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VIEWPOINT

The association between trace amine-associated receptor 1 (TAAR1) genetic mutations and neuropsychiatric disorders

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Trace amine-associated receptor 1 (TAAR1) is an emerging drug target for the treatment of neuropsychiatric conditions. Several TAAR1-targeted therapeutics are currently in clinical and preclinical development. Emerging studies highlight links between TAAR1 single-nucleotide variants/polymorphisms and neuropsychiatric disorders. An improved understanding of TAAR1 genetic variants and their functional impact will inform the potential role of the TAAR1 system in the pathophysiology of neuropsychiatric conditions and for better therapeutic dosing. This viewpoint examines clinical and molecular studies involving TAAR1 genetic variants and their association with neuropsychiatric disorders.

Neuropsychiatric conditions such as schizophrenia, bipolar disorder, and major depression have genetic heritability with several shared clinical symptoms. These disorders are often disabling, and together they contribute to a substantial global health burden of disease. Though these diseases are classified as distinct conditions, the overlap between the cognitive, emotional, and behavioral symptomologies often presents challenges in accurate and early diagnosis (1). Several studies have been conducted to distinguish these better, ranging from animal models to neuroimaging to genome-wide association studies (GWAS). Given their highly heritable nature (e.g., schizophrenia, approximately 80%), GWAS has been presented as a powerful way to investigate the contributions of genetic variants to a specific disorder. Further, genetic mapping has been useful in identifying shared genetic factors in bipolar disorder and schizophrenia (2, 3). However, the polygenic nature of most neuropsychiatric conditions raises challenges and reliable predictions cannot be made from a single-nucleotide variant or a low number of variants. As such, researchers developed aggregate scores such as polygenic risk scores. These scores assess the total number of risk variants and predict the likelihood of developing associated conditions. Such studies unveiled a large degree of genetic pleiotropy and commonly shared dysregulated systems between many of these conditions. For instance, dysfunction of the GABAergic system is observed in many neuropsychiatric and neurobiological conditions including schizophrenia, bipolar disorder, major depression, and others, while, dysregulated dopaminergic circuitries have been associated with schizophrenia, attention-deficit hyperactivity disorder (ADHD), substance abuse disorders, and depression (4, 5). Further, genetic variants in the dopamine 2 receptor (D2 receptor) and serotonin 1A receptor have been associated with addiction, and increased risk for depressive episodes and treatment response, respectively (6, 7). Polymorphisms in dopaminergic genes have been associated with antipsychotic drug sensitivity, adverse effects, and motor deficits (8). As a result, all major neuropsychiatric conditions such as schizophrenia, bipolar disorder, and major depression have been linked to multiple genes (2, 9, 10). Schizophrenia, for example, has been linked to more than 200 genes (9). Further, an increased risk for bipolar disorder has been observed in patients with ultra-rare protein-truncating variants of A-kinase anchoring protein 11 (AKAP11) (2). Thus, neuropsychiatry research establishing genetic associations with psychopathology of neuropsychiatric disorders is an area of significant interest.

Trace amines (TAs) are biogenic amines that exist in low concentrations (1–100 ng/g of tissue). They are structurally similar to typical neurotransmitters such as dopamine and serotonin but display a distinct potency for trace amine-associated receptors, a novel family of aminergic receptors discovered over two decades ago (11). The TAAR family encodes for six functional genes, with isoform-specific expression in neuronal and non-neuronal tissues. Among all, TAAR1 shows the highest expression in the brain, especially at the presynaptic and postsynaptic terminals of monoaminergic nuclei, responding to intracellular and extracellular trace amines, monoamines, and secondary metabolites (11, 12). In cell lines, stimulation by such ligands primarily increases the intracellular cyclic adenosine monophosphate (cAMP) levels, which prompts functional interaction with other monoaminergic systems, influencing their activity. Such observations extend to in vivo systems, especially in TAAR1 overexpressed (TAAR1-OE) and TAAR1 knockout (TAAR1-KO) models, which broadly display hyposensitivity and hypersensitivity to amphetamines, respectively (13). Similar to patients with schizophrenia, TAAR1-KO models exhibit increased levels of dopamine and serotonin, in addition to spontaneous activation of associated neural circuitries in the midbrain. By contrast, the TAAR1-OE model shows hyposensitivity to amphetamine and a decrease in baseline locomotion. In drug-induced psychotic models of mice, the administration of TAAR1 agonists provides symptom relief suggesting that TAAR1 has a neuromodulatory effect (13). As such, TAAR1 is considered an endogenous rheostat, and its function is critical for normal neurotransmission.

A wealth of studies therefore explored the utility of TAAR1 as a druggable target for treating schizophrenia and several other neuropsychiatric disorders (13). Emerging antipsychotic agents, TAAR1 agonists, show promise for treating schizophrenia and other neuropsychiatric disorders. The nonselective TAAR1 agonist ulotaront received a Breakthrough Therapy Designation from the U.S. FDA for treating schizophrenia. However, ulotaront failed two pivotal phase III clinical trials. This clinical candidate is currently in phase II/III trials for other conditions including sleep disorders, Parkinson's disease psychosis, major depression, and generalized anxiety disorders (ClinicalTrials.gov IDs NCT05015673, NCT02969369, NCT05593029, and NCT05729373, respectively). Moreover, several new TAAR1 agonists are in preclinical development (14). However, studies considering TAAR1 as a potential instigator of disease states remain understudied. Meanwhile, other members of the aminergic family which are also major pharmaceutical targets, have been associated with multiple neurobiological and neuropsychiatric conditions, as described previously. In the same context, immediate family members such as TAAR2, 4 (pseudo-gene), 5, and 6 have been studied, with associations described between schizophrenia and bipolar disorders (15–17). Notably, the TAAR1 gene is mapped to chromosome 6q23.2, which coincides with susceptibility locus for schizophrenia, bipolar and affective disorders (16). The potential clinical consequences of TAAR1 genetic

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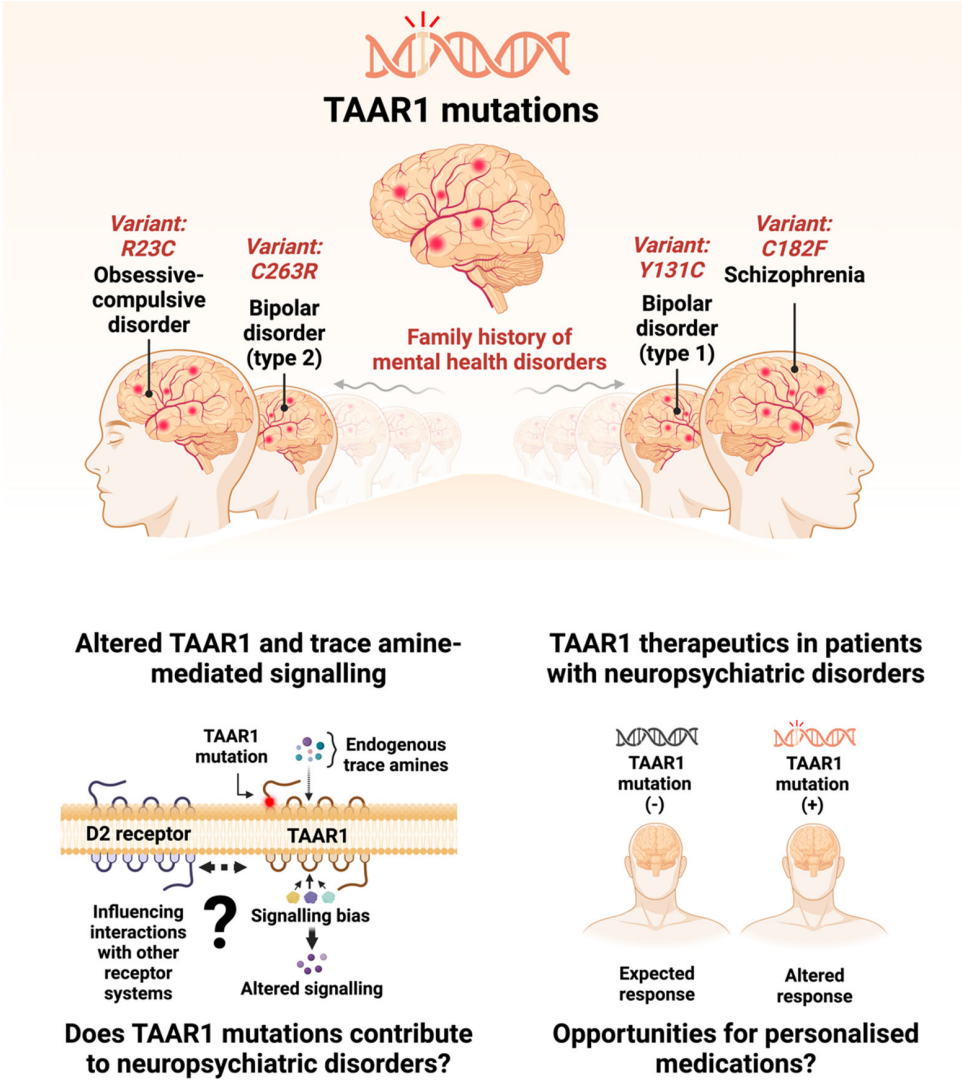

Figure 1. The association between TAAR1 variants, neuropsychiatric disorders, and therapeutic response. TAAR1 mutations (only selected mutations are shown for clarity) in patients with neuropsychiatric disorders (top panel). A model proposing altered signaling of trace amines in variant TAAR1 observed in neuropsychiatric disorders (bottom left). Treatment options are tailored to patients with TAAR1 mutations (bottom right). The figure was created with Biorender.com

variants in diverse populations may therefore be questioned. TAAR1 gene knockout studies demonstrated the critical nature of native TAAR1 function and demonstrated links with schizophrenia and other neuropsychiatric disorders. It can thus be hypothesized that TAAR1 gene variants that cause aberrations in its function may be responsible for disorders associated with dysregulated neurotransmission. Moreover, the occurrence of TAAR1 variants may display variability in therapeutic response in patients targeted with TAAR1-based medications.

Our recent work on TAAR1 identified variance in genetic differences in diverse geographical populations that can influence the structure and function of TAAR1 protein (18). We mapped over 40 rare mutations that may influence the ligand-activated mechanisms of TAAR1 including, variants in the binding pocket, microswitch regions, and signaling domains. Specifically, the D103N variant found in southeast Asian regions and Western Pacific regions completely ablate the receptor activity, with few others showing a significant impact on receptor functioning. However, the density and/or presence of such TAAR1 variants in neuropsychiatric patients remain unknown and require further study. In this viewpoint, we consolidated all literature on TAAR1 nonsynonymous variants from clinical studies and discussed the potential implications of TAAR1 mutations on disease manifestation and TAAR1-targeted therapeutics in neuropsychiatry.

Only a few studies have been reported on TAAR1 mutations in clinical samples, some of which have been reviewed previously (19). Despite limited numbers, these studies provide significant insights linking rare TAAR1 mutations with neuropsychiatric conditions (Figure 1). The first study conducted by John and colleagues on patients with sporadic schizophrenia identified several nonsynonymous variants in unrelated patients of Indian (S47C, F51L, Y294*, and L295S) and American origin (A109T and V250A). In particular, the Indian cohort reported a key variant, C182F, which disrupts the disulfide bridge that is critical for the stability and function of the receptor. This variant was found in a mother and her two children, all of whom had a diagnosis of schizophrenia. Notably, the unaffected siblings were negative for this variant or any other TAAR1 mutations, including the control subjects (20). This maternal link suggests that inherited TAAR1 variants may contribute to schizophrenia. In any case, disruption of the disulfide bridge may cause the protein to misfold or destabilize, due to a loss of structural properties facilitated by the cysteine side chain. While a true functional validation of this variant awaits, several bioinformatic functional prediction tools have predicted this allele to be damaging. Meanwhile, previous cell line studies demonstrated tyrosine variant at this position (C182Y) produces a functional knockout of the receptor, without affecting its expression levels and cellular localization (21). Other variants such as S47C, F51L, A109T, and

L295S were predicted to reduce TAAR1 activity, with no change in activity predicted for V250A (20). The variant of Y294* introduces a premature stop codon thus likely to influence receptor function. A similar phenotype in mice expressing functionally knocked-out TAAR1 gene through P77T mutation demonstrated increased methamphetamine consumption and reduced sensitivity to methamphetamine-induced hypothermia (22). Supporting, in vitro studies also demonstrated that the P77T variant produces a functional knockout of the receptor without impairing expression capabilities (22). While some may agree that functional knockouts certainly encapsulate the essence of a traditional TAAR1-KO model, it is unlikely that TAAR1's functional mechanism is merely reserved for ligand-activated signaling alone but may involve interactions with other receptors (such as D2) as demonstrated in previous studies (23). As such, functional knockouts may also have more unidentified rogue effects, which need further investigation.

The study by Mühlhaus and colleagues reported three nonsynonymous mutations in TAAR1 (24). Here, the mutations were identified from an unrelated patient cohort consisting of obese/overweight subjects with impaired glucose homeostasis. Notably, individual mutations were found in separate patients, wherein patients 1, 2, and 3 carried the variants R23C, I171L, and S49L, respectively. In vitro, studies demonstrated that two variants, R23C and S49L, significantly impair receptor response to its ligands. In a homozygous state, R23C demonstrated a complete loss of activity and the S49L variant demonstrated a 40% reduction in maximal response to 3-Iodothyronamine (T1AM). In a heterozygous state, maximal signaling for R23C and S49L peaked at 58% and 55%, respectively (relative to wild type). In addition, stimulation with β-Phenylethylamine (PEA) also demonstrated a complete loss function for the R23C variant and approximately 70% loss for S49L (24). Carriers of the variants exhibited signs of low cognition and psychiatric abnormalities, respectively. Patient 1 had a low IQ (71) at the age of 7, meanwhile, authors described patient 3 (variant S49L) as having "psychiatric problems". Conversely, in functional studies, I171L retained most of its function and was described to mimic the activity of wild type and no observations were associated with declined cognitive function or psychiatric illness. Notably, the frequency of S49L in control samples was approximately 0.38% (27/7158), meanwhile, the R23C variant only had a frequency of 0.056% (4/7181). This suggests a dichotomy where a slight loss of function may be tolerated and any significant loss may be associated with disease augmentation (24).

In another study, Rutigliano and colleagues identified 16 TAAR1 variants in the coding regions of mental health patients (25). Three were synonymous (C265C, V288V, and R312R) with the remaining 13 missense. Of these, three were further functionally evaluated in cell lines, which consisted of R23C, Y131C, and C263R. All three patients had a unique diagnosis, where the carrier of the R23C variant was symptomatic for schizoaffective, bipolar type and obsessive-compulsive disorders, the carrier of the Y131C variant was diagnosed with type 1 bipolar disorder and the carrier of the C263R variant was diagnosed with type 2 bipolar disorder. Notably, all three patients also reported family histories of schizophrenia spectrum disorders (carrier of R23C), depressive and anxiety disorders (Y131C) and a general history of mental disorders (C263R). In cell line studies, the heterozygous state, R23C, Y131C, and C263R showed significantly decreased maximal cAMP accrual in response to PEA, RO5166017, and T1AM. Meanwhile, the homozygous state is described to render the protein functionally inoperative. Notably, Mühlhaus and colleagues found the R23C TAAR1 variant in obese patients with low IQ and metabolic disorders (24), whereas Rutigliano and colleagues found the same mutation in patients with neuropsychiatric conditions (25). Therefore, TAAR1 variants may indicate genetic pathways or predisposing factors that link metabolic disorders and neuropsychiatric conditions.

In addition to genetic variants in TAAR1, studies have also shown altered levels of trace amines (TAAR1 agonists) in patients with brain disorders. Higher levels of PEA in plasma and urine samples have been noted in patients with schizophrenia (13, 26). Contrastingly, patients with ADHD were reported to have significantly lower levels of PEA in urine samples compared with control subjects (27). Similarly, decreased levels of PEA were also reported in patients suffering from depression and Parkinson's disease (28). Low concentration and rapid turnover of trace amines, coupled with a lack of sensitivity and specificity of the techniques utilized posed difficulties in accurately measuring TAs in biological fluids and tissues, resulting in differences in trace amine levels between studies (13, 26). Alterations in TAAR1 signaling that result from low ambient agonist levels may also contribute to such states, which can further be influenced by genetic variants in the protein (Figure 1). Furthermore, the current state and focus of TAAR1 therapeutics may be challenged by genetic variations, which is seemingly an unexplored area. If patients, who are recipients of these therapies are prone to genetic variants of TAAR1, it may bring significant challenges to the therapy (Figure 1). Recent molecular studies demonstrated the influence of point mutations on receptor functioning and signaling cascades (29, 30). Residue-specific interactions at the binding pockets serve as a key that influences the signaling pathways, which is critical to a compound's efficacy and to mitigate any unforeseen activities (29). Moreover, the influence of TAAR1 mutations on its interactions with other aminergic systems remains unknown. Previous accounts attributed ligand-induced activity as the key mechanism of dimerization between the D2 receptor and TAAR1, which appeared to have a significant influence on the efficacy of antipsychotics (23). In cell lines, responses to antipsychotics such as haloperidol, raclopride, and amisulpride were amplified when the D2 receptor and TAAR1 were coexpressed. In TAAR1-KO mice models, haloperidol treatment activated 30% fewer neurons, and the magnitude of haloperidol-induced catalepsy was significantly lower compared with the wild type suggesting that there is a functional interaction between both (23). Such indicators may provide opportunities for exploring personalized TAAR1 medications with studies in psychotic mice models demonstrating that activation of either Gs or Gq pathways is equally beneficial in alleviating schizophrenia-like symptoms (30). Such findings aid rational drug developmental approaches and finding alternative TAAR1 therapeutics that may find utility in patients with TAAR1 mutations.

TAAR1 disruptions may contribute to neuropsychiatric disorders, as observed in animal knockout studies and from genetic variations in patients. From a genetic perspective, further research is needed to determine whether certain rare genetic mutations in TAAR1 may predispose the development of specific psychiatric disorders. Being rare variants, larger sample sizes are required to assess the true significance of such mutations. Moreover, in vitro and in vivo studies show that TAAR1 can regulate D2-receptor activity via heterodimerization; therefore, it is essential to understand how TAAR1 variants may influence dopaminergic signaling. On the other hand, point mutations in TAAR1 have been shown to influence the selection of signaling pathways; whether this translates to in vivo remains unknown. Aberrations as such may welcome unwanted side effects from TAAR1 therapeutics. The rational development of TAAR1-based therapeutics will continue to grow with the emergence of experimental structures of TAAR1 and the significant need for better therapies for neuropsychiatric disorders. Future studies should focus on evaluating TAAR1 mutations in clinical subjects, specifically to assess the effects of these mutations on therapeutic efficacy, and adverse effects. In the future, the use of pharmacogenetic testing will facilitate determining the prevalence of mutations in TAAR1 among neuropsychiatric patients, thus supporting the development of personalized treatments for emerging TAAR1 therapeutics.

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