Literature search

The research was conducted on PubMed, Medline (Ovid), Scopus and PsyINFO (Ovid) with a dateline of February 2016, using these search filters in different combinations: ADHD or Attention-deficit/hyperactivity disorder, children, adults, gene, genetics, linkage, locus, copy number variants or CNV, genome wide association or GWA, expression, mRNA, microRNA, peripheral levels, biomarkers, plasma, serum, saliva, urine, cerebrospinal fluid; along with the consultation of database http://adhd.psych.ac.cn/index.do . Moreover we considered in our analyses seven (Lasky-Su et al. 2008; Neale et al. 2008; 2010; Mick et al. 2010; Hinney et al. 2011; Stergiakouli et al. 2012; Yang et al. 2013) and two (Lesh et al. 2008; Sanchez-Mora et al. 2015) SNPs-GWAS in children and adults with ADHD respectively, as well as ten (Elia et al. 2010; Williams et al. 2010; Elia et al. 2011; Lesch et al. 2011; Lionel et al. 2011; Stergiakouli et al. 2012; Williams et al. 2012; Yang et al. 2013; Akutagava-Martins et al. 2014; Jarick et al. 2014) and two (Akutagava-Martins et al. 2014; Ramos-Quiroga et al. 2014) CNVs-GWAS in children and adults with ADHD respectively. The most recent meta-analyses (Gizer et al. 2009; Landaas et al. 2010; Smith 2010; Reif et al. 2011; Sanchez-Mora et al. 2011; Wu et al. 2012; Shiffrin et al. 2013; Sun et al. 2014; Pan et al. 2015; Lee et al. 2015) of candidate genes have been divided into single studies.

Inclusion/exclusion criteria.

We selected articles that met the following inclusion criteria: (1) ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders—version IV (DSM-IV) or the International Classification of Diseases—10th Revision (ICD-10); (2) having a case-control or family-based study design for genomic studies, (3) having a drug free/naïve case-control study design for metabolomic studies; (4) longitudinal studies; 5) English language.

From these studies, we excluded those: a) performed on animals; b) using samples that did not separate children and adults; and c) that were reviews or case reports. To obtain a list of genes and proteins equally studied in both populations of children and adults with ADHD, we excluded the

studies where a gene or a protein was investigated or only in ADHD children or only in ADHD adults.

Methods

In relation to candidate gene association studies, the cut-off used to define a positive or negative association was set to a canonic p value < 0.05 after the correction for multiple tests. In relation to genome-wide association studies both for common (SNPs) and rare (CNVs) variants, the cut-off was set to a arbitrary p value of $1x10^{-5}$. We consulted three recent papers (Poelmans et al. 2011; Lotan et al. 2014; Hawi et al. 2015) showing the best genes associated to ADHD according to SNPs/CNVs-GWA approaches. The genes showing associations with a p value of $1x10^{-5}$ were tested if belonging to cADHD and aADHD.

For all genes/proteins, the results were obtained considering each single study, thus the meta-analyses available for each of them were divided into single studies.

A total of eligibility 350 findings from genomics and metabolomics were found for cADHD and 91 for aADHD (PRISMA Flow-chart, Figure 1).

Statistical analyses

Supplementary Table 1 shows a database that comprises all genes and proteins implicated by genomic and metabolomic studies of cADHD and of aADHD. It reports positive and negative results for each gene/polymorphism/protein. The calculations were performed considering single studies and a study performed on two populations (a replica) was calculated twice.

The histogram showed in Figure 2 was the result obtained performing the following calculations:

{[(positive findings – negative findings)]/total findings=833} x 100 in children

{[(positive findings– negative findings)]/total findings=249} x 100 in adults

Supplementary Tables 2 shows the statistical analyses (2-way Contingency Table Analysis) in relation to the different molecular pathways associated to cADHD and/or aADHD.

The analyses were performed by using the software SPSS vs 12.

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