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Influence of Genetic Variants on Risperidone-Associated Prolactin Elevation in Thai Pediatric ASD Patients

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ABSTRACT

This study explored how variations in pharmacodynamic genes influence prolactin elevation in pediatric and adolescent patients with autism spectrum disorder (ASD) receiving risperidone. Using a retrospective cohort of 124 patients treated with risperidone for at least three months, we analyzed multiple gene variants and devised a novel genetic risk scoring system for the dopamine D2 receptor (DRD2) to simplify haplotype interpretation.While single nucleotide polymorphisms (SNPs) alone did not show significant associations with prolactin levels, a specific diplotype combination (H1/H3: A2/A2-Cin/Cin-A/G) spanning DRD2 and ANKK1 Taq1A, DRD2 -141C indel, and DRD2 -141A>G—corresponding to a genetic risk score of 5.5—was linked to the highest median prolactin concentration (23 ng/ml). Patients with this diplotype also exhibited markedly higher prolactin levels in response to increasing plasma concentrations of risperidone, its active metabolite 9-OH-risperidone, and the total active moiety.Interestingly, lower prolactin levels were observed in patients who achieved favorable clinical responses, suggesting an inverse relationship between therapeutic efficacy and hyperprolactinemia. By providing a framework for scoring DRD2 haplotypes based on predicted protein expression, this study establishes a potential tool for guiding pharmacogenetic-informed dosing strategies. Incorporating such genetic information into clinical decision-making may help minimize prolactin-related adverse effects in pediatric ASD patients treated with risperidone.

Keywords: Risperidone, Prolactin, Autism spectrum disorder, Pharmacogenomics, Dopamine D2 receptor

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Introduction

Risperidone is classified as an atypical antipsychotic and is frequently used to manage symptoms of autism spectrum disorder (ASD), functioning mainly through antagonism of dopamine D2 and serotonin 5-HT2A receptors [1]. The US Food and Drug Administration has approved its use for controlling irritability in children and adolescents between 5 and 16 years old with ASD [2]. Compared to conventional antipsychotics, risperidone demonstrates superior safety and effectiveness [3]. Evidence from two pivotal clinical trials [4, 5] confirmed both the tolerability and therapeutic benefit of risperidone in ASD patients, showing significant reductions in disruptive behaviors over an 8-week period, as assessed by the irritability subscale of the Aberrant Behavior Checklist (ABC). In these trials, the treatment groups showed improvements of 56.9–64.0%, markedly higher than the 14.1–31.0% observed in placebo groups [4, 5].

Research has also investigated plasma drug monitoring as a potential biomarker to guide treatment [6, 7]. Monitoring plasma concentrations may enhance both the efficacy and safety of risperidone therapy. In adults with schizophrenia, optimal clinical outcomes were linked to plasma levels of the active moiety between 20 and 60 ng/L [6, 8]. Notably, in a 6-week risperidone trial for schizophrenia, non-responders had significantly higher

plasma concentrations than responders [7]. However, such pharmacokinetic data are lacking for pediatric ASD populations.

Variability in risperidone response is partly attributable to genetic differences in drug targets. The DRD2/ANKK1 Taq1A polymorphism (rs1800497) has been linked to clinical outcomes in risperidone-treated ASD patients [9]. Alleles such as DRD2/ANKK1 Taq1A A2 or C have been associated with higher dopamine receptor density, potentially enhancing dopaminergic blockade [10, 11]. Additional DRD2 variants, including -241A>G (rs1799978) and -141C insertion/insertion, are implicated in elevated receptor expression and increased prolactin secretion, respectively [12, 13]. Moreover, children carrying the DRD3 Gly/Gly genotype (rs6280) demonstrated superior responses to risperidone compared to Ser/Ser carriers [14]. Variations in serotonin receptor genes (HTR2A, HTR2C), ABCB1, and transporter genes (SLC6A3, 5-HTTLPR/SLC6A4) can also modulate neurotransmitter availability, influencing treatment outcomes [15-18].

Prolactin, secreted by the anterior pituitary, plays a critical role in neuroendocrine regulation and stress responses [19]. Serum prolactin levels may reflect antipsychotic responsiveness. Studies indicate that prolactin may mediate some neuropsychiatric effects of risperidone [20-22]. Zhang *et al*. [20] reported a significant correlation between changes in PANSS positive subscale scores and prolactin levels in chronic schizophrenia. Similarly, Ates *et al.* [21] found that patients with hyperprolactinemia exhibited higher PANSS negative scores than those without ($p = 0.041$). Several factors can moderate risperidone response, with lower baseline prolactin associated with better outcomes in children with ASD [22]. Genetic variants in PRL and PRLR also influence prolactin levels; for example, the PRL SNP rs2244502 (A>T) corresponds to higher levels in T carriers, and the −1149 G>T (rs1341239) genotype occurs more frequently among hyperprolactinemic patients [23-25]. Together, these findings support the potential of prolactin as a biomarker for predicting risperidone response.

Despite this, the interplay between pharmacogenetics and risperidone-induced prolactin elevation remains underexplored. Stern *et al*. [22] highlighted the occurrence of hyperprolactinemia in pediatric ASD patients receiving risperidone. Accordingly, this study aimed to investigate associations between genetic polymorphisms in pharmacodynamic genes and increases in prolactin levels induced by risperidone in children and adolescents with ASD.

Materials and Methods

Participants

This study recruited Thai children and adolescents aged 3 to 18 years diagnosed with autism spectrum disorder (ASD) at Yuwaprasart Waithayopathum Child Psychiatric Hospital, Samut Prakan, Thailand, between 2017 and 2018. ASD diagnoses were confirmed following the DSM-5 criteria. Ethical approval was obtained from both the Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand (MURA2017/556) and Yuwaprasart Waithayopathum Child Psychiatric Hospital. Prior to participation, all patients or their parents provided written informed assent or consent after receiving a full explanation of the study aims and procedures. Information regarding demographics, including age, sex, daily risperidone dose, duration of treatment, and concurrent medications, was collected using a structured questionnaire. Participants were excluded if they were taking medications known to interfere with risperidone metabolism (such as haloperidol, fluoxetine, paroxetine, carbamazepine, or phenytoin) or that could alter prolactin levels (including haloperidol, sertraline, and fluoxetine).

Study design

This retrospective analysis included 124 ASD patients who had been on risperidone for at least three months. Serum prolactin concentrations, plasma levels of risperidone, 9-hydroxy-risperidone, and the combined active moiety were measured, and genotyping was performed for selected pharmacodynamic genes. Additionally, a subset of 19 patients who had never received risperidone was evaluated at baseline prior to starting therapy and followed for 3–20 months after initiation of risperidone. Behavioral assessments, along with serum prolactin and plasma drug levels, were conducted at both baseline and follow-up visits.

Behavioral assessment

Behavior was evaluated using the Aberrant Behavior Checklist (ABC), which consists of 58 items categorized into five domains: irritability, agitation, and crying (15 items); lethargy and social withdrawal (16 items); stereotyped behavior (7 items); hyperactivity and non-compliance (16 items); and inappropriate speech (4 items).

Caregivers rated each behavior on a 4-point scale from 0 (no problem) to 3 (severe problem), with higher scores reflecting greater behavioral difficulties [26]. The irritability subscale of the ABC is widely regarded as a gold-standard measure for assessing irritability and aggression in ASD treatment trials [27]. The Thai version of the ABC-C, adapted for cross-cultural relevance and validated for reliability, was employed in this study [28]. Patients were classified as responders if their total ABC score decreased by 30% or more and as non-responders if the reduction was less than 30%.

Serum prolactin measurement

A fasting morning blood sample was analyzed with a chemiluminescent immunoassay system (IMMULITE1000, Siemens Healthcare Diagnostics Products Ltd., Erlangen, Germany) at the Yuwaprasart Waithayopathum Child and Adolescent Psychiatric Hospital, Thailand.

Plasma drug measurement

Plasma concentrations of risperidone and its primary metabolite, 9-hydroxy-risperidone (9-OH-risperidone), were determined at steady state, collected between 8:00 and 10:00 AM, roughly 12 hours after the patients' evening dose. Quantification was carried out using a validated high-performance liquid chromatography method [29, 30]. The total active moiety was calculated by summing the concentrations of risperidone and 9-OH-risperidone. To account for differences in individual dosing, all plasma levels were normalized by daily dose, resulting in dose-corrected measures for risperidone (RIS C/D), 9-OH-risperidone (9-OH-RIS C/D), and the combined active moiety (active moiety C/D).

Genetic analysis

Genomic DNA was isolated from EDTA-anticoagulated blood samples using the MagNa Pure automated extraction system (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions. A set of candidate genetic variants was selected based on their functional relevance and minor allele frequencies >5% in Asian populations [9, 14-18]. These included DRD2/ANKK1 Taq1A A2>A1 (rs1800497), DRD2 -141C insertion/deletion (rs1799732) and -241A>G (rs1799978); HTR2A -1438G>A (rs6311); HTR2C -759C>T (rs3813929); PRL 13096T>A (rs2244502); and PRLR 163444A>C (rs37364). Genotyping was performed using commercially available TaqMan assays (Life Technologies, Carlsbad, CA, USA) on a ViiA7 real-time PCR system (Applied Biosystems, Life Technologies) following standard protocols.

To evaluate variable number tandem repeats (VNTRs) in the dopamine transporter gene (DAT), PCR amplification was conducted using 60 ng of genomic DNA in 25 μL reactions containing 12.5 μL 2X Green PCR Master Mix (BiotechRabbit, Hennigsdorf, Germany) and 1 μL of each primer (10 μM; forward 5′-TCCTTGCGGTGTAGGGAACG-3′, reverse 5′-CCAGGCAGAGTGTGGTCTG-3′). PCR conditions consisted of 95°C for 2 min, followed by 35 cycles of 95°C for 30 s, 65°C for 40 s, 72°C for 1 min, with a final extension at 72°C for 10 min. The resulting fragment sizes were 263 bp (5 repeats), 423 bp (9 repeats), 463 bp (10 repeats), and 503 bp (11 repeats). Genotyping of the serotonin transporter-linked promoter region (5-HTTLPR) was performed using 8 μL PCR reactions containing 4 μL KAPA 2G Fast ReadyMix (KAPA Biosystems, Woburn, MA, USA), 0.6 μL of each 5 μM primer (forward 5′-CACAAACATGCTCATTTAAGAAGTG-3′; reverse 5′-AAAGGAAATAGCAGTGACAAGTTTG-3′), and 20 ng genomic DNA. PCR cycling included 95°C for 2 min, 40 cycles of 95°C for 15 s, 62°C for 40 s, 72°C for 30 s, and a final extension at 72°C for 1 min. Short (733 bp) and long (777 bp) alleles were separated using 2% agarose gel electrophoresis.

Haplotype-based genetic risk scoring

A haplotype-based scoring system was devised to predict genetic influence on prolactin expression. DRD2 alleles were assigned weighted values according to their expected functional impact: high-expression alleles (A2, C insertion, G) were given a score of 1, while low-expression alleles (A1, C deletion, A) were assigned 0.5 [10, 12, 31]. The cumulative haplotype score was calculated by summing these values across alleles, with higher scores corresponding to a predicted increase in prolactin levels.

Statistical analysis

All statistical procedures were performed using IBM SPSS version 24 (Armonk, NY, USA). A two-tailed p-value below 0.05 was considered statistically significant. Descriptive statistics were used to summarize participant

demographics and clinical characteristics. Continuous variables were expressed either as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for non-normal distributions.

To explore relationships between genotypes and serum prolactin or plasma drug concentrations at each assessment, parametric analyses (ANOVA for comparisons across three or more groups, and independent t-tests for two-group comparisons) were applied to normally distributed data. For non-normally distributed variables, the Kruskal-Wallis test and Mann-Whitney U test were used for multiple-group and two-group comparisons, respectively. Associations between plasma drug concentrations and prolactin levels were further evaluated using Spearman's rank correlation.

Because nine genetic variants were tested, adjustments for multiple comparisons were performed using the Bonferroni method. Corrected p-values were calculated by multiplying the original p-values by nine, and a threshold of 0.05 was applied for significance [32]. Allele and genotype frequencies, as well as Hardy-Weinberg equilibrium, were assessed using Haploview version 4.2 (Broad Institute, Cambridge, MA, USA). Haplotype reconstruction was performed using PHASE version 2.1.1 [33]. Fisher's exact test was used to examine differences in demographic and clinical variables between responders and non-responders. For analysis of DRD2 diplotypes, serum prolactin levels were compared using analysis of covariance (ANCOVA), adjusting for plasma drug concentration as a covariate. Predictive performance of prolactin cut-off values for risperidone response was assessed with receiver operating characteristic (ROC) curves, and corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using MedCalc (https://www.medcalc.org/calc/diagnostic_test.php).

Results and Discussion

Clinical characteristics

The study population comprised 124 pediatric patients with ASD, ranging in age from 3 to 18 years, with a mean age of 8.81 ± 4.04 years. All participants were undergoing risperidone treatment. Monotherapy with risperidone was administered to 74 individuals (approximately 60%), while the remaining participants received additional medications that did not interfere with either cytochrome P450 2D6 metabolism or serum prolactin levels. A summary of demographic and treatment-related characteristics is presented in **Table 1.**

Table 1. Patient demographics (n = 124).

Parameter	Median (IQR)
Age (years)	8.00 (5.00–12.00)
Males, n (%)	105 (84.68%)
Daily risperidone dosage (mg/day)	0.75 (0.50–1.00)
Duration of risperidone treatment (months)	37.94 (11.01–94.05)
Risperidone monotherapy, n (%)	74 (59.68%)
Prolactin level (ng/mL)	15.70 (8.85–22.85)
Risperidone (RIS) level (ng/mL)	0.51 (0.14–1.41)
9-OH-RIS level (ng/mL)	5.28 (2.94–9.29)
Active moiety level (ng/mL)	6.11 (3.44–11.63)
Risperidone/9-OH-RIS ratio	0.09 (0.03–0.21)
RIS concentration/dose ratio (ng/mL per mg)	0.71 (0.22–2.03)
9-OH-RIS concentration/dose ratio (ng/mL per mg)	7.72 (4.94–12.04)
Active moiety concentration/dose ratio (ng/mL per mg)	9.06 (5.82–13.14)

RIS, risperidone; 9-OH-RIS, 9-hydroxy-risperidone; Active moiety, the sum of RIS plus 9-OH-RIS; C/D, dose-corrected concentration; IQR, interquartile range [quartile 1 (Q1) and quartile 3 (Q3)].

Genetic variants, prolactin levels, and risperidone response

We examined the influence of multiple genetic variants on serum prolactin levels and risperidone treatment outcomes. No meaningful differences in prolactin concentrations were observed among carriers of DRD2/ANKK1

Taq1A A2>A1, DRD2 -141C indel, DRD2 -241A>G, HTR2A -1438G>A, HTR2C -759C>T, PRL g.13096T>A, PRLR g.163444A>C, or the variable tandem repeats in DAT and 5-HTTLPR, regardless of whether codominant, dominant, or recessive models were applied.

To explore combinatorial effects of DRD2 variants, three SNPs located on chromosome 11 (Taq1A A2/A1, -141C indel, and -241A>G) were used to construct haplotypes using PHASE v2.1.1. Six haplotypes exceeded a minor allele frequency of 1%. Four haplotypes—H1 (A2-Cin-A), H2 (A1-Cin-A), H3 (A2-Cin-G), and H4 (A2-Cdel-A)—together represented over 90% of the haplotypes in the study population **(Table 2)**. Fifteen diplotype combinations encompassed the vast majority (99.2%) of observed genotypes **(Table 3).**

Analysis of these diplotypes revealed that individuals carrying the H1/H3 combination exhibited notably higher serum prolactin levels, averaging 23.00 ng/mL, compared with other diplotype carriers ($p < 0.05$). This finding indicates that particular DRD2 haplotype pairings may contribute to the variability in prolactin elevation observed during risperidone therapy.

Table 2. *DRD2* haplotype frequencies predicted by computational phasing using PHASE v2.1.1.

Haplotype	Allele Combination	Observation (n)	Frequency (%)
H1	*2–Cn–A	86	34.68
H2	*1–Cn–A	75	30.24
H3	*2–Cn–G	35	14.11
H4	*2–Cdel–A	31	12.50
H5	*1–Cdel–A	11	4.44
H6	*1–Cn–G	10	4.03

Haplotype presented as DRD2/ANKK1 Taq1A, DRD2 -141C indel, and DRD2 -241A>G.

Table 3. Associations between *DRD2* gene diplotypes and serum prolactin levels.

Diplotype	Allele Combination	n	Frequency (%)	Genetic Risk Score	Prolactin (ng/mL), Median (IQR)
H2/H6	*1/*1–Cin/Cin–A/G	4	3.23	4.5	29.40 (15.65–67.70)
H3/H3	*2/*2–Cin/Cin–G/G	3	2.42	6.0	28.20 (16.00–29.75)
H2/H5	*1/*1–Cin/Cdel–A/A	3	2.42	3.5	25.90 (21.80–31.15)
H1/H3	*2/*2–Cin/Cin–A/G	12	9.68	5.5	23.00 (17.50–35.25) a,b,c,d
H3/H5 or H4/H6	*2/*1–Cin/Cdel–A/G	4	3.23	4.5	16.90 (13.15–25.30)
H1/H5 or H2/H4	*2/*1–Cin/Cdel–A/A	17	13.71	4.0	16.80 (12.15–21.80) a
H1/H4	*2/*2–Cin/Cdel–A/A	14	11.29	4.5	16.25 (10.10–24.00)
H3/H4	*2/*2–Cin/Cdel–A/G	2	1.61	5.0	14.40 (8.00–20.80)
H1/H6 or H2/H3	*2/*1–Cin/Cin–A/G	17	13.71	5.0	13.30 (7.50–21.40) b
H1/H2	*2/*1–Cin/Cin–A/A	23	18.55	4.5	13.00 (7.80–19.40) c
H1/H1	*2/*2–Cin/Cin–A/A	14	11.29	5.0	13.00 (9.10–24.00)
H4/H5	*2/*1–Cdel/Cdel–A/A	1	0.81	3.5	12.40 (single value)
H2/H2	*1/*1–Cin/Cin–A/A	10	8.06	4.0	10.60 (7.40–21.80) d

Diplotype presented as DRD2/ANKK1 Taq1A, DRD2 -141C indel, and DRD2 -241A>G.

[a] Significant at $p = 0.042$ when compared between H1/H3 and H1/H5 or H2/H4.

[b] Significant at $p = 0.028$ when compared between H1/H3 and H1/H6 or H2/H3.

[c] Significant at $p = 0.014$ when compared between H1/H3 and H1/H2.

[d] Significant at $p = 0.038$ when compared between H1/H3 and H2/H2.

Association between DRD2 genetic risk score and serum prolactin

A haplotype-based genetic risk scoring system was developed to estimate the influence of DRD2 expression on serum prolactin levels. Among the cohort, 45 patients (36.29%) shared the most common risk score of 4.5, with a median prolactin concentration of 16.60 ng/mL. When comparing risk groups, individuals with a score of 4.5

exhibited significantly lower prolactin levels than those with a higher score of 5.5 (n = 12, 9.68%), whose median prolactin was 23.00 ng/mL (p = 0.033), suggesting a positive correlation between predicted DRD2 expression and prolactin elevation **(Table 4)**.

Interestingly, extreme risk scores did not consistently follow this trend. Patients with the lowest score of 3.5 showed elevated prolactin (21.80 ng/mL), and those with the highest score of 6 also had high levels (28.20 ng/mL); however, these differences were not statistically significant (p > 0.05). These observations indicate that while higher DRD2 expression generally corresponds to increased prolactin, additional factors may contribute to variability at the extremes of the genetic risk spectrum.

Table 4. Associations between genetic risk scores for *DRD2* gene haplotypes and serum prolactin levels.

Genetic risk score	Diplotypes	Types	N (%) (*n* = 124)	Prolactin levels (ng/ml)	*p*-value
3.5	H2/H5, H4/H5	A1/A1-Cin/Cdel-A/A, A2/A1-Cdel/Cdel-A/A	4 (3.23)	21.80 (15.05–31.15)	0.231
4	H1/H5 or H2/H4, H2/H2	A2/A1-Cin/Cdel-A/A, A1/A1-Cin/Cin-A/A	27 (21.77)	12.70 (8.00–21.60)	0.504
4.5	H1/H2, H1/H4, H2/H6, H3/H5 or H4/H6	A2/A1-Cin/Cin-A/A, A2/A2-Cin/Cdel-A/A, A1/A1-Cin/Cin-A/G, A2/A1-Cin/Cdel-A/G	45 (36.29)	16.60 (9.00–22.70)	Reference
5	H1/H1, H1/H6 or H2/H3, H3/H4	A2/A2-Cin/Cin-A/A, A2/A1-Cin/Cin-A/G, A2/A2-Cin/Cdel-A/G	33 (26.61)	13.00 (8.00–21.40)	0.498
5.5	H1/H3	A2/A2-Cin/Cin-A/G	12 (9.68)	23.00 (17.50–35.25)	0.033 [a]
6	H3/H3	A2/A2-Cin/Cin-G/G	3 (2.42)	28.20 (16.00–29.75)	0.413

Diplotype presented as DRD2/ANKK1 Taq1A, DRD2 -141C indel, and DRD2 -241A>G respectively as follow: high expression allele (A2, Cin, G) = 1 and low expression allele (A1, Cdel, A) = 0.5. A high-risk score assumed a high prolactin level.

[a] Significant at $p < 0.05$.

Pharmacodynamic gene variants and risperidone efficacy

Examination of the selected pharmacodynamic gene polymorphisms revealed no detectable influence on clinical responsiveness to risperidone.

Serum prolactin in relation to dose-corrected plasma drug concentrations

After normalizing plasma drug levels for daily dosage, correlations between serum prolactin and plasma concentrations were analyzed. Significant positive associations emerged for risperidone (RIS C/D; rs = 0.227, p = 0.012), 9-hydroxy-risperidone (9-OH-RIS C/D; rs = 0.305, p = 0.001), and the combined active moiety (active moiety C/D; rs = 0.343, p < 0.001), indicating that higher plasma exposure corresponded with elevated prolactin levels.

DRD2 diplotype influence on prolactin levels

To disentangle the effect of DRD2 genetic variation from plasma drug concentrations, serum prolactin levels were compared across diplotypes using ANCOVA with RIS C/D, 9-OH-RIS C/D, and active moiety C/D as covariates. Participants carrying the H1/H3 diplotype displayed consistently higher prolactin concentrations than carriers of H1/H2 (F = 5.420, p = 0.026); **(Figure 1a)**, H1/H5 (F = 4.552, p = 0.042); **(Figure 1b)**, H1/H6 (F = 4.848, p = 0.037); **(Figure 1c)**, and H2/H2 (F = 5.761, p = 0.027); **(Figure 1d)**. These findings suggest that specific DRD2 diplotype combinations may predispose individuals to greater prolactin elevation during risperidone therapy, independent of plasma drug exposure.

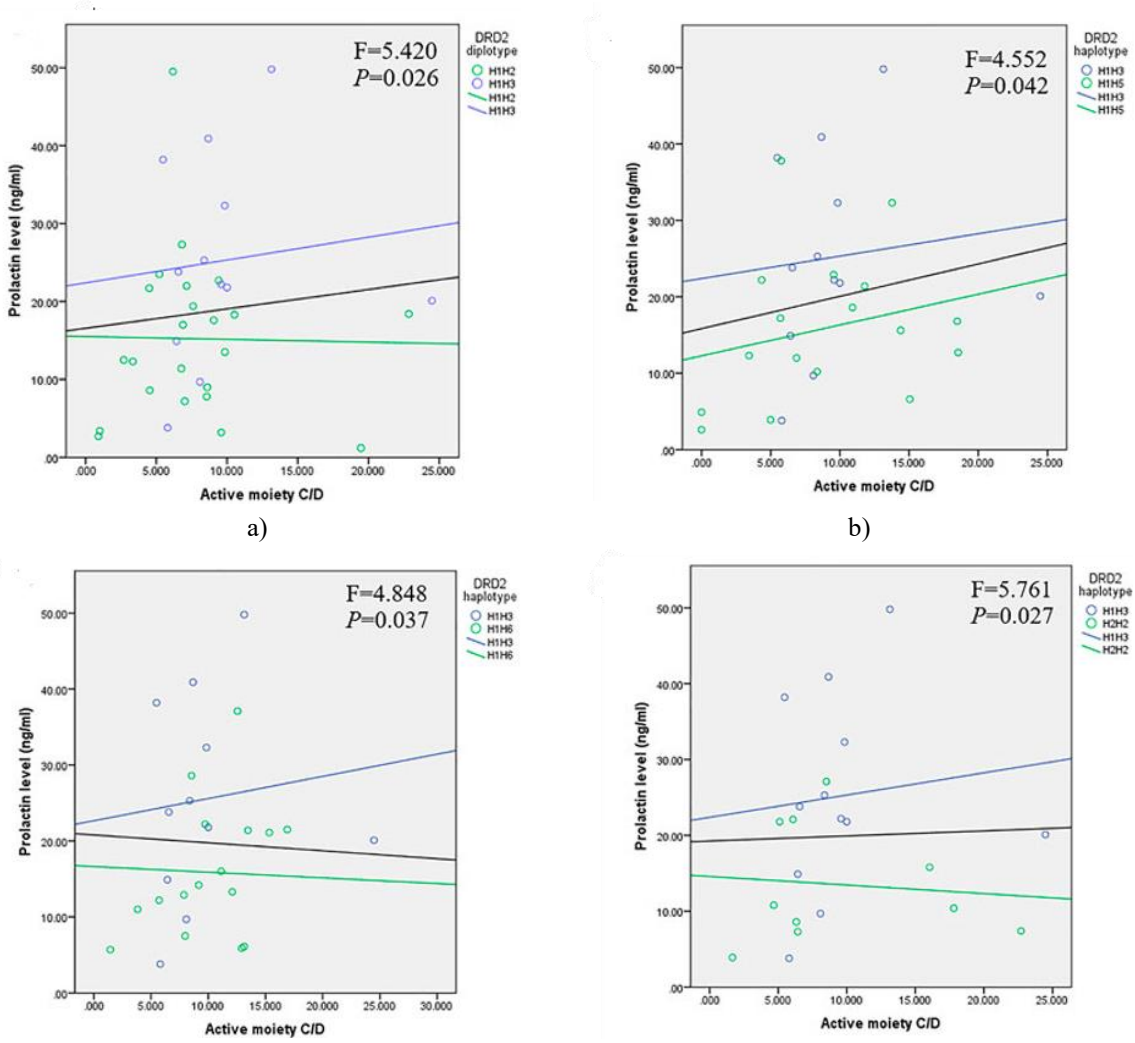

Figure 1.

Serum prolactin and risperidone treatment outcomes in pediatric ASD

Of the 124 enrolled children and adolescents, follow-up data for risperidone-naïve patients were available for a subset of 19 individuals who were assessed before starting treatment and again after a minimum of three months on risperidone. The mean age of this subgroup was 5.21 years (SD 2.82), and most participants were male (16/19, 84.2%). Treatment response was defined by a reduction in total ABC scores, and **Table 5** summarizes clinical characteristics and outcomes by responder status.

Among these 19 patients, 10 (53%) exhibited a clinically significant improvement and were classified as responders, while 9 (47%) did not achieve the threshold reduction and were considered non-responders. The average age was comparable between groups (responders: 5.50 ± 2.84 years; non-responders: 4.89 ± 2.93 years). Following three months of therapy, median prolactin levels were substantially higher in non-responders compared with responders (20.10 vs. 10.25 ng/mL, $p = 0.013$). Total ABC scores showed significant improvement across the cohort after treatment (paired t-test, $p < 0.05$).

Plasma concentrations of dose-corrected risperidone (RIS C/D), 9-hydroxy-risperidone (9-OH-RIS C/D), and the combined active moiety did not differ significantly between responders and non-responders. Among responders, prolactin levels remained largely unchanged before and after therapy (7.65 vs. 10.25 ng/mL, $p = 0.878$). In contrast, non-responders experienced a pronounced rise in prolactin post-treatment, with median levels nearly double those of responders (20.10 vs. 9.40 ng/mL, $p = 0.028$).

DRD2 diplotype influence on prolactin levels

Serum prolactin was further analyzed according to DRD2 diplotype and dose-corrected active moiety concentrations. Participants carrying the H1/H3 diplotype consistently exhibited higher prolactin levels compared with other diplotypes. Statistically significant differences were observed for comparisons with H1/H2 (F = 5.420, p = 0.026); **(Figure 1a)**, H1/H5 (F = 4.552, p = 0.042); **(Figure 1b)**, H1/H6 (F = 4.848, p = 0.037); **(Figure 1c)**, and H2/H2 (F = 5.761, p = 0.027); **(Figure 1d)**. Linear regression analyses in **Figure 1** illustrate the positive correlation between active moiety plasma levels and prolactin concentrations across diplotype groups.

Table 5. ABC score and serum prolactin levels at baseline and after 3 months of treatment between responders and non-responders (*n* = 19).

Variable	Responders (n = 10)	Non-responders (n = 9)	p-value
Demographics			
Male sex, n (%)	10 (100%)	6 (66.7%)	0.087
Age (years), median (IQR)	4.50 (4.00–6.00)	5.00 (4.00–7.00)	0.905
Baseline			
Body weight (kg), median (IQR)	17.58 (15.70–25.00)	20.00 (15.30–27.00)	0.968
Risperidone dose (mg/day), median (IQR)	0.20 (0.20–0.50)	0.25 (0.15–0.50)	0.842
Weight-adjusted dose (mg/kg/day), median (IQR)	0.01 (0.01–0.01)	0.02 (0.01–0.02)	0.315
ABC total score, mean ± SD	85.70 ± 29.73	91.22 ± 26.29	0.675
ABC-Irritability, mean ± SD	20.40 ± 8.17	21.89 ± 11.42	0.746
ABC-Social withdrawal, mean ± SD	16.80 ± 9.31	22.78 ± 6.80	0.132
ABC-Stereotyped behavior, mean ± SD	9.50 ± 6.08	9.56 ± 5.64	0.984
ABC-Hyperactivity, mean ± SD	33.10 ± 8.90	32.44 ± 5.88	0.854
ABC-Inappropriate speech, mean ± SD	5.90 ± 4.12	4.56 ± 3.32	0.448
Prolactin (ng/mL), median (IQR)	7.65 (6.00–17.70)	9.40 (7.10–16.60)	1.000
After 3 months of treatment			
Body weight (kg), median (IQR)	20.18 (17.00–30.00)	23.60 (16.70–32.00)	0.905
Risperidone dose (mg/day), median (IQR)	0.50 (0.20–0.60)	0.30 (0.20–0.50)	0.315
Weight-adjusted dose (mg/kg/day), median (IQR)	0.02 (0.01–0.03)	0.01 (0.01–0.02)	0.356
Duration of risperidone treatment (months), median (IQR)	8.64 (3.00–13.77)	4.37 (3.70–7.03)	0.780
ABC total score, mean ± SD	41.50 ± 18.00	84.67 ± 14.63	<0.001
ABC-Irritability, mean ± SD	7.90 ± 5.26	20.78 ± 11.55	0.011
ABC-Social withdrawal, mean ± SD	8.20 ± 3.94	19.89 ± 6.90	<0.001
ABC-Stereotyped behavior, mean ± SD	3.40 ± 2.68	7.78 ± 5.14	0.041
ABC-Hyperactivity, mean ± SD	18.60 ± 8.21	31.44 ± 4.98	0.001
ABC-Inappropriate speech, mean ± SD	3.40 ± 2.91	4.89 ± 3.55	0.330
Prolactin (ng/mL), median (IQR)	10.25 (6.50–16.00)	20.10 (15.80–27.40)	0.013
Risperidone level (ng/mL), median (IQR)	0.19 (0.02–0.90)	0.33 (0.12–0.58)	0.720
9-OH-Risperidone level (ng/mL), median (IQR)	3.04 (1.67–5.26)	4.57 (3.26–7.27)	0.400
Active moiety level (ng/mL), median (IQR)	3.86 (1.67–5.56)	5.41 (3.28–8.02)	0.447
Risperidone C/D ratio (ng/mL per mg), median (IQR)	23.56 (3.17–40.30)	7.19 (3.55–36.12)	0.624
9-OH-RIS C/D ratio (ng/mL per mg), median (IQR)	9.68 (7.12–18.64)	8.77 (6.52–15.09)	0.935
Active moiety C/D ratio (ng/mL per mg), median (IQR)	13.58 (9.06–19.42)	9.17 (6.77–16.90)	0.638

RIS, risperidone; 9-OH-RIS, 9-hydroxy-risperidone; Active moiety, the sum of RIS plus 9-OH-RIS; C/D, dose-corrected concentration; IQR, interquartile range [quartile 1 (Q1) and quartile 3 (Q3)]; SD, standard deviation.

Predictive value of serum prolactin for risperidone response

Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of serum prolactin levels to distinguish between responders and non-responders to risperidone therapy **(Figure 2, Table 6)**. The area under

the curve (AUC) for prolactin was 0.833 (p = 0.014), indicating good predictive performance above the conventional threshold of 0.8.

Cut-off values yielding both sensitivity and specificity above 50% ranged from 10.25 to 18.85 ng/mL. Among these, a prolactin threshold of 10.9 ng/mL demonstrated optimal performance, with a sensitivity of 100%, specificity of 60%, positive predictive value (PPV) of 69.23%, negative predictive value (NPV) of 100%, and overall accuracy of 78.95%. Alternative cut-offs at 10.25, 12.20, 15.0, and 16.8 ng/mL achieved a slightly lower but comparable accuracy of 73.68%. These findings indicate that serum prolactin is a reliable biomarker for identifying pediatric patients likely to respond to risperidone therapy.

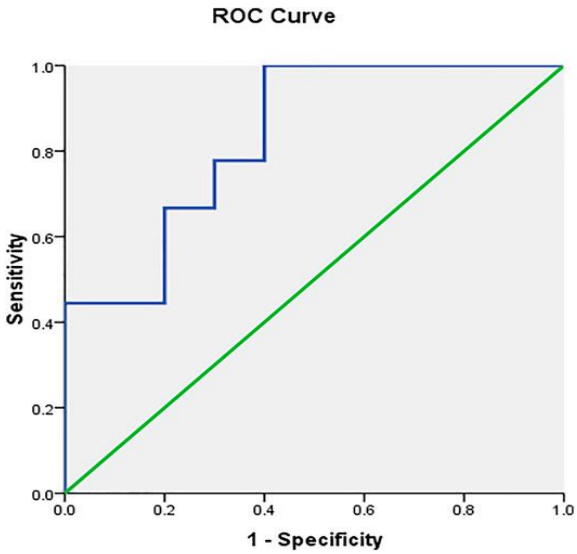

Figure 2. ROC curve analysis showing that serum prolactin level has a high accuracy (68–78%) for identifying responders and non-responders.

Table 6. Sensitivity, specificity, and accuracy of prolactin levels predicting risperidone response.

Prolactin Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
1.70	100.00	0.00	47.37	–*	47.37
3.30	100.00	10.00	50.00	100.00	52.63
5.20	100.00	20.00	52.94	100.00	57.89
6.55	100.00	30.00	56.25	100.00	63.16
8.35	100.00	40.00	60.00	100.00	68.42
10.25	100.00	50.00	64.29	100.00	73.68
10.90	100.00	60.00	69.23	100.00	78.95
12.20	88.89	60.00	66.67	85.71	73.68
13.60	77.78	60.00	63.64	75.00	68.42
15.00	77.78	70.00	70.00	77.78	73.68
15.90	66.67	70.00	66.67	70.00	68.42
16.80	66.67	80.00	75.00	72.73	73.68
18.85	55.56	80.00	71.43	66.67	68.42
20.80	44.44	80.00	66.67	61.54	63.16
21.85	44.44	90.00	80.00	64.29	68.42
23.00	44.44	100.00	100.00	66.67	73.68
25.60	33.33	100.00	100.00	62.50	68.42
28.80	22.22	100.00	100.00	58.82	63.16
30.45	11.11	100.00	100.00	55.56	57.89
31.70	0.00	100.00	–*	52.63	52.63

PPV, positive predictive value; NPV, negative predictive value.

Bold values represented cut-off value associated with higher and equal 50% in both sensitivity and specificity.

The italicized value represented the cut-off value associated with higher and equal 50% in both sensitivity and specificity with the highest degree of accuracy.

*PPV or NPV cannot be estimated.

Hyperprolactinemia is a common concern in patients receiving antipsychotic therapy, and its development during risperidone treatment has been linked to both genetic variation and plasma drug concentrations [34-39]. However, data exploring the interplay between DRD2 haplotypes, risperidone plasma exposure, and prolactin elevation in children with ASD are scarce. The current study demonstrates that carriers of the H1/H3 diplotype of DRD2 exhibited significantly higher serum prolactin levels in conjunction with increasing plasma concentrations of RIS C/D, 9-OH-RIS C/D, and the active moiety. Notably, lower prolactin concentrations were associated with a favorable response to risperidone among Thai children and adolescents with ASD.

In this cohort, 44.35% (55/124) of patients had hyperprolactinemia, emphasizing the clinical relevance of monitoring prolactin in pediatric populations treated with risperidone. These results align with previously reported prevalence rates ranging from 44% to 61% [40-42], whereas other studies have identified abnormal prolactin in approximately 27% of patients on risperidone [43]. Physiologically, hypothalamic dopamine inhibits lactotroph activity via D2 receptor signaling, thereby suppressing prolactin secretion [44, 45]. The slow dissociation of risperidone from dopamine D2 receptors and its relatively limited blood-brain barrier penetration compared with other atypical antipsychotics such as olanzapine and quetiapine [3, 46] likely contributes to prolonged D2 receptor blockade and increased prolactin release.

This study further highlights the importance of DRD2 haplotypes over individual SNPs in predicting prolactin levels. The H1/H3 diplotype was consistently associated with elevated serum prolactin, supporting prior evidence that DRD2/ANKK1 Taq1A A2 or C alleles are linked to higher dopamine receptor densities [10, 11]. The -241A>G variant in the 5′ promoter region may enhance DRD2 expression [12], and previous studies have shown that the combination of -241G with Taq1A A1 and the -141C indel results in increased receptor expression and prolactin release [13, 31, 35]. Our findings suggest that the combined effects of Taq1A, -141C indel, and -241A>G SNPs are better captured at the haplotype level than by individual SNPs, and clinicians may consider pre-emptive genetic testing to identify patients at risk for risperidone-induced hyperprolactinemia, particularly those carrying the H1/H3 diplotype.

To simplify clinical interpretation, we developed a genetic risk scoring system based on DRD2 expression, assigning 1 point for high-expression alleles (A2, Cin, G) and 0.5 for low-expression alleles (A1, Cdel, A). Higher scores were associated with elevated prolactin levels, consistent with the mechanism in which greater receptor density amplifies the inhibitory effect of risperidone on dopaminergic signaling [47]. The highest prolactin levels were observed in patients with a risk score of 6, while unexpectedly, elevated prolactin was also seen at the lowest score of 3.5. This may reflect compensatory upregulation of dopamine receptors during prolonged risperidone exposure, as previously observed in primate studies [48]. Although the sample size limited statistical power for extreme scores, the risk score system offers a practical tool for translating genotype data into clinically actionable predictions of prolactin elevation. Further validation in larger cohorts is warranted.

The present study provides evidence that both DRD2 haplotype and plasma drug exposure contribute to prolactin elevation in pediatric ASD patients treated with risperidone. Monitoring prolactin levels and considering genetic risk may help guide safer and more effective pharmacotherapy.

Implications of genetic variation and prolactin dynamics in risperidone treatment

Genetic variability in serotonin receptors, particularly HTR2A and HTR2C, has been proposed to influence antipsychotic binding and downstream physiological effects, including prolactin regulation. Prior studies in schizophrenia populations have yielded inconsistent results regarding the association between these polymorphisms and hyperprolactinemia [15, 24, 25, 49, 50]. Our findings align with those from an investigation of 289 Indian schizophrenia patients treated with risperidone, which reported no significant link between HTR2C −759 C>T variants and prolactin levels [49]. Similarly, promoter polymorphisms of HTR2C have been implicated in antipsychotic-induced weight gain [51], suggesting that the impact of these variants may be context-dependent and drug-specific.

Transporter and prolactin-related genes, including DAT (SLC6A3), 5-HTTLPR, PRL, and PRLR, have also been examined for their influence on prolactin secretion. Osmanova *et al.* [52] identified associations between DAT variants and elevated prolactin among patients receiving risperidone or paliperidone, while Smith *et al.* [53] found that the 5-HTTLPR short allele correlated with smaller increases in prolactin and cortisol relative to the long/long genotype. PRL and PRLR tagSNPs have shown nominal associations with plasma prolactin in other patient populations, such as those with advanced breast cancer [23]. Collectively, these findings illustrate that gene–

treatment interactions are complex and may vary depending on disease context, antipsychotic regimen, and population, underscoring the need for caution in extrapolating results across patient groups.

In the current study, no significant relationships were observed between the candidate genetic variants and clinical response to risperidone. While DRD2 haplotypes were predictive of prolactin elevation, they did not serve as reliable markers of therapeutic efficacy. This is consistent with previous observations in schizophrenia, where non-responders without the DRD2 -141C indel deletion exhibited greater psychiatric, extrapyramidal, and total side-effect scores compared with carriers after short-term dopamine antagonist treatment [54]. The limited sample size of 19 follow-up patients in this study likely contributed to the absence of significant associations between genetic variants and treatment response.

Pharmacokinetic monitoring has been proposed as a tool to optimize risperidone dosing in pediatric ASD populations [55-57]. In our cohort, plasma drug levels did not significantly predict clinical response, although non-responders tended to have higher mean concentrations than responders, consistent with prior studies [58, 59]. Contrastingly, other investigations have reported correlations between therapeutic drug levels and efficacy in schizophrenia [6, 7]. Such discrepancies may be attributable to differences in underlying diagnosis, timing of outcome assessment, or patient demographics. Notably, our evaluation occurred after at least three months of risperidone therapy, reflecting the trajectory of prolactin changes in children, which typically peak within the first two months and normalize over subsequent months [60]. Although plasma levels were not directly associated with clinical response, their relationship with prolactin concentrations remained robust, highlighting the potential utility of therapeutic monitoring to mitigate adverse effects such as hyperprolactinemia.

Prolactin itself may play a role in modulating neurobehavioral outcomes. As an anterior pituitary hormone under dopaminergic inhibition [61], prolactin levels provide an indirect measure of central dopamine activity. Excessive dopamine D2 receptor blockade by risperidone (occupancy 68–70% [62]) can induce hyperprolactinemia during early treatment [63]. Over prolonged therapy, compensatory upregulation of D2 receptors, consistent with the dopamine supersensitivity psychosis hypothesis, may allow effective dopaminergic blockade while promoting behavioral improvement [63]. This mechanistic framework may explain why some ASD patients initially exhibit elevated prolactin levels yet demonstrate symptom improvement over time.

Interpretation of prolactin as a biomarker for risperidone response

The observed link between elevated prolactin and poorer behavioral response may be related to the distribution of risperidone between brain and plasma compartments. Arakawa *et al.* [46] reported a brain/plasma concentration ratio of 1.61 for risperidone, calculated using dopamine D2 receptor occupancy in the temporal cortex and pituitary. This ratio indicates that risperidone concentrations in the temporal cortex are approximately 1.5-fold higher than in the pituitary, reflecting efficient brain penetration. Consequently, D2 receptor occupancy is greater in the temporal cortex than in the pituitary, which likely contributes to improved behavioral outcomes while minimizing excessive prolactin elevation. In line with these findings, our data suggest that lower serum prolactin levels may serve as an indirect indicator of positive risperidone response in children and adolescents with ASD.

This study is the first to propose a prolactin threshold for predicting poor behavioral response in patients receiving low-dose risperidone (<1 mg/day). Using ROC analysis, we identified an area under the curve of 0.833, demonstrating good discriminative accuracy. The serum prolactin cut-off range with sensitivity and specificity ≥0.5 was 10.25–18.85 ng/ml, with an optimal value of 10.9 ng/ml yielding the highest predictive accuracy of 78.95%. In clinical practice, prolactin measurement could be used to identify patients unlikely to respond to risperidone, functioning as a screening tool to reduce false negatives. For instance, with a negative predictive value of 100%, low prolactin reliably indicated a favorable treatment response, whereas a positive predictive value of 60% suggested that high prolactin identified only 60 of 100 non-responders. Such information could assist clinicians in monitoring therapy and adjusting treatment strategies, although further research is needed to establish the optimal risperidone dosing for prolactin-guided monitoring.

Limitations

Several limitations should be considered. The relatively small sample size limited our ability to detect robust genotype–phenotype associations, and findings must be interpreted cautiously. Additionally, no significant differences were observed in risperidone dose, weight-adjusted dose, or treatment duration between responders and non-responders. Since this study was conducted under naturalistic clinical conditions, risperidone dosing and treatment duration were not experimentally controlled, which may have influenced the observed associations.

Conclusion

We developed a genetic risk scoring system to represent DRD2 haplotype expression and its impact on prolactin levels. Patients carrying the H1/H3 diplotype, corresponding to a DRD2 risk score of 5.5, exhibited the highest serum prolactin levels, which correlated with increasing plasma concentrations of RIS C/D, 9-OH-risperidone C/D, and active moiety C/D. Conversely, lower prolactin levels were observed in patients demonstrating positive response to risperidone. These findings enhance our understanding of risperidone-induced hyperprolactinemia, a common adverse effect in pediatric ASD populations, and highlight the potential utility of preemptive pharmacogenetic testing. By identifying individuals at risk for elevated prolactin early in treatment, clinicians may better tailor therapy to optimize efficacy while minimizing adverse effects.

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Conflict of Interest: None

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Ethics Statement: The studies involving human participants were reviewed and approved by the Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand (MURA 2017/556) and Yuwaprasart Waithayopathum Child Psychiatric Hospital, Samut Prakan, Thailand. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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