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Molecular pathway analysis associates alterations in obesity-related genes and antipsychotic-induced weight gain

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Original Article

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Abstract

Objective: Antipsychotics often induce excessive weight gain. We hypothesised that individuals with genetic variations related to known obesity-risk genes have an increased risk of excessive antipsychotic-induced weight gain (AIWG). This hypothesis was tested in a subset of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial data set. *Methods*: The CATIE trial compared effects and side effects of five different antipsychotics through an 18-month period. Based on the maximum weight gain recorded, excessive weight gain was defined as >7% weight gain. Cytoscape and GeneMANIA were instrumental in composing a molecular pathway from eight selected genes linked to obesity. Genetic information on a total of 495.172 single-nucleotide polymorphisms (SNPs) were available from 765 (556 males) individuals. Enrichment test was conducted through ReactomePA and Bioconductor. A permutation test was performed, testing the generated pathway against 10^5 permutated pathways ($p \leq 0.05$). In addition, a standard genome-wide association study (GWAS) analysis was performed. *Result*: GWAS analysis did not detect significant differences related to excessive weight gain. The pathway generated contained 28 genes. A total of 2067 SNPs were significantly expressed ($p < 0.01$) within this pathway when comparing excessive weight gainers to the rest of the sample. Affected genes including *PPARG* and *PCSK1* were not previously related to treatment-induced weight gain. *Conclusions*: The molecular pathway composed from high-risk obesity genes was shown to overlap with genetics of patients who gained >7% weight gain during the CATIE trial. This suggests that genes related to obesity compose a pathway of increased risk of excessive AIWG. Further independent analyses are warranted that may confirm or clarify the possible reasoning behind.

Significant outcomes

- When GWAS fails to be significant, limited sample sizes can still prove useful using a hypothesis-driven molecular pathway approach.
- Already known genes involved in obesity may compose a molecular pathway at risk of excessive AIWG.
- New genes (*MRAP, SLC19A3, GPD1, NLK, ASH2L, NCOA6, PTPN1, LEPROT, GSTK1, ADIPOR1, MRAP2, RBBP5, WDR5, JAK2, CHD7, SDC3, SETDB1, PPARG* and *PCKS1*) not previously associated with AIWG have been identified.

Limitations

- With a limited sample size, some potential relevant genetic variations able to influence weight gain could have been undetected because of their limited impact on the phenotype investigated.
- The CATIE study was not designed to test the hypothesis under analysis, that is, only limited information on weight gain pattern, height (hence no BMI information) and diet, etc. was available.
- The definition of the molecular pathways is based on the current biological knowledge of gene function and our selection of target genes. Future studies may discover that genes included in the pathway backbone may not be functionally relevant after all, just as it cannot be excluded that potentially relevant genes may have been omitted in the selection process.

Introduction

According to WHO, 21 million people worldwide were affected by schizophrenia (SCZ) in 2016. It is estimated that the total amount of lost disability-adjusted life year caused by SCZ will be close to 17 million by 2020 (Murray & Lopez, 1996). SCZ affects both quality of life and lifespan

(Solanki *et al.*, 2008). Drug-induced metabolic disorders likely contribute to the reduced lifespan (11–20 years less) and high incidence of cardiovascular disorders in SCZ (Correll *et al.*, 2009; Scigliano & Ronchetti, 2013; Kredentser *et al.*, 2014). The mainstay for the treatment of SCZ is second-generation antipsychotics (SGA). Weight gain, dyslipidaemia, type II diabetes and metabolic changes are common side effects of SGA. SGA may differ within their group in terms of metabolic liability; however, no matter the drug choice, it is an expected, problematic side effect (Patel *et al.*, 2009; Bak *et al.*, 2014; Bressington *et al.*, 2016). Possible mechanisms that drive the antipsychotic-induced weight gain (AIWG) are many, involving interactions with serotonin, histamine, dopamine, adrenergic, cannabinoid and muscarinic receptors (Roerig *et al.*, 2011). Several studies support that the extend of AIWG may at least, in part, be genetically driven rendering certain individuals more susceptible than other (MacNeil & Müller, 2016; Zhang *et al.*, 2016). Nevertheless, more than every second patient will experience an excessive weight gain (>7%) when exposed to common treatments like olanzapine, quetiapine and risperidone (McEvoy *et al.*, 2007). The biological and genetic mechanisms driving excessive AIWG are not fully understood, suggesting a phenotype of a more complex genetic architecture. If the genetic make-up for AIWG were identified, protocols could be implemented to reduce the risk, with beneficial outcome for patients and society. An amount of overlap between the genes related to AIWG and genes related to obesity in general can be observed, for example, *SLC6A14, 5HTR2C, MC4R*, etc. (Shams & Müller, 2014; Miranda *et al.*, 2015; Lotta *et al.*, 2019). However, the overlap seems to go largely unnoticed as studies regarding AIWG are often contradicting at best (see Tables 1 and 2). The genetic make-up of common obesity includes alternations in genes related to energy metabolism, fatty tissue and hypothalamic function; such as: *ADIPOQ, FTO, LEP, LEPR, INSIG2, MC4R, PCSK1 and PPARG* (Walley *et al.*, 2009; Choquet & Meyre, 2011).

In this study, we hypothesise that knowledge of obesity-prone genes could have value for the identification of AIWG-prone individuals. We test the hypothesis that the genetic variations associated with common obesity might pose an increased risk of excessive AIWG. We provide new information from a sample size too small for a genome-wide association study (GWAS) approach such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial.

Methods

The CATIE trial

The sample under analysis is the NIMH CATIE sample (NIMH contract NO1 MH90001). A total of 1460 schizophrenic patients were enrolled between January 2001 and December 2004. CATIE was a multi-phase randomised controlled trial of antipsychotic medications (olanzapine, perphenazine, quetiapine, risperidone or ziprasidone) involving individuals (Table 3) with SCZ followed for up to 18 months (Stroup *et al.*, 2003; Lieberman *et al.*, 2005).

Fifty-one per cent (765 individuals, male = 556, mean age = 40.93 ± 11.03) of the CATIE participants provided a DNA sample and is the core data set of the present investigation. DNA samples were sent to the Rutgers University Cell and DNA Repository, where cell lines were established by Epstein–Barr virus (EBV) transformation. Sample DNA concentrations were quantified and normalised using PicoGreen dsDNA quantification kits (Molecular Probes, Eugene, OR, USA).

The analysis was conducted through the following steps.

GWAS

Outcome for the first-step analysis was maximum weight gain recorded during the CATIE. Clinical covariates were identified though a general linear model and were included in the genetic analysis as stratification factors when significantly associated with the outcome under analysis (Table 3). Quality checking was set as standard for this type of analysis (genotype call rate > 0.95; maf > 0.01; hwe < 0.0001), inflation factor was controlled by lambda values and imputation was run with the use of 1000 Genomes in a Plink environment. Pathway analysis was conducted at the SuperCluster PC at Aarhus University. The single variations associated with weight gain were identified (a nominal p threshold of 0.01 was chosen) together with the genes that harboured those variations. Genes were identified through the interrogation of the public available genetic data set within the specifications of R packages ReactomePA (Yu & He, 2016), Bioconductor (Huber *et al.*, 2015), biomaRt (Drost & Paszkowski, 2017) and GenABEL (Aulchenko *et al.*, 2007). Plink (Purcell *et al.*, 2007) served for the genetic association test, default settings. For a full walk-through of the methods used, please see the Supplementary Material.

Molecular pathway analysis

As a second step, genes previously related to obesity were subjected to an enrichment analysis. Genes classically associated with obesity (metabolism, fatty tissue function and hypothalamic regulation and the hypothalamic-pituitary-adrenal (HPA) axis) were chosen to create a backbone of the molecular pathway (Table 1). The genes shown in Table 1 were used as input for Cytoskape, GeneMANIA and further enriched the original pathway. As a result, a complete molecular pathway was identified by Cytoskape and then tested for enrichment in the data set.

SNPs relating to the Cytoskape-generated pathway

The enrichment analysis was conducted using the R software suite (R Foundation for Statistical Computing, 2013), through the packages Bioconductor (Huber *et al.*, 2015) and ReactomePA (Yu & He, 2016). The analysis of clinical covariates was conducted prior to the genetic tests and, when found significantly associated with the phenotype (age, years of treatment, years at the moment of presentation) under analysis was included as covariates for genetic tests.

Permutation test to confirm the validity of our findings

As a third step of the analysis, a permutation test was conducted by selecting 10^5 molecular pathways randomly identified in the CATIE genetic database and testing their enrichment against the index pathway ($p = 0.05$) generated by Cytoskape. A permutation test was deemed mandatory in order to abate the risk of false-positive findings. The selected molecular pathways had the same length and the same number of SNPs as the index pathway in order to limit the possibility of bias selection.

Result

Mean weight gain was 6.48 ± 7.50 kg throughout the study, independently from the drug treatment (olanzapine, perphenazine, quetiapine, risperidone or ziprasidone) delivered to single individuals. Significant covariates were age, years of treatment and years at the moment of presentation which were all associated with increased weight gain (see Table 3).

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Table 1. Genes previously found to be associated with obesity

Gene	Position	Start	Stop	Description	Previously associated with weight gain
ADIPOQ	3q27.3	1863842668	186858463	This gene is a protein-coding gene, and it is exclusively expressed in adipose tissue. The protein has similarities to collagen VIII and X and complement factor C1q. Circulating the plasma, it is involved in metabolic and hormonal processes	(Jassim *et al.*, 2011; Soeiro-de-Souza *et al.*, 2014; Adolph *et al.*, 2017; Li *et al.*, 2017)
PPARG	3q25.2	12287368	12471013	This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. The protein is PPAR-gamma and is a regulator of adipocyte differentiation. PPAR-gamma has been implicated in the pathology of numerous diseases including obesity, diabetes, atherosclerosis and cancer	(Franks *et al.*, 2007; Tontonoz & Spiegelman, 2008; Jeninga *et al.*, 2009; Lyche *et al.*, 2011; Bordoni *et al.*, 2017)
INSIG2	2q14.1-q14.2	118088452	118110997	This gene mediates feedback control of cholesterol synthesis. Theprotein is an endoplasmic reticulum protein that blocks the processing of sterol regulatory element-binding proteins (SREBPs)	(Le Hellard *et al.*, 2009; Koskinen *et al.*, 2016; Zhang *et al.*, 2016)
PCSK1	5q15	96390336	96434143	This gene has a crucial importance on the appetite and metabolism, because it converts insulin and glucagon to active process instead of inactive	(Choquet & Meyre, 2011; Creemers *et al.*, 2012; Choquet *et al.*, 2013; Kulanuwat *et al.*, 2014; Dušátková *et al.*, 2015; Kulanuwat *et al.*, 2015; Philippe *et al.*, 2015; Ramos-Molina *et al.*, 2016)
LEP	7q32.1	128241202	128257629	LEP is a protein-coding gene. The protein leptin is secreted by white adipocytes, which acts through the leptin receptor (LEPR), functions as part of a signalling pathway that can inhibit food intake and/or regulate energy expenditure to maintain constancy of the adipose mass, thereby playing a major role in the regulation of body weight	(Templeman *et al.*, 2005; Ellingrod *et al.*, 2007; Hart Sailors *et al.*, 2007; Kang *et al.*, 2008; Mou *et al.*, 2008; Yevtushenko *et al.*, 2008; Erez *et al.*, 2011; Wu *et al.*, 2011; Brandl *et al.*, 2012; Nurmi *et al.*, 2013; Kang *et al.*, 2014; Zhang *et al.*, 2016)
LEPR	1q31.3	65420652	65641559	This protein-coding gene codes for a protein of the gp130 family of cytokine receptors protein and is a receptor for leptin, and is involved in the regulation of fat metabolism, as well as in a novel haematopoietic pathway that is required for normal lymphopoiesis	(Gregoor *et al.*, 2009; Gregoor *et al.*, 2011; Dubern & Clement, 2012; Li *et al.*, 2015; Wasim *et al.*, 2016)
MC4R	18q21.32	60371110	60372775	MC4R is a protein-encoding gene. The protein is a membrane-bound receptor and member of the melanocortin receptor family. The encoded protein interacts with adrenocorticotropic and MSH hormones and is mediated by G proteins. Defects in this gene are a cause of autosomal dominant obesity.	(Hardy *et al.*, 2010; Lett *et al.*, 2012; Malhotra *et al.*, 2012; Czerwensky *et al.*, 2013a,b; Kao & Müller, 2013; Doulla *et al.*, 2014; Shams & Müller, 2014; Zai *et al.*, 2015; MacNeil & Müller, 2016; Zhang *et al.*, 2016; Bordoni *et al.*, 2017)
FTO	16q12.2	53701692	54158512	FTO (alpha-ketoglutarate-dependent dioxygenase) is a protein-coding gene, and the exact physiological function of this gene is not known	(Frayling *et al.*, 2007; Tanofsky-Kraff *et al.*, 2009; Hardy *et al.*, 2010; Perez-Iglesias *et al.*, 2010; Wangensteen *et al.*, 2010; Gaillard *et al.*, 2013; Reynolds *et al.*, 2013; Yeo, 2014; Zhao *et al.*, 2014; Kvaløy *et al.*, 2015; Wang *et al.*, 2015; Jiao *et al.*, 2016; Martins *et al.*, 2016; Bordoni *et al.*, 2017)

GWAS analysis

Initially, a set of 495.172 SNPs were available from the CATIE study, after pruning and quality assessment 170.841 SNPs were imputed, resulting in a total of 4.268.977 SNPs. As a result, from the first step of the analysis, none of the variations under analysis reached a genome-wide significant level when tested for weight gain throughout the trial. The Manhattan plot illustrates that no SNP was of significance; however, a trend of association was observed for both rs822391 (*ADPIOQ*) and rs2071045 (*LEP*). A lambda value of 1.002 allowed for the ruling out of major stratification factors. From the Q–Q plot, a good correlation between expected values and observed values indicates a high-quality data, see Fig. 1 for the result of the GWAS and Fig. 2 for the Q–Q plot.

Hypothesis-driven enrichment analysis

ADIPOQ, LEP, LEPR, PPARG, FTO, MC4R, PCKS1 and *INSIG2* are considered classical genes associated with obesity (Hinney & Hebebrand, 2008; Enns *et al.*, 2011; Sarzynski *et al.*, 2011; Kasim *et al.*, 2016). Based on the 8 backbone genes, a molecular pathway was created with 20 new genes giving a total of 28 genes (Fig. 3 and Table 4): *MRAP, SLC19A3, GPD1, NLK, POMC, ASH2L, NCOA6, PTPN1, LEPROT, GSTK1, ADIPOR1, MRAP2, RBBP5, WDR5, AGRP, SOCS3, JAK2, CHD7, SDC3* and *SETDB1*. A total of 2067 SNPs were harboured by genes belonging to the pathway under analysis. The prevalence of variations significantly associated with the outcome under analysis (significance level set at 0.01, not GWAS significance level) was higher than expected by chance ($n = 44$, expected $= 21$ ($= 0.01 \times 2067$)).

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Table 2. Previous reports of SNPs and their association with AIWG

Gene	SNP	Associated with AIWG	Not associated with AIWG
ADIPOQ	rs12495941, rs6773957, rs3821799, rs822396, rs3774261, rs1501299, rs1063539, rs9882205, rs822393, rs2036373, rs16861210, rs182052, rs17366743, rs7627128, rs822391, rs1656930, rs266729		(Brandl *et al.*, 2014)
	rs2241766	(Wu *et al.*, 2011)	
	rs17300539	(Jassim *et al.*, 2011)	
INSIG2	rs7566605	(Doudney *et al.*, 2009)	(Opgen-Rhein *et al.*, 2010)
	r17587100, rs10490624	(Le Hellard *et al.*, 2009)	(Opgen-Rhein *et al.*, 2010; Tiwari *et al.*, 2010; Zhang *et al.*, 2016)
	rs12151787, rs17047733, rs10490624	(Koskinen *et al.*, 2016; Zhang *et al.*, 2016)	
	rs17047764	(Le Hellard *et al.*, 2009; Tiwari *et al.*, 2010; Zhang *et al.*, 2016)	(Opgen-Rhein *et al.*, 2010)
LEP	rs7799039	(Brandl *et al.*, 2012; Nurmi *et al.*, 2013)	
LEPR	rs1137101	(Wasim *et al.*, 2016)	
MC4R	rs489693	(Czerwensky *et al.*, 2013a,b)	
	rs8087522A	(Chowdhury *et al.*, 2013)	
	rs279858	(Zai *et al.*, 2015)	
	rs17782313	(Chowdhury *et al.*, 2013)	(Zhang *et al.*, 2016)
FTO	rs9939609 (A*/TT)	(Perez-Iglesias *et al.*, 2010; Song *et al.*, 2014)	(Jassim *et al.*, 2011)
PPARG	rs2920500, rs2960421, rs2920502, rs17036160, rs2120825, rs3856806, rs1797912, rs4135268, rs4135247, rs12629751, rs7620165, rs4135256, rs10865710, rs7645903, rs4135275, rs6782475, rs1801282, rs4135258, rs1175542, rs7650895, rs17793693, rs709149, rs1177809, rs1152003		(Brandl *et al.*, 2014)
PCSK1	–	–	–

ADIPOQ, Adiponectin, C1Q And Collagen Domain Containing; *FTO*, FTO, Alpha-Ketoglutarate-Dependent Dioxygenase; *LEP*, Letpin; *LEPR*, Letpin receptor; *INSIG2*, Insulin-Induced Gene 2; *MC4R*, Melanocortin 4 Receptor; *PCSK1*, Proprotein Convertase Subtilisin/Kexin Type 1; *PPARG*, Peroxisome Proliferator-Activated Receptor Gamma.

Table 5 reports a selection of SNPs associated with the hypothesis-driven genes found in the CATIE sample associated with the weight gain. These SNPs can be prioritised in further research for their functional role and their association with the risk of gaining weight when patients are treated with antipsychotics.

Confirmation/permutation analysis

As a result, from the third step of analysis, the higher prevalence of SNPs associated with excessive AIWG retrieved from the second step of analysis resisted the permutation test (a permutated p-value = 0.05 for enrichment was retrieved from the pathway under analysis).

Discussion

With a molecular pathway approach, we were able to show a significant enrichment in variations harboured by a selected group of genes with relevance to common obesity. The results strengthen the hypothesis that genetic pre-disposition for obesity may increase the risk of excessive AIWG.

From the molecular pathway generated, the genes *ADIPOQ, INSIG2, LEP, LEPR, MC4R, FTO, AGRP, POMC* and *SOCS3* (Piao *et al.*, 2014) all have previously been associated with AIWG. *PCSK1* and *PPARG* showed to be significantly enriched in variations in the current molecular pathway and although associated with weight gain and obesity, this is to our knowledge the first time *PCSK1* and *PPARG* are associated with AIWG. *PCSK1* has a crucial importance on the appetite and metabolism regulation, as the protein (PC1/3) coded by *PCSK1* converts the proteins of proinsulin and proglucagon to their active biological forms (Rouillé *et al.*, 1997). Genetic variations in *PCSK1* have been associated, although heavily debated, with sensitivity to obesity and in particular childhood obesity, severe obesity and race (Choquet & Meyre, 2011; Choquet *et al.*, 2013; Kulanuwat *et al.*, 2014; Dušátková *et al.*, 2015; Kulanuwat *et al.*, 2015; Nordang *et al.*, 2017). In relation to AIWG, the presence of a catecholamine like dopamine or antipsychotics like haloperidol has shown to influence the levels of PC1/3 and could point towards a possible connection with AIWG not yet discovered (Day *et al.*, 1992; Oyarce *et al.*, 1996; Helwig *et al.*, 2011). *PPARG* encodes a member of the peroxisome proliferator-activated receptor subfamily of nuclear receptors. PPARG plays a key role in the regulation of lipid and glucose metabolism (Franks *et al.*, 2007). It is assumed that PPARG expresses its role in regulation of weight through a modulation of genes associated with body weight homeostasis and insulin

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Table 3. Sample descriptions

Variable	Descriptive	Statistics	*p*
Gender	F = 206; M = 559	T = 0.41	0.6
Age	**40.92 ± 11.03**	**R = −0.16**	**1.02E-05**
White	Yes = 508; No = 257	T = 0.52	0.59
Marital status	Divorced = 171; married = 83; never married = 451; separated = 45; widowed = 15	F = 0.42	0.79
Path of education	Advanced degree = 1; college graduate = 50; college graduated and master level = 6; community college = 46; did not complete high school = 202; high school diploma = 264; master's degree = 11; some college, did not graduate = 184	F = 0.31	0.93
Years of education	12.12 ± 2.21	T = −0.22	0.82
Years of treatment	**16.59 ± 11.2**	**R = −0.16**	**0.000006**
Years at the moment of presentation	**14.25 ± 10.82**	**R = −0.14**	**0.00012**
Employment	Unemployed = 645; full time = 48; part time = 68; unknown = 4	F = 0.88	0.44
Max weight change (kg)	6.48 ± 7.50	/	/

(F = female; M = male; when the ± symbol is present, the mean and the standard deviation are reported on the left and on the right, respectively) – in order to conduct the covariate analysis, clinical variables found to be significantly associated with the outcome under analysis were used as covariates in the model – the statistics (T = student; R = correlation; F = ANOVA). Values are reported in bold when significantly associated with the outcome under analysis.

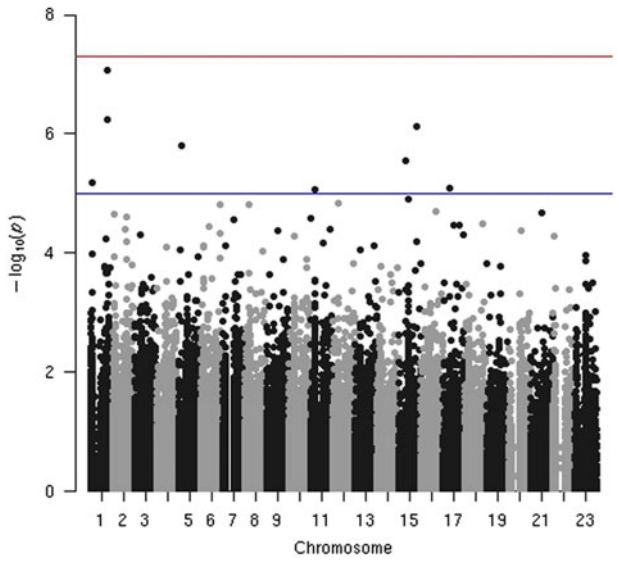

Fig. 1. GWAS results of Manhattan plot. It is illustrated that no single SNP was of significance; however, a trend of association was observed for both rs822391 (ADPIOQ) and rs2071045 (LEP).

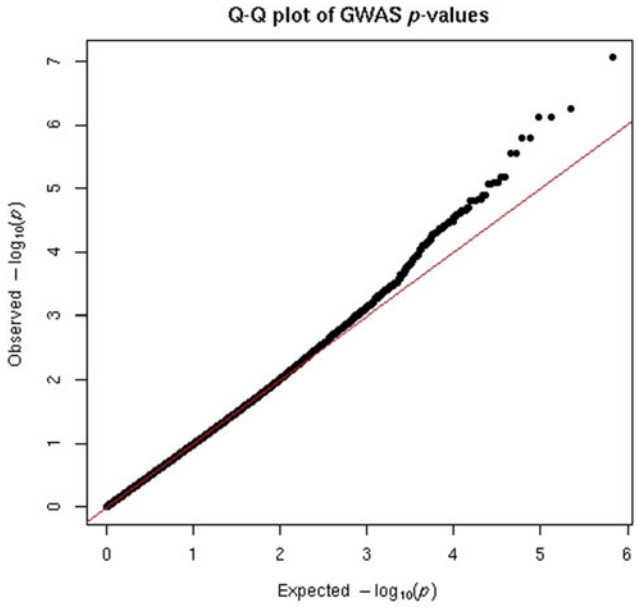

Fig. 2. Q–Q plot analysis. The R qqman package (Turner, 2017) was instrumental for creating the picture. Estimated λ for the *p* distribution was 1002. This was calculated using the GenABEL package, 'estlambda' function (Aulchenko *et al.*, 2007).

signalling (Lyche *et al.*, 2011). PPARG is a main regulator for the development of adipose cells as well as a factor in the pathology of numerous diseases including obesity, atherosclerosis and cancer (Tontonoz & Spiegelman, 2008; Hetherington & Cecil, 2010). Frequently used medicines that target the receptor cover areas of diabetes mellitus, atherosclerosis and lately as an anticancer drug (Dang *et al.*, 2018). Although variations in *PPARG* are well documented for influencing weight gain, its contribution to AIWG seems so far to be less obvious (Brandl *et al.*, 2014). This could be due to the complexity of gene–gene interactions. For instance, through inhibition of PPARG, a reduction of *LEP* expression takes place, when the patient is administered the antidiabetic thiazolidinediones (Catalano *et al.*, 2011). Alternatively, activation of PPARG and the membrane receptor GRP120 ameliorates the adipose inflammation and insulin resistance caused by local hypoxia in adipocytes (Hasan *et al.*, 2015). Hence, in the case of *PPARG*, obesity and AIWG are not a simple activation/inhibition model.

Interestingly, of the 20 new genes identified, 3 (*SOCS3*, *AGRP* and *POMC*) had previously been associated with AIWG. Suppressor of cytokine signalling 3 (*SOCS3*) is a negative regulator of leptin signalling (Piao *et al.*, 2014). The protein from agouti-related neuropeptide (*AGRP*) antagonises melanocortin-4 and melanocortin-4 receptors, thereby regulating the hypothalamic feeding behaviour, previously associated with obesity and obesity susceptibility (Krashes *et al.*, 2011). ***POMC*** encodes a preproprotein, and deficiencies in this gene are associated with obesity and adrenal insufficiency. A complex protein depending on its cleavage site influences energy metabolism, pigmentation and inflammation. Deficiencies in this gene among others are associated with obesity and adrenal insufficiency. Interestingly, up/down regulations of *POMC* and *AGRP* seem to depend on acute/chronic administration and drug choice (Fernø *et al.*, 2011; Ehrlich *et al.*, 2012; Weston-Green *et al.*, 2012; Kursungoz *et al.*, 2015; Lian *et al.*, 2015; Rojczyk *et al.*, 2015), and the reason behind this observation could be due to different experimental set-ups or perhaps that antipsychotics need to be administered at threshold levels to influence

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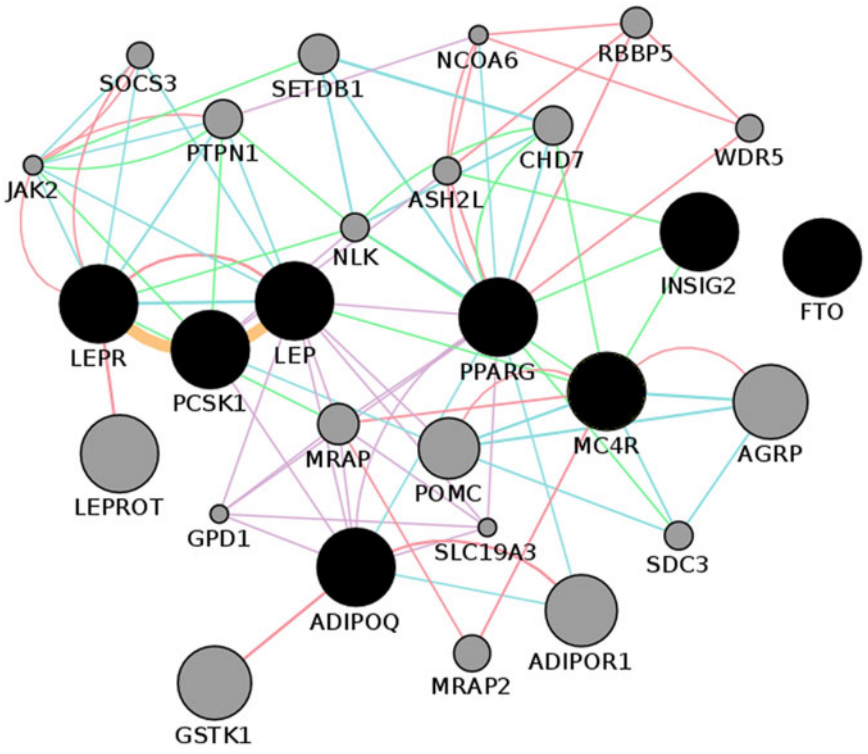

Fig. 3. The molecular pathway under analysis: A graphic representation by clusters of molecular pathways associated with weight gain. The picture provides a representation of the molecular pathways that are in strict functional association with those found to be associated with weight gain during antipsychotic treatment. Dark circles are the initial eight genes, where the grey circles are suggested genes by Cytoscape and their molecular pathways.

the anorexigenic *POMC*, while *AGRP* may be affected earlier or more potent by other factors, for example, leptin or reduced response from *MC4R*. No clear SNPs significance to AIWG has been observed (Chowdhury *et al.*, 2014). So far, this leaves an unclear picture of function and relevance of *POMC* and *AGRP* in regard to AIWG.

In the molecular pathway generated, *FTO* is the sole gene, not directly connected to the other genes. The reason for this could either be that *FTO*s full function yet to be understood or that the mechanisms behind its role in obesity are more elusive than that of the other genes in the molecular pathway. ***FTO*** encodes the FTO alpha-ketoglutarate-dependent dioxygenase exact, and the physiological function of this gene is not completely known. Evidence links FTO with BMI, obesity and a possible participation in central energy homeostasis, as an upregulation of 41% of FTO in the hypothalamus is observed in food-deprived rats (Fredriksson *et al.*, 2008; Zhao *et al.*, 2014). It is, however, known that an increased function of *FTO* is associated with obesity in both humans and animals, whereas a reduced function results in growth retardation (Yeo, 2014; Zhao *et al.*, 2014). The *FTO* genotype has a major effect on body weight in chronically treated patients with SCZ, something not observed in first-episode patients (Reynolds *et al.*, 2013). One could speculate that the inconsistent findings reflect a biphasic correlation with other factors throughout the life of patients, for example, between alleles and BMI (Hardy *et al.*, 2010).

The hypothesis-driven pathway was emulated from current knowledge in the field. The genes selected for the backbone of the molecular pathway are in concordance with previous articles of similar type (Enns *et al.*, 2011; Sarzynski *et al.*, 2011; Kang *et al.*, 2014). Genes were chosen that are related to energy metabolism, feeding behaviour, adipose tissue and leptin response, but excluding genes with inconclusive reports and genes belonging to vast molecular pathways, for example, tropic factors *SH2B1* (Choquet & Meyre, 2011). While our molecular pathway gives statistical sound evidence, the embracement of an increasing number of genes and their variations will at the same time escalate the complexity in how the variations relate to functional changes. This makes it possibly less useful in a clinical setting, at least at the current time.

Simultaneously, a hypothesis-driven molecular pathway approach is of course subjected to selection bias as a major limitation. The bias will have a high impact on the results and a molecular pathway analysis is by itself a less precise tool than, for example, GWAS. With this in mind, and based on the assumption of a polygenetic risk of drug-induced weight gain and the limited power of the sample, as expected, no single SNP was significant when using a GWAS approach. A trend of association was observed for both rs2071045 (*LEP*, $p = 0.091$) and rs822391 (*ADPIOQ*, $p = 0.078$) (Fig. 1). These findings are of particular relevance, as *LEP* was previously found to be associated with weight gain in animal and human investigations (Erez *et al.*, 2011); however, more studies lean towards the idea that the contribution from polymorphisms in *LEP* may be of minor relevance for AIWG (Creta *et al.*, 2015; Klemettilä *et al.*, 2015; Vasudev *et al.*, 2017).

The rs822391 SNP in *ADPIOQ* (adiponectin) has been related to body size in pre-menopausal women (Slattery *et al.*, 2015). Other *ADPIOQ* SNPs studies have showed an association with AIWG, but nothing of significance (Jassim *et al.*, 2011; Wu *et al.*, 2011; Brandl *et al.*, 2014). However, *ADIPOQ* may be affected directly by drugs, and independent reports show a negative correlation between weight gain and serum adiponectin (ADPIOQ) when treating with neuroleptica *in vivo* (Cuerda *et al.*, 2011; Soeiro-de-Souza *et al.*, 2014). Similar was shown *in vitro*, when stimulating cultured adipose cells with imipramine or lithium at therapeutic levels (Löffler *et al.*, 2016). To summarise, the data for *ADIPOQ* and its alleles are conflicting at best as well as when serum levels of *ADPIOQ* are monitored directly. Possible explanation for the discrepancies could be lack of multiple testing in

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Table 4. Genes under analysis in the molecular pathway

ensembl_gene_id	external_gene_name	Description	chromosome_name	start_position	end_position	phenotype_description
ENSG00000159346	ADIPOR1	adiponectin receptor 1	1	202940823	202958572	NA
ENSG00000159723	AGRP	agouti-related neuropeptide	16	67482571	67483813	OBESITY LEANNESS INCLUDED
ENSG00000129691	ASH2L	ASH2 like histone lysine methyltransferase complex subunit	8	38105242	38144076	NA
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	CHARGE SYNDROME
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	Kallmann Syndrome
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	Normosmic congenital hypogonadotropic hypogonadism
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	OMENN SYNDROME
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	CHARGE SYNDROME
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	Idiopathic hypogonadotropic hypogonadism (IHH)
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	Kallmann syndrome type 5 (KAL5)
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	HYPOGONADOTROPIC HYPOGONADISM 5 WITH OR WITHOUT ANOSMIA
ENSG00000171316	CHD7	chromodomain helicase DNA-binding protein 7	8	60678778	60868028	TRACHEOESOPHAGEAL FISTULA WITH OR WITHOUT ESOPHAGEAL ATRESIA
ENSG00000167588	GPD1	glycerol-3-phosphate dehydrogenase 1	12	50103819	50111319	Transient infantile hypertriglyceridemia and hepatosteatosis
ENSG00000167588	GPD1	glycerol-3-phosphate dehydrogenase 1	12	50103819	50111319	HYPERTRIGLYCERIDEMIA TRANSIENT INFANTILE
ENSG00000197448	GSTK1	glutathione S-transferase kappa 1	7	143244093	143270854	NA
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	BUDD–CHIARI SYNDROME
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	Essential thrombocythemia
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	Familial thrombocytosis
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	POLYCYTHEMIA VERA
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	Primary myelofibrosis
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	BUDD–CHIARI SYNDROME
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	ERYTHROCYTOSIS FAMILIAL 1
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	MYELOFIBROSIS WITH MYELOID METAPLASIA INCLUDED
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	POLYCYTHEMIA VERA
ENSG00000096968	JAK2	Janus kinase 2	9	4984390	5128183	THROMBOCYTHEMIA 3
ENSG00000213625	LEPROT	leptin receptor overlapping transcript	1	65420587	65436007	NA
ENSG00000170262	MRAP	melanocortin 2 receptor accessory protein	21	32291813	32314784	Familial glucocorticoid deficiency
ENSG00000170262	MRAP	melanocortin 2 receptor accessory protein	21	32291813	32314784	GLUCOCORTICOID DEFICIENCY 2
ENSG00000135324	MRAP2	melanocortin 2 receptor accessory protein 2	6	84033756	84090881	BODY MASS INDEX QUANTITATIVE TRAIT LOCUS 18
ENSG00000198646	NCOA6	nuclear receptor coactivator 6	20	34689097	34825649	NA
ENSG00000087095	NLK	nemo like kinase	17	28041737	28196381	NA

(*Continued*)

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Table 4. (*Continued*)

ensembl_gene_id	external_gene_name	Description	chromosome_name	start_position	end_position	phenotype_description
ENSG00000115138	POMC	proopiomelanocortin	2	25160853	25168903	Obesity due to proopiomelanocortin deficiency
ENSG00000115138	POMC	proopiomelanocortin	2	25160853	25168903	OBESITY LEANNESS INCLUDED
ENSG00000115138	POMC	proopiomelanocortin	2	25160853	25168903	PROOPIOMELANOCORTIN DEFICIENCY
ENSG00000196396	PTPN1	protein tyrosine phosphatase, non-receptor type 1	20	50510321	50585241	DIABETES MELLITUS NONINSULIN-DEPENDENT
ENSG00000117222	RBBP5	RB binding protein 5, histone lysine methyltransferase complex subunit	1	205086142	205122015	NA
ENSG00000162512	SDC3	syndecan 3	1	30869467	30908761	OBESITY LEANNESS INCLUDED
ENSG00000143379	SETDB1	SET domain bifurcated 1	1	150926263	150964744	NA
ENSG00000135917	SLC19A3	solute carrier family 19 member 3	2	227685210	227718012	Biotin-responsive basal ganglia disease
ENSG00000135917	SLC19A3	solute carrier family 19 member 3	2	227685210	227718012	Infantile spams psychomotor retardation-progressive brain atrophy-basal ganglia disease syndrome
ENSG00000135917	SLC19A3	solute carrier family 19 member 3	2	227685210	227718012	Leigh syndrome with leukodystrophy
ENSG00000135917	SLC19A3	solute carrier family 19 member 3	2	227685210	227718012	Thiamine-responsive encephalopathy
ENSG00000135917	SLC19A3	solute carrier family 19 member 3	2	227685210	227718012	THIAMINE METABOLISM DYSFUNCTION SYNDROME 2 (BIOTIN- OR THIAMINE-RESPONSIVE TYPE)
ENSG00000184557	SOCS3	suppressor of cytokine signaling 3	17	78356778	78360077	NA
ENSG00000196363	WDR5	WD repeat domain 5	9	134135365	134159968	NA

Table generated using R to access gene_ensembl.

Table 5. Single-nucleotide polymorphisms of the chosen genes, with the strongest statistical association with weight gain in the CATIE sample

Gene symbols	Gencode ID	Gene extended name and function	SNP	*p* value (expression)	T-statistic (expression)	BETA-statistic (weight)	*p* value (weight)	Tissue
FTO	ENSG00000140718.14	FTO, alpha-ketoglutarate-dependent dioxygenase, function not yet fully understood, may be involved in demethylating of 3meT and 3emU	rs17819033	0.013	−2.5	−420	0.0016	Adipose – Visceral (Omentum)
			rs7188300	0.013	−2.5	−420	0.0016	Adipose – Visceral (Omentum)
			rs11861870	0.023	2.3	−1220	0.0163	Adipose – Visceral (Omentum)
			rs12932373	0.05	2.0	−210	0.0058	Adipose – Visceral (Omentum)
LEPR	ENSG00000116678.14	Leptin receptor	rs6690625	0.023	2.3	−6640	0.0028	Adipose – Visceral (Omentum)
			rs3828039	0.024	2.3	32300	0.0028	Adipose – Visceral (Omentum)
			rs4655555	0.033	2.1	48000	0.0022	Adipose – Visceral (Omentum)
PCSK1	ENSG00000175426.6	Proprotein convertase subtilisin/Kexin type 1, the protein is involved in the processing of hormone and other protein precursors	rs1498928	0.029	2.2	−995	0.0021	Adipose – Visceral (Omentum)
FTO	ENSG00000140718.14	FTO, alpha-ketoglutarate-dependent dioxygenase, function not yet fully understood, may be involved in demethylating of 3meT and 3emU	rs17819033	0.0059	−2.8	−420	0.0016	Adipose – Subcutaneous
			rs7188300	0.0059	−2.8	−420	0.0016	Adipose – Subcutaneous
			rs12932373	0.010	2.6	−210	0.0058	Adipose – Subcutaneous
CHD7	ENSG00000171316.7	Chromodomain helicase DNA-binding protein 7	rs11997122	0.032	−2.2	−1320	0.0024	Adipose – Subcutaneous
			rs11990117	0.032	−2.2	−1340	0.0028	Adipose – Subcutaneous

ECM, extracellular matrix; SNP, single-nucleotide polymorphism.
Variations with a significant impact on expression adipose tissue and with a strong statistically significant association with the weight gain in CATIE trials. EQTLs data were retrieved from https://www.gtexportal.org/.

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previous studies, different ethnicities between studies and the heterogeneities of samples (Jassim *et al.*, 2011; Wu *et al.*, 2011; Li *et al.*, 2017).

Lastly, some of the variations found to be significantly associated with the phenotype under analysis were also reported to have a functional role in the expression of the genes they are harboured by, in the adipose tissue. This finding may be interpreted as a consistent and independent report of the relevance of a list of SNPs in driving the AIWG. The results are reported in Table 5.

Conclusion

The results from the current contribution confirm that variations in the genes related to obesity and the molecular pathway composed from them increase the risk of AIWG. Despite decades of research in genetics, we are currently not able to identify patients at risk of excessive AIWG, supporting the notion of a complex polygenetic nature of this phenomenon. Even in larger studies, the panoramic view of GWAS has so far provided limited evidence for easily identifiable phenotypes. As to why this is, one could speculate that the AIWG phenotype is seen in individuals where the total genetic make-up, from combined variations in metabolically important genes, exceeds a 'threshold'. In which case, it would be impossible to locate a SNP 'culprit'. This is similar to what is generally known of pharmacological effect/side effect, that is, 20–40% of all side effects are caused by gene variations identifiable in just one individual (Ingelman-Sundberg, 2001). Therefore, as shown in the current work, a molecular pathway approach may be a more proficient tool for describing complex polygenetic phenotypes even with limited sample sizes. Hence, downstream effects when introducing medicine to genetic alterations become increasingly complex.

Supplementary material. For supplementary material for this article, please visit https://doi.org/10.1017/neu.2019.41

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