Associations between the LEP -2548G/A Promoter and Baseline Weight and between LEPR Gln223Arg and Lys656Asn Variants and Change in BMI z Scores in Arab Children and Adolescents Treated with Risperidone

Noor B. Almandil a, b, Rohit J. Lodhi c, Hongyan Ren c, Frank M.C. Besag b, d, David Rossolatos c, Ruth Ohlsen e, Caitlin Slomp c, Diego L. Lapetina c, Giona Plazzotta c, Macey L. Murray b, f, Abdulsalam A. Al-Sulaiman g, Paul Gringras h, Ian C.K. Wong b, i, Katherine J. Aitchison c, j

a Department of Clinical Pharmacy Research, Institute for Research and Medical Consultation, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; b Centre for Paediatric Pharmacy Research, Research Department of Practice and Policy, UCL School of Pharmacy, London, UK; c Departments of Psychiatry and Medical Genetics, University of Alberta, Edmonton, AB, Canada; d Child and Adolescent Mental Health Service, Learning Disability Team (CAMHS LD), South Essex Partnership NHS Trust, Wickford, UK; e Department of Post-Graduate Research (affiliated with Mental Health), Florence Nightingale School of Nursing and Midwifery, King’s College London, London, UK; f The Comprehensive Clinical Trials Unit (part of the Institute of Clinical Trials and Methodology), UCL, London, UK; g Vice Rector for Graduate Studies and Scientific Research, University of Dammam, Dammam, Saudi Arabia; h Evelina London Children’s Hospital, Guy’s and St Thomas’ NHS Trust, London, UK; i Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, China; j Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK

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Abstract
Data on baseline (antipsychotics-naïve) age, weight, and height, and change in these at 3 subsequent follow-up time points up to 313.6 days (95% CI 303.5–323.7) were collected from 181 risperidone-treated children and adolescents (mean age 12.58 years, SD 4.99, range 2.17–17.7) attending a pediatric neurology clinic in Saudi Arabia. Owing to differences in genotypic distributions in the subsamples, results are reported for the white Arab population (n = 144). Age- and gender-normed body mass index (BMI)-standardized z scores (BMI z) were calculated (LMSgrowth program). Linear regression was performed for baseline weight and BMI z, while change in BMI z was assessed using random effects ordered logistic regression. The following single nucleotide polymorphisms (SNPs) were analyzed: rs7799039 in the LEP promoter, rs1805094 (previously rs8179183), rs1137100 and rs1137101 in the LEPR, and rs1414334 in HTR2C. We found a nominally significant association between rs7799039 and baseline weight, adjusting for height, age, gender, and diagnosis (A/G, p = 0.035, β = −3.62 vs. G/G). The rs1137101 (G/G, p = 0.018, odds ratio [OR] = 4.13 vs. A/A) and rs1805094 C al-
lele carriers \( (p = 0.019, \text{OR} = 0.51) \) showed nominally significant associations with change in BMI \( z \) categories. Our data support and replicate previous relevant associations for these variants (including with weight gain when on risperidone), whilst being the first report of such associations in patients of Arab ethnicity.

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Introduction

Antipsychotics are now relatively commonly used in children and adolescents for a variety of indications including mood disorders, disruptive behavior disorders, developmental disorders, and psychosis [1–4]. While weight gain when on antipsychotics has received greater attention in adults, it is also a relatively common adverse effect in children and adolescents [1]. The distribution of such weight gain tends to be central (abdominal), which is associated with dysregulation of adipokines including leptin, ghrelin, and adiponectin. Such dysregulation may be associated with cognitive impairment as well as with long-term adverse health outcomes (diabetes, cardiovascular disease, and some forms of cancer) [5–7]. Risperidone is the most frequently prescribed atypical antipsychotic in children and adolescents [1–4].

There are clear interindividual differences in the magnitude of weight gain in patients treated with antipsychotics. Underlying these differences are both genetic and environmental factors, such as diet and sedentary lifestyle and the interaction between these [8, 9]. The leptin \( (\text{LEP}) \), leptin receptor \( (\text{LEPR}) \), and serotonin 5-HT2C receptor \( (\text{HTR2C}) \) genes are among those with the strongest evidence for association with antipsychotic-induced weight gain [10–16], including specifically in risperidone-treated patients [17–20].

Markers rs7799039, rs1137101, and rs1805094 are single nucleotide polymorphisms (SNPs) in the \( \text{LEP} \) promoter and \( \text{LEPR} \) with previously identified relevant associations [21, 22], although results have been variable [23–26]. SNP rs7799309 (-2548G/A) is located in the \( \text{LEP} \) promoter. In a study of the \( \text{LEP} \)-2548G/A variant in risperidone-treated children and adolescents, a lele carriers showed a steeper rate of increase in weight gain and G/G genotype carriers were 2 times less likely to be overweight [17]. This marker has also been associated with a measure of metabolic dysfunction, cholesterol/high density cholesterol ratio, in adult male patients using atypical antipsychotics who were at a relatively early phase (<1 year) of treatment [24]. Other studies in adults did not find any association between rs7799309 and obesity after 3 months of using antipsychotics [27], or weight gain after being on antipsychotics [28]. To our knowledge, only one study has examined rs7799309 and antipsychotic related weight gain in children and adolescents, and it reported that A allele carriers had steeper weight gain [17]. The \( \text{LEP} \) rs1137101 and rs1805094 (into which rs8179183 has been merged) are functional variants encoding amino acid changes: the former \( (\text{c.668A>G}) \) encodes a glutamine to arginine substitution at amino acid 223 \( (\text{Q223R}) \), and the latter \( (\text{c.1968G>C}) \) encodes a lysine to asparagine substitution at amino acid 656 \( (\text{K656N}) \). In a study of \( \text{LEP} \) Q223R in 200 adult patients treated for a psychotic disorder with antipsychotics, in females, the average body weight was 13.6 kg more (95% CI 1.11–26.1) in the \( \text{LEP} \) Q223R group than in the \( \text{LEP} \) Q223R group [27]. In a previous study of 13 SNPs and weight profile in olanzapine- and risperidone-treated patients [26], the strongest genetic association for the risperidone-treated group was found with rs8179183 \( (\text{the minor allele C being protective against weight with a frequency of 20% in those with a weight of 40–60 kg and approaching 0% for those weighing >100 kg}) \). We herein report genetic association analysis of the above SNPs in \( \text{LEP} \) and \( \text{LEPR} \) and of rs1414334 in \( \text{HTR2C} \) in white Arab children and adolescents with various diagnoses treated with risperidone.

Materials and Methods

Sample

Children and adolescents aged ≤18 years who were taking risperidone were eligible for inclusion. The following patients were excluded: those with anorexia or bulimia nervosa, those taking > 1 antipsychotic drug, those taking other medications that could affect weight gain \( (\text{e.g., corticosteroids, valproic acid, or methylphenidate}) \), and those with concurrent medical conditions that could affect weight gain \( (\text{e.g., diabetes, Cushing’s syndrome, or renal disease}) \).

Ethics approval was obtained from the Department of Neurology, King Fahd Hospital of the University of Damman in Saudi Arabia. Study information sheets and consent forms were provided in multiple versions: for parents or guardians, and in age-appropriate versions so that participants could also understand \( (\text{children aged <8, 8–11, and 12–15 years; adolescents aged 16–18 years; with additional assent forms for those >8 years}) \). N.B.A. or the physician provided verbal translations for the study information sheets and consent forms as required. Informed consent was obtained from the parents or guardians for all participants included and children with capacity also gave their assent.

Eligible participants were identified from the Pediatric Neurology Clinic, Department of Neurology, King Fahd Hospital. All were seen at the hospital by the researcher \( (\text{N.B.A.}) \) with the responsible physician. Data on the following were extracted from

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patient clinical records: age, gender, date of birth, ethnicity, diagnosis, risperidone dose, weight, and height. Dates of clinic visits were recorded from baseline (when risperidone was first prescribed, all patients being antipsychotic-naive at baseline, visit 0) to the third visit (visit 3). The time between visits was 3–6 months depending on the patient’s condition.

Age- and gender-normed body mass index (BMI)-standardized $z$ scores (BMI $z$) were generated using the LMSgrowth program, designed for use with growth references based on the LMS method [29]. In brief, the LMS method summarizes BMI data in terms of three smooth age-specific curves called $L$ (lambda), $M$ (mu), and $S$ (sigma). The $M$ and $S$ curves correspond to the median and coefficient of variation of BMI at each age whereas the $L$ curve allows for the substantial age-dependent skewness in the distribution of BMI. The values for $L$, $M$, and $S$ can be tabulated for a series of ages. Patient ID, date of birth, age, sex, height and weight were inputted into the program and BMI standard deviation score (SDS-BMI, or BMI $z$) was calculated [29].

Genetic Analysis

DNA was extracted from buccal swabs at the Institute of Psychiatry, Psychology and Neuroscience, London, UK, as previously described [30]. Genotyping for 5 SNPs, i.e., the $2548G/A$ promoter SNP (rs7799039) for $LEP$, K109R (rs1137100), Q223R (rs1137101), K656N (rs1805094) for $LEPR$, and the $HTR2C$ rs1414334 C/G intronic polymorphism, was performed using TaqMan SNP genotyping assays on a ViiaTM 7 real-time polymerase chain reaction (PCR) system (Applied Biosystems/Life Technologies/Thermo Fisher, Canada) at the University of Alberta, Edmonton, ON, Canada. Although the $D’$ between rs1137101 and 1137100 was high at 0.84 and that between rs1137101 and 1137100 was high at 0.84 and that between rs1137101 and 1137100 was high at 0.84 and that between rs1137101 and 1137100 was high at 0.84 and that between rs1137101 and 1137100 was high at 0.84, the $r^2$ between these pairs of markers in our data was $<0.5$ (0.15 and 0.08, respectively), so all markers were taken forward for analysis.

Statistical Analysis

STATA 15.1 was used to conduct the analyses. One-way ANOVA was initially used to examine the effects of potential covariates on baseline weight. Linear regression was performed for the baseline outcome variables, weight and BMI $z$, to explore which of the two should be used for the repeated measures analysis. The linear regression model was as follows: baseline weight as the dependent variable and the following as independent variables: age in years, gender, diagnosis (psychosis vs. the rest), height, and genotype. Separate regressions were run for each of the 4 markers analyzed.

For the longitudinal analysis, preliminary linear mixed model analyses of change in BMI $z$ revealed a poor distribution of the residuals. BMI $z$ was therefore converted into an ordinal variable for ordered logistic regression as follows: 0, 1, 2, and 3 for BMI $z$ scores $<-2$, $-2$ to $-1.99$, $-2$–$-2.99$, and $\geq 2$, respectively, based on previous literature [31]. Analysis of change in BMI $z$ (thus-categorized) over visits was conducted using random effects ordered logistic regression. Random effects ordered logistic regression in STATA is an efficient method to test longitudinal trends in an ordered variable [32]. The predictors in all such analyses were: genotype, baseline BMI $z$ and diagnosis. To assess the effect of genotype over visits on BMI $z$, an interaction term between genotype as a factorial predictor and visit as a continuous predictor was employed, adjusting for baseline BMI $z$, with each genotypic analysis being run separately. In the random effects ordered logistic regression STATA analysis settings, subjects were used for the “panel ID variable” and visit was the “time variable”. Results are reported using the odds ratio (OR) and $p$ value, without adjustment for multiple testing and therefore termed nominally significant.

Results

Of the 181 Arab patients approached, all provided consent, and usable data were available for 162 (144 white and 18 black Arabs). Minor allele frequencies differed significantly between black and white Arabs (data not shown), and so, given their relatively small numbers, the black Arabs were excluded from further analyses. The diagnostic distribution in the 144 white Arabs (98 boys and 46 girls) was as follows: 23 (15.97%) had autism, 65 (45.14%) had attention deficit hyperactivity disorder (ADHD), 50 (34.72%) had a psychotic disorder (schizophrenia/schizoaffective disorder/bipolar disorder/psychosis not otherwise specified), 3 (2.08%) had disruptive behavioral disorders or aggression, and 3 (2.08%) had developmental disorders. The mean age was 12.58 (SD 4.99) years and there was a significant difference in age between the different diagnostic groups ($p < 0.001$). The mean age of those with autism, ADHD, psychotic disorder, disruptive behavior disorders, and developmental disorders was 12.01, 10.26, 15.92, 16.43, and 7.69 years, respectively. The mean number of days between baseline and the first, second, and third follow up visits was 106.7 (95% CI 102.1–111.4), 209.7 (CI 202.9–216.5), and 313.6 (CI 303.5–323.7), respectively.

The genotyping call rate was 100%. All SNPs were in Hardy-Weinberg equilibrium ($p = 0.58, 0.82, 0.21, 0.18, and 0.42$ for rs7799039, rs1137101, rs1805094, rs1137100, and rs1414334, respectively, with the Hardy-Weinberg $p$ value for the last being calculated from the subgroup of girls). As rs1414334 is an X-linked SNP, genotypes for boys were coded as 0 and 1 and for girls as 0, 1, or 2.

On examination by ANOVA of potential covariates (height, age, gender, and diagnosis) to include in the linear regression model of baseline weight, there were significant effects of height ($F = 598.04, p < 0.0001$), diagnosis ($F = 9.53, p < 0.0001$), age ($F = 357.8, p < 0.0001$), and gender ($F = 4.27, p = 0.04$). Risperidone dose was not included in this baseline analysis as all patients were drug-naïve at baseline. Owing to the significant difference in age between the different diagnostic groups, graphical visual inspection of weight by diagnostic group was performed, which showed that those with a psychotic disorder had a higher baseline weight. The mean weight of

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those with a psychotic disorder was 68.20 kg (95% CI 65.89–70.50), while that of the rest was 48.26 kg (95% CI 46.04–50.48). The diagnosis variable was therefore dichotomized into psychosis versus the rest of the diagnoses.

Linear regression analyses of baseline weight by genotype showed a nominally significant effect of rs7799039 A/G genotype ($p = 0.035$, $\beta = –3.62$) with a trend for A/A genotype ($p = 0.097$, $\beta = –4.34$), both being associated with lower baseline weight than G/G (Table 1). The proportion of the variance in weight ($R^2$) accounted for by the model was high at 81%, and the residual distribution good (Fig. 1). There was no effect of the other genotypes: for rs1414334, no difference in baseline weight between C/G ($p = 0.666$, $\beta = –0.625$) and C/C ($p = 0.216$, $\beta = –0.848$) versus A/G; for rs1137100, no difference for A/G ($p = 0.528$, $\beta = –1.36$) versus A/A; and for rs1805094, no difference for C/G ($p = 0.066$, $\beta = –0.228$) and C/C ($p = 0.918$, $\beta = 0.417$) versus G/G. By contrast, although linear regression of baseline BMI $z$ (without gender, age, and height, since BMI $z$ takes these variables into account) gave a significant $p$ value for the A/G genotype for rs7799039 ($p = 0.049$, $\beta = –0.604$), the model adjusted $R^2$ was low at 3.5%, and the residual distribution poor (data not shown).

In the random effects ordered logistic regression analysis of change in BMI $z$ category over time, we observed the following: a significant effect of rs1137101 G/G ($p = 0.018$, OR = 4.13) versus A/A, but not of A/G ($p = 0.826$, OR = 1.06) versus A/A (Table 2). A significant effect of rs1805094 C/G ($p = 0.042$, OR = 0.547) and a trend level effect of C/C ($p = 0.083$, OR = 0.27) versus G/G was also seen (Table 3). Given the previous literature [26] and this pattern in our data, we grouped the C/G and C/C genotypes together, and re-ran the ordered logistic regression, which resulted in a $p$ value of 0.019 and an OR of 0.55. In the rs7799039 analysis, a trend level effect for individuals of A/G genotype ($p = 0.068$, OR = 1.72) compared to G/G was seen, with no such trend being seen for the A/A group ($p = 0.678$, OR = 0.84). For rs1414334, there was no significant effect of C/G ($p = 0.431$, OR = 0.72) or C/C ($p = 0.431$, OR = 0.79) compared to G/G genotype. Similarly, for rs1137100, there was no significant effect for A/G ($p = 0.128$, OR = 1.85) compared to A/A. All results are for genotype by visit interaction for change in BMI $z$ category over time.

**Table 1.** Linear regression showing the nominally significant association between baseline weight and rs7799039 genotype (with G/G as the reference genotype)

|                  | $\beta$ | $t$  | $p$     | 95% CI          |
|------------------|---------|------|---------|-----------------|
| rs7799039        |         |      |         |                 |
| A/G              | –3.62   | –2.13| **0.035**| –6.97 to –0.266 |
| A/A              | –4.34   | –1.67| 0.097   | –9.48 to 0.801  |
| Age (years)      | 0.001   | 0.9  | 0.372   | –0.001 to 0.004 |
| Gender           | 0.383   | 0.21 | 0.833   | –3.19 to 3.96   |
| Diagnosis        | –2.50   | –1.32| 0.188   | –6.24 to 1.24   |
| Baseline height  | 0.71    | 7.90 | <**0.001**| 0.533 to 0.889  |

Bold type denotes significance.

**Table 2.** Ordered logistic regression analysis of BMI $z$ category, showing a nominally significant rs1137101 by time interaction

|                  | OR   | $z$  | $p$     | 95% CI          |
|------------------|------|------|---------|-----------------|
| rs1137101        |      |      |         |                 |
| A/G              | 0.857 | –0.19| 0.852   | 0.169–4.34      |
| G/G              | 0.163 | –1.16| 0.245   | 0.008–3.48      |
| Time             | 2.00  | 3.61 | <**0.001**| 1.37–2.92      |
| rs1137101*Time   |      |      |         |                 |
| A/G              | 1.06  | 0.22 | 0.826   | 0.612–1.85      |
| G/G              | 4.13  | 2.37 | **0.018**| 1.28–13.38     |
| Diagnosis        | 2.95  | 1.53 | 0.127   | 0.734–11.82     |
| Baseline BMI $z$ | 21.15 | 7.54 | <**0.001**| 9.57–46.75     |

Bold type denotes significance.
Table 3. Ordered logistic regression analysis of BMI $z$ category, showing a nominally significant rs1805094 (previously rs8179183) by time interaction for the C/G genotype and a nominal trend for the C/C genotype.

|                 | OR   | $z$  | $p$    | 95% CI       |
|-----------------|------|------|--------|--------------|
| rs1805094       |      |      |        |              |
| C/G             | 1.63 | 0.57 | 0.568  | 0.304–8.71   |
| C/C             | 1.58 | 0.22 | 0.824  | 0.028–90.43  |
| Time            | 2.86 | 5.47 | <0.001 | 1.96–4.17    |
| rs1805094*Time  |      |      |        |              |
| C/G             | 0.547| −2.04| 0.042  | 0.307–0.978  |
| C/C             | 0.269| −1.74| 0.083  | 0.061–1.19   |
| Diagnosis       | 2.80 | 1.46 | 0.145  | 0.70–11.21   |
| Baseline BMI $z$| 19.75| 7.63 | <0.001 | 9.17–42.51   |

Bold type denotes significance.

Discussion

We observed a nominally significant association between LEP rs7799039 and baseline weight, with the A/G genotype being nominally associated ($p = 0.035$) with lower baseline weight and the A/A genotype having a trend level association ($p = 0.097$). In a sensitivity analysis entering all diagnoses into the model, the $p$ values were similar (0.037 and 0.12 for the A/G and A/A genotypes, respectively). The rs7799039 A/G genotype also had a trend level association ($p = 0.068$) with increase in BMI $z$ category over the 3 follow up time points (which also remained similar at $p = 0.074$ when entering all diagnoses into the model). In a previous study of risperidone in this age group by Calarge et al. [17], rs7799039 genotypes containing the A allele were associated with more weight gain. Their study did not find an association with baseline weight but, of note, the ethnicity of their sample ($n = 74$) was different from ours (84% non-Hispanic Caucasian, 12% African American, 3% Hispanic, 1% Other).

In the random effects ordered logistic regression, we observed nominally significant effects for the LEPR Gln223Arg and Lys656Asn variants. The rs1137101 G/G ($p = 0.018$, OR = 4.13) genotype encoding 223QQ increased the odds of an increase in BMI $z$ compared to A/A. In the sensitivity analysis entering all diagnoses rather than the dichotomized variable, this result remained similar ($p = 0.021$, OR = 3.91). Moreover, this finding is consistent with previous literature. Meta-analytic evidence suggests that rs1137101 (G/G) increases the odds of type 2 diabetes mellitus, and other studies suggest a role for the same in obesity [33, 34]. For rs1805094 (previously rs8179183), C allele carriers ($p = 0.019$, OR = 0.51) had reduced odds of BMI $z$ increase compared to G/G (and in the sensitivity analysis entering all diagnoses, the results were the same: $p = 0.019$, OR = 0.51). Interestingly, this is consistent with the results of Ruano et al. [26], who found that the strongest association with weight profile (out of 29 SNPs tested in 13 candidate genes) in the risperidone-treated group was with rs8179183 C allele carriers (encoding 656N), who, like in our sample, were relatively protected against weight gain compared to those of rs8179183 G/G genotype.

We included children treated with only one antipsychotic medication (risperidone), all of whom were antipsychotic-naive at baseline, unlike other studies in which adults treated with a variety of antipsychotics were pooled into a single analysis [26, 27, 35, 36]. This is the first report of associations of genetic markers with weight gain in Arab children and adolescents treated with risperidone. Of note, there is a relative paucity of publicly available data on DNA sequence variation in Arabs, so any contribution to genetic associations in this population is valuable. The fact that our findings are largely consistent with those of previous investigators despite differing ethnicities is also noteworthy.

The limitations of this study include sample size, gender distribution (low proportion of girls), and no measures of compliance or of activity level. Limited sample sizes increase the risk not only of finding a spurious positive association (a type I error) but also of missing genetic associations with small effect sizes (type II errors). However, a power analysis using Quanto 1.2.4 [37] revealed that, for a sample size of 130, with a SNP minor allele frequency of 0.28–0.29 (the frequency range for rs1137101), there was 80% power using an OR of 1.60 (in fact, substantially less than our OR for this marker) for the risk genotype in an additive model with $\alpha$ set at 0.05 (without adjustment for multiple testing); our sample was therefore sufficiently powered to generate a result of nominal significance. We did not adjust for multiple testing and hence report our findings as of nominal significance. An adjustment for multiple testing such as the Bonferroni correction would be too conservative, as this assumes independence of tests conducted. In fact, the variants are both statistically (in terms of linkage disequilibrium) and functionally significantly related (including the HTR2C polymorphism being associated with circulating levels of leptin [38]). Another potential criticism could be the focus on baseline weight rather than baseline BMI $z$ for the baseline analysis. We have justified this by presentation of the adjusted $R^2$ for both. Of relevance to

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the BMI z calculations, the Centers for Disease Control and Prevention 2000 growth charts do not include Arab ethnicity, which may explain why the use of the weight variable, adjusting for age, gender, height and diagnosis, was appropriate for the baseline analysis in our sample.

**Conclusion**

Our investigation of baseline weight and change in BMI z and relevant genetic variants in Arab children and adolescents treated with risperidone revealed associations with functional genetic variants in the leptin pathway. Specifically, baseline weight was nominally associated with SNP rs7799039 encoding LEP -2548G/A, while change in BMI z category was nominally associated with the LEPR 223QQ (rs1137101) and 656N (rs1805094/rs8179183) variants, the latter replicating an earlier report of this variant being protective against risperidone-associated weight gain. Further replication and extension to more diverse demographic groups are desirable. Specifically, we recommend further studies of this and other variants in the LEP promoter and LEPR versus baseline weight and BMI z category on treatment with risperidone and other antipsychotics in individuals of Arab and other ethnicities in this age group and in adults.

Given the association between markers in the leptin pathway and relevant Mendelian genetic disorders, it will also be interesting to see if such markers are associated with persistent weight gain on psychotropics despite interventions aimed at reducing weight gain, and (in a larger sample) whether they are associated with weight gain to an unhealthy extent (to an at least obese level). More thorough analysis of this gene including sequencing and haplotype analysis might result in the identification of other functionally relevant variants in this ethnic group. Although often difficult in practice, replication studies should ideally use protocols with antipsychotic monotherapy, especially for children and adolescents in their first psychotic episode, and, like our study, ideally commence data collection when patients are antipsychotic-naïve. Additionally, extending the analysis to other antipsychotics and to more genes, as well as conducting more complex analyses including consideration of gene-environment interactions including epigenetics and gene-gene interactions models, could shed further light on relevant biological mechanisms [39]. As patients and their caregivers are certainly interested in preventing and ameliorating antipsychotic-associated weight gain and predicting who will respond well to interventions for this and who will not, further collaborative research efforts in this area are indicated.

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**Statement of Ethics**

All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments, or comparable ethics standards.

**Disclosure Statement**

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