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Variants in the *DRD2* locus and antipsychotic-related prolactin levels: A meta-analysis

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ABSTRACT

Background: Although dopamine D2 receptor antagonists lead to dose-dependent prolactin (PRL) elevations proportionate to their D2 affinity, considerable inter-individual differences exist. We conducted a *meta*-analytic review of associations between genetic variations in the dopamine D2 receptor gene (*DRD2*) and PRL levels in antipsychotic-treated subjects.
Methods: Systematic literature search (5/8/2015) was performed to find published studies of pharmacogenetic associations between two *DRD2* variants, Taq1A (rs1800497) and −141C Ins/Del (rs1799732), and PRL levels during antipsychotic treatment (excluding aripiprazole). Patients were included independent of age or diagnosis. Random effects models were used and Hedges' g was calculated as the effect size measure. Subgroup analyses explored the effect of sex and diagnosis, (males vs females; schizophrenia vs non-schizophrenia).
Results: Altogether, 11 studies (n = 1034, schizophrenia-spectrum = 475) for Taq1A polymorphism, and 4 studies (n = 451, schizophrenia-spectrum = 274) for −141C Ins/Del polymorphism, each reporting on PRL levels but not on the proportion of patients with hyperprolactinemia, were *meta*-analyzed. Across all patients, there was no statistically significant association between PRL levels and either *DRD2* Taq1A genotype or *DRD2* −141C Ins/Del genotype. However, in patients with schizophrenia, PRL levels were significantly higher in *DRD2* Taq1A A1 carriers than A1 non-carriers (studies = 5, n = 475, Hedges' g = 0.250, 95% CI = 0.068–0.433, p = 0.007, I^2 = 0%).
Discussion: Although there was no significant association between either *DRD2* Taq1A genotype or *DRD2* −141C Ins/Del genotype and PRL levels in all included patients, our results suggest that *DRD2* Taq1A genotype may affect antipsychotic-related PRL levels in patients with schizophrenia. Because of the small sample size, further studies are needed to confirm these results.

1. Introduction

Hyperprolactinemia is one of the common side effects of antipsychotics (Peuskens et al., 2014), which is associated with various secondary problems, such as amenorrhea, galactorrhea, sexual dysfunction (De Hert et al., 2014), and osteoporosis (Kishimoto et al., 2012; Peuskens et al., 2014). Additionally, concerns have been raised about a potential association between hyperprolactinemia and breast cancer, which according to the most updated *meta*-analysis fortunately appears to be small to negligible though (De Hert et al., 2015). First-generation antipsychotics (FGAs) induce a significant rise in serum prolactin (PRL) levels, which are around two to three times higher than the reference values (Peuskens et al., 2014). Hyperprolactinemia was found in 71% of patients treated with FGAs (Montgomery et al., 2004). A recent *meta*-analysis showed that haloperidol was associated with significantly increased PRL levels compared with placebo (standard mean differences (SMD) = 0.70, 95% confidence interval (CI) = 0.56–0.85), whereas chlorpromazine

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was not (SMD = 0.16, 95%CI = −0.48–0.80) (Leucht et al., 2013). Although second-generation antipsychotics (SGAs) are characterized by fewer PRL-related side effects compared with FGAs (Madhusoodanan et al., 2010), risperidone has been associated with more hyperprolactinemia (73.8%) than haloperidol (49.8%) in patients with psychosis (Schooler et al., 2005). Furthermore, olanzapine increases plasma PRL levels in a dose-dependent manner (Suzuki et al., 2011), although olanzapine clearly has less effect on plasma PRL levels than risperidone (Lieberman et al., 2005; Fraguas et al., 2011). In a recent network *meta*-analysis and using placebo as the reference, risperidone (SMD = 1.23, 95%CI = 1.06–1.40) and paliperidone (SMD = 1.30, 95%CI = 1.08–1.51) were associated with significantly greater PRL increases than all other antipsychotics, whereas aripiprazole (SMD = −0.22, 95%CI = −0.46–0.03,) and quetiapine (SMD = −0.05, 95%CI = −0.23–0.13) were not associated with significantly increased PRL levels compared to placebo (Leucht et al., 2013). Accordingly, hyperprolactinemia is still a relevant side effect of antipsychotic treatment of schizophrenia and other psychiatric diseases.

PRL secretion is regulated by dopamine in the anterior pituitary gland (Peuskens et al., 2014). Antipsychotics, except aripiprazole, are antagonists at the dopamine D2 receptors. Since stimulation of the D2 in the pituitary gland by dopamine suppresses PRL secretion, antipsychotics that block D2 lead to increased PRL release that is roughly proportional to the affinity to the D2 and the antipsychotic serum concentration at the pituitary gland, which is outside of the blood-brain barrier (Peuskens et al., 2014). However, there are also substantial inter-individual differences in the PRL release across subjects taking the same antipsychotic and dose, suggesting an interaction between the antipsychotic and other relevant biological factors. Due to the tight correlation between D2 blockade and therapeutic as well as adverse effects of antipsychotics, pharmacogenetic research has focused on the association between the *DRD2* gene and efficacy as well as tolerability of antipsychotics, including extrapyramidal side effects (Güzey et al., 2007; Zivković et al., 2013), tardive dyskinesia (Bakker et al., 2008) and PRL elevation (Peuskens et al., 2014). The Taq1A and the −141C Ins/Del polymorphisms in *DRD2* are the most studied polymorphisms of antipsychotic response in schizophrenia (Suzuki et al., 2000; Lencz et al., 2006; Zai et al., 2007; Bakker et al., 2008; Ikeda et al., 2008; Kwon et al., 2008; Zhang et al., 2010; Miura et al., 2012, 2015). The Taq1A (rs1800497) is located 10 kb downstream of *DRD2*, and causes an amino substitution within the 11th ankyrin repeat of ankyrin repeat and kinase domain containing 1 (*ANKK1*), which may affect substrate-binding specificity (Neville et al., 2004). The −141C Ins/Del (rs1799732) represents a deletion of cytosine at position −141, located in the 5′ promoter region of the *DRD2* (Arinami et al., 1997). Previous studies reported that both Taq1A and −141C Ins/Del polymorphisms influence D2 density in the brain (Noble et al., 1991; Thompson et al., 1997; Jönsson et al., 1999). Furthermore, a *meta*-analysis showed that −141C Ins/Del polymorphism was associated with antipsychotic response in schizophrenia (6 studies, N = 687, pooled odds ratio = 0.65, 95%CI = 0.43–0.97), whereas Taq1A polymorphism was not associated with antipsychotic response (8 studies, N = 748, pooled odds ratio = 1.30, 95%CI = 0.92–1.84 for the comparison between A1 allele carriers and non-carriers) (Zhang et al., 2010).

The association between elevated PRL levels and polymorphisms in *DRD2* has been investigated in individual studies of adults with schizophrenia (Mihara et al., 2000, 2001; Young et al., 2004; Kwon et al., 2008; Yasui-Furukori et al., 2008; Zhang et al., 2011; Nagai et al., 2012) as well as in children and adolescents treated with antipsychotics (Anderson et al., 2007; Calarge et al., 2009; Correia et al., 2010; Roke et al., 2013). Some studies have shown significant associations between the A1 allele of Taq1A polymorphism and increased PRL levels (Mihara et al., 2000, 2001; Young et al., 2004; Calarge et al., 2009), although subsequent studies did not show a significant association between serum PRL levels and the A1 allele of the Taq1A polymorphism (Anderson et al., 2007; Yasui-Furukori et al., 2008; Zhang et al., 2011). Similarly, Zhang et al. (2011) showed a significant association between the −141C Ins/Del polymorphism and plasma PRL levels, whereas other studies investigating this polymorphism and PRL have shown inconclusive results (Anderson et al., 2007; Yasui-Furukori et al., 2008; Calarge et al., 2009; Nagai et al., 2012). Because of such heterogeneous findings in often small samples, we performed a *meta*-analysis to investigate the association between polymorphisms in *DRD2* and increased PRL levels to overcome the limitation of small samples and effects in individual studies.

2. Methods

2.1. Search, inclusion criteria, and data extraction

To examine the effects of the Taq1A and −141C Ins/Del polymorphisms in *DRD2* on plasma PRL levels or changes in plasma PRL levels after the antipsychotic exposure or on the proportion of patients with hyperprolactinemia, we conducted a systematic literature review using PubMed, Web of Science, and PsycINFO until May 8, 2015 with the following keywords: (*DRD2* or dopamine D2 receptor or Taq1A or −141C Ins/Del) and (prolactin or hyperprolactinemia). To complement the electronic search; we performed a hand search of reference lists of relevant studies and reviews. Furthermore; when required data were missing or not available; we contacted authors for additional and unpublished information. Included in this *meta*-analysis were: studies reporting on the association between the Taq1A or −141C Ins/Del polymorphism in *DRD2* and plasma PRL levels (endpoint or change); or patients with hyperprolactinemia during treatment with antipsychotics. There were no restrictions regarding the age or diagnoses of patients treated with antipsychotics. Excluded were studies that studied aripiprazole because aripiprazole has a unique pharmacological profile as a D2 partial agonist (Burris et al., 2002); and can decrease plasma PRL levels (Peuskens et al., 2014); studied patients treated with antipsychotics for less than 5 half-lives (basically; single dose antipsychotic studies); or that did not report quantitative *meta*-analyzable data. Two authors (I.M. and C.U.C) checked the inclusion and exclusion criteria; and independently extracted data. Any disagreements were resolved by discussion.

2.2. Data synthesis and statistical analysis

The outcome measures included both the changes in plasma PRL levels from baseline to endpoint and cross-sectional plasma PRL levels. For Taq1A polymorphism, statistical analyses were performed for dominant (A1/A1 + A1/A2 vs. A2/A2) and recessive (A1/A1 vs. A1/A2 + A2/A2) genetic models. For −141C Ins/Del polymorphism, we pooled the Del/Del and Ins/Del genotype groups into one group (Del allele carriers) because of the low frequency of the Del/Del genotype. Accordingly, statistical analyses were performed for the dominant (Del/Del + Ins/Del vs. Ins/Ins) genetic model for −141C Ins/Del polymorphism. Data were entered into and analyzed by Comprehensive Meta-Analysis Version 2.0 (http://www.meta-analysis.com; Borenstein et al., 2005). Random effects model was used to combine studies, and Hedges' g was used as the effect size measure for differences between groups. Heterogeneity between studies was tested by using the Q and I^2 statistics, with p-values < 0.05 and I^2 values of ≥50% indicating significant heterogeneity. In addition to the overall analyses, we analyzed males and females separately because PRL levels differ between males and females, being higher in women due to

estrogen effects (Haddad and Wieck, 2004; Peuskens et al., 2014). Furthermore, we performed a second *a priory* defined subgroup analyses comparing patients with schizophrenia with those with non-schizophrenia diagnoses, as patients with schizophrenia may have specific dopamine related pathology and may receive higher antipsychotic doses. Because possible racial effects may exist for variants of *DRD2* in its association with the side effects of antipsychotics, including sexual dysfunction (Alenius et al., 2008), we performed subgroup analyses to compare the different racial subgroups. Finally, we conducted subgroup analyses comparing the studies that measured PRL changes during antipsychotic treatment with those measuring cross-sectional PRL levels. Furthermore, we performed three exploratory *meta*-regression analyses, investigating percent male, mean age of the study population, and percent schizophrenia as moderator variables. Begg's funnel plot, Egger's test (Egger et al., 1997), and the Duval and Tweedie "trim and fill" method (Duval and Tweedie, 2000) were used to explore the possibility of publication bias. We used Bonferroni correction for multiple comparisons, and significance level was set at $p < 0.025$ (2 markers, 0.05/2 = 0.025).

3. Results

3.1. Search results

Supplementary Fig. 1 shows the flowchart of study selection and inclusion. The electronic search yielded a total of 1872 potential studies. Among the 1872 identified hits, 853 articles were duplicates between the databases. Of the 1019 unique studies, we excluded 989 articles based on title and abstract review. Based on full-text inspection, we excluded another 19 references because of the following reasons: the reference was a meeting abstract for the same study included in this *meta*-analysis (articles = 6); plasma PRL levels were not measured (articles = 5); the study reported the results of single dose administration (articles = 3; Aklillu et al., 2007; López-Rodríguez et al., 2011; Cabaleiro et al., 2013); patients received a partial D2 agonist aripiprazole (articles = 2); patients were not treated with antipsychotics (articles = 2); the reference was a review article (articles = 1). Finally, 11 studies including 1034 patients for Taq1A polymorphism, and 4 studies including 451 patients for −141C Ins/Del polymorphism were *meta*-analyzed.

3.2. Study, patient and treatment characteristics

Study, patient and treatment characteristics are summarized in Table 1. The mean age of the included patients was 32.5 ± 17.5 years, 64.4% were male, 63.4% Caucasians, and 33.4% Asians. Out of 11 studies, 5 included patients with schizophrenia (Mihara et al., 2000, 2001; Young et al., 2004; Yasui-Furukori et al., 2008; Zhang et al., 2011), 4 included children and adolescents (Anderson et al., 2007; Calarge et al., 2009; Correia et al., 2010; Roke et al., 2013) with predominantly autism-spectrum and disruptive behavior-spectrum disorders, and 2 included patients with mood disorder or personality disorders (Houston et al., 2010, 2011). The sample size per study ranged from 25 to 239. Antipsychotics included risperidone in 5 studies, first-generation antipsychotics (bromperidol and nemonapride) in 2 studies, mixed first- and second-generation antipsychotics in 2 studies, olanzapine in one study, and olanzapine and fluoxetine combination (OFC) in one study. Five of 11 studies were cross-sectional, 4 studies were prospective, and 2 were genetic association studies using data of randomized controlled trials. Four studies included only Asian patients, 3 studies included only Caucasian patients, and 4 studies included mixed racial/ethnic patients. Seven of 11 studies measured cross-sectional PRL levels, and 4 studies assessed changes in PRL levels over the treatment period. No studies reported on the genotype effect on the proportion of patients with study-defined hyperprolactinemia.

3.3. DRD2 Taq1A genotype and antipsychotic-related PRL levels

In the total population, there was a trend in the difference in plasma PRL levels between A1 carriers and A1 non-carriers (studies = 11, n = 1034, Hedges' g = 0.157, 95%CI = −0.022 to 0.336, p = 0.086; Fig. 1, Table 2). However, there were no significant associations in the total population between DRD2 Taq1A genotype and PRL levels when comparing A2 carriers and A2 non-carriers (studies = 7, n = 736, Hedges' g = 0.081, 95%CI = −0.198–0.36, p = 0.568; Table 2). Significant heterogeneity was not present in two genetic comparisons (Table 2). In *meta*-regression analyses, no significant associations were found in the 2 genetic comparisons between either percent males, mean age of patients in the study samples, or percent schizophrenia and PRL levels.

In patients with schizophrenia, A1 carriers had significantly higher PRL levels than A1 non-carriers (studies = 5, n = 475, Hedges' g = 0.250, 95%CI = 0.068–0.433, p = 0.007; Table 2), whereas there were no significant associations between DRD2 Taq1A genotype and plasma PRL levels in non-schizophrenia patients (Table 2). The association between A1 carriers and A1 non-carriers remained significant after Bonferroni correction.

Dividing the subjects by sex, no significant associations were found in males or females between the DRD2 Taq1A genotype and PRL levels in any of the 2 genetic comparisons, which all yielded non-heterogeneous results (Table 2). In Asian patients, there was a trend level difference between A1 carriers and A1 non-carriers (studies = 4, n = 331, Hedges' g = 0.216, 95%CI = −0.020–0.451, p = 0.073; Table 2), whereas there were no significant associations between DRD2 Taq1A genotype and plasma PRL levels in Caucasian or mixed racial/ethnic patients (Table 2). In the PRL measurement subgroup analysis, no significant associations were found in both genetic comparisons for either study subgroup measuring cross-sectional PRL levels or PRL changes during treatment (Table 2).

3.4. DRD2 −141C Ins/Del genotype and antipsychotic-related PRL levels

In the total population, there were no significant associations between DRD2 −141C Ins/Del genotype and PRL levels when comparing Del carriers and Del non-carriers (studies = 4, n = 451, Hedges' g = −0.070, 95%CI = −0.423–0.283, p = 0.698; Fig. 2, Table 3). Significant heterogeneity was present in this comparison of Del carriers and Del non-carriers (Q = 7.409, df = 3, p = 0.06, I^2 = 59.5%; Table 3). In *meta*-regression analyses, there was a significant association between male sex and PRL levels (slope = −0.009, 95%CI = −0.0176–0.0005, p = 0.038), indicating that a greater proportion of male patients was related to a smaller effect of the Del carriers on PRL levels. There was no significant association between either mean age or percent schizophrenia and PRL levels in the genetic comparisons.

In subgroup analyses, there were also no significant associations between DRD2 −141C Ins/Del genotype and PRL levels. Significant heterogeneity was present in the schizophrenia subgroup (Q = 5.333, df = 1, p = 0.021, I^2 = 81.3%). Dividing the subjects by sex, there were no significant associations between DRD2 −141C Ins/Del genotype and PRL levels in males or females (Table 3). Significant heterogeneity was present in males (Q = 4.359, df = 2, p = 0.113, I^2 = 54.1%) (Table 3). There were no significant associations between the DRD2 −141C Ins/Del genotype and plasma PRL levels in Asian or mixed racial/ethnic patients (Table 3). Because all 4 studies measured cross-sectional PRL levels, we could not

Table 1
Studies investigating the association between the DRD2 polymorphisms and antipsychotic-related prolactin levels.

study	Ethnicity	Country	patients	study design, duration	prolactin measurement	APs	Sample size	mean age (years)	% Male	polymorphism	genotype, N(%)		
Schizophrenia													
Mihara et al. (2000)	Asian: 100%	Japan	SCZ (DSM-IIIR) inpatients received no medication for at least 1 month	Prospective study, 3 weeks	Changes over prospective study period	Nemonapride, 18 mg/day	25	34.7 ± 11.2	52	Taq1A	A1/A1 2 (8.0)	A1/A2 12 (48.0)	A2/A2 11 (44.0)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
Mihara et al. (2001)	Asian: 100%	Japan	SCZ (DSM-IIIR) inpatients received no medication for at least 1 month	Prospective study, 2 weeks	Changes over prospective study period	Bromperidol, 6 mg/day (n = 10), 12 mg/day (n = 13), 18 mg/day (n = 9)	32	37.2 ± 13.0	50	Taq1A	A1/A1 4 (12.5)	A1/A2 17 (53.1)	A2/A2 11 (34.4)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
Young et al. (2004)	Caucasian: 100%	Australia	SCZ (DSM-IV) inpatients (n = 61) and outpatients (n = 83), who received AP for at least 1 month at a stable dosage	Crosssectional study	Crosssectional levels	CLO (n = 31), OLZ (n = 31), RIS (n = 49), typical (n = 33)	144	36.4 ± 12.0	85.4	Taq1A	A1/A1 7 (4.9)	A1/A2 55 (38.2)	A2/A2 82 (56.9)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
Yasui-Furukori et al. (2008)	Asian: 100%	Japan	SCZ (DSM-IV) inpatients, who received 6 mg/day of RIS for 4–79 weeks	Crosssectional study	Crosssectional levels	RIS, 6 mg/day	174	43.2 ± 18.9	39.1	Taq1A	A1/A1 12 (6.9)	A1/A2 68 (39.1)	A2/A2 94 (54.0)
										−141C Ins/Del	Ins/Ins 121 (69.5)	Ins/Del 50 (28.7)	Del/Del 3 (1.7)
Zhang et al. (2011)	Asian: 100%	China	Married remitted male SCZ (DSM-IV) outpatients, who received single AP for at least 6 months	Crosssectional study	Crosssectional levels	CLO (n = 37), RIS (n = 30), CPZ (n = 21), HPD (n = 9), OLZ (n = 3)	100	40.8± 4.9	100	Taq1A	A1/A1 17 (17.0)	A1/A2 46 (46.0)	A2/A2 37 (37.0)
										−141C Ins/Del	Ins/Ins 86 (86.0)	Ins/Del 13 (13.0)	Del/Del 1 (1.0)
N = 5	Asian: n = 331 (69.7%) Caucasian: n = 144 (30.3%)	Japan: N = 3; Australia: N = 1; China: N = 1	SCZ: N = 5	Crossectional study: N = 3; Prospective study: N = 2	Crosssectional levels: N = 3; Changes over prospective study period: N = 2	RIS: n = 253; CLO: n = 37; OLZ: n = 34; BRO: n = 32; NEM: n = 28; CPZ: n = 21; HPD: n = 9; other typical AP: n = 33	475	39.8 ± 14.4	67.4	Taq1A	A1/A1 42 (8.8)	A1/A2 198 (41.7)	A2/A2 235 (49.5)
										−141C Ins/Del	Ins/Ins 207 (75.5)	Ins/Del 63 (23.0)	Del/Del 4 (1.5)
Non-schizophrenia													
Anderson et al. (2007)	Mixed: White (n = 67), Black (n = 11), Asian (n = 8), Hispanic (n = 7), other (n = 7)	US	5 to 17 years old medication-free (except for unchanged dose of AED) autism (DSM-IV) outpatients	Prospective study, 6 months	Crosssectional levels	RIS 1.8 ± 0.7 mg/day (mean ± SD)	101	8.8 ± 2.7	81.2	Taq1A	A1/A1 2 (2.9)	A1/A2 31 (45.6)	A2/A2 35 (51.5)
										−141C Ins/Del	Ins/Ins 51 (72.9)	Ins/Del 18 (25.7)	Del/Del 1 (1.4)
Calarge et al. (2009)	Non-Hispanic Caucasian (n = 90) and other (n = 17)	US	7 to 17 years old outpatients (irrespective of diagnosis) who received RIS for 6 months or more	Crosssectional study	Crosssectional levels	RIS, 0.03 mg/kg/d (median, A1 allele carriers); 0.02 mg/kg/day (median, A1 allele non-carriers)	107	12.1± 2.8	86.9	Taq1A	A1/A1 4 (3.7)	A1/A2 35 (32.7)	A2/A2 68 (63.6)
										−141C Ins/Del	Ins/Ins 80 (74.8)	Ins/Del 25 (23.4)	Del/Del 2 (1.9)

Table 1 (*Continued*)

study	Ethnicity	Country	patients	study design, duration	prolactin measurement	APs	Sample size	mean age (years)	% Male	polymorphism	genotype, N(%)		
Correia et al. (2010)	Caucasian (n = 44, 97.8%) and African (n = 1, 2.2%)	Portugal	Autistic outpatients (ADIR and ADOS), who received no medication for at least 3 months	Prospective study, 12 months	Changes over prospective study period	RIS 1.34 ± 0.7 mg/day (at 12months)	45	8.7 ± 4.3	75.6	Taq1A	A1/A1 2 (4.9)	A1/A2 18 (43.9)	A2/A2 21 (51.2)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
Houston et al. (2010)	Caucasian: 100%	US/Canada	Treatment resistant MDD (DSM-IV) outpatients/BP I, depressed (DSM-IV) outpatients and inpatients	Genetic association study using data of 2 RCTs, 15.9 weeks	Crosssectional levels	OFC (OLZ 6–18 mg/day and FLU 25–50 mg/day)	239	42.8 ± 10.9	37.2	Taq1A	A1/A1 11 (4.6)	A1/A2 84 (35.1)	A2/A2 144 (60.3)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
Houston et al. (2011)	Caucasian: 100%	US/Europe	BPD (DSM-IV) outpatients/acute bipolar manic or mixed episode (DSM-IV-TR) inpatients and outpatients	Genetic association study using data of 3 RCTs, 12 weeks	Changes over prospective study period	OLZ 2.5–20 mg/day	59	35.6 ± 11.0	44.1	Taq1A	A1/A1 4 (6.8)	A1/A2 11 (18.6)	A2/A2 44 (74.6)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
Roke et al. (2013)	Caucasian (n = 46, 97.9%) and other (n = 1, 2.1%)	Netherlands	10 to 20 outpatients (autism spectrum disorder and/or disruptive behavior disorder), who received any potential prolactin-elevating antipsychotic medication for more than 16 months	Crosssectional study	Crosssectional levels	RIS 1.6 ± 1.0 mg/day	47	14.7 ± 2.1	100	Taq1A	A1/A1 1 (2.1)	A1/A2 15 (31.9)	A2/A2 31 (66.0)
										−141C Ins/Del	Ins/Ins –	Ins/Del –	Del/Del –
N = 6	Caucasian: n = 545 (91.2%); African: n = 12 (2.0%); Asian: n = 8 (1.3%); Hispanic: n = 7 (1.2%); other: n = 24 (4.2%)	US: N = 2; Portugal: N = 1; Netherlands: N = 1; US/Canada: N = 1; US/Europe: N = 1	Autism: N = 2; autism spectrum disorder and disruptive behavior disorder: N = 1; mixed child and adolescents psychiatric disorders: N = 1; Treatment resistant MDD and BP I, depressed: N = 1; BPD and bipolar manic or mixed episode: N = 1	Crosssectional study: N = 2; Prospective study: N = 2; Genetic association study using data of RCT: N = 2	Crosssectional levels: N = 4; Changes over prospective study period: N = 2	RIS: n = 300; OLZ: n = 239; OFC: n = 59	598	26.0± 17.4	62	Taq1A	A1/A1 24 (4.3)	A1/A2 194 (34.6)	A2/A2 343 (61.1)
										−141C Ins/Del	Ins/Ins 131 (74.0)	Ins/Del 43 (24.3)	Del/Del 3 (1.7)
total N = 11	Caucasian: n = 643 (63.4%); Asian: n = 339 (33.4%); African: n = 12 (1.2%); Hispanic: n = 7 (0.7%); other: n = 24 (2.4%)	Japan: N = 3; US: N = 2; Australia: N = 1; China: N = 1; Portugal: N = 1; Netherlands: N = 1; US/Canada: N = 1; US/Europe: N = 1	SCZ: N = 6; SCZ + SCZAD + SCZPD: N = 1; Autism: N = 2; mixed child and adolescents psychiatric symptoms: N = 1; Treatment resistant MDD and BP I, depressed: N = 1; BPD and bipolar manic or mixed episode: N = 1	Crosssectional study: N = 5; Prospective study: N = 4; Genetic association study using data of RCT: N = 2	Crosssectional levels: N = 7; Changes over prospective study period: N = 4	RIS: n = 553; CLO: n = 37; OLZ: n = 273; OFC: n = 59; BRO: n = 32; NEM: n = 28; CPZ: n = 21; HPD: n = 9; other typical AP: n = 33	1073	32.1 ± 17.5	64.4	Taq1A	A1/A1 66 (6.4)	A1/A2 392 (37.8)	A2/A2 578 (55.8)
										−141C Ins/Del	Ins/Ins 338 (74.9)	Ins/Del 106 (23.5)	Del/Del 7 (1.6)

Abbreviations: SCZ, schizophrenia; SCZAD, schizoaffective disorder; SCZPD, schizophreniform disorder; MDD, major depressive disorder; BP I, bipolar I disorder; BPD, borderline personality disorderAP, antipsychotic; ADIR, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; CLO, clozapine; OLZ, olanzapine; RIS, risperidone; APZ, aripiprazole; QTP, quetiapine; HPD, haloperidol; CPZ, chlorpromazine; NEM, nemonapride; BRO, bromperidol.

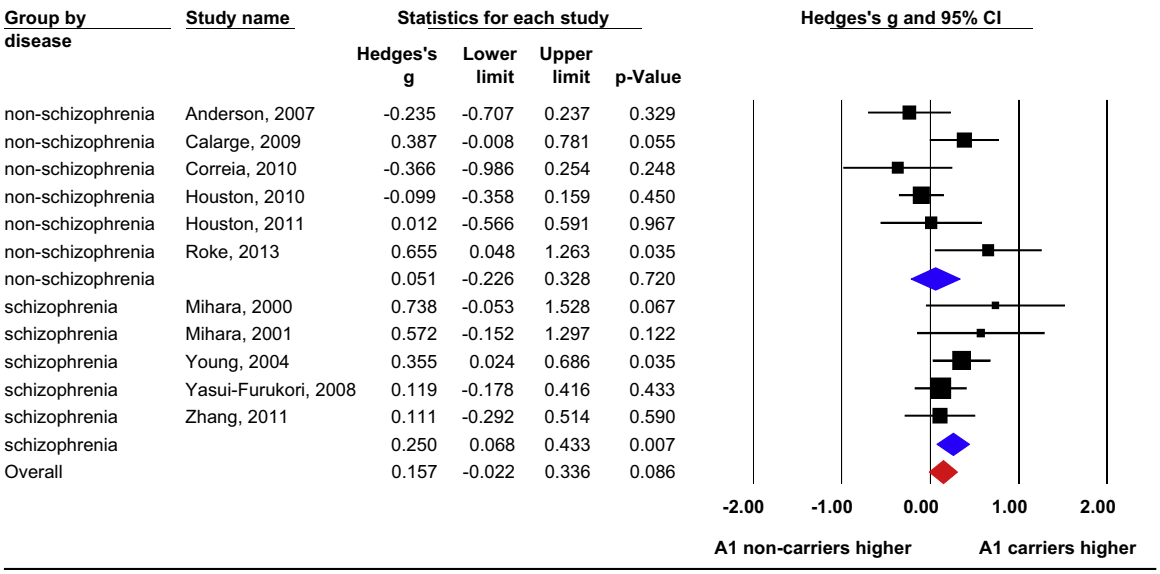

Fig. 1. Forest plot for the association with DRD2 Taq1A polymorphism (A1 carriers vs. A1 non-carriers) and antipsychotic-related PRL levels using random effects model. Legend: Blue diamond represents effect size of each diagnostic subgroup (non-schizophrenia and schizophrenia); red diamond represents effect size of overall subjects (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Table 2
Meta-analysis of the association between DRD2 Taq1A polymorphism and plasma PRL levels.

Comparisons of genetic groups	Subjects	Sample size	No. ofstudies	Association			Test of heterogeneity			
				Random model Hedges' g (95% CI)	Z value	P value	Q value	df(Q)	P value	I^2(%)
A1 carriers vs. A1 non-carriers	Overall	1034	11	0.157 (−0.022, 0.336)	1.718	0.086	17.939	10	0.056	44.3
	Male	481	9	0.019 (−0.191, 0.230)	0.181	0.857	9.175	8	0.328	12.8
	Female	341	7	−0.003 (−0.263, 0.256)	−0.025	0.98	6.229	6	0.398	3.67
	schizophrenia	475	5	0.250 (0.068, 0.433)	2.694	**0.007**	3.818	4	0.431	0
	non-schizophrenia	559	6	0.051 (−0.226, 0.328)	0.359	0.72	10.951	5	0.052	54.34
	Asian	331	4	0.216 (−0.020, 0.451)	1.794	0.073	3.266	3	0.352	8.131
	Caucasian	442	3	0.089 (−0.227, 0.406)	0.552	0.581	4.544	2	0.103	55.98
	Mixed ethnicity	261	4	0.116 (−0.334, 0.567)	0.506	0.613	9.249	3	**0.026**	67.56
	crosssectional PRL levels	879	7	0.152 (−0.043, 0.347)	1.524	0.128	11.62	6	0.071	48.36
	PRL changes over treatment	155	4	0.194 (−0.293, 0.681)	0.782	0.434	6.303	3	0.098	52.41
A2 carriers vs. A2 no-carriers	Overall	736	7	0.081 (−0.198, 0.360)	0.571	0.568	4.945	6	0.551	0
	Male	392	6	0.013 (−0.364, 0.391)	0.07	0.944	2.943	5	0.709	0
	Female	317	5	0.114 (−0.346, 0.574)	0.486	0.627	2.167	4	0.705	0
	schizophrenia	331	4	−0.049 (−0.405, 0.308)	−0.268	0.788	3.05	3	0.384	1.65
	non-schizophrenia	405	3	0.298 (−0.161, 0.757)	1.274	0.203	0.531	2	0.767	0
	Asian	331	4	−0.049 (−0.405, 0.308)	−0.268	0.788	3.05	3	0.384	1.65
	Caucasian	298	2	0.372 (−0.146, 0.889)	1.408	0.159	0.17	1	0.68	0
	Mixed ethnicity	107	1	0.029 (−0.963, 1.020)	0.057	0.955	0	0	1	0
	crosssectional PRL levels	620	4	0.165 (−0.145, 0.475)	1.043	0.297	1.11	3	0.775	0
	PRL changes over treatment	116	3	−0.295 (−0.997, 0.407)	−0.824	0.41	2.357	2	0.308	15.14

Bolded *p*-value < 0.05.

perform a subgroup analysis according to the type of PRL measurement.

3.5. Publication bias

There was asymmetry for the A1 carriers vs. A1 non-carriers comparison in females (Egger's test: p = 0.032). Using the Duval and Tweedie trim and fill method, three additional potentially unpublished studies were missing for the A1 carriers vs. A1 non-carriers comparison in female subjects. After filling in the three missing studies, the genotype effect on PRL levels also remained non-significant (Hedges' g = −0.072, 95%CI = −0.373–0.230). There was no asymmetry for other Taq1A genotype comparisons depicted in Table 2 (supplementary Fig. 2 for A1 carriers vs. A1 non-carriers in all subjects). Funnel plot inspection revealed no asymmetry for −141C Ins/Del genotype comparisons depicted in Table 3 (Supplementary Fig. 3 for Del carriers vs. Del non-carriers in overall subjects).

4. Discussion

To our knowledge, this is the first comprehensive *meta*-analysis of the association between *DRD2* polymorphisms and PRL levels or changes during treatment with D2 antagonist antipsychotic treat-

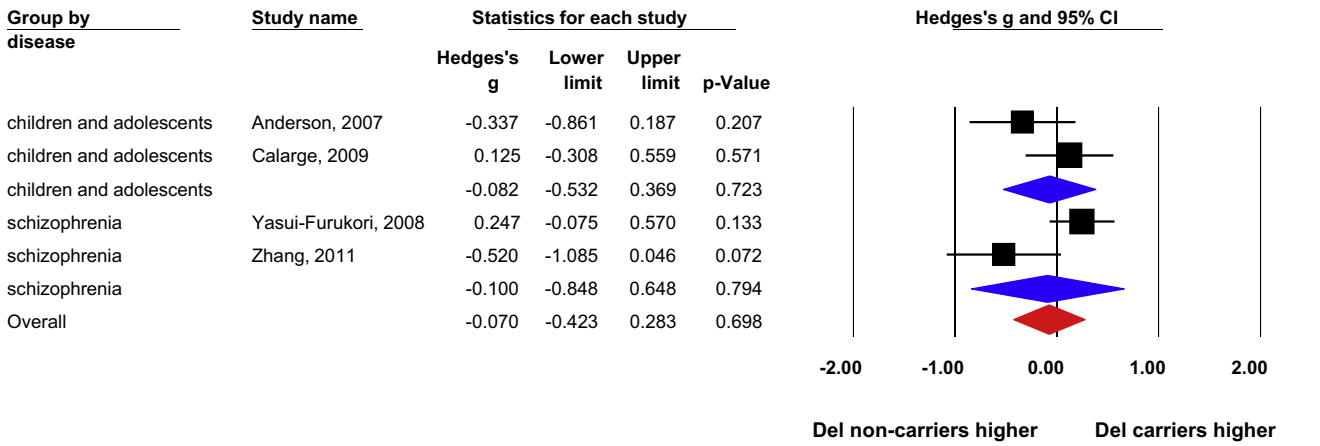

Fig. 2. Forest plot for the association with DRD2 −141C Ins/Del polymorphism (Del carriers vs. Del non-carriers) and antipsychotic-related PRL levels using random effects model. Legend: Blue diamond represents effect size of each diagnostic subgroup (non-schizophrenia and schizophrenia); red diamond represents effect size of overall subjects (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

Table 3
Meta-analysis of the association between DRD2 −141C Ins/Del polymorphism and plasma PRL levels.

Comparisons of genetic groups	Subjects	Sample size	No. of studies	Association			Test of heterogeneity			
				Random model Hedges' g (95% CI)	Z value	P value	Q value	df(Q)	P value	I^2(%)
Del carriers vs. Del non-carriers	Overall	451	4	−0.070 (−0.423, 0.283)	-0.388	0.698	7.409	3	0.06	59.51
	Male	261	3	0.065 (−0.326, 0.457)	0.327	0.744	4.359	2	0.113	54.11
	Female	120	2	0.146 (−0.235, 0.528)	0.752	0.452	0.279	1	0.597	0
	schizophrenia	274	2	−0.100 (−0.848, 0.648)	-0.261	0.794	5.333	1	**0.021**	81.25
	non-schizophrenia	177	2	−0.082 (−0.532, 0.369)	-0.354	0.723	1.779	1	0.182	43.79
	Asian	274	2	−0.100 (−0.848, 0.648)	-0.261	0.794	5.333	1	**0.021**	81.25
	Mixed ethnicity	177	2	−0.082 (−0.532, 0.369)	-0.354	0.723	1.779	1	0.182	43.79

Bolded *p*-value < 0.05.

ment. In this *meta*-analysis of 11 studies with a total of 1073 antipsychotic-treated patients, we found no significant associations between the *DRD2* Taq1A or −141C Ins/Del polymorphism and PRL levels in all studies and patients pooled together. However, when conducting subgroup analyses by disease, we did find a significant difference in plasma PRL levels between Taq1A A1 carriers and A1 non carriers in patients with schizophrenia, with A1 carriers showing higher PRL levels. By contrast, no significant effects were found in studies with non-schizophrenia patients.

These null findings in all patients from our *meta*-analysis were contrary to our expectations that were based on the well-known and well-replicated relationship between full antidopaminergic antipsychotic affinity for the DRD2 and prolactin elevation (Peuskens et al., 2014). The non-significant findings are either due to small effects of DRD2 polymorphisms or other, more important genetic and/or non-genetic factors. The possibility that the DRD2 polymorphism effects could be present but small is raised by the fact that the number of studies and patients included in this *meta*-analyses was still quite small. Moreover, in pooled analyses, there was a trend level difference in plasma PRL levels between A 1 carriers and A1 non-carriers ($p = 0.086$). Furthermore, it is also possible that higher doses of antipsychotics increase chances of identifying DRD2 polymorphism effects on PRL levels. A potential dose effect is suggested by the significantly higher PRL levels in DRD2 Taq1A A1 carriers than A1 non-carriers in patients with schizophrenia, who generally receive higher antipsychotic doses than in patients with mood disorders/personality disorders. However, based on the reported data, it was not possible to calculate and compare chlorpromazine equivalences across the diagnostic subgroups. Furthermore, since different antipsychotics possess different PRL raising effects, the mixture of antipsychotic agents could have made it more difficult to find a genotype effect in this *meta*-analysis. Moreover, comedications can also have affected the results. For example, in 3 of the 4 studies of children and adolescents and the 2 studies with mood and personality disorders, co-medications, such as psychostimulants or antidepressants were used, whereas only benzodiazepines and anticholinergics were allowed in the studies including schizophrenia patients.

Nevertheless, our trend-level findings in all patients and the significant results in those with schizophrenia, indicating significantly higher PRL levels in A1 carriers than in A1 non-carriers, are consistent with previous single dose administration studies (Aklillu et al., 2007; López-Rodríguezet al., 2011; Cabaleiro et al., 2013), which demonstrated that the A1 allele was associated with greater PRL response to antipsychotics in healthy subjects. Furthermore, previous PET studies (Noble et al., 1991; Thompson et al., 1997; Pohjalainen et al., 1998; Jönsson et al., 1999) indicated that A1 allele carriers had lower DRD2 density than A1 allele non-carriers. If A1 allele carriers have fewer DRD2 than A1 allele non-carriers, antipsychotics may bind to relatively more DRD2, which may lead to increased PRL levels. Interestingly, a previous study showed that Taq1A polymorphism may be associated with changes in plasma levels of homovanillic acid, a metabolite of dopamine, during antipsychotic treatment of schizophrenia (Miura et al., 2012). In that study, the changes of plasma homovanillic acid levels differed significantly between responders and nonresponders in A1 allele

carriers but not in A1 allele non-carriers, and plasma homovanillic acid levels decreased significantly in responders with A1 allele carriers. Taken together, despite our overall negative findings, we cannot exclude that Taq1A polymorphism may affect the dopaminergic neural response to DRD2 binding by antipsychotics, showing a greater response in A1 allele carriers than A1 allele non-carriers and being possibly associated with modestly increased PRL levels. Larger studies and *meta*-analyses are required to investigate this question further.

We also did not detect a relationship between antipsychotic-related PRL levels and the −141C Ins/Del polymorphism, yet the analyses were limited by the small number of available studies (N = 4) and patients (n = 451). The 141C Ins/Del SNP is located in the 5′ promoter region of DRD2 gene, and may have effects on transcriptional activities (Arinami et al., 1997). Although −141C Ins/Del polymorphism has also been reported to influence DRD2 density, indicating that Del allele carriers had higher DRD2 density than Del allele non-carriers (Jönsson et al., 1999), although one other study reported no association between this polymorphism and DRD2 density (Pohjalainen et al., 1999). Our results suggest that −141C Ins/Del is not associated with plasma PRL levels during antipsychotic treatment, although additional studies are needed to fully confirm this.

In exploratory *meta*-regression analyses investigating percent male and mean age as moderators, we found significant association between male sex and PRL levels when comparing Del carriers and Del non-carriers of −141C Ins/Del polymorphism, whereas there were no significant associations between mean age and PRL levels. Female sex has been associated with hyperprolactinemia (Kinon et al., 2003; Bushe and Shaw, 2007), which may have affected our *meta*-analytic results, although the small number of studies and small sample size limited the power for these analysis.

There are several limitations of this study. First, despite pooling data from 11 studies, only 1034 and 451 patients, respectively contributed to each of the 2 DRD2 polymorphism analyses. Second, the study samples, antipsychotic treatments, treatment durations and doses as well as comedications were heterogeneous and not always detailed to allow for *meta*-regression analyses. Furthermore, due to insufficient information in the included studies, we were unable to perform subgroup analyses by specific antipsychotic or group of antipsychotics with similar PRL raising effects that differ across different antipsychotics (Peuskens et al., 2014; Leucht et al., 2013; Suzuki et al., 2013). Third, this *meta*-analysis focused only two DRD2 polymorphisms and gene–gene interactions could not be examined. Thus, other polymorphisms that have not been widely investigated may have relevant effects on PRL levels, and investigating gene–gene interactions may be helpful for clarifying the genetic underpinnings of antipsychotic-related PRL changes. Furthermore, haplotype analysis between the two DRD2 genotypes may be helpful to investigate genetic effects on PRL levels. However, the small sample size and *meta*-analytic study design precluded adding this analysis to our study. Finally, based on the published data, we were only able to assess DRD2 effects on PRL levels. However, it is possible that the examination of subgroups of patients, including those with clinically relevant hyperprolactinemia or the examination of tails of the PRL distribution may yield stronger effects. Future studies should report findings both for continuous PRL levels as well as for the subgroup of patients with hyperprolactinemia as well as those with symptomatic hyperprolactinemia, indicated by sexual and/or reproductive system adverse effects.

In summary, we found no significant associations between the two DRD2 polymorphisms and PRL levels in patients treated with various antidopaminergic antipsychotics. In the subgroup of schizophrenia patients, however, there was significant difference between the DRD2 Taq1A polymorphisms and higher plasma PRL levels during antipsychotic treatment. However, caution is needed in interpreting the results of this *meta*-analysis because of the small sample size, variety of antipsychotic drugs and heterogeneity across studies and samples that could result in both a type I and type II error. Therefore, additional studies with larger sample sizes that report more detailed information about potential moderators and confounders as well as PRL levels, changes and subgroups with hyperprolactinemia are needed to confirm and extend or refute our results. Furthermore, studies or subgroup analyses of single antipsychotics are needed to investigate the effect of individual antipsychotics. Finally investigating the effect of combinations of Taq1A and −141C Ins/Del polymorphisms on plasma PRL levels may be helpful for dissecting the genetic risk underlying antipsychotic-related PRL changes and hyperprolactinemia.

Contributions

Dr. Miura conducted the literature search, extracted the data, conducted the statistical analysis and wrote the first draft of the manuscript. Drs. Zhang and Hagi helped with the statistical analysis and helped editing the content of the manuscript. Drs. Lencz, Kane, Malhotra, and Yabe helped reviewing the content of the manuscript. Dr. Correll designed the study, helped with data extraction and literature search, and helped editing the content of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Dr. Miura has received speaker's honoraria from Dainippon Sumitomo, Janssen, Meiji Seika, Otsuka, and Yoshitomi. He had received grant support from Janssen, Hoshi General Hospital Foundation, and the Eli Lilly Fellowship for Clinical Psychopharmacology.

Dr. Zhang has received grant support from Genomind, Inc.

Dr. Hagi is an employee of Dainippon Sumitomo Pharma.

Dr. Lencz declares no conflict of interest.

Dr. Kane reports consulting fees for Alkermes, Bristol-Myers Squibb, Eli Lilly, Forrest, Forum, Genentech, ITI, Janssen, Johnson and Johnson, Lundbeck, Novartis, Otsuka, Roche, Sunovion, Reviva, and Pierre Fabre.

Dr. Yabe declares no conflict of interest.

Dr. Malhotra has been a consultant to Genomind, Inc. and Forum Pharmaceuticals.

Dr. Correll has received research grants from Bristol-Myers Squibb Company, Novo Nordisk, AstraZeneca Pharmaceuticals LP, and Otsuka Pharmaceuticals Co., Ltd., and served as member of the Data Safety Monitoring Board of Eli Lilly and Company; Cephalon; Janssen; Lundbeck, Inc.; Pfizer, Inc.; and Takeda Pharmaceuticals North America, Inc.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.06.002.

References

Aklillu, E., Kalow, W., Endrenyi, L., Harper, P., Miura, J., Ozdemir, V., 2007. CYP2D6 and DRD2 genes differentially impact pharmacodynamic sensitivity and time course of prolactin response to perphenazine. Pharmacogenet. Genom. 17, 989–993.

Alenius, M., Wadelius, M., Dahl, M.L., Hartvig, P., Lindström, L., Hammarlund-Udenaes, M., 2008. Gene polymorphism influencing treatment response in psychotic patients in a naturalistic setting. J. Psychiatr. Res. 42, 884–893.

Anderson, G.M., Scahill, L., McCracken, J.T., McDougle, C.J., Aman, M.G., Tierney, E., Arnold, L.E., Martin, A., Katsovich, L., Posey, D.J., Shah, B., Vitiello, B., 2007. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. Biol. Psychiatry 61, 545–550.

Arinami, T., Gao, M., Hamaguchi, H., Toru, M., 1997. A functional polymorphism in the promoter region of the dopamine receptor gene is associated with schizophrenia. Hum. Mol. Genet. 6, 577–582.

Bakker, P.R., van Harten, P.N., van Os, J., 2008. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. Mol. Psychiatry 13, 544–556.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H. (Eds), 2005. Comprehensive Meta-analysis. 2. Biostat, New Jersey.

Burris, K.D., Molski, T.F., Xu, C., Ryan, E., Tottori, K., Kikuchi, T., Yocca, F.D., Molinoff, P.B., 2002. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J. Pharmacol. Exp. Ther. 302, 381–389.

Bushe, C., Shaw, M., 2007. Prevalence of hyperprolactinemia in a naturalistic cohort of schizophrenia and bipolar outpatients during treatment with typical and atypical antipsychotics. J. Psychopharmacol. 21, 768–773.

Cabaleiro, T., López-Rodríguez, R., Ochoa, D., Román, M., Novalbos, J., Abad-Santos, F., 2013. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum. Psychopharmacol. 28, 205–214.

Calarge, C.A., Ellingrod, V.L., Acion, L., Miller, D.D., Moline, J., Tansey, M.J., Schlechte, J.A., 2009. Variants of the dopamine D2 receptor gene and risperidone-induced hyperprolactinemia in children and adolescents. Pharmacogenet. Genom. 19, 373–382.

Correia, C.T., Almeida, J.P., Santos, P.E., Sequeira, A.F., Marques, C.E., Miguel, T.S., Abreu, R.L., Oliveira, G.G., Vicente, A.M., 2010. Pharmacogenetics of risperidone therapy in autism: association analysis of eight candidate genes with drug efficacy and adverse drug reactions. Pharmacogenomics J. 10, 418–430.

De Hert, M., Detraux, J., Peuskens, J., 2014. Second-generation and newly approved antipsychotics: serum prolactin levels and sexual dysfunctions: a critical literature review. Expert Opin. Drug Saf. 13, 605–624.

De Hert, M., Peuskens, J., Sabbe, T., Mitchell, A.J., Stubbs, B., Neven, P., Wildiers, H., Detraux, J., 2015. Relationship between prolactin, breast cancer risk and antipsychotics in patients with schizophrenia: a critical review. Acta Psychiatr. Scand., http://dx.doi.org/10.1111/acps.12459 (Epubaheadofprint).

Duval, S., Tweedie, R., 2000. A nonparametric trim and fill method of accounting for publication bias in meta-analysis. J. Am. Stat. Assoc. 95, 89–98.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.

Fraguas, D., Correll, C.U., Merchán-Naranjo, J., Rapado-Castro, M., Parellada, M., Moreno, C., Arango, C., 2011. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. Eur. Neuropsychopharmacol. 21, 621–645.

Güzey, C., Scordo, M.G., Spina, E., Landsem, V.M., Spigset, O., 2007. Antipsychotic-induced extrapyramidal symptoms in patients with schizophrenia: associations with dopamine and serotonin receptor and transporter polymorphisms. Eur. J. Clin. Pharmacol. 63, 233–241.

Haddad, P.M., Wieck, A., 2004. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs 64, 2291–2314.

Houston, J.P., Fijal, B., Heinloth, A.N., Adams, D.H., 2010. Genetic associations of prolactin increase in olanzapine/fluoxetine combination-treated patients. Psychiatry Res. 175, 171–172.

Houston, J., Dharia, S., Bishop, J.R., Ellingrod, V.L., Fijal, B., Jacobson, J.G., Hoffmann, V.P., 2011. Association of DRD2 and ANKK1 polymorphisms with prolactin increase in olanzapine-treated women. Psychiatry Res. 187, 74–79.

Ikeda, M., Yamanouchi, Y., Kinoshita, Y., Kitajima, T., Yoshimura, R., Hashimoto, S., O'Donovan, M.C., Nakamura, J., Ozaki, N., Iwata, N., 2008. Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. Pharmacogenomics 9, 1437–1443.

Jönsson, E.G., Nöthen, M.M., Grünhage, F., Farde, L., Nakashima, Y., Propping, P., Sedvall, G.C., 1999. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol. Psychiatry 4, 290–296.

Kinon, B.J., Gilmore, J.A., Liu, H., Halbreich, U.M., 2003. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 28 (Suppl. 2), 55–68.

Kishimoto, T., De Hert, M., Carlson, H., Manu, P., Correll, C.U., 2012. Osteoporosis and fracture risk in people with schizophrenia. Curr. Opin. Psychiatry 25, 415–429.

Kwon, J.S., Kim, E., Kang, D.H., Choi, J.S., Yu, K.S., Jang, I.J., Shin, S.G., 2008. APLUS study group.,. Taq1A polymorphism in the dopamine D2 receptor gene as a predictor of clinical response to aripiprazole. Eur. Neuropsychopharmacol. 18, 897–907.

López-Rodríguez, R., Román, M., Novalbos, J., Pelegrina, M.L., Ochoa, D., Abad-Santos, F., 2011. DRD2 Taq1A polymorphism modulates prolactin secretion induced by atypical antipsychotics in healthy volunteers. J. Clin. Psychopharmacol. 31, 555–562.

Lencz, T., Robinson, D.G., Xu, K., Ekholm, J., Sevy, S., Gunduz-Bruce, H., Woerner, M.G., Kane, J.M., Goldman, D., Malhotra, A.K., 2006. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. Am. J. Psychiatry 163, 529–531.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382, 951–962.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209–1223.

Madhusoodanan, S., Parida, S., Jimenez, C., 2010. Hyperprolactinemia associated with psychotropics—a review. Hum. Psychopharmacol 25, 281–297.

Mihara, K., Kondo, T., Suzuki, A., Yasui, N., Nagashima, U., Ono, S., Otani, K., Kaneko, S., 2000. Prolactin response to nemonapride a selective antagonist for D2 like dopamine receptors, in schizophrenic patients in relation to Taq1A polymorphism of DRD2 gene. Psychopharmacology (Berl.) 149, 246–250.

Mihara, K., Suzuki, A., Kondo, T., Yasui-Furukori, N., Ono, S., Otani, K., Kaneko, S., Inoue, Y., 2001. Relationship between Taq1 A dopamine D2 receptor (DRD2) polymorphism and prolactin response to bromperidol. Am. J. Med. Genet 105, 271–274.

Miura, I., Takeuchi, S., Katsumi, A., Mori, A., Kanno, K., Yang, Q., Mashiko, H., Numata, Y., Niwa, S., 2012. Effects of aripiprazole and the Taq1A polymorphism in the dopamine D2 receptor gene on the clinical response and plasma monoamine metabolites level during the acute phase of schizophrenia. J. Clin. Psychopharmacol. 32, 106–109.

Miura, I., Kanno-Nozaki, K., Hino, M., Horikoshi, S., Ota, T., Mashiko, H., Niwa, S., Yabe, H., 2015. Influence of −141C Ins/Del polymorphism in DRD2 gene on clinical symptoms and plasma homovanillic acid levels in the treatment of schizophrenia with aripiprazole. J. Clin. Psychopharmacol. 35, 333–334.

Montgomery, J., Winterbottom, E., Jessani, M., Kohegyl, E., Fulmer, J., Seamonds, B., Josiassen, R.C., 2004. Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment. J. Clin. Psychiatry 65, 1491–1498.

Nagai, G., Mihara, K., Nakamura, A., Suzuki, T., Nemoto, K., Kagawa, S., Ohta, I., Arakaki, H., Kondo, T., 2012. Prolactin concentrations during aripiprazole treatment in relation to sex, plasma drugs concentrations and genetic polymorphisms of dopamine D2 receptor and cytochrome P450 2D6 in Japanese patients with schizophrenia. Psychiatry Clin. Neurosci. 66, 518–524.

Neville, M.J., Johnstone, E.C., Walton, R.T., 2004. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23. 1. Hum. Mutat. 23, 540–545.

Noble, E.P., Blum, K., Ritchie, T., Montgomery, A., Sheridan, P.J., 1991. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch. Gen. Psychiatry 48, 648–654.

Peuskens, J., Pani, L., Detraux, J., De Hert, M., 2014. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs 28, 421–453.

Pohjalainen, T., Rinne, J.O., Någren, K., Lehikoinen, P., Anttila, K., Syvälahti, E.K., Hietala, J., 1998. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol. Psychiatry 3, 256–260.

Pohjalainen, T., Någren, K., Syvälahti, E.K., Hietala, J., 1999. The dopamine D2 receptor 5′-flanking variant, −141C Ins/Del, is not associated with reduced dopamine D2 receptor density in vivo. Pharmacogenetics 9, 505–509.

Roke, Y., van Harten, P.N., Franke, B., Galesloot, T.E., Boot, A.M., Buitelaar, J.K., 2013. The effect of the Taq1A variant in the dopamine D2 receptor gene and common CYP2D6 alleles on prolactin levels in risperidone-treated boys. Pharmacogenet. Genom. 23, 487–493.

Schooler, N., Rabinowitz, J., Davidson, M., Emsley, R., Harvey, P.D., Kopala, L., McGorry, P.D., Van Hove, I., Eerdekens, M., Swyzen, W., De Smedt, G., 2005. Early Psychosis Global Working Group.,. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am. J. Psychiatry 162, 947–953.

Suzuki, A., Mihara, K., Kondo, T., Tanaka, O., Nagashima, U., Otani, K., Kaneko, S., 2000. The relationship between dopamine D2 receptor polymorphism at the Taq1 A locus and therapeutic response to nemonapride, a selective dopamine antagonist, in schizophrenic patients. Pharmacogenetics 10, 335–341.

Suzuki, Y., Ono, S., Sugai, T., Fukui, N., Watanabe, J., Tsuneyama, N., Sawamura, K., Someya, T., 2011. Dose-dependent effects of olanzapine on QT intervals and

plasma prolactin levels in Japanese patients with stable schizophrenia. Hum. Psychopharmacol. 26, 440–443.
Suzuki, Y., Sugai, T., Fukui, N., Watanabe, J., Ono, S., Tsuneyama, N., Saito, M., Someya, T., 2013. Differences in plasma prolactin levels in patients with schizophrenia treated on monotherapy with five second-generation antipsychotics. Schizophr. Res. 145, 116–119.
Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E.K., Morris, C.M., Perry, R.H., Ferrier, I.N., Court, J.A., 1997. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 7, 479–484.
Yasui-Furukori, N., Saito, M., Tsuchimine, S., Nakagami, T., Sato, Y., Sugawara, N., Kaneko, S., 2008. Association between dopamine-related polymorphisms and plasma concentrations of prolactinduring risperidone treatment in schizophrenic patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1491–1495.
Young, R.M., Lawford, B.R., Barnes, M., Burton, S.C., Ritchie, T., Ward, W.K., Noble, E.P., 2004. Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the DRD2*A1 allele. Br. J. Psychiatry 185, 147–151.
Zai, C.C., De Luca, V., Hwang, R.W., Voineskos, A., Müller, D.J., Remington, G., Kennedy, J.L., 2007. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. Mol. Psychiatry 12, 794–795.
Zhang, J.P., Lencz, T., Malhotra, A.K., 2010. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. Am. J. Psychiatry 167, 763–772.
Zhang, X.R., Zhang, Z.J., Zhu, R.X., Yuan, Y.G., Jenkins, T.A., Reynolds, G.P., 2011. Sexual dysfunction in male schizophrenia: influence of antipsychotic drugs, prolactin and polymorphisms of the dopamine D2 receptor genes. Pharmacogenomics 12, 1127–1136.
Zivković, M., Mihaljević-Peles, A., Bozina, N., Sagud, M., Nikolac-Perkovic, M., Vuksan-Cusa, B., Muck-Seler, D., 2013. The association study of polymorphisms in DAT, DRD2, and COMT genes and acuteextrapyramidal adverse effects in male schizophrenic patients treated with haloperidol. J. Clin. Psychopharmacol. 33, 593–599.