SDC Text 2 Discussion on variants with suggestive association signal for paliperidone response

Other candidate variants associated with paliperidone efficacy included variants in *ANO4* (also known as *TMEM16D*) encoding Anoctamin 4, which belongs to a family of novel Cl^- channels transiently activated by an increase in intracellular Ca^{2+} that play important roles in cell physiology including regulation of neuronal excitability.[1, 2] Another variant rs1399439 (not in LD with the top variant rs644939 from this study $r^2 = 0.0004$, D' = 0.18) in *ANO4* was identified as suggestively associated with rate of cognitive decline in Alzheimer's Disease ($p = 3.51 \times 10^{-7}$) though this finding was not replicated in independent samples.[3] Although not highlighted in the tables, a variant in the intergenic region 10p11.23 between *CKS1BP2*/*SVIL* and *KIAA1462* exhibited suggestive association (rs2986961, $p = 5 \times 10^{-7}$) in a meta-analysis[4] of 5,118 European ancestry migraine cases and 74,239 European ancestry controls. The same variant also exhibited suggestive association signals in the paliperidone efficacy analysis (rs2986961, p = 8.82×10^{-6}, 0.01, 8.44×10^{-5}, and 0,03 for change in Marder positive factor score, Marder negative factor score, total PANSS score, and CGI-S, respectively). In addition, a variant in polymerase (DNA directed) nu (*POLN*) with suggestive association (4p16.3, rs1923775, $p = 6 \times 10^{-6}$) in Alzheimer disease[5] in African Americans also was also found to show a marginal association (GLM/MLM p-values are 0.0007/0.0003, 7.93×10^{-5}/4.07×10^{-5}, 2.5×10^{-5}/8.51×10^{-6}, and 0.0001/6.37×10^{-5} for each of the four paliperidone efficacy endpoints above). Furthermore, 4p16.3 was one of the linkage peaks associated with bipolar. Putative damaging yet common variants (MAF > 5%) was reported under the 4p16.3 linkage peak in the *POLN* gene.[6] Clark et al.,[7] identified *PDE4D* (5q12.1) as a potential mediator of the effect of quetiapine on patient-reported severity ($p = 4.2 \times 10^{-8}$, n = 238) as measured by a patient global impression of illness. It is intriguing that rs2127826 in *PDE5A* was found to have suggestive associations (p = 0.00095, 0.0048, 0.0003, and 2.97×10^{-6} with each of the four paliperidone efficacy endpoints above). Phosphodiesterase inhibitors have been considered as possible therapeutic agents to treat impaired memory function linked to several disorders, including depression, schizophrenia and

Alzheimer's disease (AD). [8] Although these overlapping findings could have occurred by chance, these findings are intriguing given the overlap in the molecular mechanism between central nervous system disease conditions and overlap in the clinical symptom (such as cognitive deficit among patients with both schizophrenia and AD).

Other candidate variants identified in cohorts from the extended-release study or palmitate formulation, have not been highlighted in this paper as we only report results of meta-analyses of all three cohorts. Nevertheless, we cannot rule out those candidate variants as they might still be valid candidate variants for paliperidone efficacy. However, the results of these analyses must be interpreted with caution since the sample size was smaller for each of these formulation strata. As palmitate is a once-monthly long-acting injectable therapy versus once-daily oral extended-release tablets, there is the potential that different genetic loci contribute to the pharmacokinetic and pharmacodynamics characteristics of each therapy. For example, genes which contribute to absorption of medication in the intestines will only impact oral paliperidone. Also, medication noncompliance may introduce heterogeneity in the extended-release cohort as participants in this cohort are expected to self-administer their own medication, while participants in the palmitate cohort are not.

References

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