Genetic determinants of eating disorders

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Chapter 7

General discussion

Eating disorders have a debilitating effect on the lives of people who suffer from these disorders, and the people surrounding them. The mortality rate is considerable and the prognosis is poor. Relapse rates are high, and after four to ten years of follow-up a substantial part of the patients has not recovered (Crow et al., 2009; Harris & Barraclough, 1998; Nielsen et al., 1998; Papadopoulos et al., 2009; Steinhausen, 2002; Steinhausen & Weber, 2009; Sullivan, 1995). Eating disorders have a large heritable component, and identification of susceptibility genes underlying these disorders will clarify which pathophysiologic mechanisms and pathways contribute to their aetiology. In the future, knowledge regarding the genetic aetiologies may open pathways for novel drug targets, enhance treatment and improve prevention. Also, an increase in knowledge regarding the extent to which disorders are influenced by genetic vulnerability may help to decrease the stigma associated with such disorders (Klump et al., 2009).

However, it is clear that the genetics of eating disorders is still in an early phase. Despite the fact that since the publication of our review (chapter 2) several twin (Bulik et al., 2006; Bulik et al., 2010) and a multitude of molecular genetic studies have been performed (see Appendix B and C), the conclusions regarding those studies remain the same. Studies have mainly been characterized by small sample sizes, inadequate statistical power and the use of diagnostic categories for phenotype assessment.

In the series of genetic studies described in this thesis, I tried to improve issues such as study design, use of phenotypes, phenotype measurements, choice of candidate genes, and genotype measurements. The main findings from our studies will be discussed in this chapter.

Study design

Figure 7.1 summarizes the design of the novel study described in this thesis. There were three groups of participants who took part in different phases of the study:

1. participants from the Genetics of Eating Disorder (GenED) study, this study was initiated as part of this thesis to collect DSM-IV eating disorder diagnoses, DNA and extensive phenotype information from a large group of participants with an eating disorder throughout the Netherlands;
2. population-based sample of twins and family members from the Netherlands Twin Registry (NTR); and
3. control participants without an eating disorder.

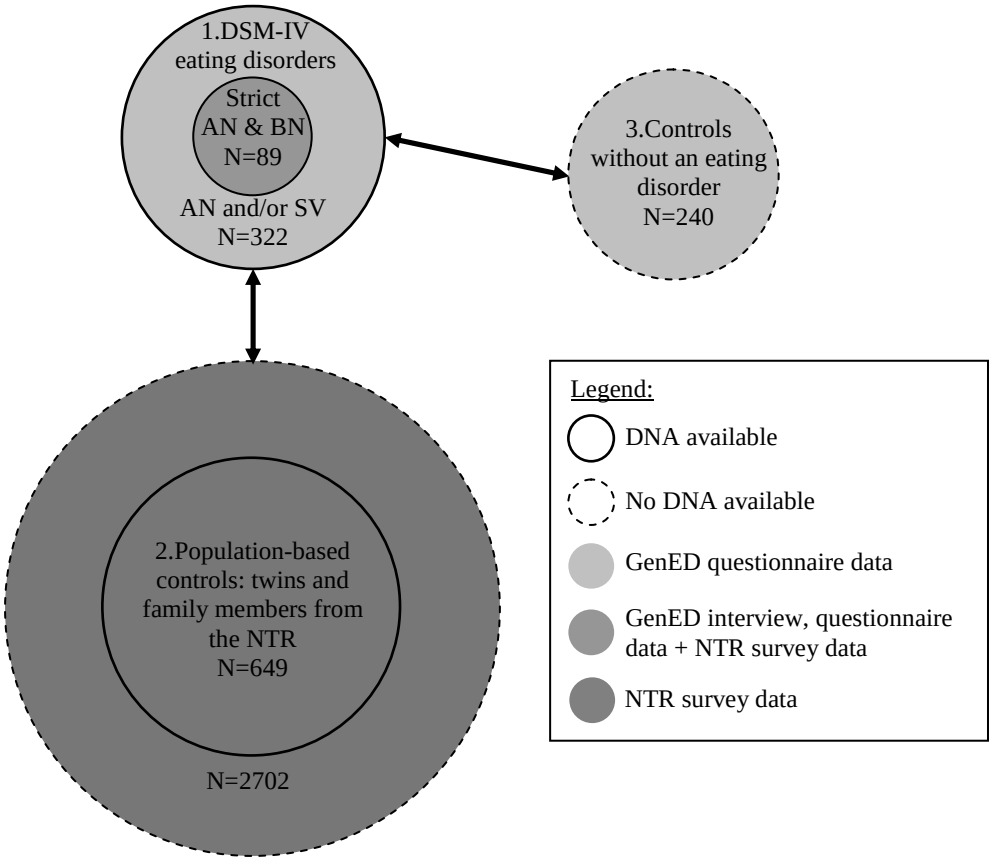

Figure 7.1 Study design used in this thesis

This design can be used for heritability studies (in group 2) and genetic association studies (in groups 1 and 2). Elaborate phenotype data were collected for the different groups by administering questionnaires and interviews. Therefore, it was not only possible to examine the genetics of DSM-IV eating disorder diagnoses, but also of related traits and possible endophenotypes like perfectionism and impulsivity (Bulik et al., 2007a).

Heritability of disordered eating behaviour

In the adolescent twins from the NTR, the Disordered Eating Behavior (DEB) scale was devised and used instead of categorical DSM-IV (1994) eating disorder diagnoses. To enhance the statistical power, an extended twin design including an additional sibling per family was applied. In addition, the psychometric quality of the DEB-scale was evaluated

by testing for measurement invariance with respect to sex (chapter 3), before performing the bivariate genetic analysis. In both adolescent men and women the different disordered eating behaviors and attitudes measured by the DEB-scale were explained by one underlying factor. This is in line with the overlap and the hypothesized shared liability between the different eating disorders. The requirements of complete measurement invariance with respect to sex could not be met for the DEB-scale. Thus scores on the DEB-scale cannot be taken to represent exactly the same underlying trait in men and women. As a consequence the genetic analysis described in chapter 4 were performed separately in men and women. We were the first to evaluate complete measurement invariance in the eating disorder field. Thus, despite the fact that sum scores on eating disorder scales are used widely to compare for example men and women, eating disorder cases and controls, or different age and ethnic groups, measurement invariance was never established for any of these grouping variables. In other words, reported similarities and differences between these groups could be a consequence of measurement bias instead of a genuine resemblance or difference in the underlying trait.

Genetic bivariate analyses as presented in chapter 4 showed that genetic factors explained a considerable part of the variance in disordered eating behavior (DEB). Heritability estimates for DEB were 0.65 in women and 0.39 in men. BMI was highly heritable in women (heritability =0.80) and men (heritability =0.76). In addition, additive genetic factors were responsible for the total overlap between the two characteristics, yielding a genetic correlation of 0.43 in women and 0.51 in men. Despite the overlap between BMI and DEB, a large part of the genetic influences on DEB was due to genetic effects that are independent of BMI in women as well as men. The heritability estimates for DEB are in line with the heritability estimates previously reported for eating disorders and eating disorder symptoms (ranging from 7 to 83%, see chapter 1).

The four DEB items are related to body weight, and in general body weight appears to be a risk factor for the development of eating disorders, especially bulimia nervosa (Jacobi et al., 2004). Therefore it is noteworthy that the genetic influence on DEB was largely independent of BMI, indicating that there are genes involved in DEB that do not seem to have an effect on body weight. On the other hand, part of the genetic factors that influence BMI also influence DEB. It would be interesting to disentangle the direction of causation of the overlap between these characteristics. Genetic influences on for example metabolism may be causal to weight gain that eventually leads to disturbed eating behavior. Genetic influences on DEB may alternatively be causal to a disturbed eating profile, leading to fluctuations in weight. Several approaches can be taken to disentangle the direction of

causation, for example phenotypic causation models (Duffy & Martin, 1994; Heath et al., 1993) and the co-twin control design (Cederlof et al., 1977; Kendler et al., 1993).

A concern with regard to the four item DEB-scale is that it might not be ideal to measure the underlying latent trait in eating disorders. However, in large epidemiological studies such as becoming common for gene finding, short scales might be a requirement to obtain phenotyping in sufficiently large samples. With the selection of the items we have tried to capture a variety of eating disorder symptoms. Three of the items (fear of weight gain, importance of body weight and shape for self-evaluation and binge eating) used in this study are based on eating disorder criteria from the DSM-IV. The fourth item (dieting) has been identified as a potent risk factor (Jacobi et al., 2004). One eating disorder symptom, compensatory behavior, is missing in our assessment instrument. Since heritability estimates for compensatory behavior and self-induced vomiting in female twins (0.50-0.70) were comparable to the estimate for DEB (Klump et al., 2000; Sullivan et al., 1998a), the inclusion of compensatory behaviors in our phenotype might not influence the results found for the women in the current study. However, we do not know what the consequences for the heritability estimates in the men would be, especially since significant gender differences have been reported for a variety of compensatory behaviors like self-induced vomiting, laxative use and fasting (Anderson & Bulik, 2004).

Genetic association study

In a two step design, the association between four candidate genes and eating disorders was investigated in chapter 5. Eating disorders included anorexia nervosa (AN) as well as eating disorders characterized by self-induced vomiting (SV). The four candidate genes were serotonin receptor 1D (*HTR1D*), stathmin (*STMN1*), brain-derived neurotrophic factor (*BDNF*) and tryptophan hydroxylase 2 (*TPH2*). To replicate previous results in ED, genes were selected for which association was observed and confirmed in studies with an adequate sample size (as discussed in Chapter 2). Both *HTR1D* and *BDNF* fulfilled these criteria (Bergen et al., 2003; Brown et al., 2006; Ribases et al., 2004; Ribases et al., 2005). Besides replication of previous results, we also aimed to evaluate the involvement of two unexplored candidate genes for ED. *STMN1* was located under the linkage peak of restrictive AN (1p33-36) (Grice et al., 2002). Because the associations with *HTR1D* and Opioid Receptor Delta-1 (genes located under the same peak) only explained part of the linkage, it was expected that additional candidate genes could underlie the linkage peak (Bergen et al., 2003). *TPH2* was selected because of the link between serotonin and eating disorders (Kaye, 2008; Lucki, 1998). To overcome the drawbacks of previous association

studies in which candidate genes were tested by single SNPs , 25 tagging SNPs were selected based on HapMap to capture the majority of the common variation within the four candidate genes. Between 71 and 91% of common variation within the four genes was captured by the tagging SNPs. In addition, replication of association was performed in two additional independent case-control samples from the Netherlands and Germany, making this one of the largest association studies performed thus far with 887 AN cases, 306 SV cases and 1914 controls.

In the first step allele frequencies of the 25 SNPs were compared between the GenED case groups (AN and SV cases) and random controls from the NTR. No association was observed for any of the *BDNF*, *HTR1D* and *STMN1* SNPs. A nominal significant association ($p<0.05$) was observed for *TPH2* rs1473473 in AN as well as SV. Subsequently this association was replicated in a meta-analysis with two additional independent eating disorder case-control samples. In the meta-analysis, the minor allele of *TPH2* SNP rs1473473 was significantly more frequent in AN cases (OR=1.25, 95% CI 1.06-1.47, $p<0.009$) and SV cases (OR=1.34, 95% CI 1.06-1.69, $p=0.013$) compared to controls. We are the first to observe an association with a genetic variant in the *TPH2* gene and eating disorders.

The *TPH2* gene encodes the main rate-determining enzyme in the synthesis of serotonin in the brain (Zill et al., 2007). Serotonin is involved in satiety, anxious and obsessional behavior, mood, and impulse control, features all linked to eating disorders (Kaye, 2008; Lucki, 1998). In long-term recovered AN and bulimia nervosa (BN) patients elevated 5-hydroxyindoleacetic acid levels in cerebrospinal fluid were detected (Kaye et al., 1991; Kaye et al., 1998). This is the major metabolite of serotonin in the brain and body and is thought to reflect extracellular serotonin concentrations. This finding thus could be indicative of an ‘overactive’ serotonin system in eating disorders, which in turn could be caused by an increased function of the *TPH2* gene.

The *TPH2* gene was also one of 182 candidate genes that were investigated for association with AN in another large collaborative study (Pinheiro et al., 2010). In this study 5151 SNPs (43 SNPs within the *TPH2* gene) were evaluated in 1085 participants with AN and 677 controls. After accounting for multiple testing, there were no statistically significant associations for any individual SNP. No association was found between the measured *TPH2* SNPs and AN, but rs1473473 was not genotyped in this study. The extent of the linkage disequilibrium between rs1473473 and the genotyped SNPs is not known, a small linkage disequilibrium could explain why the association with *TPH2* was not found in this study.

The LD block that *TPH2* rs1473473 tags spans across part of the *TPH2* gene, and is ended by a recombination hotspot on one side. Therefore it is highly likely that this SNP is in LD with a functionally relevant variant(s) in the *TPH2* gene. Rs1473473 is not in LD with known *TPH2* mutations (Haavik et al., 2008). *TPH2* SNPs in LD with rs1473473 however, have been associated with a suicidal mental condition in Finnish men (Zhou et al., 2005), with antidepressant response in depressive patients (Peters et al., 2004), and with allelic mRNA expression imbalance in sections of the human pons (Lim et al., 2007), indicating that genetic variation at this locus may contribute to mental conditions and could influence gene function.

To find yet unidentified functionally relevant variants with an effect in eating disorders, the *TPH2* gene could be sequenced in eating disorder cases and family members, for example by exon resequencing to detect rare or low frequency variants of medium effect (Gloyn & McCarthy, 2010; Johansen et al., 2010). Since a multitude of genes belong to the serotonin pathway, measuring the presence and activity of serotonin either in blood or in cerebrospinal fluid will probably not be a good representation of the *TPH2* gene per se (Kaye et al., 1998; Savelieva et al., 2008). A reliable way to evaluate the activity of the *TPH2* gene is by measuring mRNA expression levels in the brain (Lim et al., 2007). A difficulty of this approach is that brain tissue is required. When investigating gene expression in eating disorders it is important to differentiate between the secondary effects of malnutrition (for example due to fasting in AN) from effects of the disorder itself. The inclusion of a recovered eating disorder group in these studies therefore seems to be a prerequisite, which makes this approach even more difficult. Translational models might offer a solution for this problem.

Previously, a full phenotypic evaluation of the *TPH2* knock-out mouse was performed (Savelieva et al., 2008). The mice appeared largely normal both in appearance as well as behavior. In general the results indicated that the role of serotonin appears to be modulatory instead of essential in behavior. However, the results of one behavioral test suggested increased obsessive/compulsive behavior in the *TPH2* knock-out mice. This is an interesting finding, since a substantial comorbidity between eating disorders and obsessive-compulsive disorder is present (Bulik et al., 1997; Lilenfeld et al., 1998).

This is the first genetic study that used SV as a phenotype. This phenotype was chosen because there is no *a priori* reason to believe that a DSM eating disorder diagnosis represents a more ‘genetic’ syndrome than underlying core behaviors or traits. Twin studies have shown that binge-eating and vomiting represent more genetically mediated symptoms (heritability estimates ranging between 8 and 80), while genetic factors did not appear to have any effect (heritability estimate of 0) on the undue influence of weight and shape on

self-evaluation represents (Bulik et al., 1998; Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud et al., 2004b; Reichborn-Kjennerud et al., 2004a; Sullivan et al., 1998a; Wade et al., 2008b; Wade & Bulik, 2007). Because the reliability of the measurement of SV is high and the heritability of this behaviour is higher, as opposed to binge eating, it was decided to select cases based on this core behaviour in the study described in chapter 5 (Sullivan et al., 1998a; Wade et al., 2000a).

The selection of candidate genes in chapter 5 represents a choice from a larger set of possibilities. Another plausible candidate gene would have been Opioid Receptor Delta-1, since association with this gene was also observed and confirmed in two large studies (Bergen et al., 2003; Brown et al., 2006). This was not the case for the genes encoding Serotonin Receptor 2A and the Serotonin Transporter, which have been studied most intensively in eating disorders (see Table 1.4). Of course many alternatives exist for the novel candidate genes *STMN1* and *TPH2* that were currently selected. However, with the sample sizes of the current study design (Figure 7.1) only a few candidate genes could be evaluated with a good coverage rate while retaining adequate statistical power.

Despite this selection, the statistical power in the GenED study was limited. Depending on the minor allele frequency the study had adequate power (85% power at an alpha level of 0.05, log-additive or allelic model) to detect effects sizes ranging between 1.45 and 1.8 for AN and ranging between 1.48 and 1.85 for SV. This could explain why previously reported associations between *BDNF*, *HTR1D* and AN were not observed in this study (Bergen et al., 2003; Brown et al., 2006; Ribases et al., 2004; Ribases et al., 2005). The meta-analysis of *TPH2* rs1473473 had adequate power (85% power at an alpha level of 0.05, log-additive or allelic model) to detect effect sizes of at least 1.25 for AN and 1.4 for SV. This approach has led to a robust association of the *TPH2* SNP rs1473473.

Performing candidate gene studies is an outdated approach to identify susceptibility genes for eating disorders. However, at the time that this study was designed it was the available method for performing this kind of research. Since the aetiology of eating disorders is largely unknown, genomewide association studies are more appropriate for finding candidate genes in these disorders. These studies rely on the assumption that linkage disequilibrium enables one SNP to act as a surrogate marker for association to other sequence variants in the same region (Freimer & Sabatti, 2007). Currently the Genetic Consortium of Anorexia Nervosa is conducting a genomewide association study in a large group of female participants who meet DSM-IV criteria for AN and a group of female controls, all of European ancestry. The GenED study also takes part in this consortium. Although this is a huge step forward in identifying plausible candidate genes, the heterogeneity of eating disorders, including AN, should be kept in mind. Substantial

differences in genetic and environmental contributions to component *symptoms* of AN suggests that we may be obscuring our ability to detect loci that contribute to risk by focusing on a contrived and heterogeneous condition. Incorporating additional phenotypes within this study might lead to interesting findings, although the multiple testing issue should be taken into account. Additional phenotypes can be core symptoms of eating disorders, like binge eating and SV, but also personality features associated to eating disorders, like perfectionism and impulsivity.

The link between TPH2 and personality features

The substantial heritability of AN and SV may in part be explained by heritable aspects of perfectionism and impulsivity, which are consistently associated to eating disorders (Cassin & von Ranson, 2005). Both perfectionism and impulsivity remained present after recovering from an eating disorder (Bastiani et al., 1995; Kaye et al., 1998; Lilenfeld et al., 2000; Srinivasagam et al., 1995; Wagner et al., 2006). In addition, elevated levels of perfectionism were observed in relatives of individuals with AN and BN (Lilenfeld et al., 2000; Woodside et al., 2002). These findings suggest that perfectionism and impulsivity may be of potential aetiological relevance for eating disorders.

Chapter 6 explored the hypothesis that genetic variation in the TPH2 gene explains part of the overlap between eating disorders, perfectionism and impulsivity. In the phenotypic analyses, earlier observations that patients with AN and/or SV score different from healthy controls on perfectionism and impulsivity, as measured by the Multidimensional Perfectionism Scale (Frost et al., 1990) and the Dickman Impulsivity Inventory (Dickman, 1990) were confirmed. To study the involvement of four TPH2 SNPs, that were associated to AN or SV previously (chapter 5), in perfectionism and/or impulsivity in the general population, genetic association analyses were performed in a random twin-based control group (N=512) with perfectionism and impulsivity items from the Youth Self-Report (Levinson, 2005; Verhulst et al., 1997). The minor allele of rs1473473 (OR =1.49, 95% CI 1.02-2.17, p=0.04) and rs1007023 (OR=1.60, 95% CI 1.08-2.36, p=0.02) were more frequent in impulsive controls. In the eating disorder case group (N=267), an association to Dysfunctional Impulsivity, a subscale from the Dickman Impulsivity Inventory, was observed for both rs1007023 (OR=1.79, 95% CI 1.01-3.17, p=0.05) and rs1473473 (OR=1.83, 95% CI 1.08-3.08, p=0.02). The degree of perfectionism was not associated to genetic variation at the TPH2 gene.

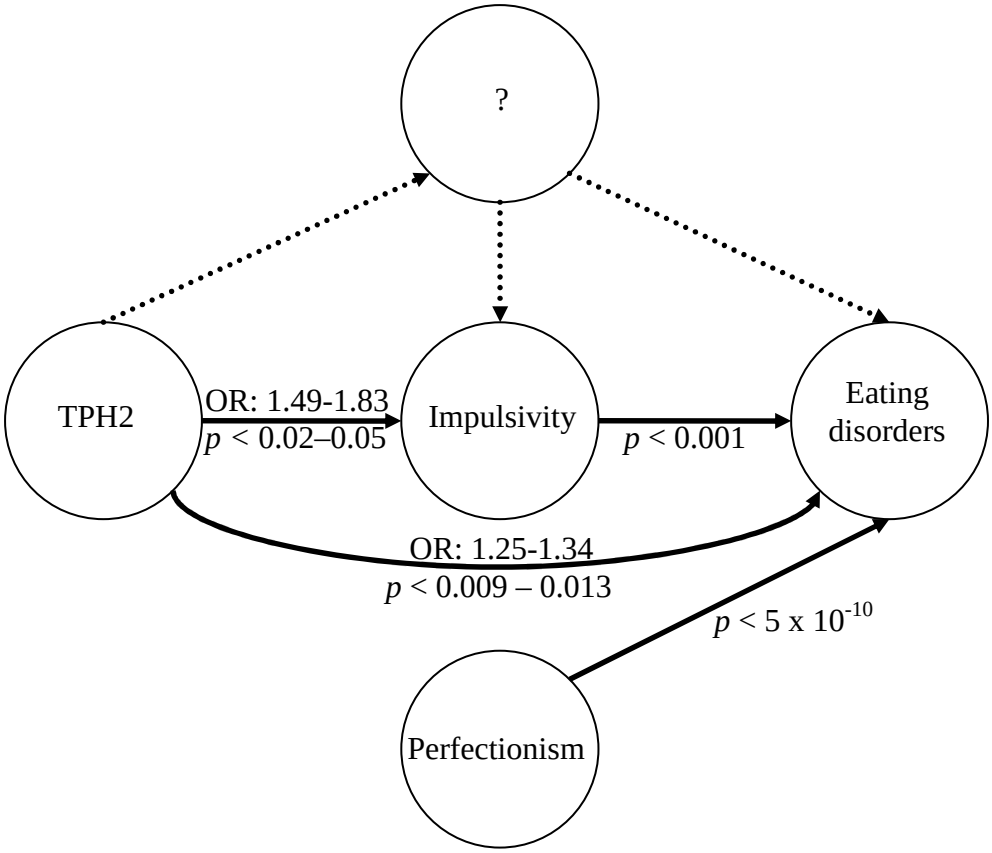

Figure 7.2 The link between TPH2, impulsivity and eating disorders. The observed associations between TPH2 and impulsivity (chapter 6), TPH2 and eating disorders (chapter 5), impulsivity and eating disorders (chapter 6), and perfectionism and eating disorders (chapter 6) are depicted with the arrows. The TPH2 gene leads to higher impulsivity which in turn might make people more susceptible for an eating disorder. An alternative explanation, a third factor that is affected by TPH2, and which in turn influences both impulsivity and eating disorders is presented by the dashed arrows.

In Figure 7.2 the results from the analyses are summarized. Both impulsivity and perfectionism were associated to eating disorders. TPH2 showed an association with eating disorders (AN and SV) and with impulsivity. Possibly there is a causal relation, thus that genetic variation at the TPH2 gene leads to higher impulsivity which in turn will make people more susceptible for developing an eating disorder. Another explanation is that TPH2 affects another unknown factor, which influences both impulsivity and eating disorders. To evaluate whether the association between TPH2 and impulsivity is underlying the association with eating disorders a longitudinal prospective study design (following up carriers of the minor alleles of rs1007023 and rs1473473) is preferred. However, because of

the low prevalence of eating disorders and the complex nature, it will be difficult to conduct this study. To overcome this, a more prevalent intermediate phenotype, for example DEB discussed in chapter 3 and 4, could be used. Another approach to test for causality is by adjusting the case-control association analysis for the impulsivity phenotype. Because the Youth Self Report impulsivity item was only measured in a small subset of the eating disorders cases, we did not have sufficient power to adjust the previous case-control association analyses with impulsivity scores.

In addition to perfectionism and impulsivity, there are other established risk factors for eating disorders that might predispose to their development, like negative self-evaluation/low self-esteem, negative body image and weight concerns (Jacobi et al., 2004). It would be interesting to find out whether one or several shared factors are underlying this overlap between personality features and eating disorders, and whether these factors have a genetic or an environmental background. Large population-based twin studies can be used to investigate these questions.

A limitation of the study design used in chapter 6 is that although there is overlap in the features that were phenotyped in the cases from the GenED study and the NTR controls, the questionnaires used to measure these features are not identical (Figure 7.1). Extensive perfectionism and impulsivity phenotypes were available for the participants with an eating disorder, whereas the available phenotypes in the NTR controls were based on single items. It is possible that despite the considerable correlation between these instruments they do not measure the same underlying construct. By recruiting the control women without eating disorders we tried to overcome this limitation. The questionnaires administered to this group were identical to the questionnaires used in the GenED study. However, because no DNA was collected from these women the utility of this group was limited (Figure 7.1). Therefore the association with Dysfunctional Impulsivity scale could not be evaluated in controls without an eating disorder.

The observed differences in perfectionism and impulsivity scores between participants with an eating disorder and controls without an eating disorder indicate that currently ill individuals are more impulsive and highly perfectionistic. Although measurement invariance with respect to disease state was not tested (the framework described in chapter 3 can be used to do this), it is likely that the scales do not measure exactly the same underlying trait in both groups (both within patient subgroups and between patients and controls). For example, someone who regularly engages in self-induced vomiting (a quite dysfunctional impulsive behavior), may have another opinion or standard on dysfunctional impulsivity compared to somebody who does not engage in self-induced vomiting. These persons will probably respond in a different matter preceding their illness or after recovery.

The previously reported elevated levels of perfectionism and impulsivity in recovered patients however, point out that the differences in perfectionism and impulsivity are not entirely disease state-dependent and may be an underlying trait preceding eating disorder onset (Bastiani et al., 1995; Kaye et al., 1998; Srinivasagam et al., 1995; Wagner et al., 2006).

Future Perspectives

In future research identical phenotypes will be available for a substantial group of cases from the GenED study and for random participants from the NTR. This will increase the possibilities for conducting studies into genetic associations, phenotype correlations and the way these influence the development of eating disorders. A major limitation of the study design thus far used is that questionnaires used in GenED and NTR controls were not identical (Figure 7.1). Both studies are however still ongoing which enable us to complete the data.

It will be interesting to evaluate the influence of disease-state on the performance of the used measurement instruments, by investigating measurement invariance (as discussed in chapter 3). For the Multidimensional Perfectionism Scale (Frost et al., 1990) and the Dickman Impulsivity Inventory (Dickman, 1990) these analyses can be performed in the cases from the GenED study and the controls without an eating disorder (group 1 and 3 depicted in Figure 7.1). In the future, it will also be possible to test for measurement invariance in the combined sample of GenED cases and NTR controls, not only for perfectionism and impulsivity but also for other personality features which are measured within the NTR survey.

Besides perfectionism and impulsivity there are other personality features that possibly predispose to the development of eating disorders, like negative self-evaluation/low self-esteem, negative body image and weight concerns (Jacobi et al., 2004). Because different types of eating disorders are characterized by a different combination of these features (for example high perfectionism, low self-esteem and negative body image in AN), it will be interesting to examine the overlap of these features, including the overlap with different types of eating disorders or different eating disorder symptoms (e.g. binge eating, SV). Within the twin sample of the NTR it will be possible to examine whether these features have a common background, and whether genetic or environmental influences are underlying this overlap. Furthermore the twin design can be used to disentangle the direction of causation, for example phenotypic causation models (Duffy & Martin, 1994; Heath et al., 1993) and the co-twin control design (Cederlof et al., 1977; Kendler et al.,

1993). The first method is a nested model of the bivariate Cholesky decomposition, in this approach the correlated traits need to have different modes of inheritance. In the co-twin control design relative risks for one feature (e.g. perfectionism) would be compared between unrelated individuals discordant for another feature (e.g. impulsivity), DZ twins discordant for impulsivity, and MZ twins discordant for impulsivity.

The next step is conducting genomewide association studies to identify genetic loci that influence the susceptibility for eating disorders, but also the susceptibility for the combined phenotype of predisposing personality features. As was shown in chapter 6, perfectionism and impulsivity scores are different in eating disorder cases compared to controls, and the same is expected for the personality features mentioned above. In order to detect genes that are involved in these personality features in the absence of disease, genomewide association studies should be performed in the twins from the NTR or in family members of eating disorder cases. As part of the GenED study first degree family members of participating individuals with an eating disorder are also approached to participate in the study. Currently, phenotype and genotype data of 161 relatives of 64 eating disorder cases have been collected. Besides for genetic association studies, this family sample can also be used to perform phenotypic studies. It can be questioned whether family members of eating disorder cases show elevated levels of for example perfectionism and impulsivity. Furthermore, in the combined sample of cases and relatives it can be examined whether these features are familial.

When genetic loci are identified by the genomewide association studies, these genes will have to be followed-up. In the first step more (preferably) functionally relevant variants within that gene will be measured. Subsequently, the gene will be sequenced to find yet unidentified variants that can explain the observed association. A recommended approach for genes associated to eating disorders is exon resequencing in severe cases and matched healthy controls, to detect rare or low frequency variants of medium effect (Gloyn & McCarthy, 2010; Johansen et al., 2010). In addition to newly identified genes based on genomewide association studies, the same approach will be used to follow up the association with the TPH2 gene in the future.

Once it is established that a gene is involved in either eating disorders or a predisposing personality feature, the activity and function of this gene can be tested by using translational models, like knock-out mice. Possibly these mice show a difference in behavior compared to wild-type mice, which can be relevant for the studied phenotype in humans. In addition to knock-out mice, the activity-based anorexia (ABA) or semi-starvation induced hyperactivity model (Kas et al., 2009), a translational model for AN, can be used to test the activity of the identified gene.

Finally, in the future more studies regarding gene-environment interaction (G x E), whereby a person's genes may influence how sensitive he or she is to the effects of the environment, should be performed. This interaction could be a potential explanatory model in eating disorders (Bulik, 2005). Despite the fact that practically every young girl in Western society is exposed to cultural standards of slenderness and attractiveness and the majority of them is or has been on a diet, only a small number ever develops an eating disorder. Possibly dieting will only trigger the development of eating disorders in girls with a large genetic vulnerability for these disorders. The underlying molecular processes of G x E, with genes mediating an individual's risk to for example stressful life events, may be elucidated by studying epigenetics (Feinberg, 2008; Schroeder et al., 2010). Epigenetics is the study of inherited changes in phenotype or gene expression caused by mechanisms other than changes in the primary underlying DNA sequence. These epigenetic alterations are potentially reversible and accessible for drug treatment. Recent findings suggest that the transmission of vulnerability for depression from parent to offspring could occur, in part, through the epigenetic modification of genomic regions that are implicated in the regulation of stress response and related processes such as neurogenesis, like the glucocorticoid receptor and brain-derived neurotrophic factor (McGowan et al., 2009; Schroeder et al., 2010). Expectancies with relation to benefits for future personalized diagnostics and therapies for psychiatric disorders from this relatively new form of genetic research are high. Epigenetic changes might also be involved in eating disorders. To examine these changes epigenetic studies can be performed in currently ill or recovered patients with eating disorders.

Clinical implications

Genetic research as discussed in this thesis will improve the knowledge regarding the genetic background of eating disorders. Once the pathways involved in these disorders and in the associated personality features are elucidated, prevention and treatment can be improved. Phenotypic studies into the shared background of eating disorders and personality features will enable us to make a risk profile for eating disorders. This will increase the chance of early recognition, and improve prevention strategies.

The knowledge that certain genes are involved in eating disorders could be used to predict the outcome of the disease if genetic variants will be found with sufficient predictive effect sizes. Carrying a number of risk alleles might worsen the prognosis of the eating disorder, because specific behaviors or eating disorder features are influenced by these genes (Hetrick et al., 2008; Maguire, 2008). Treatment programs could be adjusted

and improved based on this knowledge. Furthermore, knowledge regarding the genetic aetiologies may open pathways for novel drug targets. Since the prevalence of eating disorders is relatively low, pharmaceutical companies may not invest in the development of medications to cure or mask genetic effects specific for these disorders. However, since there is evidence for shared genetic vulnerability between eating disorders, depression and anxiety (Keel et al., 2005; Kendler et al., 1995; Wade et al., 2000b; Wade et al., 2004), genes that contribute to this spectrum of disorders might become targets for medical interventions.

Also, an increase in knowledge regarding the extent to which disorders are influenced by genetic vulnerability may help to decrease the stigma associated with such disorders. It can relief the burden of guilt with which many parents of eating disorder patients struggle (Enten & Golan, 2009; Jacobi et al., 2004; Le Grange et al., 2010). In addition, this knowledge could also change and ameliorate the attitudes towards individuals suffering from them (Crisafulli et al., 2008; Crisp, 2005; Stewart et al., 2006).