Autism Insights

SHORT REVIEW

Autism and Obesity: Prevalence, Molecular Basis and Potential Therapies

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Abstract: Studies in the past have suggested that autistic children are at higher risk of developing obesity as compared to the general population. Not enough research has been done to examine the co-existence of obesity in children with autism spectrum disorders. Although studies have attempted to define the prevalence of obesity in autism, none of these studies have explained the molecular basis of this overlap. In this review, we summarize not only the previous investigations related to autism and obesity but also present a systematic biology oriented pathway based analysis. We hypothesize that defining the common molecular gene targets as well as shared pathways between autism and obesity could be the key to develop therapies for individuals who present phenotype of autism as well as obesity.

Keywords: autism, obesity, molecular pathways, genetics

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Introduction

Obesity is a pandemic of the 21st century with more than 300 million individuals' affected worldwide.[1] It affects the people of all age groups however people with existing chronic conditions and disabilities are seen to be at the highest end of the risk curve.[2,3] Published literature offers a substantial evidence that disabled individuals are more vulnerable to obesity and associated negative consequences. This emphasizes the importance of health promotion and obesity prevention in high risk populations.[4] There are studies which have examined the prevalence of obesity in children with developmental disabilities like Down syndrome and Prader-Willi syndrome.[5–8] However, very limited amount of work has been done regarding the assessment of the prevalence of obesity in children with other developmental disabilities like autism spectrum disorders (ASDs).[9–11] Autism is a severe neurodevelopmental disorder which is characterized by social deficits, impaired communication and stereotypical, repetitive and narrow behaviors.[12,13] It has onset in childhood, usually by 3 years of age. The prevalence of ASDs is currently estimated to be one in 150 to one in 91 individuals.[14] The research focus is slowly shifting from language, psychology and behaviour of the autistic children to their body growth and nutritional status.[15–18] With alarming increase in the incidence of autism in past decade, it becomes important to study autism from different perspectives that have been neglected in past or were not considered to be of high importance. To demonstrate that obesity in autism is an understudied problem, the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was searched and we retrieved only 114 (dated March 21, 2011) results by using the keywords "autism AND obesity". Whereas the individual keywords such as "autism" and "obesity" retrieved 17175 and 144484 results from PubMed respectively. It shows that only 0.66% published journal articles available in PubMed reflect co-occurrence of words 'autism' and 'obesity'. This explains that the research exploring co-existence of obesity and autism is scarce.

This review is an attempt to explore the genetic basis of the co-existence of autism and obesity. The review starts with summarizing studies explaining prevalence of obesity in autism and the circumstantial causes for this observation at the social and environmental level. We further attempts to identity common molecular pathways prevailing in autism and obesity. The review goes one step further by emphasizing that drugs affecting molecular pathways could potentially be more useful as new treatment options for complex diseases.

Prevalence Rates and Risk of Obesity in Autism

Body Mass Index (BMI) is considered to be the most reliable index for assessment of overweight and obesity. The BMI for age charts are recommended by various scientists.[19–21] Revised growth charts from the Center for Disease Control and Prevention (CDC) include an age- and sex-specific BMI reference for children aged 2–20 years.[20] Based on the CDC references, children are classified as overweight and at-risk-of-overweight. Children who have BMI greater than or equal to 85th percentile (BMI $\geq$ 85th) are referred as at-risk-of-overweight and children having BMI at or above 95th (BMI $\geq$ 85th) percentile are considered as overweight.[22] Flagel et al (2006) used terminology where the terms 'overweight' and 'obesity' correspond roughly to the levels that would be labeled as 'at risk of overweight' and 'overweight' respectively, using CDC (2000) growth charts.[23] Only few studies (Table 1) have addressed varying prevalence's of obesity in children and adolescents with autism.[9,10,18,24–32] A secondary analysis of data from National Survey of Children's Health was done[9] and the children were classified as obese on the basis of standards provided by CDC.[22] It was concluded that children with autism were more likely to be obese than children without autism. The prevalence of obesity in children with autism was 30.4% compared to 23.6% among children without autism ($P = 0.075$). Children with autism had 1.42 times (95% CI, 1.00, 2.02, $P = 0.052$) higher risk of developing obesity as compared to non-autistic children. However, in a previous study[10] it was reported that among children with ASD, the overall prevalence at-risk-for-overweight and overweight was 35.7% and 19%, respectively, while in reference population the respective figures were 31% and 16%. Further, Xia et al (2010) reported 31.5% of obesity among Chinese children with autism.[31] An analysis of data collected by National Survey of Children's Health (NSCH-2003)[24] reported prevalence of obesity among children with autism was 23.4% which was higher as compared to their

Table 1. Prevalence of obesity among autistic children of various countries where percentages of obese individuals among different study groups are summarized.

Country	Criteria used	Autistic children % obese (age group/gender)	Healthy normal children % obese (age group/gender)	Reference
Iran	CDC	11.1 (Boys) 13.0 (Girls)	–	26
USA	CDC	30.4 (3–17 yrs)	23.6 (3–17 yrs)	10
USA	CDC	18.8 (6–11 yrs) 50.0 (12–19 yrs)	15.8 (6–11 yrs) 16.1 (12–19 yrs)	9
China	WHO (1995)	31.5 (2–9 yrs)	–	27
China	(Barlow, 2007)	23.4 (10–17 yrs)	12.2 (10–17 yrs)	28
China	Barlow and Dietz (1998)	–	17.0 (2–5 yrs) 21. 8 (6–11 yrs)	17
Canada		42.0 (11.5 yrs mean age)	–	29
Egypt	–	16.1 (Boys) (6–24 yrs) 15.8 (Girls) (6–24 yrs)	–	31
Japan	–	22.0 (Boys) (6–17 yrs) 11.0 (Girls) (6–17 yrs)	–	24
Canada	Miller and Stephens (1986)	42.6 (13.3 yrs mean age)	15.0–25.00	32
Japan	–	25.0 (7–18 yrs)		25

Note: These studies are based on several classification criteria suggested by various agencies (CDC, WHO) or independent studies.

counterparts without autism (12.2%). Similarly in Canada, Eves & Ho (2008) also reported high rates of obesity (42%) among children with autism[25] whereas this figure was 23% in 1997.[26] The evaluation of the nutritional status of children with special needs in Alexandria city estimated incidence of obesity among autistic males and females as 15.8% and 16.1%, respectively.[28] A study of 140 Japanese children (7–18 years of age) with autism revealed that 25% of the children were classified as obese.[29] The difference in prevalence estimates among children with autism from different countries might be due to various environmental factors contributing towards the development of overweight/obesity. In addition, the observed differences might have also been due to different definitions of obesity, the diagnostic category, classification criteria used, or mode of recruitment into the studies. These are the technical caveats in the planning and execution of the epidemiological studies that could potentially lead to biased results.

Personal, social and environmental factors responsible for obesity in autism

There are a number of potential variables that could account for high prevalence of overweight and obesity among autistic children. Physical growth and dietary patterns are being recognized as an important part of many learning and developmental disorders.[33–36] Excessive television viewing has been repoted to be a cause of displacement of physical activity.[37] Several studies have given substantial evidence that people with disabilities are more likely to be sedentary[38–40] and experience substantially more barriers to physical activity participation compared to the general population.[39,40] In addition to this the observed low levels of physical activity might occur due to their impairments in social skills which may limit participation in structured activities with peers. It is also reported that children with ASDs have aversions to specific textures, colors, smells, temperatures, and brand names of foods, with some preferences for soft and sweet foods.[41–43] In a larger study[13] it was documented that autistic children had typical food preferences and they preferred energy dense foods within food groups (e.g., chicken nuggets, hotdogs, peanut butter, cake, etc.). Overprotective parents sometimes use highly dense caloric foods as reinforcers for good behaviour.[44] It is possible that these eating patterns might have their contribution to the development of obesity in this population of children.

It has also been reported that use of certain weight gaining medications may also cause significant increases in obesity particularly among people with mental illness, where these drugs are used on a

regular basis.[45,46] For example, some medications like sodium valproate or resperidone which are normally prescribed among children with intellectual disabilities are associated with excess weight gain.[47,48]

These studies have contributed significantly to establish a connection between autism and obesity at a quantitative level. The root-cause of this connection is unclear and we investigated the genetic basis of these disorders in order to get clues about their co-existence.

Genetic Basis of Autism

A number of studies have provided ample evidence for the biological basis of autism.[49–54] It has been proven in various studies that the risk of being diagnosed with autism is relatively high among children having affected sibling.[55–57] Furthermore, evidences of genetic basis of autism comes from various twin and epidemiological studies[50,58–60] which show that there are higher concordance rates (70%–90%) in monozygotic twins as compared to dizygotic twins (20%–30%), which makes autism as the most heritable of all other complex neuropsychiatric disorders. The genetic linkage studies[49,57,61–67] have indicated that many loci (2q32, 7q21-q22, 7q32 and 15q11-q13) might contribute towards risk of autism. Various studies have pointed towards the long arm of chromosome 7 as a strong candidate region.[68,69] Numerous candidate genes have been tested for their association with autism for example, reelin,[70,71] sertonin transporter gene[72–76] and contactin associated protein like-2 (CNTNAP2),[61,77] neurologin 4 (NLGN4), neuroligin 3 (NLGN3), neurorexin1 (NRXN1), neurexin 3 (NRXN3),[78–80] SHANK3,[81,82] FOXP2,[83] CD38,[84] Cadherins (CDH9, CDH10) and PTEN,[85] amyloid precursor protein-binding protein A2(APBA2),[86] acetylserotonin O-methyltransferase gene (ASMT),[87] Oxytocin receptor (OXTR) gene,[88] Disrupted-in-Schizophrenia 1(DISC1),[89] WNT2,[90] LAMB1,[91] UBE2H,[92] Engrailed 2 (EN2),[93] Tuberous sclerosis (TSC1), UBE3A, ATP 10A.[94]

Many chromosomal abnormalities like fragile X syndrome,[95–99] Down syndrome,[100] Turner syndrome,[101] Ret syndrome[102] and single gene disorders like tuberus sclerosis have also shown association with autism. Studies have also reported several chromosomal rearrangements like deletions and duplications in children diagnosed with autism.[103] The most frequent are maternal 15q11-13 duplications, duplications of 17p12, and deletions of 7q11.23, 17p11.2 and 22q11.2.[104] Many genes[105] and rare copy number variants (CNVs, lost or duplicated segments of chromosomes) have also been linked with autism.[106]

Genetic Basis of Obesity

Initially, obesity was considered to be a disease that follows the rules of Mendelian inheritance, but the advancement of molecular biology tools has revealed the polygenic nature of obesity. More than 430 genes or chromosomal regions have been associated with obesity.[107] It has become evident from numerous candidate gene association studies that there is an association between single nucleotide polymorphisms and obesity phenotypes.[107–110] Various twin and adoption studies have also shown the heritable nature of obesity.[111–113] The heritability values ranged from 6%–85% among various populations. Various genome wide linkage studies have also determined number of loci showing linkage with obesity phenotypes.[114–117] It has also been discovered that CNVs, can be responsible for obesity.[93] For example, the deletion on chromosome 16p11.2 has been reported as most common CNV in obesity.[118–120] The same deletion has also been reported in autistic individuals.[106,121] Recurrent deletions in this region enclosing the SH2B1 gene were also reported in early-onset obesity and in individuals suffering from neurodevelopmental disorders associated with phenotypic variability.[121] Another study done by Walters et al showed that high frequency of 16p11.2 deletion in cohorts was ascertained for both cognitive disability and obesity (2.9%) as compared to cohorts having either of phenotypes (0.4% 0.6%, respectively).[122] It is reported in various studies that there is a significant association between serotonin transporter promoter gene and obesity.[123–126] This point further strengthens the evidence that both autism and obesity may have a functional interrelationship but the extent of overlap between these two disorders at genetic level needs further exploration. In the light of above presented studies, it can be hypothesized that there may be some common genes or polymorphisms or mutations which could be responsible for both obesity and autism. In order to complement this hypothesis and in order to provide more clues about molecular interactions at gene level in autism and

obesity, a brief pathway based analysis is presented in the next section.

Potential Molecular Links between Autism and Obesity

In this section, we provide insights into the key molecular pathways contributing to both autism and obesity. We collected the lists of genes linked with autism and obesity. We curated 155 genes from published literature that have been experimentally linked with autism. We collected 305 genes from AutDb database (http://autism.mindspec.org/autdb/), 284 genes from SFARI gene (https://gene.sfari.org/autdb/HG_Home.do) and 195 genes from Entrez using keywords "autism Homo sapiens" (http://www.ncbi.nlm.nih.gov/sites/entrez). We could generate a list of 541 unique genes for autism.The search in Entrez Gene database using the relevant keywords "obesity Homo sapiens" retrieved 412 genes linked to obesity. The analysis is based on the assumption that the genes involved in specific pathways related to both autism and obesity could prove to be a link between these two diseases. Based on this assumption, a list of 36 common genes known to be involved in autism as well as obesity has been identified which is further referred to as 'test gene set' in the following text (see additional file 1). This test gene set was further used for the functional annotation analysis by software tool DAVID (Database for Annotation, Visualization, and Integrated Discovery).[127] The pathway analysis revealed that 27.8% of genes were involved in neuroactive ligand-receptor interaction, 16.7% in cytokine-cytokine receptor interaction, 11.1% in calcium signaling pathway, 11.1% in gap junction and and 8.3% in tyrosine metabolism. Since most of the genes from test gene set were mapped to 'Neuroactive ligand pathway', we tried to establish a link of this pathway with autism and obesity.

The PubMed search using keywords "neuroactive ligand receptor" retrieved 167 records while keywords 'neuroactive ligand receptor autism' and 'neuroactive ligand receptor obesity' retrieved two[128,129] and one[102] records respectively. A putative link was described[128] between cholesterol metabolism and autism explaining the role of cholesterol for production of neurosteroids as well as modulation of the oxytocin receptor, ligand activity and G-protein coupling of the serotonin-1A receptor. The study does not explain any direct role of the neuroactive ligand receptor pathway in autism. Das et al (2007) explained the role of neuroactive ligand receptor pathway in obesity which is found to be upregulated in obesity during the comparison of the genes' expression profiles of obese and diabetic individuals.[130] Notable point is that there is no experimental study available that could link autism and obesity based on shared molecular pathways however systems biology approach has attempted to link different pathways to psychiatric and metabolic disorders.[131] They observed that the pathways (neuroactive ligand receptor interactions, calcium signaling, as well as tryptophan and tyrosine metabolism) linked to neuropsychiatric disorders such as depression and anxiety disorder are also significantly associated with obesity, hypertension etc. We also found similar results in our analysis of test gene set. and we hypothesize that common molecular pathways contribute to co-existence of autism and obesity.

The search in Pubmed is not sufficient to support the proposed hypothesis, therefore, to test our results from above described analysis, we generated a network of functional classes that affect the expression of the test gene set using Pathway Studio software (Ariadne Genomics I (2010) Pathway Studio™. 8.0 ed.). Figure 1 represents the network of complex molecular interactions among members of test gene set and functional classes in a cell. These interactions are derived from published literature thus represent valid interactions among different biological entities. It can be clearly observed that the expression of this set of genes is affected by several types of receptors and protein kinases. The receptors generally bind to ligands and show their downstream effects in the cell.

Figure 1 highlights the role played by neuroactive ligand receptor interactions in molecular functioning of the cell. The role of these interactions in autism and obesity remains to be experimentally verified. Another hypothesis that arise from this brief investigation is that is there a scope or benefit of developing or testing drugs targeting the identified pathways in order to develop treatment options for a sub-set of autistic patients who are obese. The drugs targeting the components of shared pathway could work better for a sub-set of patients diagnosed with autism who are also obese.

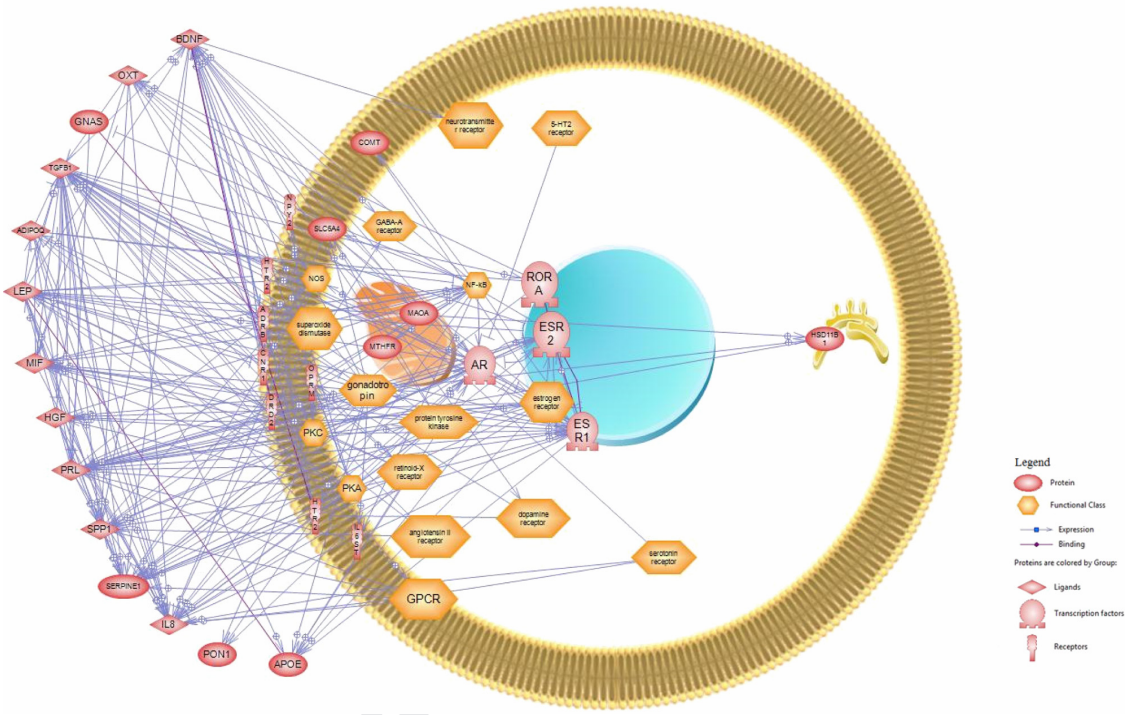

Figure 1. The network of molecular interactions of the genes common to autism and obesity. Out of 36, a list of 31 genes was mapped to different functional classes.
Abbreviations: PKA, Protein Kinase A; PKC, Protein Kinase C; GPCR, G-Protein Coupled Receptors.

Therapeutic implications of molecular pathways for autism and obesity

Let us now look if the hypothesis drawn on the basis of above analysis has any potential use in identifying the drugs that can offer new treatment options for patients with autism and obesity. The importance of usage of pathway based drugs has been emphasized previously.[132] The results presented in next sections also address an issue raised by previous studies where one of the most commonly used medication "risperidone" leads to weight gain in autism patients. We looked for the genetic targets of the drug risperidone and found that pharmacodynamics of risperidone is affected by polymorphisms in several genes including HTR2A, HTR2C, BDNF. The weight gain associated with risperidone therapy has been linked with polymorphisms in HTR2C.[133] All these genes affected by risperidone (as mentioned above) are also present in our test gene set. If we assume that these genes are among the key targets of risperidone in the cell then can we identify other drugs having same molecular targets for potential use to treat autism related symptoms. We searched the Cancer Resource database (http://bioinf-data.charite.de/cancerresource/).[134] This database is a collection of 2,716 drugs and 4244 targets leading to 11535 redundant drug target interactions. We used this database for two reasons; (a) there is no autism specific drug database available, (b) this database is a comprehensive resource where information about marketed drugs and compounds under testing is available and we are looking for drugs that target specific genes in a cell and not a specific disease. We mapped the test gene set of 36 genes in Cancer Resource database and the list of 314 drugs interacting with different genes (28 in number) has been presented (see additional file 2). For example, the drug 'minaprine' is an antidepressant and binds to serotonin type 2 receptors, dopamine D1 and D2 type receptors and the serotonin reuptake pump. It has the ability to block the reuptake of both dopamine and serotonin. The genes from the test gene set interacting with this drug are HTR2A, HTR2C, DRD2 and SLC6A4. All these are genes involved in serotonin system in the brain and are crucial for serotonin signaling in the brain.[135] Minaprine affects functioning of some of the genes in test gene set (associated with autism) and has been reported to be free of cardiotoxicity, drowsiness, and weight gain (http://www.drugbank.ca/drugs/DB00805). This sug-

gests that minaprine could be tested as a new drug for treatment of autism since no study is available in PubMed that explains testing of minaprine for treatment of autism. This drug could be more useful for autistic patients with obesity since no weight gain has been associated with minaprine therapy. DrugBank[136] explains that minaprine is a reversible inhibitor of MAOA—an enzyme that degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin, which is another gene in our test gene set. This discussion points out that minaprine could treat behavioural symptoms associated with autism by targeting the genes involved in serotonin signaling system and could have additional benefits for obese autistic patients by preventing excess weight gain associated with therapy.

Proof of concept in support of re-positioning of drugs based on pathway based analysis

To support the above-presented hypothesis of re-positioning of drugs based on genetic targets (drug-gene interactions), we performed an analysis using Ingenuity Pathway Analysis (http://ingenuity.com/) tool. The analysis was performed on 'test gene set' and the several pathways were mapped (Figure A1). The genes involved in these pathways were further overlaid with biological functions, diseases and drugs (Figure A2). This figure shows that the genes are involved in several neurological diseases and involved in brain activity or structure related functions. In Figure A2, three drugs are shown that have interactions with genes in the overlaid pathway. The target genes, actions and indications/status are shown in (additional file 3). The drug 'aripiprazole' was approved by FDA for treatment of autism in 2009 (http://www.medscape.com/viewarticle/713006) and was proved to reduce symptoms of irritability in children with autism of ages 6–17 years.[137] The additional file 3 also shows that this drug is also in various phases of studies for treatment of Alzheimer's disease, Asperger's syndrome and weight gain. Similarly, other two drugs 'risperidone' and 'sertraline' are in different phases of investigation for treatment of autism, obesity and other disorders. If we look closely then aripripazole, risperidone and sertraline have one, three and one gene targets respectively (additional file 3). Our argument in this manuscript is that if the drugs with single target can be used or tested for treatment of various diseases then why not drugs with multiple targets (for example—adaphostin targets eight genes and minaprine targets four genes in our analysis (additional file 2)) can be used for pre-liminary testing for potential treatment of both autism and obesity.

Conclusions and Future Directions

Obesity is now a general problem that is replacing the mere traditional public health concerns, including under nutrition and infectious diseases, and has proven to be one of the most significant contributors of ill health globally. This review suggests that obesity is a significant problem among individuals with autism. Furthermore the population data outlined above might have underestimated the magnitude of problem because the people who live in group homes or supporting facilities might have been excluded. Moreover, self report or parental report of height, weight could produce higher error rate. More research is needed to establish firm evidence of higher prevalence of obesity among individuals with autism and to examine factors that could explain higher incidence of obesity in this population. One more urgent area of study is the need to examine various co-morbodities associated with obesity and some of the challenges that these autistic individuals could face in maintaining a normal life style.

Alternately, more studies are needed to explore the molecular basis of co-existence of autism and obesity. This might provide insights into the relevant molecular mechanisms contributing to these diseases and also it may be possible to identify new drugs that could be better options for treating autistic patients with obesity. The pathway based approach used in the present investigation has provided clues for further research in the field. It is logical since both autism and obesity are polygenic diseases and genetic basis of these diseases is well studied but not well defined. The merger of genetic information along with targeted drugs could lead to personalized medicine for these individuals. The insights presented above warrant further experimental investigation and could open up a whole new area of research targeting a specific category of drugs in order to treat these complex conditions to improve lives in terms of physical and mental conditions of individuals with autism as well as obesity.

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Author Contributions

Conceived and designed the study: MK. Analysed the data: JRS, SS, MK. Wrote the first draft of the manuscript: JRS, ZA, MK. Contributed to the writing of the manuscript: SS. Agree with manuscript results and conclusions: JRS, ZA, SS, MK. Jointly developed the structure and arguments for the paper: JRS, SS, MK. Made critical revisions and approved final version: JRS, SS, MK. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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Additional Files

Additional File 1

Title: List of common genes between autism and obesity. The file presents the Entrez gene IDs and symbols of the genes that are found to be common between autism and obesity.

Additional File 2

Title: List of drug-gene interactions identified from Cancer Resource database. The matrix represents the interactions among drugs and common genes (between autism and obesity).

Additional File 3

Title: Overview of drugs targeting genes in pathway generated using IPA tool. File lists the genes used for pathway generation and their interaction with drugs. File lists the diseases which are under clinical investigation for treatment using drugs aripiprazole, resperidone and sertraline.

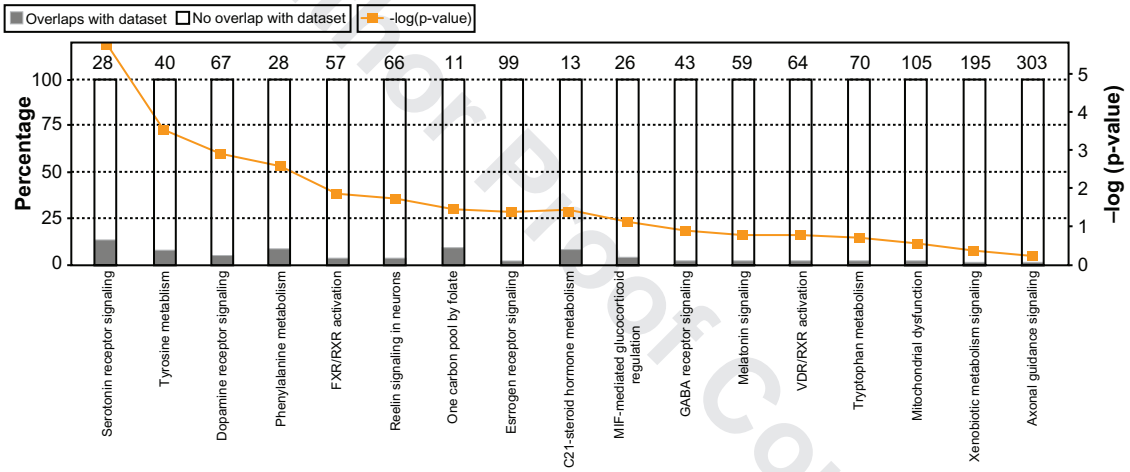

Figure A1. The graph shows the mapping of 'test gene set' into various pathways using IPA tool.
Note: The graph shows percent maaping along with number of total genes present in the pathway at top of each bar.

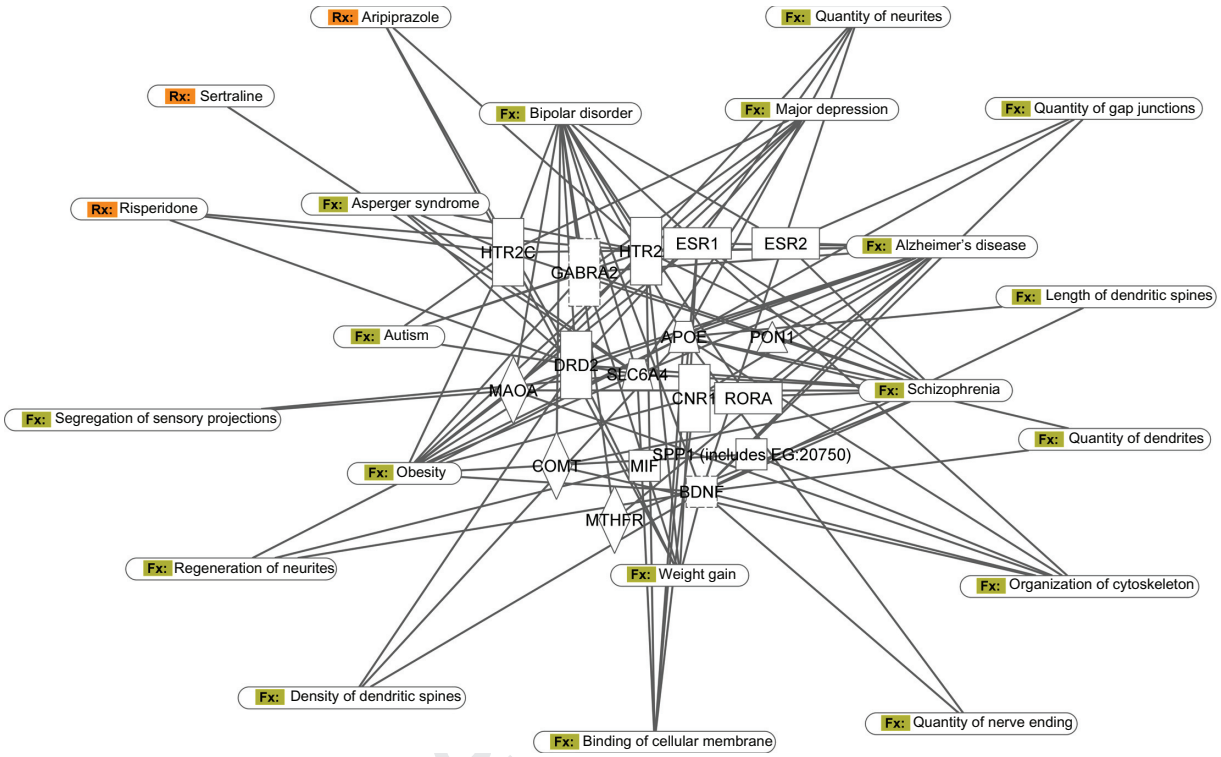

Figure A2. Overlaid pathway generated using IPA tool.
Note: The genes mapped on pathways (Figure A1) were used for building pathways by overlaying with different functional classes, drugs and diseases.