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Meta-analyses of 4 *CFTR* variants associated with the risk of the congenital bilateral absence of the vas deferens

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Abstract

Aims: The aim of our study was to evaluate the relationship between four *CFTR* variations and the congenital bilateral absence of the vas deferens (CBAVD).

Methods: A systematic search was performed in the literature databases for the case-control studies of *CFTR* variations with the risk of CBAVD. A total of 29 studies among 1139 controls and 1562 CBAVD patients were gathered for the meta-analyses of three commonly tested variations (5T, Δ F508 and M470V) with CBAVD.

Results: Our meta-analyses observed significant associations between CBAVD and all the three variations, including 5T ($P < 0.001$, OR = 8.35, 95% CI = 6.68-10.43), M470V ($P = 0.027$, OR = 0.74, 95% CI = 0.60-0.91) and Δ F508 ($P < 0.001$, OR = 22.20, 95% CI = 7.49-65.79).

Conclusion: In the current study, we demonstrated a significant association between *CFTR* variations and CBAVD. Our results showed that the 5T variation was a risk factor of CBAVD in French, Spanish, Japanese, Chinese, Iranian, Indian, Mexican and Egyptian populations. *CFTR* Δ F508 was another important risk factor in Caucasians, including Slovenians, Canadians, Iranians, and Egyptians. In addition, M470V was a protective factor among French, Chinese, Italian and Iranian populations.

Keywords: Congenital bilateral absence of the vas deferens, Meta-analysis, *CFTR* gene, 5T, Δ F508, M470V

Introduction

Congenital bilateral absence of the vas deferens (CBAVD, MIM: #277180) is one of the abnormal forms in the male reproductive system, causing obstruction to sperm outflow into the urethra. CBAVD is responsible for 1-2% of male infertility [1]. CBAVD was widely considered as an atypical symptom of cystic fibrosis (CF, MIM: #219700) [2,3], which was a severe recessive disease characterized by obstructive chronic lung disease, pancreatic disease and abnormal concentrations of electrolytes in the sweat in clinical studies [4]. Approximately 97% of the male CF patients also suffered from CBAVD [5].

CF is a severe genetic disease with a incidence of 1/2500 births every year in Caucasians [6]. CF patients are often carriers of *CFTR* gene variations [7] that were originally found in CBAVD patients [8,9]. The *CFTR* gene encodes a glycosylated transmembrane protein that is a chloride channel conducts the regulation of other transport pathways. *CFTR* was widely expressed in epithelial cells of exocrine tissues, such as the sweat glands, lungs, and vas deferens [10]. Published studies have shown evidence that abnormal expression of *CFTR* contributed to the dysfunction of body organs, including the sweat glands, respiratory system and reproductive systems. CBAVD is one of the generally acknowledged monosymptomatic *CFTR*-related disorders [11].

Located on chromosome 7q31.2, the *CFTR* gene contains 27 exons and 1945 polymorphisms according to the Cystic Fibrosis Variations Database [12]. There are four commonly tested variations (Δ F508, 5T, M470V and R1117H) in CBAVD.

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The abnormal fold of the Δ F508-CFTR protein triggered the activity of proteasomes for degradation, which caused a lower open probability than normal [13]. Another common variations, IVS8-Tn, had three forms containing five, 7 seven, or 9 nine thymidine residues in this locus, which is considered an incomplete penetrance [14]. The 5T allele especially produces high levels of CFTR transcript without exon 9, resulting in variable phenotypes which were observed in CBAVD or mild CF patients [4]. Experimental evidence indicates that 5T carriers have a decreased splicing efficiency of intron 8 [15,16]. M470V (1540A/G in exon 10) is in a strong linkage disequilibrium with the 5T locus in the CBAVD population, and has become a commonly tested locus [17-19]. The 470V-CFTR protein has lower function than the 470M-CFTR protein [20]. There were arguments on the role of M470V in the CBAVD, although M470V might increase the penetrance of 5T and lead to an obvious association between 5T and Val470 alleles in CBAVD but not in fertile males.

CBAVD incidence is rare (1-2%) in the patients with male infertility [1]. Most genetic studies only involved a few number of individuals. Meanwhile, there was large ethnic difference for the CFTR variations that were more frequent in Caucasians than in other populations, such as Asians. Meta-analysis has an advantage in the sample size by pooling all the relational studies. In the present study, we performed a comprehensive search for the eligible case-control studies on the association between CBAVD and three CFTR variations, including F508del, IVS8-Tn, and M470V. The goal of our study was to evaluate the overall contribution of the three CFTR variations to the risk of CBAVD in different ethnic groups through systematic meta-analyses.

Materials and methods

Literature search and study selection

The search terms including CBAVD, SNP or variations and CFTR gene were used in the literature search on the PubMed. We investigated all publications on the association between CFTR variants and CBAVD disease from 1993 to 2013. Reference lists in the harvested literatures were explored for additional relevant studies suitable for inclusion in our meta-analysis. The selection criteria of studies for our meta-analysis were as follows: (1) CBAVD patients with typical CF were excluded; (2) complete data with allele or genotype in the case-control studies was available; (3) only CBAVD diagnosis for studies with physical examination, semen analysis and ultrasonography were considered. The retrieved information consisted of author, year of publication, ethnicity, and the number of participants with different alleles.

Statistical analysis

All the eligible case-control studies were involved in the meta-analysis done by Stata software (version 11.0, Stata Corporation, College Station, TX) [21]. Total odd ratios (OR) and 95% confidence intervals (CIs) were estimated to assess the association between CFTR variations and CBAVD risk. Cochran's Q statistic and I^2 test were used to test heterogeneity in our study. The Fixed-effect model was used for meta-analysis with moderate heterogeneity ($I^2 < 50\%$). Otherwise, a random-effect model was adopted for the meta-analysis with significant heterogeneity ($I^2 \geq 50\%$) [22,23]. Z-test with a two-sided P value < 0.05 was used to determine the significance of the total ORs. The publication bias in the meta-analysis was evaluated by the funnel plot and Egger's test. Summary analysis of the overall frequency of all the studies was executed to show the frequency for all four variations [24]. Subgroup analysis was performed by ethnicity to evaluate the effect of different ethnicity on total ORs.

Results

Our comprehensive literature search returned a total of 149 articles on the association between CFTR and CBAVD from PubMed and two studies from CNKI. A total of 104 studies was harvested after being filtered by their titles and abstracts. Among those articles, we removed four family studies and three reviews or meta-analysis. Consequently, 26 studies without obtainable allele or genotype data were removed. Among them, there were 29 studies on three CFTR variations. Our meta-analyses of three CFTR variations were performed among 1139 cases and 1563 controls (Figure 1, Table 1).

A strong association between the CFTR 5T variant and CBAVD was observed in the meta-analysis of 19 studies

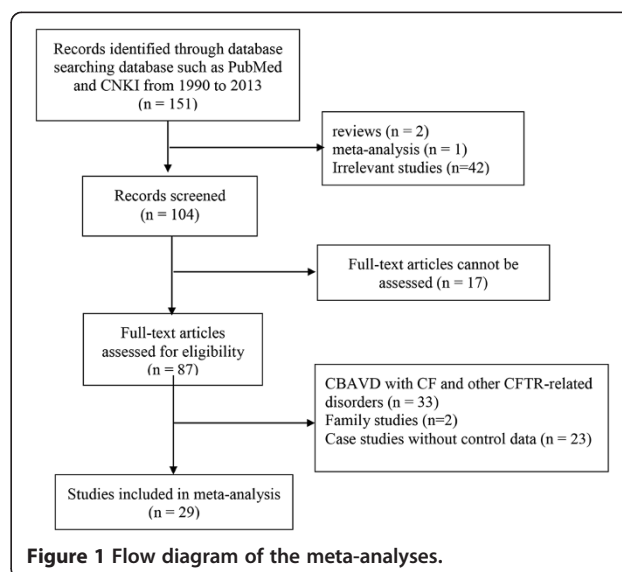


Figure 1 Flow diagram of the meta-analyses.

Table 1 The characteristics of the enrolled mutation for OR meta-analysis

| Mutation | Author | Ethnic | Year | Total (case/control) | Allele (case/control) | Total1 | Allele1 | Total2 | Allele2 |
|-----------------|-----------------|-----------|---------|----------------------|-----------------------|--------|---------|--------|---------|
| 5T | Costes | French | 1995 | 45/66 | 23/7 | 90 | 23 | 131 | 7 |
| | Chillon | Spanish | 1995 | 102/46 | 42/5 | 204 | 42 | 92 | 5 |
| | de Meeus | French | 1998 | 60/133 | 20/11 | 120 | 20 | 266 | 11 |
| | Casals | Spanish | 2000 | 104/200 | 41/20 | 208 | 41 | 400 | 20 |
| | Ravnik-Glavac | Slovenia | 2001 | 7/95 | 3/8 | 14 | 3 | 190 | 8 |
| | Anzai | Japanese | 2003 | 19/53 | 11/0 | 38 | 11 | 106 | 0 |
| | Grangeia | Caucasian | 2004 | 31/114 | 17/8 | 62 | 17 | 228 | 8 |
| | Wu, C. C. | Chinese | 2004 | 27/46 | 34/5 | 54 | 34 | 92 | 5 |
| | Wu, C. C. | Chinese | 2005 | 36/23 | 21/1 | 72 | 21 | 46 | 1 |
| | Radpour, R. | Iranian | 2006 | 106/43 | 55/0 | 212 | 55 | 86 | 0 |
| | Wilschanski | Canadian | 2006 | 60/31 | 22/2 | 120 | 22 | 62 | 2 |
| | Radpour, R. | Iranian | 2007 | 112/84 | 61/0 | 224 | 61 | 168 | 0 |
| | Costa | NA | 2008 | 68/62 | 33/6 | 136 | 33 | 124 | 6 |
| | Chiang | Chinese | 2009 | 63/86 | 42/6 | 126 | 42 | 172 | 6 |
| | Sharma | Indian | 2009 | 39/50 | 21/5 | 78 | 21 | 100 | 5 |
| | Sachdeva | Indian | 2011 | 35/50 | 19/1 | 70 | 19 | 100 | 1 |
| | Hussein | Egyptian | 2011 | 30/30 | 16/3 | 60 | 16 | 60 | 3 |
| Saldana-Alvarez | Mexican | 2012 | 16/103 | 1/3 | 32 | 1 | 206 | 3 | |
| LU | Chinese | 2013 | 109/104 | 97/28 | 218 | 97 | 208 | 28 | |
| ΔF508 | Ravnik-Glavac | Slovenia | 2001 | 7/95 | 2/3 | 14 | 2 | 190 | 3 |
| | Kusic, J. | NA | 2002 | 10/11 | 5/1 | 20 | 5 | 22 | 1 |
| | Wilschanski, M. | Canadian | 2006 | 60/31 | 30/1 | 120 | 30 | 62 | 1 |
| | Radpour, R. | Iranian | 2007 | 112/84 | 28/0 | 224 | 28 | 168 | 0 |
| | Hussein, T. M. | Egyptian | 2011 | 30/30 | 12/0 | 60 | 12 | 60 | 0 |
| M470V | de Meeus, A. | French | 1998 | 60/133 | 52/158 | 120 | 52 | 266 | 158 |
| | Wu, C. C. | Chinese | 2005 | 36/53 | 35/61 | 72 | 35 | 106 | 61 |
| | Stuppia, L. | Italian | 2005 | 13/54 | 4/38 | 26 | 4 | 108 | 38 |
| | Radpour, R. | Iranian | 2006 | 106/43 | 69/21 | 212 | 69 | 86 | 21 |
| | Du, Qing | Chinese | 2013 | 95/135 | 99/158 | 190 | 99 | 270 | 158 |

among 1069 cases and 1419 controls (OR = 8.35, 95% CI = 6.03-10.81, Figure 2). Our results also found that ΔF508 was a risk factor of CBAVD (OR = 22.2, 95% CI = 7.49-65.79, Figure 2). Our meta-analysis showed the M470V variation was associated with CBAVD (OR = 0.74, 95% CI = 0.60-0.91, Figure 2). Future study is required to explore whether there are other causal variants in high linkage disequilibrium with M470V.

As shown in Figure 2, moderate heterogeneity was observed for *CFTR* 5T ($I^2 = 44.0\%$), M470V ($I^2 = 61.0\%$) and ΔF508 ($I^2 = 0.00\%$). Furthermore, subgroup meta-analyses of the 5T variations by ethnicity showed that the heterogeneity mainly came from Asians ($I^2 = 71.5\%$) instead of Caucasians ($I^2 = 30.0\%$). Our results indicated that 5T was a risk factor of CBAVD in Caucasians (OR = 8.07, 95% CI = 6.03-10.81, P = 0.00, Figure 2), as well as in Asians (OR = 9.31, 95% CI = 6.42-13.49, P = 0.00, Figure 2).

As shown in the funnel plot, no obvious publication bias was observed for the meta-analyses (Figure 3). The results of meta-analyses were robust after the removal of individual studies (Figure 4).

Discussion

In the present study, we carried out a systematic overview of the studies for a genetic link with CBAVD. Significant evidence was observed (that showed) the strong association with CBAVD onset with the risk of CBAVD for all the three variations, including 5T (OR = 8.35, 95% CI = 6.03-10.81, Figure 2), M470V (OR = 0.74, 95% CI = 0.60-0.91, Figure 2) and ΔF508 (OR = 22.2, 95% CI = 7.49-65.79, Figure 2).

Among the tested variations, M470V was the only one with the protective role of CBAVD. V470 carriers tended to have a higher fertility than other carriers, suggesting that there might be competing and evolutionary forces

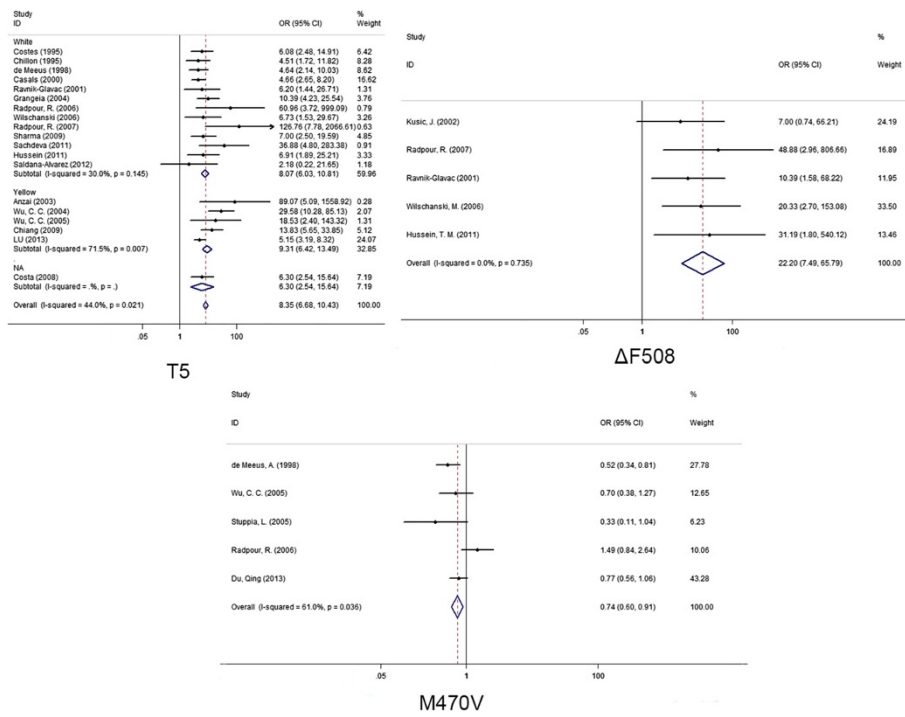


Figure 2 Forest plots for the relationship between 3 variations and CBAVD in the meta-analyses and subgroup meta-analyses.

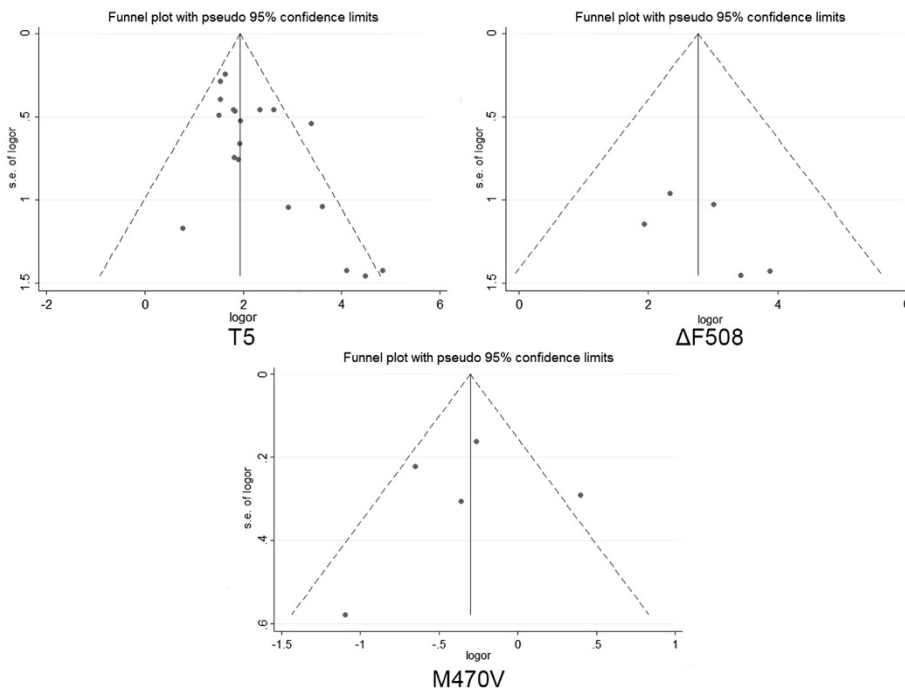


Figure 3 Funnel plots for the relationship between 3 variations and CBAVD in the meta-analyses.

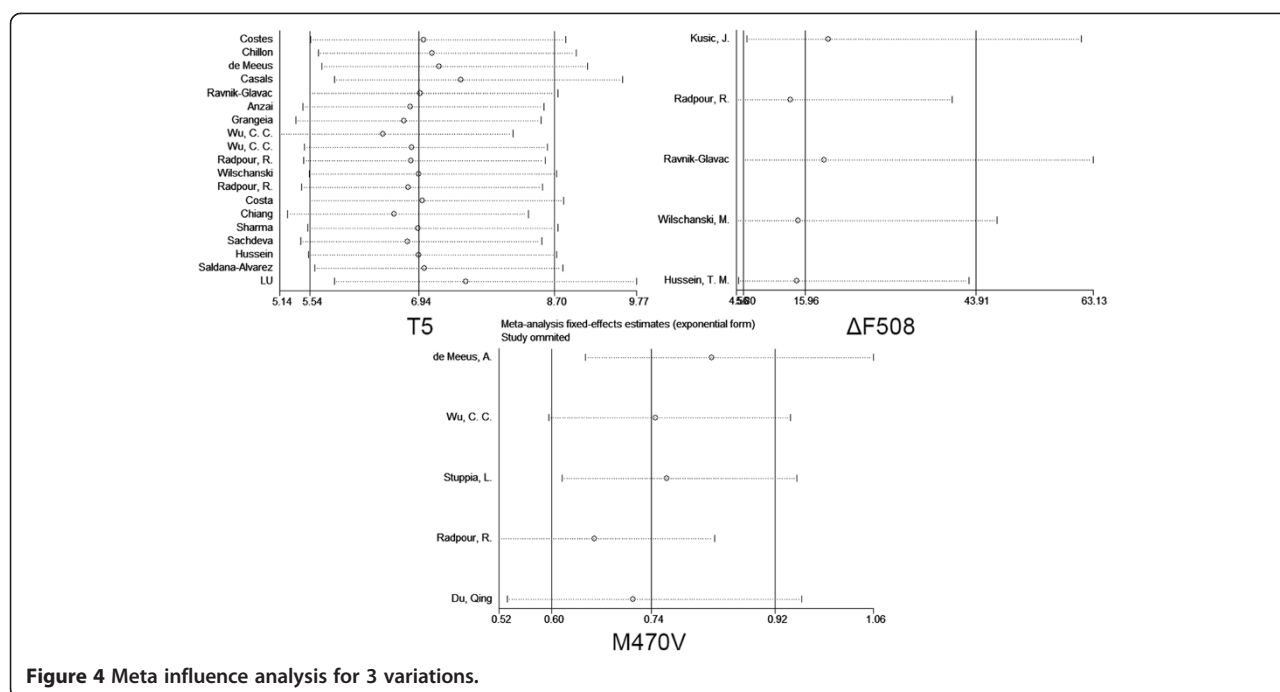


Figure 4 Meta influence analysis for 3 variations.

acting on the *CFTR* gene [25]. Furthermore, the interaction of the variations might affect the risk of CBAVD [26,27]. In addition, the haplotypes of these variations can significantly contribute to the susceptibility of CBAVD alone or together with the *SPINK1* locus [11]. Further detailed studies are required to provide evidence that independent CBAVD rather than CBAVD with CF is associated with *CFTR* variations.

Several limitations in our meta-analyses were taken into consideration as followed. Firstly, some studies did not reveal whether CBAVD patients were isolated CBAVD patients or patients with CF symptoms for the incomplete information. This might potentially interfere with the results of our meta-analyses. Secondly, the power of our meta-analyses is still low due to low allele frequency of these variations. Under a moderate risk of OR (OR = 1.2), power analysis showed a lack of power in the meta-analyses, including 5T (47.3%), ΔF508 (7.1%) of LPL, and M470V (52.1%). Thirdly, there was a lack of haplotype information among these loci in most of involved studies. Reports have shown there were interactions among these variations [28-30]. We discontinued the further analysis for examining variables, including interaction between the two or three loci.

In conclusion, the present study demonstrated an association between *CFTR* variants and CBAVD risk. Our meta-analysis among 1069 cases and 1418 controls showed that 5T was a risk factor of CBAVD in the combined populations, including French, Spanish, Japanese, Chinese, Iranian, Indian, Mexican and Egyptian. Meta-analysis among 60 cases and 133 controls confirmed that *CFTR* ΔF508 was another important risk factor in

Caucasian populations including Slovenian, Canadian, Iranian and Egyptian. In addition, M470V was shown to be a protective factor by our meta-analysis among 10 cases and 11 controls from French, Chinese, Italian and Iranian populations.

Abbreviations

SNP: Single nucleotide polymorphism; CBAVD: Congenital bilateral absence of the vas deferens; CF: Cystic fibrosis; OR: Odds ratio; 95% CI: 95% confidence interval; I²: Inconsistency index.

Competing interests

All authors declare no competing financial interests.

Authors' contributions

XTX drafted the manuscript; JZ and QL were responsible for analysis; HZ and HX participated in literature search. SJ and SD carried out language editing. All authors read and approved the final manuscript.

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