Genetic and epigenetic interactions in adaptive thermogenesis pathways in association with obesity from a Public Health Genomics perspective

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SUPPLEMENTARY MATERIALS

Figures 1-3

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Figure 1. Selection of studies regarding the association between -3826 (A->G) polymorphism in the UCP1 gene and obesity phenotypes

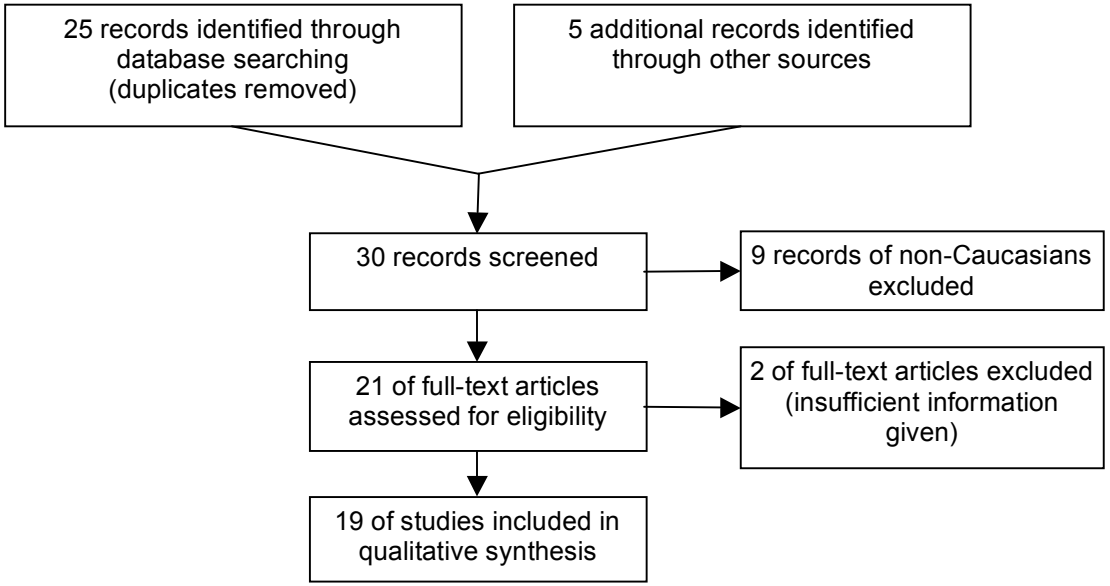

Figure 2. Selection of scientific evidence showing epigenetic regulation of PPARγ

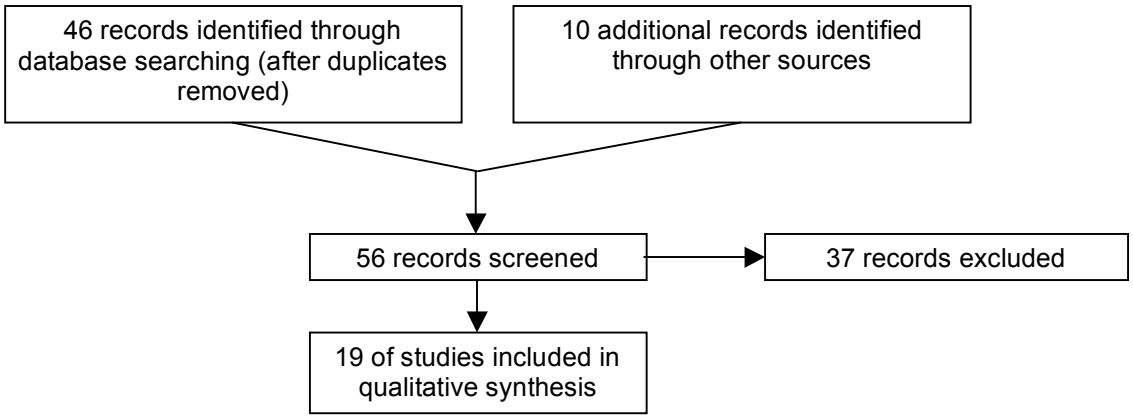

Figure 3. Selection of studies showing an association between rs4994 polymorphism in the ADRB3 gene and obesity phenotypes

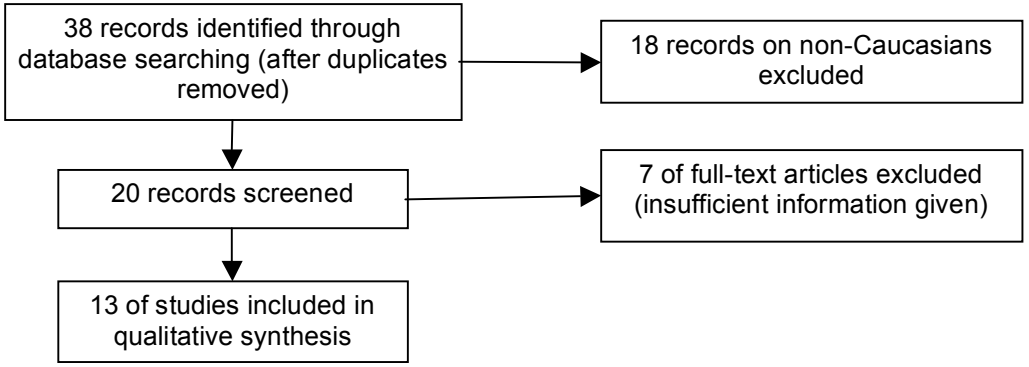

Table 9. Studies observing additive effects of the -3826 A→G in the UCP1 gene and rs4994 in the ADRB3 gene and associations with obesity phenotypes

Phenotype	+/-	P	Study design	Study population			Additional information	Ref.
				Ethnicity	Female	Male		
BMI	-		Case-control	German	343		Subjects were participants in the Diabetomobile study cohort	(70)
			Case-control	Polish	80	38	Participants were overweight or obese	(71)
Higher weight gain	+	0.05	Case-control	French	238 91 controls		Cases were morbidly obese	(67)
		0.051	Case-control	Finnish	85		Participants were healthy, obese, premenopausal women. They underwent a 12 weeks energy restriction diet and were followed over a subsequent 40 weeks weight maintenance phase. Results are significant for faster weight gain after a VLCD	(75)
Low basal metabolic rate	+	0.002	Case-control	Finnish	141 59 controls	29 53 controls	Cases were obese	(74)

Table 10. Studies observing associations between SNPs in the C/EBPα gene and obesity phenotypes

SNP	Phenotype	+/−	P	Subjects	Additional information	Ref.
rs12691	BMI	−	−.	147 male 381 female	SOS study	(69)
		−	−	2 248 male 2 618 female	Botnia study 30 % diabetes mellitus 2 patients	
rs41490344	WHR	+	0.02	537	Leeds family study	(80)
rs41504144		−	−			
rs41344151						
rs16967952						
rs34508287						
rs41428545						
rs34529039						
rs41367646						
rs1049969						
rs707656						

Table 11. Evidence on DNA methylation in the C/EBPα gene

Tissue	Evidence	Ref.
Granulocytes from human acute myeloid leukaemia patients	Aberrant gene methylation is infrequent	(81)
Endometrial cancer cell line	DNA methyltransferases inhibitor increased gene expression	(82)
Human hepatoma cell line	Gene expression was not induced after treatment with DNA methyltransferase inhibitor but together with HDAC inhibitor	(83)
Lung cancer cell lines and human lung primary tumour	Methylation in upstream promoter region is associated with low or absent gene expression Treatment with DNA methyltransferases inhibitor increased gene expression	(84)
Bone marrow samples from acute myeloid leukaemia	No correlation with upstream promoter methylation and gene expression level	(85)
Placenta and Cord blood		(86)
Bone marrow or spleen from leukemic, transgenic mice	Downregulation of expression is due to methylation, but not to HDAC	(87)
Human head and neck squamous cell carcinoma	Downregulation of expression is due to methylation in upstream promoter region	(88)
Pancreatic cancer cell line	Upregulated gene expression after treatment with DNA methyltransferases inhibitor due to upstream promoter demethylation. Effect was greater in combination when additionally treated with HDAC inhibitor	(89)
Hematopoietic tumour cell line	Hypermethylation of proximal promoter is association with transcriptional silencing	(90)
Human hepatocellular carcinomas	Expression regulation due to methylation of upstream promoter region	(91)

Table 12. Evidence on histone modifications of the C/EBPα gene

Modification	Tissue	Evidence	Ref.
H3 acetylation	Lung cancer cell lines and human lung primary tumour	Histone acetylation was directly associated with DNA methylation of the upstream promoter and inversely with gene expression	(84)
	Pancreatic cancer cell line	HDAC inhibitors increase gene expression	(89)
	Pancreatic cancer cell line	Upregulated gene expression after treatment with HDAC inhibitor. Effect was enhanced in combination with DNA methyltransferases inhibitor	(89)
	Human hepatocellular carcinomas	Upregulation of expression depends on deacetylation of H3	(91)
-	Human hepatoma cell line	HDAC inhibitor increases gene expression	(83)
H3K4me3	Mouse embryonic fibroblasts and preadipocytes	Enrichment of trimethylation of H3K4 in promoter region ends up in defects in adipogenesis	(57)
H4 acetylation	Lung cancer cell lines and human lung primary tumour	Histone acetylation was directly associated with DNA methylation of the upstream promoter and inversely with gene expression	(84)

Table 13. Studies observing associations between SNPs in the LPL gene and obesity phenotypes

SNP	Phenotype	+/−	P	Subjects	Additional information	Ref.
rs285	Abdominal ob	+	0.013	58 female 47 male	No information about ethnicity	(92)
rs320	BMI Lower risk ov	+	<0.02	587 female	Association only in female	(93)
		−	−	476 male		
rs328	BMI FM	+	0.01	249 female	20 weeks physical activity Association only in female	(94)
		−	−	231 male		

Table14 Evidence for epigenetic regulation of the LPL gene

Modification	Tissue	Evidence	Ref.
CpG methylation	Human adipose stem cells	Promoter hypomethylation in clonally cultured adipose stem cells	(95)
		Promoter hypermethylation in senescent undifferentiated adipocytes	(51)
	Human prostate cancer cells	Promoter methylation observed in prostate cancer cells vs. no methylation in controls	(96)
H3 acetylation	3T3-L1 treated with diallyldisulfide	Decreased HDAC activity upon treatment correlates with gene expression	(97)
	Murine embryonic fibroblasts	Recruitment of HDAC1, HDAC3 and histone methyltransferase upon induction of adipogenesis	(98)
H3K4 methylation	Differentiated adipose stem cells	No change of trimethylation in promoter region when differentiated	(59)
	Undifferentiated adipose stem cells	Enrichment in promoter	
H3K9 acetylation	Murine embryonic fibroblasts	Recruitment of HDAC1, HDAC3 and histone methyltransferase upon induction of adipogenesis	(98)
	Undifferentiated adipose stem cells	No modification in promoter region	(59)
	Differentiated adipose stem cells	Hyperacetylation of H3K9 and demethylation of H3K27 in promoter region	
H3K9 methylation	Undifferentiated adipose stem cells	No modification in promoter region	
H3K27 methylation	Differentiated adipose stem cells	Hyperacetylation of H3K9 and demethylation of H3K27 in promoter region	
	Undifferentiated adipose stem cells	Enrichment in promoter	
H4 acetylation	3T3-L1 treated with diallyldisulfide	Decreased HDAC activity upon treatment correlates with gene expression	(97)

Table 15. Evidence for epigenetic regulation of the FABP4 gene

Modification	Tissue	Evidence	Ref.
CpG methylation	adipose stem cells	Promoter hypermethylation remains stable upon differentiation	(95)
	Senescent undiff. adipose stem cells	Variation in promoter methylation	(51)
	Adipose stem cells	Promoter region is largely unmethylated	(53)
H3 acetylation	3T3-L1	Decreased HDAC activity upon treatment with diallyldisulfide correlates with gene expression	(97)
H3K4 methylation	Mouse embryonic fibroblasts	Methylation is essential for PPARγ-dependent adipogenesis	(99)
	Undiff. adipose stem cells	Enrichment in promoter	(59)
	Differentiated adipose stem cells	No change of trimethylation upon differentiation	
H3K9 acetylation	Differentiated adipose stem cells	Hyperacetylation of H3K9 in promoter region	
	Undiff. adipose stem cells	No modification in promoter region	
H3K9 methylation	Undiff. adipose stem cells	No modification in promoter region	
H3K27 methylation	Undiff. adipose stem cells	Enrichment in promoter	
	Differentiated adipose stem cells	Demethylation of H3K27 in promoter region	
H4 acetylation	3T3-L1	Decreased HDAC activity upon treatment with diallyldisulfide correlates with gene expression	(97)

Table 16. Studies observing the association of joint effects of SNPs and obesity phenotypes

Phenotype	+/−	P	Study design	Study population				Additional information	Ref.
				Ethnicity	Female	Male	Children		
rs4994 (ADRB3) and rs1801282 (PPARγ)									
BMI	+	0.039	Case-control	Spanish			185 185 control	Cases were obese (5-18 yrs old) with sex- and age-matched controls	(100)
rs1801282 (PPARγ) and rs8192678 (PGC1α)									
BMI	-	-	Case-control	Danish	254 270 controls	430 239 controls		The association study focused on type 2 diabetes mellitus in a 2 level study design. Cases suffered from type 2 diabetes mellitus	(101)
rs4994 (ADRB3) and rs320 (LPL)									
BMI	+	0.026	Cross-sectional	Spanish	587			Gender specific effect	(138)
	-					476			