HTR3A as a Druggable Target in Chronic Pruritus: A Phenome-Wide Association Study

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Background: Few therapies are FDA-approved for chronic pruritus, with management relying heavily on off-label medications with variable efficacy. 5-HT3 receptor antagonists, approved for nausea and vomiting, have also shown benefit for uremic and morphine-induced pruritus. We investigated whether genetic variation in the 5HT3 receptor is associated with pruritus to support repurposing 5HT3 antagonists such as palonosetron for treatment-resistant itch.

Methods: A Phenome-Wide Association Study (PheWAS) was performed using Vanderbilt Health's (VH) Synthetic Derivative (nearly 4 million de-identified EHRs) and BioVU (a biobank of over 300,000 de-identified genotyped patients), examining the 5HTR3 single nucleotide polymorphism rs35815285, which is known to increase ion channel opening time and neuronal depolarization.

Results: The PheWAS identified a significant association between the rs35815285 variant and pruritus (OR = 4.687, P = .003518), consistent with a mechanism in which prolonged 5HTR3 channel opening increases neuronal depolarization and itch. This genetic signal converged with transcriptomic evidence from single-nucleus RNA sequencing of human dorsal root ganglia, showing HTR3A expression enriched specifically within itch-specific neuronal clusters and largely absent from pain, mechanosensory, and

proprioceptive clusters. Together, these findings elevate the 5HT3 receptor from a transcriptomic candidate to a genetically validated target for chronic pruritus.

Conclusion: This genetic association supports blocking the 5-HT3 receptor as a strategy for reducing chronic itch and supports evaluating palonosetron, a second-generation 5-HT3 antagonist with a strong safety profile, as a repurposed treatment. To translate this target, we utilized VH's TAILOR (Treatment Assessments in the Individual Leading to Optimal Regimens) tool, a clinical quality improvement infrastructure aimed at enhancing personalized treatment decision making based on PROs and informed by PheWAS, to provide patients and providers with the resources to systematically evaluate the off-label prescribing of palonosetron for treatment resistant pruritus. Adults with chronic refractory pruritus of neuropathic or neurogenic etiology (CKD, cutaneous T-cell lymphoma, or cholestatic liver disease) will receive palonosetron (0.5 mg orally or 0.25 mg intravenously, per FDA labeling and antiemetic guidelines) and share information on their itch symptoms using the TAILOR assessments as part of their usual course of clinical care. Itch severity, quality of life, and side effects are captured through daily surveys via the MyCap mobile application over an initial one-month window, yielding within-patient treatment-effect estimates that providers and patients jointly review to continue, adjust, or deprescribe. Altogether, information gleaned from the TAILOR assessments could inform off-label prescribing and identify a novel palonosetron indication for future randomized controlled trials.

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