Genetic determinants of eating disorders

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Appendix A: DSM-IV criteria for eating disorders

Anorexia nervosa

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
B. Intense fear of gaining weight or becoming fat, even though underweight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)

Specify type:

Restricting Type: during the current episode of Anorexia Nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)
Binge-Eating/Purging Type: during the current episode of Anorexia Nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

Bulimia nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   (1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
   (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)

B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of Anorexia Nervosa.

Specify type:
Purging Type: during the current episode of Bulimia Nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
Nonpurging Type: during the current episode of Bulimia Nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

Eating disorder not otherwise specified
Eating disorder not otherwise specified includes disorders of eating that do not meet the criteria for any specific eating disorder.

1. For female patients, all of the criteria for anorexia nervosa are met except that the patient has regular menses.
2. All of the criteria for anorexia nervosa are met except that, despite significant weight loss, the patient's current weight is in the normal range.
3. All of the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur less than twice a week or for less than 3 months.
4. The patient has normal body weight and regularly uses inappropriate compensatory behavior after eating small amounts of food (e.g., self-induced vomiting after consuming two cookies).
5. Repeatedly chewing and spitting out, but not swallowing, large amounts of food.
6. Binge-eating disorder is recurrent episodes of binge eating in the absence if regular inappropriate compensatory behavior characteristic of bulimia nervosa.

Appendix B: Overview of genetic association studies performed since 2005 with adequate statistical power.

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
Serotonin						
Serotonin Receptor 1D, HTR1D, 1p36	Rs652783	RAN	122	NS	(1)	UK
		BPAN	104			
		Controls	678			
	Rs604030	RAN	122	NS	(1)	UK
		BPAN	104			
		Controls	678			
	T-1123C (rs674386)	RAN	122	0.03	(1)	ANr vs ctrl OR 1.44 UK
		BPAN	104			
		Controls	678			
	Rs856510	RAN	122	0.02, 0.04 (geno)	(1)	ANr vs ctrl OR 1.51 UK
		BPAN	104			
		Controls	678			
Serotonin Receptor 3A, HTR3A, 11q23	p.L459L (exon 9)	German AN	265	NS	(2)	Germany, Spain
		German BN	91			
		German Controls	191			
		Spanish AN	78			
		Spanish BN	119			
		Spanish Controls	331			

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	c.-42C>T (rs1062613)	German AN German BN German Controls Spanish AN Spanish BN Spanish Controls	265 91 191 78 119 331	German sample: ANr vs ctrl 0.04 (geno, N=138)	(2)	Pooled data NS Germany, Spain
	IVS1-19G>A (rs1176722)	German AN German BN German Controls Spanish AN Spanish BN Spanish Controls	265 91 191 78 119 331	German: 0.03 (geno) ANr vs ctrl 0.006 (geno, N=138) BN vs ctrl 0.01 BNP vs ctrl 0.008 (geno, N=80)	(2)	Pooled data NS Germany, Spain
	IVS3+7A>C	German AN German BN German Controls Spanish AN Spanish BN Spanish Controls	265 91 191 78 119 331	NS	(2)	Germany, Spain
Serotonin Receptor 3B, HTR3B, 11q23	p.Y192S (rs1176744)	German AN German BN German Controls Spanish AN Spanish BN Spanish Controls	265 91 191 78 119 331	German: 0.004 (geno) ANr vs ctrl 0.007 (genotypic, N=138)	(2)	Pooled ANr vs ctrl p<0.002 Germany, Spain

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	c.-104_-102 delAGA (‘5 untransl region)	German AN	265	NS	(2)	Germany, Spain
		German BN	91			
		German Controls	191			
		Spanish AN	78			
		Spanish BN	119			
		Spanish Controls	331			
	IV6+72A>G	German AN	265	NS	(2)	Germany, Spain
		German BN	91			
		German Controls	191			
		Spanish AN	78			
		Spanish BN	119			
		Spanish Controls	331			
Catecholamine						
Beta 3 adrenergic receptor, ADRB3, 8p11-12	Trp64Arg	AN	96	NS	(3)	Japan
		BN	116			
		Controls	284			
Dopamine D2 Receptor, DRD2, 11q23	-141C/Indel (rs1799732)	AN	191	NS	(4)	TDT 0.01 USA, UK and Germany
		Parents & aff rel	457			
		Controls	98			
	T2730C (rs1800498)	AN	191	NS	(4)	USA, UK and Germany
		Parents & aff rel	457			
		Controls	98			

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	C932G (rs1801028)	AN Parents & aff rel Controls	191 457 98	NS	(4)	USA, UK and Germany
	C939T (rs6275)	AN Parents & aff rel Controls	191 457 98	NS	(4)	USA, UK and Germany
	C957T (rs6277)	AN Parents & aff rel Controls	191 457 98	NS	(4)	TDT 0.006 USA, UK and Germany
	Rs6278	AN Parents & aff rel Controls	191 457 98	ANp vs ctrl 0.04 (geno, N=88)	(4)	USA, UK and Germany
	C10620T (rs1800497)	AN Parents & aff rel Controls	191 457 98	ANp vs ctrl 0.05 (geno, N=88)	(4)	USA, UK and Germany
Dopamine D4 Receptor, DRD4, 11p15	C-521T	AN (trios) Controls (fam)	202 418	0.009	(5)	TDT Israel
	C-616G	AN (trios) Controls (fam)	202 418	NS	(5)	TDT Israel
	A-809G	AN (trios) Controls (fam)	202 418	NS	(5)	TDT Israel
	120 bp tandem repeat dupl	AN (trios) Controls (fam)	202 418	NS	(5)	TDT Israel

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	Exon III repeat	AN (trios)	202	NS	(5)	TDT
		Controls (fam)	418			Israel
Noradrenaline transporter, SLC6A2, 16q12	S4/L4 (promoter)	RAN	67	NS	(6)	Austria, UK
		BPAN	48			
		AN subtype n.a.	27 (trios)			
Neuropeptide & feeding regulation						
Cholecystokinin, CCK, 3p21	Rs6791019	AN	165	NS	(7)	Netherlands
		Controls	283			
	Rs7611677	AN	165	NS	(7)	Netherlands
		Controls	283			
	Rs6809785	AN	165	NS	(7)	Netherlands
		Controls	283			
	Rs6801844	AN	165	NS	(7)	Netherlands
		Controls	283			
	Rs11129946	AN	165	0.0001 (geno)	(7)	AC genotype OR 2.64
		Controls	283			Netherlands
Ghrelin, GHRL, 3p25-26	Gln90Leu	AN	366	NS	(8)	Austria, France,
		BN	326			Germany, Italy,
		AN and BN (trios)	529			Slovenia, Spain,
		Controls	342			and UK

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	Leu72Met	AN Controls	196 98	NS	(8)	Austria, France, Germany, Italy, Slovenia, Spain, and UK
	Arg51Gln	AN Controls	196 98	NS	(8)	Austria, France, Germany, Italy, Slovenia, Spain, and UK
	T171C (rs495225)	AN BN Controls	96 116 284	BN vs ctrl 0.04	(3)	Japan
	Rs17700633	AN Controls	267 1636	NS	(9)	Netherlands
	Rs17782313	AN Controls	267 1636	NS	(9)	Netherlands
Opioid receptor delta-1 OPRD1, 1p35	Rs569356	RAN BPAN Controls	122 104 678	0.007, 0.0003 (geno) 0.05, 0.04 (geno) AN vs ctrl 0.0008, 0.001 (geno)	(1)	AN vs ctrl OR 1.67, ANr vs ctrl OR 1.77 ANbp vs ctrl OR 1.57 UK
	Rs204047	RAN BPAN Controls	122 104 678	NS	(1)	UK

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	Rs204055	RAN	122	NS	(1)	UK
		BPAN	104			
		Controls	678			
	Rs2298896	RAN	122	NS	(1)	UK
		BPAN	104			
		Controls	678			
	Rs521809	RAN	122	0.02 (geno)	(1)	UK
		BPAN	104			
		Controls	678			
	Rs4654327	RAN	122	0.03, 0.03 (geno)	(1)	ANr vs ctrl OR 1.42
		BPAN	104			UK
		Controls	678			
Other candidate genes						
Brain Derived Neurotrophic Factor, BDNF, 11p13-14	C-270T	AN	195	NS	(10)	Netherlands
		Schizofrenia	273			
		Controls	580			
	Val-66-Met (rs6265)	AN	195	NS	(10)	Netherlands
		Schizofrenia	273			
		Controls	580			
	20 kb upstr ATG	AN	195	NS	(10)	Netherlands
		Schizofrenia	273			
		Controls	580			

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	33 kb downstr exon 2	AN Schizofrenia Controls	195 273 580	NS	(10)	Netherlands
	Rs1488830	AN Controls	267 1636	NS	(9)	Netherlands
	Rs925946	AN Controls	267 1636	NS	(9)	Netherlands
Cannabinoid receptor 2, CNR2, 1p36	R63Q	AN BN Controls	94 111 1867	ED vs ctrl 0.04	(11)	ED vs ctrl OR 1.24 Japan
Estrogen receptor 1, ESR1, 6q25	Rs488133	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs11155819	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs12199722	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs188405	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs726281	French AN (fam) German RAN (fam)	321 41	French AN 0.02 French RAN 0.005 German RAN 0.03	(12)	France and Germany
	Rs3020407	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
	Rs17081994	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs2981712	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs3020371	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs2228480	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
	Rs3798577	French AN (fam) German RAN (fam) French women (population-based)	321 41 693	French RAN 0.02 ED in population-based women 0.008	(12)	France and Germany
	Rs2295193	French AN (fam) German RAN (fam)	321 41	French AN 0.02 French RAN 0.007	(12)	France and Germany
	Rs2252837	French AN (fam) German RAN (fam)	321 41	NS	(12)	France and Germany
ETS variant gene 5, ETV5, 3q28	Rs7647305	AN Controls	267 1636	NS	(9)	Netherlands
Fat mass- and obesity associated gene, FTO, 16q12	Rs1121980	AN Controls	267 1636	NS	(9)	Netherlands

Gene	Polymorphism	Phenotype	N	*p*-value[a]	Ref	Note
Glucosamine-6-phosphate deaminase 2, GNPDA2, 4p13	Rs10938397	AN Controls	267 1636	NS	(9)	Netherlands
G-Protein coupled receptor 55, GPR55, 2q37	Gly195Val (rs3749073)	AN Controls	235 1244	0.02	(13)	OR 1.31 OR 2.41 (p<0.005) Val195 homozygotes Japan
Potassium channel tetramerisation domain, KCTD15, 19q13	Rs368794	AN Controls	267 1636	NS	(9)	Netherlands
Mitochondrial carrier homolog 2, MTCH2, 11q12	Rs10838738	AN Controls	267 1636	NS	(9)	Netherlands
Neurol growth regulator 1, NEGR1, 1p31	Rs2568958	AN Controls	267 1636	NS	(9)	Netherlands
SH2B adaptor protein 1, SH2B1, 16p11	Rs7498665	AN Controls	267 1636	NS	(9)	Netherlands
Transmembrane protein 18, TMEM18, 2p25	Rs6548238	AN Controls	267 1636	NS	(9)	Netherlands

AN=Anorexia Nervosa, BN=Bulimia Nervosa, RAN= Restrictive Anorexia Nervos, BPAN= Binge-purge Anorexia Nervosa

Appendix B: Reference list large genetic association studies since 2005

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Curriculum vitae

Margarita Cornelia Theodora Slof (-Op ‘t Landt) was born August 20th, 1980 in Ter Aar, the Netherlands. She attended secondary school in Alphen aan den Rijn at the Groene Hart Lyceum, where she passed her exams (atheneum) in 1998. In that same year she started her study Nutrition and Health at Wageningen University and Research centre (Netherlands). During this study she did an internship at the Virginia Institute for Psychiatric and Behavioral Genetics of the Virginia Commonwealth University (United States of America). She received her degree in September 2002. January 2003 she started working as a researcher at the Center for Eating Disorders Ursula on a project on the genetics of eating disorders. This was a PhD project in collaboration with the department of Molecular Epidemiology of the Leiden University Medical Center and the department of Biological Psychology of the VU University Amsterdam. She was supervised by Prof. dr. P.E. Slagboom and Dr. I. Meulenbelt at the department of Molecular Epidemiology (Leiden University Medical Center), by Prof. dr. D.I. Boomsma and Dr. M. Bartels at the department of Biological Psychology (VU University) and by Dr. E.F. van Furth at the Center for Eating Disorders Ursula. The results of the research performed during the project are described and discussed in this thesis. Rita will continue to work at the Center for Eating Disorders Ursula in Leidschendam.