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Methods

Psychiatric samples

Demographic data, history of treatment and co-medications were obtained from medical files. At inclusion, body weight and height were measured with participants standing without shoes in light indoor clothes. Body weight was measured in kilograms to the nearest kg. Body weight was available for at least two different time points during their current psychotropic treatment. Height was measured to the nearest cm using a height gauge. Body mass index (BMI) was defined as weight/height^2 (kg/m^2). BMI values between 25-30 kg/m^2 and equal or higher than 30 kg/m^2 were used to define overweight and obese patients, respectively.[1] The percent of body fat mass was calculated for the Caucasian psychiatric patients based on Gallagher equation (percentage body fat = 76.0 -1097.8· (1/BMI) -20.6·sex + 0.053·age + 154·sex· (1/BMI) + 0.034·sex·age, where sex = 1 for male and 0 for female).[2] Psychiatric diagnoses were established by physicians according to the ICD-10 classification,[3] in which F2 includes predominantly psychotic disorders such as schizophrenia and schizoaffective disorders and F3 includes mood disorders. Disorders not listed in F2 or F3 were considered as other diagnoses.

Patients were included in the present study only if their drug plasma levels were above an arbitrary threshold at 10% of the minimal value of the therapeutic range[4] (i.e. 15, 35, 2, 7, 2, 5, 0.05 mmol/L and 5 mg/L for aripiprazole, clozapine, olanzapine, quetiapine, risperidone + 9-hydroxy-risperidone, sertindole, lithium, and valproate, respectively). This threshold was chosen to indicate a suspicion of compliance issue and/or a rapid metabolism and/or pharmacokinetics drug interaction and/or low dose prescription (e.g. prescription of 50 mg/day of quetiapine for sleep disorders).

Drug intake was assessed by measuring plasma concentration using previously described liquid chromatography / mass spectrometry methods for AP,[5, 6] a specific electrode system (EasyLyte, Medica, Châtel-St-Denis, Switzerland) for lithium and a Cobas Integra 400 instrument (Roche Instrument Diagnostic, Basel, Switzerland) for valproate. As the study included different psychiatric centers with different treatment strategies and given that each psychotropic drug has its own mechanism of action, drug doses were standardized and calculated separately for each psychiatric center and for each psychotropic drug as follows: (dose - mean dose)/Standard deviation of the prescribed dose.

Population-based sample (CoLaus)

Participants came from a random sample of the population aged 35-75 years living in the city of Lausanne, Switzerland. Participation rate was 41%. All subjects were of Caucasian origin. Participants attended the outpatient clinic of the University Hospital of Lausanne in the morning after an overnight fast. Data were collected by trained field interviewers in a single visit lasting about 60 min. All participants provided written informed consent. Smoking status was classified as never, former or current smokers. For female subjects, contraceptive use and menopausal status were self-reported. Participants self-reported all their drug treatments. Body weight and height were measured with participants standing without shoes in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a Seca_scale (Seca Switzerland, Reinach, Switzerland), which was calibrated regularly. Height was measured to the nearest 5 mm using a Seca height gauge. Fat and lean mass (bioimpedance) were measured as previously described.[7]

GIANT consortium

The GIANT consortium performed a meta-analysis of GWAS data with a discovery set of 123'865 individuals of European ancestry from 46 studies for height,[8] BMI[9] and waist-to-hip ratio.[10] In each of the participating studies, genotype data were imputed to ~2.8M SNPs present in HapMap Phase 2 European-American reference panel and the effects and standard errors of all SNPs were adjusted by genomic control method.

CRTC1 polymorphism analyses

Psychiatric patients' genomic DNA was extracted from whole blood and genotyping was performed using Taqman allelic discrimination assay (ABI PRISM 7000 Sequence Detection System; Applied Biosystems, Rotkreuz, Switzerland). All SNPs were tested for Hardy-Weinberg equilibrium and linkage disequilibrium, as defined by the values of D' and r^2. A Custom Taqman SNP Assay including the primer sequences TGGCTCCTCTCCACAGCA (forward), CTGAGTGATGGGTGACAGC (reverse), and labeled probes FAM-ATCGCCCGCCCTGT and VIC-CATCGCCCACCCTGT was used to analyze *rs3746266A>G* polymorphism. Taqman SNP Genotyping Assay ID: C____26737143_10, ID: C__32455030_10 and ID: C__29217720_10 were used for *rs8104411C>T, rs10402536G>A* and *rs6510997C>T* SNPs, respectively. All reagents were obtained from Applied Biosystems (Rotkreuz, Switzerland), and genotyping was performed according to the manufacturer's protocol. To validate *rs3746266A>G* assay, control samples of the 3 genotypes were sequenced using an ABI BigDye terminator version 1.1 kit on an ABI PRISM 3100 automated sequencer, as previously described.[11]

Nuclear DNA from the CoLaus subjects was extracted from whole blood for whole-genome scan analysis using Nucleon® genomic DNA extraction kit (Tepnel life sciences, Manchester, UK) according to the manufacturer's recommendations. Genotyping was performed using the Affymetrix GeneChip® Human Mapping 500K array set, as recommended by the manufacturer. Genotypes were called using BRLMM (http://www.affymetrix.com/support/technical/whitepapers/brlmm_whitepaper.pdf).

Autosomal SNPs were imputed as follows. CoLaus genotypes with >90% call rate, >1E-7 HWE P-value were selected for phasing. SNP coordinates were converted to NCBI build 37 using the liftover tool from UCSC and sorted according to chromosomal position. Phasing was done for each chromosome separately using MACH with parameters of 20 rounds and 200 states. The resulting phased CoLaus target haplotypes along with the 2010-August release 1000G reference haplotypes were entered into the minimac for imputation. Duplicate individuals, and first and second degree relatives, were identified by computing genomic identity-by-descent coefficients, using PLINK. The younger individual from each duplicate or relative pair was removed. SNPs with call rate <70% and individuals with call rate <90% were excluded from further analysis. *Rs3746266A>G* significantly associated with BMI in psychiatric patients was not genotyped, but among the *CRTC1* SNPs genotyped in CoLaus, the intronic SNP *rs6510997C>T* was found to be an adequate proxy (r^2=0.7, D'=1, and eTable 7) of *rs3746266A>G*. Since probe *rs6510997* showed mild deviation from HWE, we repeated the genotype calling using all CoLaus individuals together with a more stringent cluster separation threshold than for the original genotype data set. Thus, for this particular SNP, we used the newly performed genotype calls that do not violate HWE. The minor allele frequency of *rs6510997C>T* was 20% and the SNP was in Hardy-Weinberg equilibrium (p>0.1).

Sequence capture and Exome sequencing

We used variation data observed in 413 exomes from the CoLaus study, which were sequenced at the Wellcome Trust Sanger Institute (WTSI) as part of a partnership between the Institute, the CoLaus principal investigators and the Quantitative Sciences department of GlaxoSmithKline (ODEX team, see below).

Following Agilent's SureSelect protocol,[12] 10 μg of sheared DNA were end repaired and polyA tailed, and Illumina-sequencing adapters were ligated to the resulting fragments using the Illumina (San Diego, CA, USA). Paired-End DNA Sample-Prep protocol, except that the gel-size selection step was replaced with a purification using magnetic bead-based solid phase reversible immobilization (SPRI) beads (following Agilent's protocol).

PCR products were purified using SPRI beads before sequencing. All data represent results of one capture reaction for each sample. Captured libraries were sequenced on the Illumina Genome Analyzer 2 platform as paired-end 54-bp reads according to the manufacturer's protocol. The standard Illumina data processing pipeline[13] was used to generate quality scored base calls from the raw image data.

The purity filtered reads from the standard Illumina processing pipeline were aligned to the NCBI36 human reference genome (1000 genomes pilot paper version) using both MAQ v0.7.1 [14] and BWA v0.5.7,[15] generating a BAM[16] alignment file per sample for each aligner. The duplicate fragments in each BAM file were then marked using Picard v1.27 [17] and base qualities were recalibrated using GATK v1.0.4269M.[18] SNVs were called on the MAQ and BWA alignments independently, per sample, using samtools v0.1.7 [16] and filtered using a minimum read depth of 4x, minimum consensus base quality of 20, minimum SNV quality of 30, minimum root mean squared (RMS) mapping quality of reads covering the site of 30 and excluded if outside relevant target calling regions.

Results:

Additional GAMM analyses:

For the psychiatric samples, at the study inclusion, setting the limit at 10% of the minimal value of the therapeutic range, 96%, 90% and 84% of samples 1, 2 and 3, respectively, met this threshold criterion for medication compliance. After raising the threshold to 50% and 100% of the minimal value of the therapeutic range, patients who met these thresholds were 82% and 66% of sample 1, 74% and 60% of sample 2 and 82% and 57% of sample 3, respectively. By setting the threshold at 50% as an indicator of medication compliance, the associations between *CRTC1 rs3746266A>G* and BMI remained significant in the 3 psychiatric samples and in the combined sample (eTable 8). The same significant association between *CRTC1 rs3746266A>G* and BMI was also observed at the threshold of 100% of the minimal value of the therapeutic range (data not shown).

In order to only focus on psychotic disorders and mood disorders (F2 and F3 classifications), additional GAMM analysis including only these 2 diagnosis showed the same significant association between *CRTC1 rs3746266A>G* and BMI (data not shown).

Appetite and physical activity in the psychiatric cohorts:

Data regarding the appetite and physical activity were available at different time points in the prospective study (sample 2). For this sample, appetite data were dichotomized into normal or moderately increased appetite versus strongly increased appetite, whereas physical activity was dichotomized into ≤ 60 min or > 60 min of physical activity per day. To examine the association between appetite or physical activity with the CRTC1 SNP, chi2 tests were performed and then multilevel mixed models for binary responses were used to control for non-genetic factors. The multilevel mixed model showed appetite to be associated with age, BMI and standardized antipsychotic doses, but not with the *CRTC1 rs3746266A>G*. Regarding physical activity, this variable was not associated with the *CRTC1 rs3746266A>G*, or any non-genetic factor included in the multilevel mixed model.

For samples 1 and 3, only data regarding change in appetite and/or physical activity related to the current psychiatric treatment were available. These data were taken only once at the time of inclusion. To examine the association with CRTC1 SNP, chi2 test was applied and then a logistic regression was used to control for non-genetic factors. In both samples, no association was observed between appetite change and *CRTC1 rs3746266A>G*, whereas appetite change was associated with age, smoking status and BMI according to the logistic regression model. Similarly, in both samples, physical activity was associated with the BMI but not the *CRTC1 rs3746266A>G.*

Members of the ODEX team include:

The GSK members that meet authorship criteria:
Linda C. McCarthy, Judong Shen, Matthew R. Nelson, Peter M. Woollard, Keith L. Nangle, Kijoung Song, Dawn M. Waterworth, John C. Whittaker.

The Wellcome Trust Sanger Institute members that meet authorship criteria:
Inês Barroso, Eleftheria Zeggini, Aaron Day-Williams, Margarida C Lopes, Lorraine Southam, Ioanna Tachmazidou, Jennifer Asimit, Eleanor Wheeler, Carol E Scott, Alison J Coffey, Chris Tyler-Smith, Yali Xue, Yuan Chen, Jillian Durham and Felicity Payne (also Sarah Hunt, who has now left the institute and is working at the European Bioinformatics Institute).

The CoLaus members that meet authorship criteria (alphabetical order):
Jacques S. Beckmann, Sven Bergmann, Murielle Bochud, Zoltan Kutalik, Pedro Marques-Vidal, Vincent Mooser, Peter Vollenweider, Gérard Waeber.

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