Schizophrenia: a neurodevelopmental disorder - integrative genomic hypothesis and therapeutic implications from a transgenic mouse model


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Abstract: Schizophrenia is a neurodevelopmental disorder featuring complex abnormalities in the structure, wiring, and chemistry of multiple neuronal systems. The detrimental developmental impact of the brain appears to be established by fetal gene expression, leading to channelopathies, neuronal migration and gliogenesis issues, and altering the formation of molecular networks. The manifestation of the disease in this early stage has been shown to correlate with the development of molecular networks in the schizophrenia brain. The genetic landscape of the preclinical stages of schizophrenia is likely to be influenced by the dysregulation of transcriptional programs that ultimately affect the overall cellular functions and molecular interactions. Our current understanding of the dysregulation of gene networks in schizophrenia is likely to be based on the dysregulation of transcriptional programs that ultimately affect the overall cellular functions and molecular interactions. Our current understanding of the dysregulation of gene networks in schizophrenia is likely to be based on the dysregulation of transcriptional programs that ultimately affect the overall cellular functions and molecular interactions.

Integrative Nuclear Fibroblast Growth Factor Receptor 1 Signaling (INF) - a point of convergence in neurodevelopmental pathways affected in Schizophrenia

3. Figure 2: Dravins malformations in the glial (g-1)-kox mice. Brain structures: 1-5V, 2-2V, 3-3V, 4-4V, 5-5V: structures 1-5V, 2-2V, 3-3V, 4-4V, 5-5V are brain structures observed in the schizophrenia brain. The genetic landscape of the preclinical stages of schizophrenia is likely to be influenced by the dysregulation of transcriptional programs that ultimately affect the overall cellular functions and molecular interactions. Our current understanding of the dysregulation of gene networks in schizophrenia is likely to be based on the dysregulation of transcriptional programs that ultimately affect the overall cellular functions and molecular interactions. Our current understanding of the dysregulation of gene networks in schizophrenia is likely to be based on the dysregulation of transcriptional programs that ultimately affect the overall cellular functions and molecular interactions.

4. **Figure 5:** Tjg-Nrtrb improves the accuracy of cognition that is impaired in the g-1-kox mice. During Phase I, mice were placed into the arena for 10 minutes and allowed to investigate four identical "old" objects. Subjects were then returned to their home cage for 24 minutes. During Phase II, four "new" identical objects were placed in the arena and mice were given 10 minutes to explore the objects. After returning to their home cages again, mice were then injected with other saline or Tjg-Nrtrb (1 mg/kg p.o.). 40 minutes after injections, mice were placed in the arena for Phase III and investigation time of each object ("old" and "new") was measured. In mice with no injection, it is common to spend more time investigating the old objects presented in Phase I, which are less familiar than the new recent objects from Phase II ("new" objects). With saline, male g-1-kox mice cannot distinguish between objects presented in the recent Phase II ("new" objects) and the distant past Phase I ("old" objects). This deficit may reveal working memory impairment. In mice administered Tjg-Nrtrb, this deficit was alleviated. Bars represent means ± SEM of significantly greater than recent, one-way ANOVA (p<0.05). Preliminary account of these observations was given in (Tang, 2010)

5. **Figure 6:** Effects of treatment with Tjg-Nrtrb and Clonazepam on social interaction score in drug injections. In the absence of both social and anxiety-induced behaviors, both Tjg-Nrtrb (1 mg/kg) and Clonazepam (1 mg/kg) increase the time that mice spend investigating the social stimuli. There is no difference in social interaction (time between drug-treated control and drug-treated mice). Levels of Clonazepam (0.3 mg/kg or 0.9 mg/kg) alone have no effect on social interaction time between control and drug-treated mice (Figure 6A). Levels of Clonazepam (0.3 mg/kg or 0.9 mg/kg) alone have no effect on social interaction time between control and drug-treated mice (Figure 6B). These data indicate that the social interaction deficits observed in Tjg-Nrtrb and Clonazepam-treated mice are likely to be due to a more subtle dysfunction in the human brain. We also show the nicotinic acetylcholine system has the potential to alleviate symptoms associated with both cortical and subcortical malfunctions by mediating subcortical DA release and possibly the activity of other neurological networks impaired in schizophrenia.

6. **Figure 7:** Effects of treatment with Tjg-Nrtrb and Clonazepam on social interaction score in drug injections. In the absence of both social and anxiety-induced behaviors, both Tjg-Nrtrb (1 mg/kg) and Clonazepam (1 mg/kg) increase the time that mice spend investigating the social stimuli. There is no difference in social interaction (time between drug-treated control and drug-treated mice). Levels of Clonazepam (0.3 mg/kg or 0.9 mg/kg) alone have no effect on social interaction time between control and drug-treated mice (Figure 6A). Levels of Clonazepam (0.3 mg/kg or 0.9 mg/kg) alone have no effect on social interaction time between control and drug-treated mice (Figure 6B). These data indicate that the social interaction deficits observed in Tjg-Nrtrb and Clonazepam-treated mice are likely to be due to a more subtle dysfunction in the human brain. We also show the nicotinic acetylcholine system has the potential to alleviate symptoms associated with both cortical and subcortical malfunctions by mediating subcortical DA release and possibly the activity of other neurological networks impaired in schizophrenia.

7. **Figure 8:** Effects of treatment with Tjg-Nrtrb and Clonazepam on social interaction score in drug injections. In the absence of both social and anxiety-induced behaviors, both Tjg-Nrtrb (1 mg/kg) and Clonazepam (1 mg/kg) increase the time that mice spend investigating the social stimuli. There is no difference in social interaction (time between drug-treated control and drug-treated mice). Levels of Clonazepam (0.3 mg/kg or 0.9 mg/kg) alone have no effect on social interaction time between control and drug-treated mice (Figure 6A). Levels of Clonazepam (0.3 mg/kg or 0.9 mg/kg) alone have no effect on social interaction time between control and drug-treated mice (Figure 6B). These data indicate that the social interaction deficits observed in Tjg-Nrtrb and Clonazepam-treated mice are likely to be due to a more subtle dysfunction in the human brain. We also show the nicotinic acetylcholine system has the potential to alleviate symptoms associated with both cortical and subcortical malfunctions by mediating subcortical DA release and possibly the activity of other neurological networks impaired in schizophrenia.

8. **Summary:** In conclusion, inhibition of INFs that integrates several schizophrenia related pathways, recapitulates several anatomical, neurochemical and behavioral features of the human disease. Targeting of the domains negative FGFRI(K)-transgenic mouse in which the INFs mechanism is activated impairs their development producing hypoplastic and hyperactive DA neurons. This initial abnormality is accompanied by secondary changes in other neuronal systems including brain stem serotonergic neurons and cortical neurons, which was most clearly targeted by FGFRI(K)-transgenic mouse. Thus, in schizophrenia, malformation of DA neurons could be the initial defect that gradually affects other monoaminergic and cortical circuits underwirng the progression of the disease and gradual behavioral deterioration. Importantly, the onset of sensorimotor gating impairments in thg-fg(1):kox mice parallels the time course of positive symptom propagation of the human disease. We also show the nicotinic acetylcholine system has the potential to alleviate symptoms associated with both cortical and subcortical malfunctions by mediating subcortical DA release and possibly the activity of other neurological networks impaired in schizophrenia.