Elsevier Science Direct and China National Knowledge Infrastructure (CNKI) databases for all articles related to mood disorders and the WFS1 gene H611R polymorphism that had been published through April 15, 2014. In order to perform an exhaustive search, we enlarged our searching items and used “Wolfram syndrome 1” or “wolframin” or “WFS1” or “rs734312”, “mood” or “affective” or “depressive” or “bipolar” or “unipolar”, and “gene” or “allele” or “polymorphism” or “variation” or “mutation”. Review articles and original studies on the association of WFS1 gene polymorphisms with mood disorders were hand-searched to find additional eligible studies. Eligible studies fulfilled the following inclusion criteria: 1) it involved cases with clinically diagnosed mood disorders and controls who were free of psychiatric disorders; 2) it was a case–control study of the WFS1 gene H611R polymorphism with mood disorders risk. When there were multiple studies from the same population, only the largest study was used in this meta-analysis.

Data extraction
Two authors independently extracted the data with the standard protocol. Discrepancies about inclusion of studies and interpretation of data were resolved by discussion with our research team. The following information from each publication was collected: the first author’s name, year of publication, source of publication, ethnicity, number of cases and controls, and available allele and genotype frequencies information. If original data were not reported in articles, a request for original data were sent to the authors.

Statistical analysis
Analyses were performed using the software Review Manager (v4.2; The Cochrane Collaboration, Oxford, UK) and Stata statistical software (v10.0; StataCorp, College Station, Texas, USA). Pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of association. We evaluated the allele contrast (R vs. H), the dominant model (HR+RR vs. HH), the recessive model (RR vs. HH+HR) and the codominant model (RR vs. HH and HR vs. HH), respectively. The statistical heterogeneity among studies was assessed with chi square-test based Q-statistic (20). P<0.10 was interpreted as significant heterogeneity among the studies. A significant Q-statistic indicated heterogeneity across studies, and then the result of the random effect model (DerSimonian–Laird method) was selected (21). Otherwise, the result of the fixed effect model (Mantel–Haenszel method) was selected (22). F was also used to measure the effect of heterogeneity (23). Meta-regression was conducted to explore potential sources of heterogeneity (24). We performed subgroup analyses by ethnicity and types of mood disorders. Publication bias was estimated using Egger’s linear regression test by visual inspection of funnel plot (25). Hardy–Weinberg equilibrium (HWE) for genotype frequencies was checked in the control groups of each study by chi square-test. Sensitivity analysis was performed by excluding the studies not in HWE. P<0.05 (two-sided) was considered statistically significant.

Results

Characteristics of eligible studies
We found 635 articles relevant to the searching terms (PubMed: 43; EMBASE: 50; Elsevier Science Direct: 513; CNKI: 29). The study selection process is shown in Fig. 1. Based on our search criteria, eight studies examined the association between WFS1 gene polymorphisms and mood disorders (12–18, 26). Among them, one study did not explore the H611R polymorphism and was excluded (26). Finally, a total of seven studies including 1318 cases and 1252 controls were included in the present meta-analysis. Detailed characteristics of identified studies are listed in Table 1 (12–18).

Of eligible studies, six studies reported allele and genotype frequencies of WFS1 gene H611R polymorphism (12, 13, 15–18). The genotype distributions in the controls of these six studies were in agreement with HWE. One study only reported allele frequency of WFS1 gene H611R polymorphism (14). Thus, we could not perform HWE test for the study. Table 1 shows the results of HWE test for genotype distributions in the controls. Of eligible studies, four studies were conducted in Caucasian populations (12, 13, 16, 18), three studies...
The summary of the meta-analysis for WFS1 gene H611R polymorphism and mood disorders is shown in Table 2. Overall, we did not detect a significant association of WFS1 gene H611R polymorphism with mood disorders (R vs. H: OR = 0.93, 95% CI = 0.82 – 1.05, P = 0.22; HR vs. HH: OR = 0.98, 95% CI = 0.82 – 1.17, P = 0.80; RR vs. HR vs. HH: OR = 0.84, 95% CI = 0.67 – 1.04, P = 0.11; RR vs. HH: OR = 0.86, 95% CI = 0.67 – 1.10, P = 0.24; HR vs. HH: OR = 1.03, 95% CI = 0.78 – 1.36, P = 0.83). In overall analysis, significant between-study heterogeneity existed in the contrast of HR vs. HH (P = 0.09). No significant between-study heterogeneity was found in other contrasts.

We also performed subgroup analyses by ethnicity and types of mood disorders. In subgroup analyses by

**Table 1. Characteristics of studies included in the meta-analysis of WFS1 gene H611R polymorphism with mood disorders.**

| Author/year | Ethnicity | Disease | Sample size (case/control) | Case | Control | p_HWE-value for control |
|-------------|-----------|---------|----------------------------|------|---------|-------------------------|
| Zalsman/2009 (12) | Caucasian | BD, MDD | 314 (201/113) | HH: 58, HR: 113, RR: 30 | HH: 49, HR: 47, RR: 17 | 0.309 |
| Koido/2005 (13) | Caucasian | BD, MDD | 384 (224/160) | HH: 51, HR: 123, RR: 50 | HH: 32, HR: 78, RR: 50 | 0.874 |
| Kawamoto/2004 (14)* | Asian | BD | 143 (47/96) | | | |
| Kato/2003 (15) | Asian | BD | 391 (184/207) | HH: 139, HR: 40, RR: 5 | HH: 153, HR: 48, RR: 6 | 0.354 |
| Middle/2000 (16) | Caucasian | BD | 613 (312/301) | HH: 91, HR: 149, RR: 72 | HH: 79, HR: 157, RR: 65 | 0.430 |
| Ohtsuki/2000 (17) | Asian | MDD | 91 (30/61) | HH: 24, HR: 5, RR: 1 | HH: 44, HR: 16, RR: 1 | 0.739 |
| Furlong/1999 (18) | Caucasian | BD, MDD | 634 (320/314) | HH: 104, HR: 163, RR: 53 | HH: 96, HR: 149, RR: 69 | 0.437 |

WFS1, Wolfram syndrome 1; HWE, Hardy–Weinberg equilibrium; BD, bipolar disorder; MDD, major depressive disorder.

*Only allele frequency was extracted from the study.


NO ASSOCIATION BETWEEN WOLFRAMIN GENE H611R POLYMORPHISM AND MOOD DISORDERS

Table 2. Meta-analysis of WFS1 gene H611R polymorphism and mood disorders association.

| Comparison | Number of studies | Sample size | Test of heterogeneity | Test of association |
|------------|------------------|-------------|-----------------------|---------------------|
|            |                  | Case | Control | $I^2$ (%) | $\chi^2$ | $P$-value | Model | OR (95% CI) | $P$-value |
| R vs. H    |                   |      |         |           |         |          |       |             |           |
| All        | 7                 | 2636 | 2504    | 27.8      | 8.31    | 0.22     | F      | 0.93 (0.82–1.05) | 0.22 |
| Caucasian  | 4                 | 2114 | 1776    | 54.3      | 6.56    | 0.09     | R      | 0.95 (0.79–1.16) | 0.64 |
| Asian      | 3                 | 522  | 728     | 0.0       | 1.41    | 0.49     | F      | 0.83 (0.59–1.18) | 0.30 |
| BD         | 6                 | 1576 | 2382    | 0.0       | 3.88    | 0.57     | F      | 0.91 (0.79–1.05) | 0.21 |
| MDD        | 4                 | 1060 | 1296    | 60.3      | 7.56    | 0.06     | R      | 0.95 (0.70–1.28) | 0.73 |
| RR vs. HH  |                   |      |         |           |         |          |       |             |           |
| All        | 6                 | 1271 | 1156    | 43.0      | 8.78    | 0.12     | F      | 0.98 (0.82–1.17) | 0.80 |
| Caucasian  | 4                 | 1057 | 888     | 29.4      | 4.25    | 0.24     | F      | 0.83 (0.67–1.03) | 0.10 |
| Asian      | 2                 | 214  | 268     | 0.0       | 0.26    | 0.61     | F      | 1.05 (0.35–3.18) | 0.93 |
| BD         | 5                 | 741  | 1095    | 41.1      | 6.79    | 0.15     | F      | 0.81 (0.62–1.05) | 0.11 |
| MDD        | 4                 | 530  | 648     | 0.0       | 1.70    | 0.64     | F      | 0.79 (0.59–1.07) | 0.13 |
| RR vs. HH+HR |                |      |         |           |         |          |       |             |           |
| All        | 6                 | 678  | 661     | 0.0       | 4.65    | 0.46     | F      | 0.86 (0.67–1.10) | 0.24 |
| Caucasian  | 4                 | 552  | 534     | 3.3       | 3.10    | 0.38     | F      | 0.92 (0.69–1.21) | 0.54 |
| Asian      | 2                 | 126  | 127     | 0.0       | 0.53    | 0.47     | F      | 0.66 (0.37–1.17) | 0.15 |
| BD         | 5                 | 413  | 613     | 0.0       | 2.35    | 0.67     | F      | 0.82 (0.60–1.13) | 0.23 |
| MDD        | 4                 | 265  | 358     | 41.4      | 5.12    | 0.16     | F      | 0.84 (0.59–1.20) | 0.34 |
| HR vs. HH  |                   |      |         |           |         |          |       |             |           |
| All        | 6                 | 1060 | 948     | 47.2      | 9.46    | 0.09     | R      | 1.03 (0.78–1.36) | 0.83 |
| Caucasian  | 4                 | 852  | 687     | 63.0      | 8.11    | 0.04     | R      | 1.11 (0.78–1.58) | 0.57 |
| Asian      | 2                 | 208  | 261     | 0.0       | 0.57    | 0.45     | F      | 0.85 (0.55–1.32) | 0.46 |
| BD         | 5                 | 628  | 888     | 0.0       | 3.89    | 0.42     | F      | 1.02 (0.82–1.28) | 0.85 |
| MDD        | 4                 | 432  | 511     | 65.5      | 8.71    | 0.03     | R      | 1.07 (0.64–1.78) | 0.60 |

WFS1, Wolfram syndrome 1; OR, odds ratio; CI, confidence interval; BD, bipolar disorder; MDD, major depressive disorder; R, random effect model; F, fixed effect model.

No association between Wolframin gene H611R polymorphism and mood disorders association. For most of contrasts, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry (funnel plots not shown). These results were further supported by evaluation of publication bias, heterogeneity and sensitivity analysis.

For most of contrasts, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry (funnel plots not shown). These results were further supported by evaluation of publication bias, heterogeneity and sensitivity analysis.
analyses via Egger's linear regression test (Table 3), but funnel plot and Egger's linear regression test were not applied in several contrasts (Asian: HR + RR vs. HH, RR vs. HH + HR, RR vs. HH, and HR vs. HH) due to the small number of studies. In overall analysis, significant between-study heterogeneity was found in the contrast of HR vs. HH ($I^2 = 47.2\%$, $P = 0.09$), thus meta-regression was conducted to explore potential sources of heterogeneity. The confounding factors included year of publication, ethnicity, types of mood disorders and sample size. However, the result of meta-regression did not indicate that any of these potential factors was a major source of heterogeneity ($P > 0.05$). The small number of included studies could be very limited for efficient assessment of potential sources of heterogeneity. Additionally, other factors that regretfully remain undefined due to insufficient data, such as the severity of symptoms, may contribute to the heterogeneity. One study only reported allele frequency of $WFS1$ gene H611R polymorphism, and we could not perform HWE test for the study. We conducted the sensitivity analysis by excluding the study, which did not change the present results (R vs. H: OR = 0.94, 95% CI = 0.83–1.06, $P = 0.29$).

**Discussion**

The present meta-analysis of seven case–control studies including 1318 cases and 1252 controls provides the most comprehensive assessment for the association between $WFS1$ gene H611R polymorphism and the risk of mood disorders. The meta-analysis did not detect any significant association between $WFS1$ gene H611R polymorphism and mood disorders, which were further supported by subgroup analyses and sensitivity analysis. In subgroup analyses by ethnicity, we did not detect any significant association of this polymorphism with mood disorders in Caucasian and Asian populations. Similarly, in subgroup analyses by types of mood disorders, no significant association of this polymorphism with BD or MDD was detected. To the best of our knowledge, this is the first meta-analysis assessing the association between $WFS1$ gene H611R polymorphism and mood disorders.

Mood disorders are a common group of diseases characterized by a significant disturbance in a person's persistent emotional state or mood, and social as well as economic impact of these diseases is extremely high and may be even higher in coming years (1, 2). It is clear from family, twin and adoption studies that genetic factors play an important role in these diseases (27). Many association studies have been conducted to assess the association between $WFS1$ gene H611R polymorphism and mood disorders (12–18), but these studies had relatively small sample sizes and their results vary from study to study. Meta-analysis is a statistical method for combining the results of several studies to produce a single estimate of the major effect with enhanced precision (28). Our meta-analysis suggests that $WFS1$ gene H611R polymorphism is not associated with mood disorders. Evidence showed that there was no significant difference of expression levels of $WFS1$ mRNA among patients with mood disorders and normal individuals (15), which supports our results, but there is some evidence to show that $WFS1$ gene may be involved in the pathogenesis of mood disorders (7, 8). Thus, the results of the present meta-analysis should be treated with caution. Our results are based on unadjusted estimates, and the H611R polymorphism may only play a role in conjunction with environmental factors. An analysis stratified by environmental factors may provide more definitive conclusion. Mood disorders development is a complex process in which multiple genes are involved (4, 29, 30). We investigated only a single polymorphism, which might have a limited impact on mood disorders etiology. More comprehensive multiple polymorphisms-based or haplotype-based or multigenic-based studies may provide more precise information. Finally, mood disorders are a group of heterogeneous diseases. The sample size of study must be larger and the phenotype must be more robust if a significant association is to be found. The sample sizes of studies included in the meta-analysis were relatively small. Further studies based on larger sample size, case–control design and stratified by ethnicity as well as types of mood disorders could provide more definitive conclusion.

Some limitations should be acknowledged in the current meta-analysis. First, we detected significant between-study heterogeneity in some contrasts, and may be distorting the meta-analysis. Second, funnel plot and Egger's linear

**Table 3. Egger's linear regression test to measure the funnel plot asymmetry.**

| Comparison        | All          | Caucasian       | Asian          | BD         | MDD        |
|-------------------|--------------|-----------------|----------------|------------|------------|
| R vs. H           | -0.62 (-3.43 to 2.19) | 4.04 (-15.77 to 23.86) | -1.43 (-10.18 to 7.32) | -1.21 (-3.35 to 0.91) | 0.33 (-11.77 to 12.43) |
| HR + RR vs. HH    | -0.01 (-5.78 to 5.76) | 4.32 (-16.90 to 25.54) | NA             | 1.23 (-1.90 to 4.36) | 0.38 (-16.57 to 15.79) |
| RR vs. HH + HR    | 0.52 (-2.09 to 3.13)  | -0.07 (-16.94 to 16.78) | NA             | -1.63 (-5.54 to 2.27) | 1.13 (-2.03 to 4.30)  |
| RR vs. HH         | 0.75 (-1.91 to 3.42)  | 2.51 (-13.41 to 18.45) | NA             | -0.91 (-3.51 to 1.69) | 1.30 (-6.32 to 8.93)  |
| HR vs. HH         | -0.19 (-6.19 to 5.80) | 5.04 (-14.96 to 25.05) | NA             | 2.39 (-1.22 to 6.02)  | 0.93 (-16.07 to 14.19) |

BD, bipolar disorder; MDD, major depressive disorder; NA, not applicable.
regression test were not applied in several contrasts due to the small number of studies. Thus, publication bias may occur. Finally, of eligible studies, one study did not report genotype frequency of WFS1 gene H611R polymorphism, and may be influencing the results.

To summarize, our meta-analysis suggests that there is no association between WFS1 gene H611R polymorphism and the risk of mood disorders. However, more epidemiologic studies based on larger sample size, case-control design and stratified by ethnicity, types of mood disorders as well as environmental factors are still needed.

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Supplementary material available online
Supplementary Table 1. PRISMA checklist.