Get to know a gene: DRD2

What is DRD2?

The dopamine D2 receptor, encoded by the DRD2 gene, plays a critical role in response to antipsychotic medications. All antipsychotic medications bind to the D2 receptor, underscoring its importance in treating psychotic symptoms. Several polymorphisms have been identified in this gene, but the best studied has been a single nucleotide insertion/deletion known as the -141C indel polymorphism (-141C Ins/Del), which has been proposed to modulate antipsychotic efficacy and side effect burden.

What do the studies say about the DRD2 -141C Ins/Del polymorphism and antipsychotic efficacy?

We reviewed 18 publications that examined the effect of the DRD2 -141C Ins/Del polymorphism on antipsychotic efficacy. Five publications (n=377) demonstrated that the Ins allele showed a statistically significant association with greater response to antipsychotics.[1–5] However, sample sizes tended to be small, with 4 studies enrolling between 49-72 patients. The largest positive study (n=135) by Wu et al. evaluated chlorpromazine response over 8 weeks, and found that the insertion allele was more common in responders vs non-responders, but this finding did not survive correction for multiple testing.[5] In contrast, 12 publications (n=1,736) showed no significant association between -141C Ins/Del genotype and antipsychotic response[6–17], while one other study (n=83) showed that the Del allele was associated with greater response to antipsychotics[18].

What do the studies say about the DRD2 -141C Ins/Del polymorphism and antipsychotic-induced adverse events?

We reviewed 15 publications that examined the effect of the DRD2 -141C Ins/Del polymorphism on antipsychotic-induced movement disorders. Fourteen (n=3,427) showed no significant association.[13,19–31] The lone positive study (n=126) showed an association with rigidity subscales, which did not survive correction for multiple testing.[32] We also reviewed 5 publications (n=457) that examined the effect of the DRD2 -141C Ins/Del polymorphism on hyperprolactinemia, and all 5 showed no association.[33–37] Finally, of the 4 publications that examined the effect of the DRD2 -141C Ins/Del polymorphism on antipsychotic-induced weight gain, 1 (n=58) showed a significant association[38], while 3 studies (n=520) showed no association[31,39,40].

What is the clinical significance of the DRD2 -141C Ins/Del polymorphism?

While initial studies of the DRD2 -141C Ins/Del polymorphism were positive, subsequent studies have failed to replicate the initial findings. Extensive data regarding the effect of the DRD2 -141C Ins/Del polymorphism on antipsychotic response or antipsychotic-induced adverse events show no significant association. These data suggest a very modest, if any, impact of the DRD2 -141C Ins/Del polymorphism on either antipsychotic efficacy or adverse events. While DRD2 remains a very important target for pharmacogenomic research, this particular polymorphism in isolation does not appear to be clinically significant as a marker for antipsychotic response and is therefore not currently included on the GeneSight® panels.

Methodology

The search was conducted within the PubMed database. Results were limited to English studies and focused on antipsychotic efficacy and tolerability, including antipsychotic-induced weight gain, movement disorders, and hyperprolactinemia. After redundant and irrelevant studies were eliminated, a total of 18 publications (n=2,196) entered the efficacy review, 15 publications (n=3,553) entered the antipsychotic-induced movement disorders review, 5 publications (n=457) entered the hyperprolactinemia review, and 4 publications (n=578) entered the weight gain review.

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