

Review Article

5-HTTLPR L Allele Gene may be a Protecting Factor for Eating Disorder -- A Meta-Analysis

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Abstract

Objective: Eating disorders are conditions defined by abnormal eating habits that may involve either insufficient or excessive food intake to the detriment of an individual's physical and mental health, which might be associated with the gynecological endocrinological conditions (amenorrhea, infertility) in young women. Some studies have revealed that there were a relationship between 5-HTTLPR gene and eating disorders. However, no clear conclusion has been offered addressing this issue. Therefore, we investigated the relationship of the 5-HTTLPR polymorphisms and eating disorders by meta-analysis.

Methods: PubMed, Medline, Psych INFO of web knowledge, and CNKI (Chinese National Knowledge Infrastructure) were searched before April 2012. Eighteen studies involving 2567 subjects. Data were entered into the Cochrane Collaboration review manager software (RevMan version 5). Individual and pooled 95% confidence intervals (CIs) were calculated.

Results: The results showed that the 5-HTTLPR L polymorphism was associated with significantly less risk of eating disorders (EDs) (including EDs, anorexia nervosa (AN) and Bulimia nervosa (BN)) [LL vs. SS (homozygote model), EDs: odds ratio (OR) = 0.53, confidence interval (CI): 0.36-0.78; LL vs. SS, BN: OR=0.25, CI=0.11-0.57; LS vs. SS (heterozygote), AN, Asians: OR= 0.62, 95% confidence interval (CI): 0.46-0.85; LS vs. SS (heterozygote), BN: OR= 0.56, 95% CI: 0.39-0.79].

Conclusions: These results suggested that the 5-HTTLPR gene polymorphisms might be related with EDs under some conditions.

Keywords

- 5-HTTLPR
- Polymorphism
- Eating disorder
- Anorexia nervosa
- Bulimia nervosa
- Bing eating disorder

INTRODUCTION

Eating disorders (ED) form a series of Behavioral disorders diagnosed in young women (the age of onset is 16-17 years (rarely >30 years)) who share some syndromes associated with psychological disturbance and physical factors: distortion idea of body image and weight, and pathological eating behaviors. The Mortality of EDs is 10-15% (2/3 physical complications and 1/3 suicide) [1]. ED includes anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorders and so on. Importantly, the women with ED may suffer from the gynecological endocrinological conditions (amenorrhea, infertility), such as: women who suffered from binge eating have more risk of suffering from amenorrhea and oligomenorrhea than females who reported no binge eating [2]; AN patients has profound low leptin levels which increase pulsatile LH, leading to ovaries enlarging, levels of estradiol increasing which suggest that treating amenorrhea might be key strategy for AN patients [3]; Leptin level was significantly low in AN patients even compared with underweight controls which support that leptin predict AN independently from low BMI [4].

Moreover, EDs are often regarded analogous to cancer among all psychological disorders because people who suffer from it know exactly that their behavior might lead great harm to their body but they could do nothing to stop them, they felt depressed, feared, struggle and hopeless.

Generally, EDs were traditionally thought as influenced by the social expectation and literature excessive emphasizes the beauty of thinness among culture of upper/ middle class in western countries. However, recent evidence from family and twin studies suggests that genetic variances account for 50-70% factors for AN and 28-83% for BN [5].

5-HTTLPR gene which was widely reported associated with human's behaviors, psychological conditions, psychological disorders [6-8], which located on the SERT gene promoter as a functional polymorphism because of a 44-bp insertion (5-HTTLPR-L) or deletion (5-HTTLPR-S). The transcriptional activity of S is less than L which might be the reasons of 5HTTLPR playing an important role in humans' psychological features [9].

Past studies showed that 5-HTTLPR might be the most associated gene with the heredity of EDs, but they does not talk about the results systematic by five different gene models, different races and subtypes of EDs . The present study tries to further clear the relationship between 5-HTTLPR polymorphism and EDs systematically.

MATERIALS AND METHODS

An electronic search of the literature was performed to identify association studies investigating the influence the 5-HTTLPR polymorphisms on EDs. Pubmed, Medline, PsychINFO of web knowledge, and CNKI (Chinese National Knowledge Infrastructure) were searched until April 2012. The search terms were "5-HTTLPR", "gene", "Eating disorder", "Anorexia Nervosa", and "Bulimia nervosa". Reference lists from identified articles and reviews were used as well to find additional studied to be included.

Inclusion criteria of studies in the meta-analysis

Studies fulfilled the following criteria were included: a) they were published studies; b) they were case-control studies and the genetic frequencies of the 5-HTTLPR could be got; c) they were written in English or Chinese; d) the participants for studies are unrelated and does not have other special including criteria expect for the diagnosis of EDs. Studies were excluded if: a) no 5-HTTLPR genotypic frequencies were given for patients; b) the participants has other special including criteria; c) the participants are related (for example family members).

Data extraction

The following information was extracted from each study: name of first author, diagnosis for including participants and control group, publication year, country, diagnosis and assessment criteria, number of sample and control group.

In this meta-analysis, one included paper had participants of EDNOS (Bingeing type) and EDNOS (Purging type), while another included paper involved participants of sub-clinical bulimia nervosa. For convenience, we call BN, EDNOS (Bingeing type), EDNOS (Purging type) and sub-clinical BN as BN related in this paper.

Statistical analysis

Five models were used in this study: L allele vs. S allele, LL genotype vs. SS genotype, LS genotype vs. SS genotype, LL genotype vs. SS+SL genotype and LL+LS genotype vs. SS genotype. The present study also talks EDS as a whole, AN and BN related. The studies also divide participants into two groups: western population (Caucasian, European, Poland, Italian, German, Australian) and Asians (Japanese and Chinese) to study about because the researchers noticed that the frequencies of L allele and S allele in those two kinds of population are significantly different. Not all figures are included in this paper because of the limitation of length of paper. A random-effects model was used for analyses where there was significant heterogeneity between studies. Hardy-Weinberg equilibrium was examined in all studies included in the meta-analysis.

Data were entered into the Cochrane Collaboration review

manager software (RevMan version 5). Individual and pooled 95% confidence intervals (CIs) were calculated. For studies not including controls, we use the data of control group from other studies which has similar participants (ethnic) with them: The Steiger's study published in 2008 [10] get control group from his study published in 2009 [11]. Paper of Ribases published in 2008 [12] gets control group data from paper of Lauzurica [13]. Both the two studies were taken in Spain. The data control group in [14] data were applied in three studies Frieling, 2006 [15], Urwin, [16], Wonderlich, 2005 [17].

RESULTS

Study characteristics

the initial search yielded 23 papers and the abstracts were carefully reviewed in order to investigate if they fulfill the inclusion criteria. Of the 23 articles, four were excluded because they were reviews Martásková, 2009 [18], Calati, 2011 [19], Polsinelli, 2012 [20], Castellini, 2012 [21]. One paper [22] Hinney, 1997 was excluded because the participant were all obese populations. One was excluded because the participants were adolescent and young adult female twins and female non-twin siblings Munn-Chernoff, 2012 [23]. After all, 17 articles were included in this study. The information from these studies was summarized in (Table 1).

Meta-analysis

Data from the 17 samples were not all analyzed because some data are absence, for example, in Ribasés's study of 2008 [12], only the number of LL genotype participants and the total number of all participant could be got from the article? Therefore, that paper only analyzed the model of LL genotype vs. SS+LL genotype.

L Allele vs. S Allele Model

Eating bisorders: In fixed effect model, $I^2=81\%$, indicating high heterogeneity, random-effects model was selected. However, no significant association was found ($Z=1.33$, $p=0.19$).

Anorexia nervosa: We include 10 papers [14-16], [21], [24-29] (In following 4 models about AN we include the same 10 papers)

We use random-effects model: No significant association was ($Z = 1.55$, $P = 0.12$),

Heterogeneity was high: $\text{Tau}^2 = 0.14$; $\text{Chi}^2 = 38.66$, $df = 9$ ($P < 0.001$); $I^2 = 77\%$

BN Related: We include 8 papers [10,13,15,17,25,28,30,31], (In following 4 models about BN, we include the same papers).

No significant association was found ($Z=1.35$, $p=0.18$). There was high between -study heterogeneity ($\text{Tau}^2 = 0.23$; $\text{Chi}^2 = 45.70$, $df = 7$ ($P<0.001$); $I^2 = 85\%$)

LL VS. LS+SS Model

Eating disorders: We use random effect model. No significant association was found ($Z=0.70$, $p=0.48$). There was high between -study heterogeneity ($\text{Tau}^2 = 0.38$; $\text{Chi}^2 = 72.28$, $df = 7$ ($P<0.001$); $I^2 = 78\%$)

Table 1: Basic information of included studies.

Author	Classification	Country	Diagnostic and assessment criteria	Sample size	
				Case	Control
Steiger 2009	EDs ¹	Canada	EDE ²	185	93
Steiger 2008	BN ³ , EDNOS ⁴	Canada	DSM-IV-TR ⁵ , EDE, EDE-Q ⁶ , CES-D ⁷ , BASIS-32 ⁸ , BIS-11 ⁹	111	
Ribases 2006	EDs	Spain	DSM-IV, SCID-I ¹⁰ , SCL90-R ¹¹	82	
	AN ¹²			46	
	BN			36	
Rybakowski 2006	AN	Poland	DSM-IV, TCI	132	93
Frieling 2006	AN and BN	Germany	DSM-IV, SCID-I, SCID-II; EDI-2 ¹³	40	
Urwin. 2005	AN	Australia	DSM-IV	109	
Wondelich 2005	BN	US	DSM-IV, SCID-IP ¹⁴ , DAPP-BQ ¹⁵ , IBS ¹⁶ , EDEQ-4 ¹⁷ ; MAST/AD ¹⁸ ; IDS-SR ¹⁹ ; STAI ²⁰ ; MOCI ²¹	178	
Monteleone 2006	BN	Italy	DSM-IV, SCID-I, SCID-II ²² , MINI ²³ , TCI-R ²⁴	125	94
Monteleone 2006.	BED ²⁵	Italy	DSM-IV, SCID-IP, SCID-I, SCID-II	77	61
Matsushita 2004	ED	Japan	DSM-IV	195	
	AN			77	
	BN			118	
Lauzurica 2003	BN	Spain	DSM-IV	102	
Fumeron 2001	AN	France	DSM-IV	67	
Sundaramurthy 2000	AN	UK	DSM-IV	138	90
Di Bella 2000	AN and BN	Italy	DSM-IV	106	
Castellini 2012	ED	Italy	DSM-IV	201	
	AN			113	
	BN			88	
Yue et 2012	AN	China			
F-50		Eating disorders			
F-50.0	307.1	Anorexia nervosa			
F-50.1	307.1	Atypical anorexia nervosa			
F-50.2	307.51	Bulimia nervosa			
F-50.3	307.51	Atypical bulimia nervosa			
F-50.4	307.5	Over eating associated with other psychological disturbances			
F-50.5	307.5	Vomiting associated with other psychological disturbances			
HAMD ²⁶ , HAMA ²⁷ , EDE-Q, Y-COBS ²⁸ , EDI-II	198				
Chen 2006	AN	China	HAMD, HAMA, EDE-Q, Y-COBS, SCID-II	54	36

(Endnotes)

- i. EDs: Eating Disorders
- ii. EDE: Eating disorder Examination (EDE: Fairburn and Cooper, 1993)
- iii. BN: Bulimia Nervosa
- iv. EDNOS: Eating Disorder Not otherwise specified
- v. DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision)
- vi. EDE-Q: Eating Disorder Examination Questionnaire
- vii. CES-D: The Center for Epidemiologic Studies Depression Scale
- viii. BASIS-32: The Behavior and symptoms Identification Scale
- ix. BIS-11: The Barratt Impulsivity Scale-version 11
- x. SCID-I: Structured Clinical Interview for DSM-IV Axis-I disorders
- xi. SCL-90R: Symptom Checklist90 Revised
- xii. AN: Anorexia Nervosa
- xiii. EDI-2: Eating Disorder Inventory -2
- xiv. SCID-IP: Structured Clinical Interview for DSM-IV Patient Edition (First et al, 1997)
- xv. DAPQ: Dimensional Assessment of Personality Pathology Basic Questionnaire (DAPP- BQ)
- xvi. IBS: Impulsive Behavior Scale
- xvii. EDE-Q4: Eating Disorder Examination Questionnaire 4
- xviii. MAST/ AD: Michigam Assessment Screening Test/ Alcohol- Drug
- xix. IDS-SR: Inventory for Depressive Symptomatology - Self Report
- xx. STAI/SSAI: Spielberger Stait- Trait Anxiety Inventory
- xxi. MOCI: Maudsley Obsessive- Compulsive Inventory Table 2:
- xxii. SCID-II: Structured Clinical Interview for DSM-IV Axis-II disorders
- xxiii. MINI: Mini International Neuropsychiatric Interview
- xxiv. TCI-R: Temperament and Character Inventory Revised
- xxv. BED: Binge Eating Disorder
- xxvi. HAMD: Hamilton Depression Scale
- xxvii. HAMA: Hamilton Anxiety Scale

Anorexia nervosa: We use random-effect model. No significant association was found ($Z=1.04$, $p=0.30$). There was high between -study heterogeneity ($\text{Tau}^2=0.24$; $\text{Chi}^2=24.71$, $\text{df}=9$ ($P=0.001$); $I^2=67\%$)

BN Related: We use random-effect model. No significant association was found ($Z=0.60$, $p=0.55$). There was high between -study heterogeneity ($\text{Tau}^2=0.63$; $\text{Chi}^2=39.90$, $\text{df}=6$ ($P<0.001$); $I^2=85\%$)

LL+LS vs. SS Model

Eating disorders: We use random-model. No significant association was found ($Z=1.79$, $p=0.07$). There was high between -study heterogeneity ($\text{Tau}^2=0.46$; $\text{Chi}^2=84.42$, $\text{df}=15$ ($P<0.00001$); $I^2=82\%$). P is extremely close to the 0.05, it suggest that LL+LL might be the protector factor for EDs. When delete some article from the list (one or some of the [16,24,30,31]), the P does down below 0.05, suggest there was significant association between L carriers and people who has less possibility to suffer from EDs. So including L in the genotype might be the protector factor in EDs.

Anorexia nervosa: We use random-effect model. There was nearly significant association was found ($Z=1.86$, $p=0.06$). There was middle between -study heterogeneity ($\text{Tau}^2=0.01$; $\text{Chi}^2=28.53$, $\text{df}=9$ ($P=0.0008$); $I^2=68\%$).

When delete one or all of the articles ([16,24]) from the list, the P goes down below 0.05.

BN related: We use random-effect model. No significant association was found ($Z=0.79$, $p=0.43$). There was high between -study heterogeneity ($\text{Tau}^2=0.59$; $\text{Chi}^2=30.24$, $\text{df}=5$ ($P<0.00001$); $I^2=83\%$)

LL vs. SS Model

Eating disorders: We use random-effect model. No

significant association was found ($Z=1.10$, $p=0.27$). There was high between -study heterogeneity ($\text{Tau}^2=0.66$; $\text{Chi}^2=74.38$, $\text{df}=15$ ($P<0.00001$); $I^2=80\%$)

Delete four articles: Delete ([16,24,30,31]) from the list the p becomes 0.001. It suggested that people whose genetic type is LL has significantly less possibility to suffer from EDs. (Figure 1).

Anorexia nervosa: We use random-effect model. No significant association was found ($Z=1.50$, $p=0.13$). There was high between -study heterogeneity ($\text{Tau}^2=0.44$; $\text{Chi}^2=28.63$, $\text{df}=9$ ($P=0.0007$); $I^2=69\%$)

Delete two articles: When delete ([16,24]) from the list, the P becomes 0.0003 which suggest that persons whose 5-HTTLPT genetic type is LL has significantly less possibility to suffer from the AN.

BN related: We use random-effect model. No significant association was found ($Z=1.05$, $p=0.29$). There was high between -study heterogeneity ($\text{Tau}^2=1.76$; $\text{Chi}^2=49.83$, $\text{df}=5$ ($P<0.00001$); $I^2=90\%$)

Delete two articles: When delete ([30,31]) from the list, the P became 0.001 and suggested that people of LL gene have significantly possibility to suffer from BN.

LS vs. SS Model

Eating disorders: We use random-effect model. No significant association was found ($Z=0.21$, $p=0.84$). There was high between -study heterogeneity ($\text{Tau}^2=0.52$; $\text{Chi}^2=18.54$, $\text{df}=15$ ($P=0.24$); $I^2=19\%$)

AN : We use random-effect model. No significant association was found ($Z=1.13$, $p=0.26$). There was high between -study heterogeneity ($\text{Tau}^2=0.19$; $\text{Chi}^2=23.27$, $\text{df}=9$ ($P=0.006$); $I^2=61\%$)

Asian ethnics: For only the three Asian articles: [24,25,27].

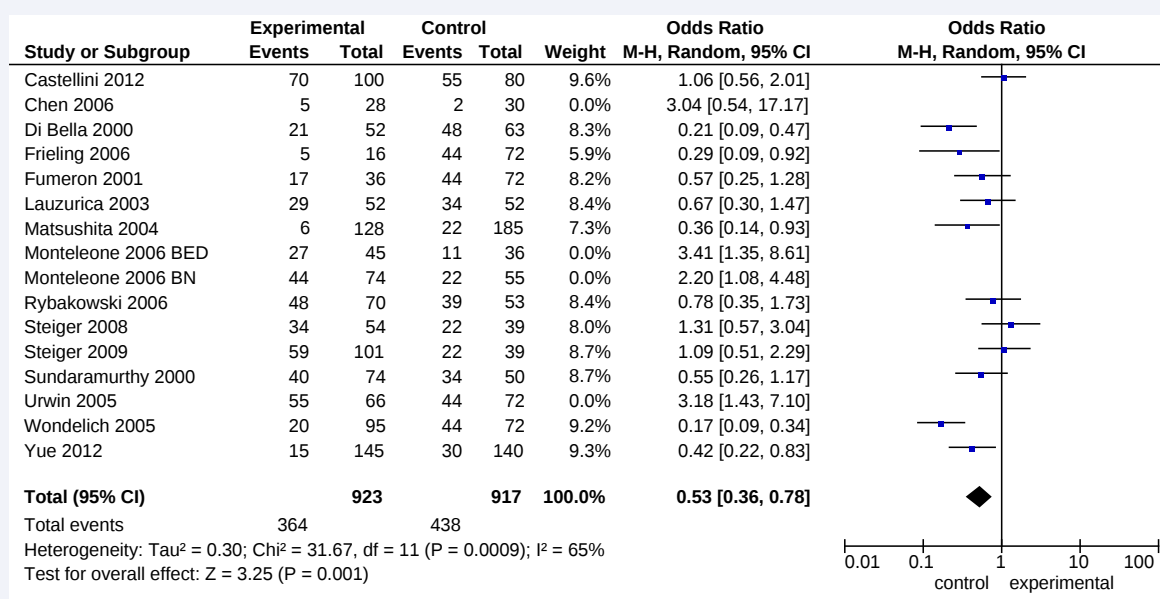


Figure 1 Association between 5-HTTLPR polymorphisms and eating disorders risks (LL vs. SS: homozygote model).

We use fixed-effect model. No significant association was found ($Z=3.00$, $p=0.003$). There was low between-study heterogeneity ($\chi^2 = 3.31$, $df=2$ ($P=0.19$); $I^2=40\%$). It suggested that in Asian populations: people have LS genetic type has significantly less possibility to suffer from. (Figure 2)

BN related: We use random-effect model. No significant association was found ($Z=0.77$, $p=0.44$). There was high between-study heterogeneity ($\tau^2=0.23$; $\chi^2=13.60$, $df=5$ ($P=0.02$); $I^2=63$

Delete two articles: Delete ([30,31]) from the list, the P became 0.001 and suggested that people of LL gene have significantly possibility to suffer from BN. (Figure 3)

DISCUSSION

The aims of this meta-analysis were (1) to determine the association between 5-HTTLPR and eating disorders as a whole, AN and BN related (including BN and BED).

CONCLUSION

Eating disorders are coding as F50 in ICD-10 and are coding

from 307.1 to 307.50 as shown in (Table 2) [1]. The human 5-HTTLPR is located on chromosome 17q11.1 to 17q12. The 5-HTTLPR polymorphism consisted of two forms S variant (short) or L variant (long). S form is associated with a lower transcriptional activity compared with L's. [32]. So the aim of this meta-analysis was to further clarify the association between the 5-HTTLPR and eating disorders using all dominant model, recessive model and additive models. We also compare the gene frequencies of L and S in different eating disorders. These results are different in different genetic comparing models. In some situations where some articles were detected, the L gene was proved to be the protecting factor for different eating disorders.

Compared with the [19] Meta-analysis, which was published in 2010, this review adds three new articles: [21,27] and [24]. Among these three articles, [27] and [24] were taken in Chinese population, which were different from all previous meta-analysis. The paper of Yue (2012) [27] proved that the L was the protecting factor for BN. Chen (2012) [24] reported that AN might also was related with morbid personality, and personality disorder might increase the severity of patients' EDs, which allow we make further studies in the future.

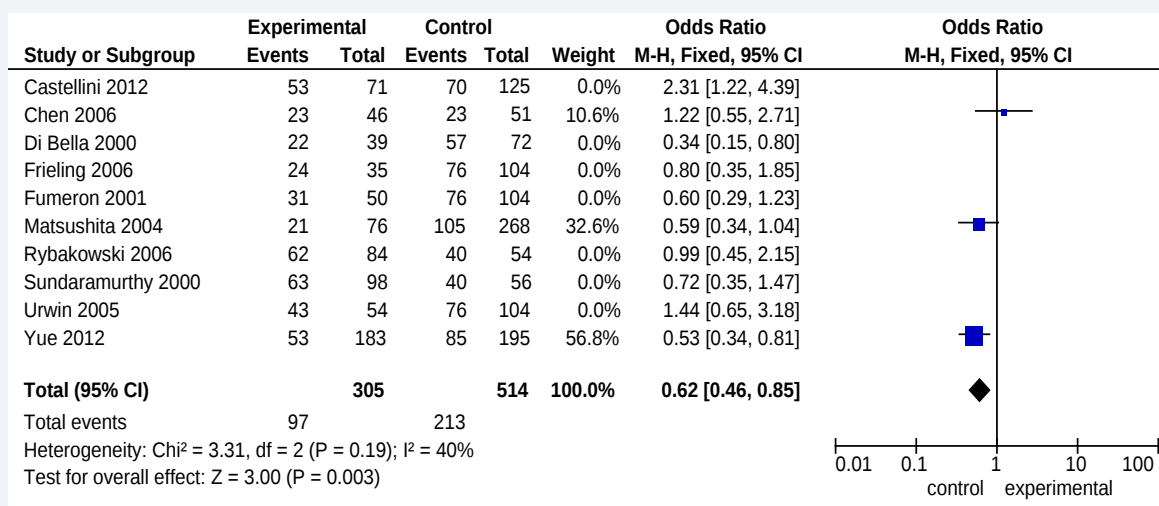


Figure 2 Association between 5-HTTLPR polymorphisms and eating disorders risks: (LS vs. SS: heterozygote) for Anorexia Nervosa in Asians.

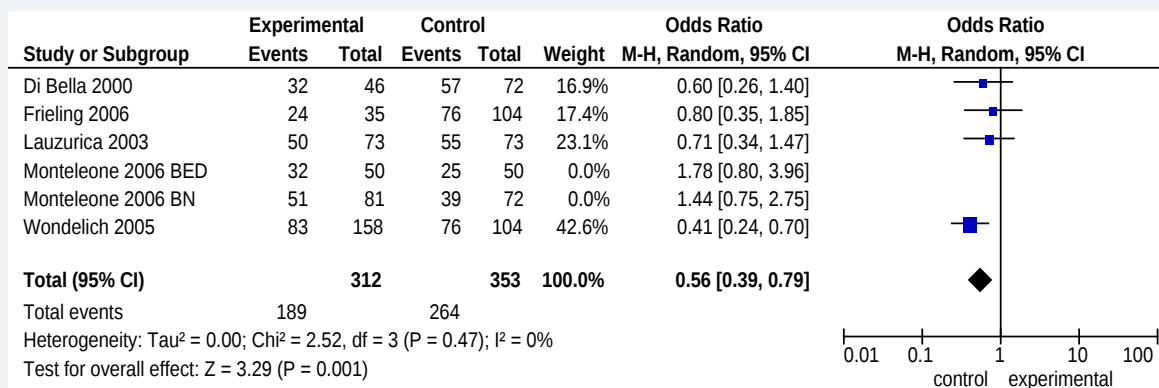


Figure 3 Association between 5-HTTLPR polymorphisms and eating disorders risks: (LS vs. SS: heterozygote) for BN related: delete two articles (Monteleone 2006 BED, Monteleone 2006 BN).

Table 2: Eating disorders classifications in ICD-10.

ICD-10	DSM-IV	Disorder
F-50		Eating disorders
F-50.0	307.1	Anorexia nervosa
F-50.1	307.1	Atypical anorexia nervosa
F-50.2	307.51	Bulimia nervosa
F-50.3	307.51	Atypical bulimia nervosa
F-50.4	307.5	Over eating associated with other psychological disturbances
F-50.5	307.5	Vomiting associated with other psychological disturbances

In LL+LS Vs SS model, When delete some article from the list (one or some of [16,24,30,31]), then the P value goes down below 0.05, suggest the P was the protecting factor for the EDs. Why we deleted those four articles? The [30-31] were taken in Italian, which might suggest 5HTTLPR gene plays a different role in Italian populations compared with other ethnics. In addition, In the paper of [31], the distribution of the 5HTTLPR genotypes was found to be linked with body mass index, body fat mass values and harm avoidance score. So the body mass index, body fat mass and avoidance score might contribute to the BN together with other factors which factors are not significant in the paper of Monetleone 2006 [31], for example eating habits, social culture, community environment and so on. We suggest further research to be done in Italian to find out the factors stop the significant relationship between 5HTTLPR genes distribution and BN. In addition, further research could be taken in other demographic population to find out whether body mass index, body fat mass values and harm avoidance score are important intermediate variable between 5HTTLPR genotypes distribution and BN. For the paper of Monetleone BED [30], binge eating disorder has features of recurrent episodes of binge eating without compensatory behaviors which make it different all other eating disorder (significant restrict behavior features), which might make this paper not suitable to be included to the analyze the ED as a whole. In addition, BED patients has higher mean weight, which make the BED populations different from other eating disorder populations in many places, such as, physical fitness, internal secretion, blood glucose, social function, self-confidence and so on. So, further study could be taken to find out what factors affect the BED together with 5HTTLPR genotype distributions. In Urwin 2005 [16] 114 anorexia nervosa patients have both parents, which seems to be normal in general, population but should be abnormal in eating disorder patients. Most eating disorder patients have family problems, which mean that some of ED patients do not have both biological parents and even none of them. So the patients in Urwin should have different family background with patients in other studies. So the family factor interfere the 5HTTLPR genotype distribution affect the occurrence of EDs as an immediate reason. Further, more study could be taken to find out the in the different family backgrounds, the relationship between 5HTTLPR genotype distribution and EDs.

In conclusion, most studies have suggested that L allele is the protecting factor for eating disorders. The conclusion of the meta-analytic results was: The results showed that the 5-HTTLPR L polymorphism was associated with significantly less risk of

eating disorders (EDs) (including EDs, anorexia nervosa (AN) and Bulimia nervosa (BN)) [LL vs. SS (homozygote model), EDs: odds ratio (OR) =0.53, confidence interval (CI): 0.36-0.78; LL vs. SS, BN: OR=0.25, CI=0.11-0.57; LS vs. SS (heterozygote), AN, Asians: OR= 0.62, 95% confidence interval (CI): 0.46-0.85; LS vs. SS (heterozygote), BN: OR= 0.56, 95% CI: 0.39-0.79].

Some reasons why we get significant statistic results when we delete these four articles (2 about BN: [30-31]) and 2 about AN ([16,24]) have been stated in the beginning of the discuss section (such as the ethnics difference, BED's differences with other eating disorders and different family background in Urwin 2005 [16] paper.

In addition Urwin 2005's [16] participants are all Australian, which is hard for us to get suitable control group data from other papers.

Chen 2006 [24] use medical students as the control group, which could not present the general population, which might affect the comparing result.

ADVANTAGES

The advantages of this meta-analysis include that (1) It include the most papers until April 4, 14 among all meta-analysis about eating disorders and 5-HTTLPR (2)It is the first article discuss 3(EDs, AN related, BN related)*5(L vs. S, LL vs. SS, LS vs. SS, LL vs. SS+SL and LL+LS)*3(All ethnics, western ethnics and Asians ethnics)=40 tree diagrams, especially we found for Asians, people who have LL genetic type has less possibility to suffer from BN.

FUTURE

Besides the further studies we might consider to take in the above of the paper, because of the limitation of time and ability, there were something left to be clarified in the further: (1) What make BED and BN (purging type) different from other AN in 5-HTTLPR gene distribution (2) We want to talk about the relationship with different features of ED with 5-HTTLPR (3) We also want to talk about why the genetic type in Asians and Caucasians have different BN risk factors? (4) It will be better if we could include more participants (different country, ethnic, and other background) and more random control group. (5) The relationship among 5-HTTLPR, AN and other background data need to be further analyzed to clarify the pathologies of AN.

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