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A mouse model of 22q11.2 deletions: Molecular and behavioral signatures of Parkinson's disease and schizophrenia

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Individuals with chromosome 22q11.2 deletions are at increased risk of developing psychiatric conditions, most notably, schizophrenia (SZ). Recently, clinical studies have also implicated these recurrent 22q11.2 deletions with the risk of early-onset Parkinson's disease (PD). Thus far, the multiple mouse models generated for 22q11.2 deletions have been studied primarily in the context of congenital cardiac, neurodevelopmental, and psychotic disorders. One of these is the *Df1/+* model, in which SZ-associated and developmental abnormalities have been reported. We present the first evidence that the mouse model for the 22q11.2 deletion exhibits motor coordination deficits and molecular signatures (that is, elevated α -synuclein expression) relevant to PD. Reducing the α -synuclein gene dosage in *Df1/+* mice ameliorated the motor deficits. Thus, this model of the 22q11.2 deletion shows signatures of both SZ and PD at the molecular and behavioral levels. In addition, both SZ-associated and PD-relevant deficits in the model were ameliorated by treatment with a rapamycin analog, CCI-779. We now posit the utility of 22q11.2 deletion mouse models in investigating the mechanisms of SZ- and PD-associated manifestations that could shed light on possible common pathways of these neuropsychiatric disorders.

INTRODUCTION

Microdeletions within the chromosome 22q11.2 region represent the most frequent pathogenic interstitial deletions found in humans, occurring in approximately 1 in 4000 live births (1). Previous studies have identified 22q11.2 deletions as a strong genetic risk factor for psychiatric conditions, most notably, schizophrenia (SZ) (2, 3). Thus, 22q11.2 deletions have been shown to confer susceptibility to SZ and related neurodevelopmental disorders in humans, and mouse models of 22q11.2 deletions have proven valuable in providing insights into the pathophysiological mechanisms underlying these conditions along developmental trajectories (4).

Recent studies have now reported an increasing number of individuals with 22q11.2 deletions who developed early-onset Parkinson's disease (PD) (5–8), including those confirmed by postmortem brain studies (7). A genetic association study estimated that 22q11.2 deletions increase the risk of early-onset PD by 20-fold (9). To our knowledge, however, no study has yet addressed the pathological signatures possibly relevant to PD in a mouse model of 22q11.2 deletions.

We therefore investigated a mouse model of 22q11.2 deletion, *Df1/+* (10), known to display anatomical and behavioral abnormalities, including defective interneuron migration (11), deficits in sensorimotor gating (12), and psychostimulant-induced hyperlocomotion (13). Using this model, we have reproduced key phenotypes relevant to psychotic symptoms and, for the first time, also demonstrated

the presence of significant motor coordination deficits and elevated expression of α -synuclein and p62 proteins, major constituents of Lewy bodies that are well-accepted signatures relevant to PD (14, 15). Reducing the α -synuclein gene dosage in *Df1/+* mice ameliorated the motor deficits. Furthermore, we report that both SZ-associated and PD-relevant deficits in this model were ameliorated by treatment with a rapamycin analog, CCI-779.

RESULTS

Df1/+ mice display both motor and psychiatric deficits

Df1/+ mice have been studied from SZ-associated dimensions in the context of developmental trajectories (11–13). On the basis of recent clinical findings that the 22q11.2 deletion is also associated with PD (5–9) and that motor deficits exist in adults with 22q11.2 deletions (16, 17), we examined whether *Df1/+* mice might also display motor deficits. To assess motor functions of *Df1/+* mice, we used the rotarod test, which has been used to evaluate motor coordination and motor learning in PD mouse models (18). Latency to fall from an accelerating rotarod was measured over nine trials at 3.5 months of age. *Df1/+* mice stayed at a significantly shorter time on the rotating bar than wild-type (WT) control mice ($F_{1,18} = 14.09$, $P = 0.0015$) (Fig. 1A), demonstrating the existence of motor coordination deficits. Motor learning did not appear to be impaired, as the *Df1/+* mice showed an increase in latency to fall over successive trials (Fig. 1A). The observed motor deficits in *Df1/+* mice were not apparently due to impairment in basic locomotive function because voluntary locomotor activities in *Df1/+* mice were equivalent to those in WT in the open-field box (0 to 60 min; Fig. 1B).

Meanwhile, we successfully replicated behavioral deficits in *Df1/+* mice associated with psychiatric manifestations previously reported for this and other 22q11.2 mouse models (4, 12, 13, 19, 20). More specifically, *Df1/+* mice showed exacerbated responses to the psychostimulant MK-801, exhibiting higher locomotor activities than

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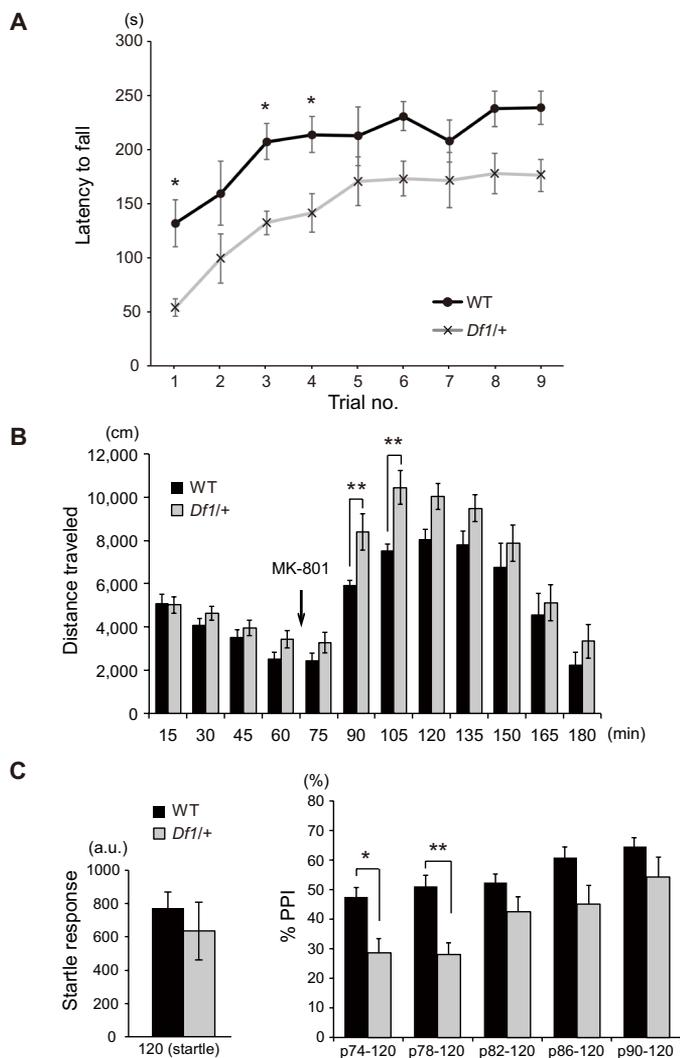


Fig. 1. Motor coordination deficits, psychostimulant hypersensitivity, and sensorimotor gating deficits in *Df1*^{+/+} mice. (A) Latency to fall (in seconds) from the rotarod was scored three times per day over three consecutive days. WT control ($n = 10$) and *Df1*^{+/+} ($n = 10$) mice were tested at 3.5 months of age. Statistical significance [two-way analysis of variance (ANOVA) with repeated measures: $F_{1,18} = 14.09$, $P = 0.0015$]; * $P < 0.05$ (Bonferroni post hoc test). (B) Locomotor activities [distance traveled (in centimeters)] measured in the open-field box before and after MK-801 challenge were plotted in 15-min bins. WT ($n = 10$) and *Df1*^{+/+} ($n = 10$) mice were tested at 2 months of age. Statistical significance (two-way ANOVA with repeated measures: $F_{1,18} = 4.763$, $P = 0.0426$); ** $P < 0.01$ (Bonferroni post hoc test). (C) Acoustic startle response (left) and PPI (%) of startle response (right) were evaluated. WT ($n = 10$) and *Df1*^{+/+} ($n = 10$) mice were tested at 2 months of age. Statistical significance (two-way ANOVA with repeated measures: $F_{1,18} = 8.528$, $P = 0.0091$); * $P < 0.05$ and ** $P < 0.01$ (Bonferroni post hoc test). a.u., arbitrary units.

WT in the open-field box ($F_{1,18} = 4.763$, $P = 0.0426$) (60 to 180 min; Fig. 1B). *Df1*^{+/+} mice also showed evidence of impaired sensorimotor gating, as demonstrated by reduced levels of prepulse inhibition (PPI) of acoustic startle responses compared with WT ($F_{1,18} = 8.528$, $P = 0.0091$) (Fig. 1C). These two changes are commonly regarded as mouse behavioral phenotypes relevant to psychiatric disorders, including SZ (4). A previous study reported a possibility that *Df1*^{+/+} mice have altered hearing thresholds or hearing loss (21), which may confound interpretation of the PPI results. To address this is-

sue, we quantified the responses to nonstartle sound stimuli (65 to 90 dB) delivered to each mouse during the PPI assays. The amplitude of responses to these stimuli in *Df1*^{+/+} mice was equivalent to that in control mice (fig. S1), suggesting that both *Df1*^{+/+} and control mice were equally capable of sensing rather small stimulus sound used in the assays and that attenuated PPI observed in *Df1*^{+/+} mice was not likely due to hearing loss.

Expressions of α -synuclein and p62 are elevated in *Df1*^{+/+} mice

As motor deficits possibly relevant to PD were observed, we next addressed the question of whether PD-related neuropathological and molecular changes may exist in *Df1*^{+/+} mice. We conducted immunohistochemistry with markers for Lewy bodies (α -synuclein and p62), a pathological hallmark of PD. We analyzed the anterior cingulate cortex (ACC), caudate putamen (CPU), and substantia nigra pars compacta (SNc) because Lewy bodies are frequently observed in these regions of PD brains (14, 15). Functional deficits in the ACC and CPU are also linked to SZ (22, 23). Brain sections at the ACC, CPU, and SNc were costained with anti-calcium/calmodulin-dependent protein kinase II (CaMKII), anti-dopamine- and cAMP-regulated phosphoprotein 32 kDa (DARPP-32), and anti-tyrosine hydroxylase (TH) antibodies, respectively, to mark the most abundant neuronal cell type in each brain region. We analyzed brains at 3.5 and 8 months of age, which correspond to the earliest age of onset (that is, 20s) and to the mean age of onset (that is, 40s), respectively, of PD with 22q11.2 deletions (16, 17). We found that expression of α -synuclein was significantly elevated in these brain regions at 3.5 months of age (1.77-, 1.50-, and 1.61-fold increase in the ACC, CPU, and SNc, respectively, compared with WT) (Fig. 2A), and at 8 months of age (1.73-, 1.30-, and 1.50-fold increase in the ACC, CPU, and SNc, respectively, compared with WT) (fig. S2A; summarized in Table 1). In addition, expression of p62 was also increased, compared with WT (1.88-, 1.66-, and 1.17-fold increase in the ACC, CPU, and SNc, respectively, at 3.5 months of age; Fig. 2B; 2.42-fold increase in the ACC at 8 months of age; fig. S2B) (summarized in Table 1). However, we did not observe apparent signs of inclusion body formation. To further validate these findings, we quantified the fluorescence intensities of the cell type markers used for the assays. The relative fluorescence intensities per soma for each cell type marker were equivalent between WT and *Df1*^{+/+} mice. The intensities of CaMKII in the ACC of WT versus *Df1*^{+/+} mice were 1.00 ± 0.04 versus 0.98 ± 0.05 at 3.5 months of age ($P > 0.5$) and 1.00 ± 0.03 versus 0.98 ± 0.04 at 8 months of age ($P > 0.5$); the intensities of DARPP-32 in the CPU of WT versus *Df1*^{+/+} mice were 1.00 ± 0.04 versus 1.01 ± 0.03 at 3.5 months of age ($P > 0.99$) and 1.00 ± 0.03 versus 0.99 ± 0.04 at 8 months of age ($P > 0.99$); and the intensities of TH in the SNc of WT versus *Df1*^{+/+} mice were 1.00 ± 0.01 versus 1.01 ± 0.01 at 3.5 months of age ($P > 0.99$) and 1.00 ± 0.02 versus 0.97 ± 0.05 at 8 months of age ($P > 0.5$). Together, the data support the conclusion that the expression levels of α -synuclein and p62 levels are specifically elevated in *Df1*^{+/+} mice when compared with control mice of the same age group.

Motor coordination deficits in *Df1*^{+/+} mice are ameliorated by reducing α -synuclein gene dosage

Increased expression of α -synuclein has been linked to pathophysiology of PD; recent clinical studies have reported that prodromal stages of PD show increased levels of α -synuclein microaggregates,

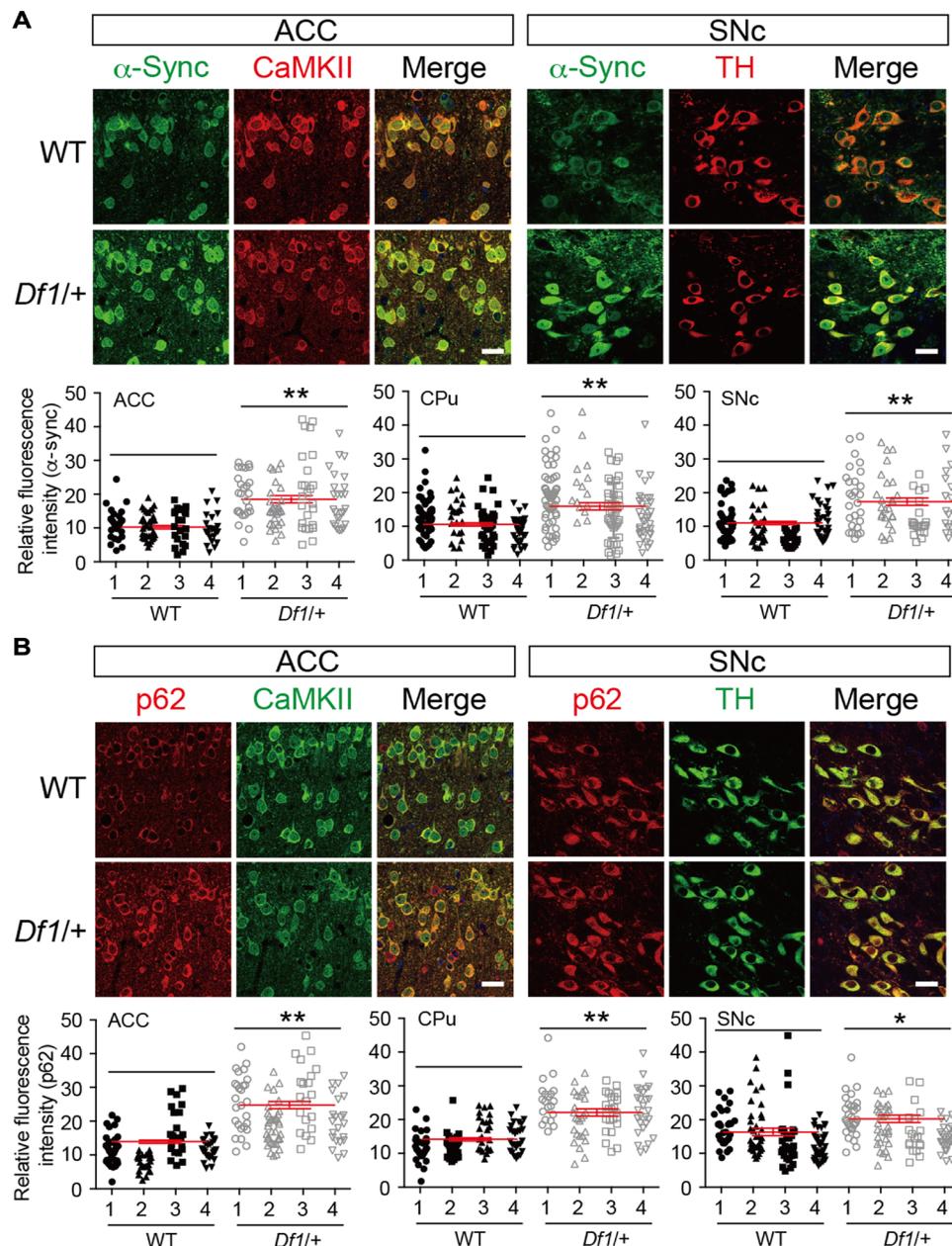


Fig. 2. Elevated expression of α -synuclein and p62 proteins in *Df1/+* mice. (A and B) The ACC, CPu, and SNc in *Df1/+* mice ($n = 4$) and the WT littermates ($n = 4$) (3.5 months old) were immunostained with anti- α -synuclein (α -Syn) (A) or anti-p62 (B) antibodies, together with anti-CaMKII, anti-DARPP-32, and anti-TH antibodies, which label the most abundant neuronal cell type in the ACC, CPu, and SNc, respectively. Images were acquired by a confocal microscope using the same parameters across multiple specimens. Images in the ACC and SNc are shown. Scale bars, 20 μ m. Relative fluorescence intensities (arbitrary units) of α -synuclein or p62 immunostaining were measured from each soma colabeled with the neuronal marker (30 to 50 soma per section) and plotted in the graph. Overall average fluorescence intensities (\pm SEM) calculated across three to four serial sections per animal from all animals used ($n = 4$ per group) are shown in red in the graph. * $P < 0.05$ and ** $P < 0.01$ (two-tailed Mann-Whitney test).

with no apparent sign of Lewy body formation (24, 25). Besides, overexpression of α -synuclein in mice serves as a model for PD (26–28). To investigate whether increased expression of α -synuclein in *Df1/+* mice is pathophysiologically relevant to PD, we sought to test the impact of reducing the dosage of α -synuclein gene (*Snca*) on motor deficits in *Df1/+* mice. We crossed *Df1/+* mice with *Snca*-knockout (KO) mice to generate WT, *Df1/+*, *Df1/+;Snca/+*, and *Snca/+* mice and tested their motor function in rotarod assays at 3.5 months of age. While *Df1/+* mice showed motor coordination

deficits ($F_{3,28} = 9.552$, $P = 0.0250$), the *Df1/+;Snca/+* mice showed motor function equivalent to that of WT and *Snca/+* mice (Fig. 3A).

PD-relevant and SZ-associated changes found in *Df1/+* mice are ameliorated by pharmacological treatment with a rapamycin analog

In the first half of the present study, we observed PD-relevant behavior (motor deficits) and molecular signatures (increase in the expression of α -synuclein and p62) in *Df1/+* mice. To our knowledge,

Table 1. Expression of α -synuclein and p62 proteins in *Df1/+* mice. ND, not determined; \uparrow , up-regulated ($>1.5\times$, compared with WT); \nearrow , up-regulated ($<1.5\times$, compared with WT); \rightarrow , unchanged (compared with WT).

	ACC		CPu		SNc	
	α -Synuclein	p62	α -Synuclein	p62	α -Synuclein	p62
2 months	ND	\uparrow	ND	\nearrow	ND	\rightarrow
3.5 months	\uparrow	\uparrow	\uparrow	\uparrow	\uparrow	\nearrow
8 months	\uparrow	\uparrow	\nearrow	\rightarrow	\uparrow	\rightarrow

this is the first study that reports these PD-relevant changes in 22q11.2 mouse models. In parallel, we also observed SZ-associated behavioral changes (for example, psychostimulant hypersensitivity and deficits in sensorimotor gating), which have been previously reported by other groups as relevant to psychiatric disorders, including SZ (4, 12, 13, 19, 20).

We then questioned whether PD-relevant and SZ-associated changes found in *Df1/+* mice might stem from common pathological pathways. Although this is an ambitious question for which long-term studies are needed in the future, elucidating pathological mechanisms in the 22q11.2 deletion model is critical in identifying potential targets for therapeutic interventions. To obtain initial clues to address this issue, we conducted a hypothesis-driven approach by selecting a specific pharmacological agent to test whether this could ameliorate either or both the PD-relevant and SZ-associated changes observed in the mouse model.

Recently, elevated mammalian target of rapamycin (mTOR) activity has been shown to play a role in the pathophysiology of PD (29, 30) and SZ (31). As a proof of concept for this finding, pharmacologically inhibiting mTOR activity ameliorated PD-related phenotypes in PD models (29, 30). Notably, a recent proteomic analysis reported up-regulated expression of proteins in the mTOR signaling pathway in another 22q11.2 deletion mouse model called *Df(16)A^{+/-}* (32). Thus, our working hypothesis for this study was that up-regulation of a pathway involving mTOR may commonly underlie the pathophysiologies of the expression of SZ- and PD-associated phenotypes in *Df1/+* mice.

Treatment of *Df1/+* mice with CCI-779, a rapamycin analog that inhibits mTOR activity, significantly rescued motor coordination deficits at 3.5 months of age ($F_{2,27} = 4.34$, $P = 0.0232$) (Fig. 3B). This treatment also normalized MK-801-induced hyperlocomotion ($F_{3,36} = 3.132$, $P = 0.0374$) (Fig. 3C) and PPI deficits ($F_{3,36} = 4.347$, $P = 0.0103$) (Fig. 3D) at 2 months of age. Thus, at least for these phenotypes, CCI-779 appears to ameliorate both PD-relevant and SZ-associated changes in *Df1/+* mice.

To evaluate the pharmacological effect of CCI-779 in the brain, we quantified the levels of p62 protein in the ACC of *Df1/+* mice after CCI-779 treatment. The treatment significantly attenuated the levels of p62 in *Df1/+* mice to the levels equivalent to WT at 2 months of age (fig. S3), consistent with the effect of mTOR inhibition on the level of p62 expression (33). To further validate the effect of CCI-779 on mTOR inhibition, we also quantified the levels of phosphorylated S6 ribosomal protein in the ACC of *Df1/+* mice (2 to 3 months of age) after CCI-779 treatment. The ratio of phospho-S6 to total S6 was significantly elevated by $\sim 28\%$ in *Df1/+* mice compared with WT, and CCI-779 treatment suppressed it to the level equivalent to WT (fig. S4), indicating that CCI-779 can normalize elevated mTOR activity in *Df1/+* mice.

DISCUSSION

Here, we showed for the first time that a 22q11.2 deletion mouse model (*Df1/+* mice) displays significant motor coordination deficits, as well as elevated expression of α -synuclein and p62 proteins. Moreover, reducing the α -synuclein gene dosage in *Df1/+* mice rescued deficits in motor coordination, demonstrating the causal role of elevated α -synuclein expression in the manifestation of this phenotype. The data provide a possible link between 22q11.2 deletions and PD-related pathobiology. In parallel, we also confirmed SZ-associated behavioral changes in *Df1/+* mice, consistent with the previous findings by others (4, 12, 13, 19, 20). A rapamycin analog, CCI-779, ameliorated both motor coordination deficits and SZ-associated behavioral changes. These data suggest a possible common pathway that may underlie both SZ-associated and PD-relevant manifestations in the context of 22q11.2 deletions.

Motor dysfunction of 22q11.2 deletion mouse models has not been intensively studied before; most investigators have used these models to study behavioral changes thought to represent psychiatric conditions in conjunction with the developmental trajectory. A previous study that reported no apparent motor deficits in *Df1/+* mice (12) was performed using mice on a mixed genetic background, which can result in variable animal behavioral phenotypes, including motor, mood, and cognitive functions (34). In contrast, the present study used a mouse model fully backcrossed to a congenic C57BL/6J background. A congenic background is recognized as important to delineate the effects of specific genomic alterations on animal behaviors.

We observed elevated levels of α -synuclein and p62 expression in brain regions, including the ACC, CPu, or SNc, but no apparent sign of Lewy body–like inclusions in the *Df1/+* mice, as also reported in other currently available mouse models of PD (28). Recent clinical studies have reported that prodromal stages of PD show microaggregates of α -synuclein with no apparent sign of Lewy body formation, as well as increased p62 expression, in several brain regions, including the SNc, striatum, and frontal cortex (24). Increased expression of α -synuclein has also been reported for PD patients (35). Given these lines of evidence, the phenotypes observed in the *Df1/+* mice might represent pathophysiological conditions relevant to prodromal PD. Alternatively, the motor coordination deficits observed in *Df1/+* mice may provide us with an opportunity to understand mild motor dysfunctions frequently observed in patients with neurodevelopmental and psychiatric conditions, including SZ (36, 37), as well as those with 22q11.2 deletions (16, 17). Conversely, SZ-relevant phenotypes observed in *Df1/+* mice may help us understand the mechanisms underlying the psychiatric symptoms frequently observed in PD. Note that nonmotor deficits, especially psychiatric symptoms, are clinically observed in individuals in prodromal stages of PD (38).

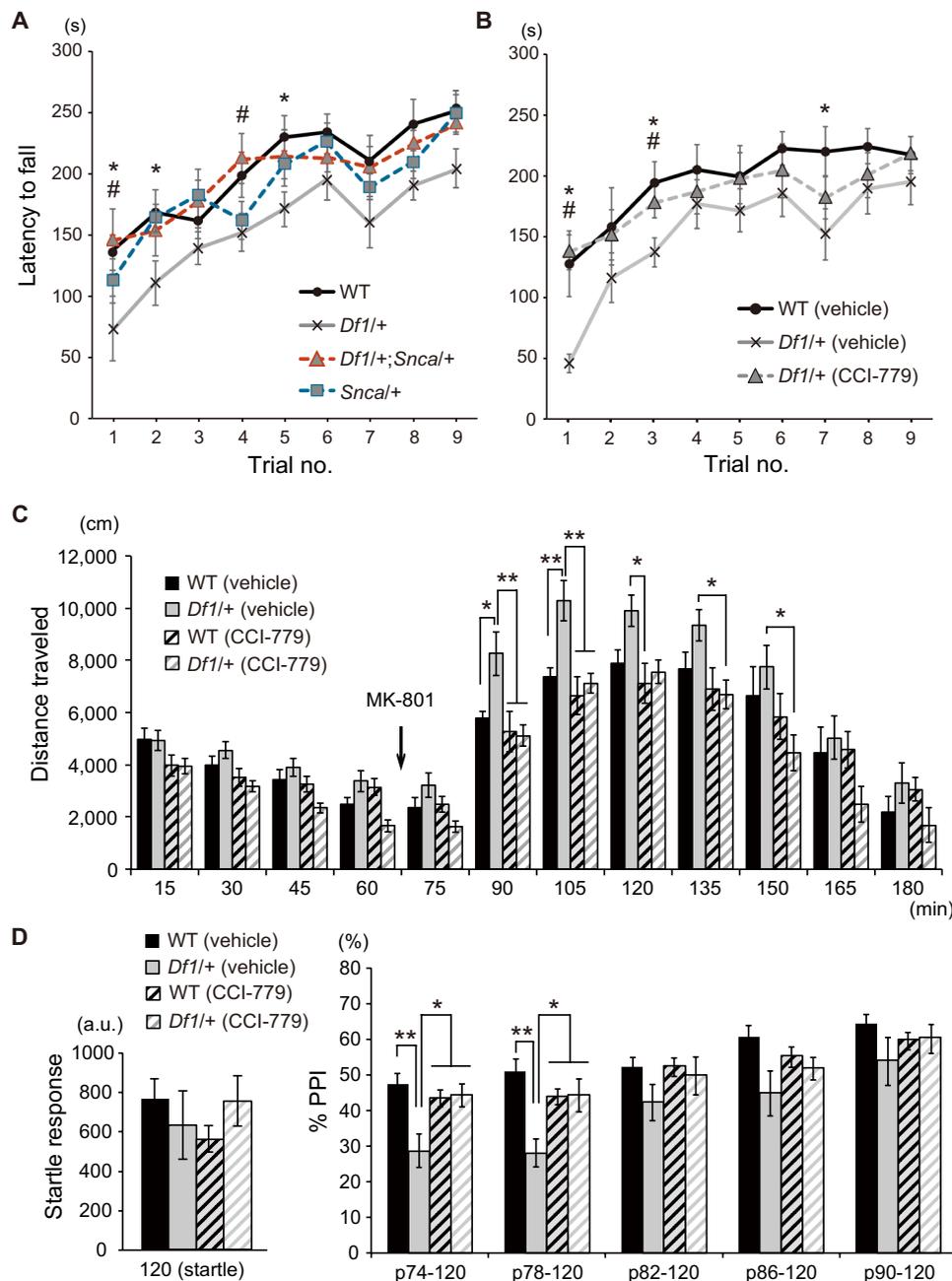


Fig. 3. Genetic or pharmacological rescue of motor coordination deficits, psychostimulant hypersensitivity, and sensorimotor gating deficits in *Df1*⁺ mice.

(A) Latency to fall (in seconds) from the rotarod was scored three times per day over three consecutive days. WT control ($n = 8$), *Df1*⁺ ($n = 8$), *Df1*⁺;*Snca*⁺ ($n = 8$), and *Snca*⁺ ($n = 8$) mice were tested at 3.5 months of age. Statistical significance (two-way ANOVA with repeated measures: $F_{3,28} = 9.552$, $P = 0.0250$); $^*P < 0.05$ (*Df1*⁺, as compared to WT) and $^{\#}P < 0.05$ (*Df1*⁺, as compared to *Df1*⁺;*Snca*⁺) (Bonferroni post hoc test). (B) Latency to fall (seconds) from the rotarod was scored three times per day over three consecutive days. WT mice treated with vehicle ($n = 12$), and *Df1*⁺ mice treated with CCI-779 ($n = 8$) were tested at 3.5 months of age. Statistical significance (two-way ANOVA with repeated measures: $F_{2,27} = 4.34$, $P = 0.0232$); $^*P < 0.05$ (*Df1*⁺ mice treated with vehicle, as compared to WT) and $^{\#}P < 0.05$ (*Df1*⁺ mice treated with CCI-779, as compared to *Df1*⁺ mice treated with vehicle) (Bonferroni post hoc test). (C) Locomotor activities [distance traveled (in centimeters)] measured in the open-field box before and after MK-801 challenge were plotted in 15-min bins. WT mice treated with vehicle ($n = 10$), WT mice treated with CCI-779 ($n = 10$), *Df1*⁺ mice treated with vehicle ($n = 10$), and *Df1*⁺ mice treated with CCI-779 ($n = 10$) were tested at 2 months of age. Statistical significance (two-way ANOVA with repeated measures: $F_{3,36} = 3.132$, $P = 0.0374$); $^*P < 0.05$ and $^{**}P < 0.01$ (Bonferroni post hoc test). (D) Acoustic startle response (left) and PPI (%) of startle response (right) were evaluated. WT mice treated with vehicle ($n = 10$), WT mice treated with CCI-779 ($n = 10$), *Df1*⁺ mice treated with vehicle ($n = 10$), and *Df1*⁺ mice treated with CCI-779 ($n = 10$) were tested at 2 months of age. Statistical significance (two-way ANOVA with repeated measures: $F_{3,36} = 4.347$, $P = 0.0103$); $^*P < 0.05$ and $^{**}P < 0.01$ (Bonferroni post hoc test).

Although we observed motor coordination deficits in *Df1/+* mice at 3.5 months of age with α -synuclein protein levels less than two times that of control mice, PD mouse models that overexpressed α -synuclein transgene generally had greater levels of the overexpression (1.5- to 3.4-fold at the protein level compared to the control) (26, 27) and exhibited later onset of motor deficits (after 7 months to 1 year of age) (27, 28). We postulate that the amount of α -synuclein overexpression necessary to cause motor deficits and the age of onset of PD-related motor phenotypes may differ, depending on the genetic mechanism of each model. For example, the *Df1/+* mice tested in this study have a hemizygous deletion of ~30 genes, resulting in downstream elevated expression of not only α -synuclein but also p62 proteins and possibly other proteins as well. In addition, the 22q11.2 region notably contains genes (for example, *PRODH* and *TXNRD2*) that were suggested to affect motor functioning (39). In contrast, the genetic mutation of α -synuclein transgenic mice is restricted to the transgene integration sites on the mouse genome, presumably resulting in specific overexpression of the transgene. Besides the elevated α -synuclein levels, the genetic, biochemical, or circuit-wide changes in *Df1/+* model versus α -synuclein transgenic mice may explain phenotypic differences among these models.

Genetic evidence has shown that 22q11.2 deletions are a susceptibility factor for SZ and PD (2, 3, 9), and we tested deregulated mTOR as a candidate common pathway shared between these two under this genetic condition. However, this does not mean that SZ pathophysiology generally contributes to PD pathophysiology and vice versa. 22q11.2 deletions represent only a small portion of SZ susceptibility among the entire SZ populations, and many additional genetic alterations have been suggested to serve as SZ risk factors (2, 3). Likewise, 22q11.2 deletions represent only a small portion of PD susceptibility, and many others, including mutations in *Parkin*, *PINK*, *PARK2*, *PARK7*, or *LRRK2* genes, serve as PD risk factors that are not considered as SZ susceptibility factors (9). Nonetheless, we predicted that 22q11.2 deletions may provide a unique opportunity to test whether there is some level of overlap, if any, in the pathophysiological mechanisms shared across these two distinct disease categories associated with 22q11.2 deletions. Elevated expression of α -synuclein and p62 proteins that we observed in *Df1/+* brains could result from attenuated activity of the cellular recycling machinery due to elevated mTOR activity (33), and we detected a steady-state increase in mTOR activity in *Df1/+* brains. Administration of the rapamycin analog in *Df1/+* mice normalized mTOR activity and concomitantly rescued both the motor- and non-motor-related behavioral deficits. Together, these lines of evidence suggest that elevated mTOR activity causes, at least in part, both the motor and nonmotor deficits in *Df1/+* mice.

To further delineate SZ and PD pathobiology associated with 22q11.2 deletions, future studies will need to investigate where, when, and how much of these pathological abnormalities (that is, elevated mTOR signaling or elevated expression of α -synuclein or p62 proteins) may occur within the human brains with 22q11.2 deletions. Depending on the cell types (for example, excitatory or inhibitory neuron), the brain regions (for example, ACC, CPU, or SNc), or the circuits (for example, corticolimbic, corticostriatal, or nigrostriatal pathway) that are principally affected, we predict seeing a range of phenotypic consequences, including SZ or PD.

There are several limitations to our study. First, motor dysfunctions observed in PD, including resting tremor and bradykinesia,

are more complex than the motor coordination deficit we showed in the *Df1/+* model. *Df1/+* mice may not be suited to model these cardinal motor features of PD. Second, our current immunofluorescence analyses were designed to compare levels of α -synuclein or p62 proteins across genotypes within the same age group instead of following longitudinal changes in their expression levels for each genotype. Given that aggregate-prone proteins tend to accumulate during aging (14, 15), questions remain as to whether α -synuclein or p62 would show an accelerated increase in *Df1/+* mice relative to WT mice and, if so, at which age this would begin. To address these questions, we will need to directly compare the expression levels over additional longitudinal age groups in one experimental cohort. Third, elevated α -synuclein expression levels alone may not fully explain pathophysiological mechanisms for early-onset PD associated with 22q11.2 deletions. Although human genetic studies and postmortem analyses have demonstrated the association of recurrent 22q11.2 deletions with early-onset PD (7, 9), the detailed mechanisms underlying this comorbidity remain to be elucidated. While a high proportion (that is, up to 30%) of patients with 22q11.2 deletions are shown to develop psychiatric conditions, a smaller proportion (~5%) of those with 22q11.2 deletions are estimated to develop PD (7). This suggests that additional pathogenic events, such as age-related stresses, environmental risk factors, or other genetic alterations, may interact with 22q11.2 deletions to contribute to the development of PD. For example, some chronic insults that would disrupt metabolic homeostasis of dopaminergic neurons (16), coupled with elevated α -synuclein in SNc due to 22q11.2 deletions, may culminate in dopaminergic neuron death, leading to full-blown PD pathology. In this regard, the present study provides initial evidence that 22q11.2 deletion mouse models may be useful to investigate how the biological disturbances elicited by 22q11.2 deletions could underlie both neurodevelopmental conditions, such as SZ, and neurological conditions, such as early-onset PD, at the mechanistic levels. The preliminary findings of the current study support the possibility that deregulated mTOR signaling may represent a joint mechanism, providing a working hypothesis for future research.

There is precedence that molecular mechanisms underlying both psychiatric and nonpsychiatric (for example, motor) symptoms are delineated in the same animal model. For example, the R6/2 model, a representative mouse model for Huntington's disease with respect to its polyglutamine pathology, displays motor deficits and anhedonia-like manifestations: The mutant huntingtin protein with a polyglutamine stretch causes both motor and psychiatric symptoms through distinct molecular mechanisms (40). Likewise, we cautiously but optimistically propose that the animal models of 22q11.2 deletions will become important tools for studying mechanisms not only for neurodevelopmental conditions, such as SZ, but also for neurodegenerative pathologies, such as PD.

MATERIALS AND METHODS

Experimental design

On the basis of the clinical evidence linking human 22q11.2 deletions not only to SZ but also to early-onset PD (7, 9), we hypothesized that a mouse model of 22q11.2 deletions could be used to investigate pathobiological mechanisms underlying the early-onset PD associated with the 22q11.2 deletions. The *Df1/+* mouse line (10, 12) was used as a representative model because this line has been extensively characterized to address the pathophysiology of SZ. The

Df1/+ mouse line was maintained on the C57BL/6J genetic background for >12 generations. *Snca*-KO mice were obtained from the Jackson Laboratory (stock #016123 maintained on C57BL/6NJ). Animal handling was performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and approved by the Animal Research Committee at Kyoto University.

Behavioral assays

All mice were group-housed and maintained under standard conditions (12/12-hour light/dark cycle, lights on at 7:00; 22° ± 1°C; with food and water ad libitum). Mice to be used for behavioral assays were acclimated in the test room 1 day before the assay, and all the assays were performed between 15:00 and 19:00. *Df1/+* and the littermate control mice (3.5 months old; male; *n* = 8 to 12 per group) were used for rotarod tests. Independent cohorts of mice (2 months old; male; *n* = 10 per group) were used for PPI tests, followed by locomotor tests 3 days later. Personnel performing the tests were blinded to the genotype of the mice.

Rotarod

Mice were tested for their ability to stay on a rotating bar (rotarod, Harvard Apparatus), which accelerated from 4 to 50 rpm over 5 min per trial. For each mouse, three trials were performed per day (30-min break between trials) for three consecutive days. Latency to fall (seconds) was scored in each trial.

PPI

To assess sensorimotor gating function, startle response and PPI were measured using a startle chamber (SR-LAB). Briefly, a prepulse-pulse trial started with a 50-ms null period, followed by a 20-ms prepulse white noise (74, 78, 82, 86, or 90 dB) and a 100-ms delay, and then, the startle stimulus (a 40-ms, 120-dB white noise) was presented. Six trial types (pulse-only trial and five types of prepulse-pulse trial) and six nonstartle stimuli (65, 74, 78, 82, 86, or 90 dB) were presented in a pseudorandomized order such that each trial type or nonstartle stimulus was presented once within a block of assay. %PPI = 100 – [(response on prepulse-pulse stimulus trials / startle response on pulse-only trials) × 100].

Locomotor

Each mouse was placed in the center of the open-field box ($W \times D \times H = 40 \text{ cm} \times 40 \text{ cm} \times 27 \text{ cm}$), and the baseline activities were measured over 60 min. Subsequently, MK-801 was administered intraperitoneally [0.1 mg/kg body weight, intraperitoneally (ip)], and the locomotor activities were measured over 120 min to evaluate psychostimulant sensitivity. The distance traveled (in centimeters) was analyzed in 15-min bins using EthoVision (Noldus).

Immunohistochemistry

Mice (*n* = 4 per group; male; 2, 3.5, or 8 months of age) were perfused transcardially with 4% paraformaldehyde in phosphate-buffered saline while under anesthesia [ketamine (100 mg/kg body weight) / xylazine (10 mg/kg body weight) mixture, ip]. The brains were then serially cut into 50- μm -thick coronal sections using a vibratome (VT1200 S, Leica), and the sections from one cohort of mice (a littermate pair of WT and *Df1/+* mice) were simultaneously immunostained for 16 hours at 4°C with primary antibodies anti-p62 (guinea pig, 1:400; Medical and Biological Laboratories), anti- α -synuclein (rabbit, 1:200; Immuno-Biological Laboratories), anti-CaMKII (mouse, 1:1000; StressMarq), anti-DARPP-32 (mouse, 1:1000; Calbiochem), and anti-TH (mouse, 1:3000; Abcam), followed by in-

cubation with Alexa Fluor 488- or Alexa Fluor 546-conjugated secondary antibodies (1:500; Gibco). Images of one optical section (1 μm thick) were acquired via confocal microscopy (SP8, Leica; 40 \times objective lens; numerical aperture, 1.3) from sections containing either the ACC, dorsolateral part of CPu, or SNc. For each brain region, three to four serial sections were analyzed, and three to six nonoverlapping areas were randomly chosen for image acquisition in each section. The fluorescence intensities of the α -synuclein or p62 immunostaining were measured from each neuron marker-positive soma (30 to 50 somas per section) using ImageJ (NIH), with the background levels in adjacent regions being subtracted. The average immunofluorescence intensity per soma was calculated across all serial sections from every mouse used.

Western blot

Mice (male; 2 to 3 months of age; *n* = 6 per group) were acutely sacrificed by decapitation. The brain (the ACC) was then dissected quickly within 30 s, snap-frozen in liquid nitrogen, and subsequently lysed in radioimmunoprecipitation assay buffer containing 1% Triton X-100, 0.1% SDS, protease inhibitor cocktail (Roche), and phosphatase inhibitor cocktail (Sigma-Aldrich). The extracted proteins were subjected to SDS-polyacrylamide gel electrophoresis and transferred to a polyvinylidene difluoride membrane (0.45- μm pore, Millipore), which was incubated in a membrane-blocking agent (GE Healthcare) for 30 min and probed with anti-S6 ribosomal protein (rabbit, 1:1000; Cell Signaling Technology) or anti-phospho-S6 (Ser^{235/236}) antibodies (rabbit, 1:1000; Cell Signaling Technology) and subsequently with horseradish peroxidase-conjugated anti-rabbit immunoglobulin G (1:10,000; GE Healthcare). Signals were detected with an ECL agent (GE Healthcare). Blotting images were acquired by ChemiDoc XRS imaging system (Bio-Rad), and the densitometric analysis was performed using ImageJ (NIH).

Pharmacological rescue

A water-soluble rapamycin analog, CCI-779 (Tocris), dissolved in saline (10 mg/kg body weight) or the vehicle alone was injected (intraperitoneally) once daily for eight consecutive days before behavioral testing. During the behavioral testing period, daily injection was performed 1 hour before behavioral assessment and was continued up to day 11 until all behavioral assays were completed.

Statistical analysis

Data were means ± SEM. Behavioral assay data were analyzed using a two-way ANOVA with repeated measures, followed by Bonferroni post hoc tests. Immunohistochemistry data without drug rescue were analyzed by Mann-Whitney test (two-tailed). Immunohistochemistry data with drug rescue and Western blot data were analyzed by Kruskal-Wallis test, followed by Dunn's multiple comparisons tests. Statistical significance: **P* < 0.05 and ****P* < 0.01.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at <http://advances.sciencemag.org/cgi/content/full/4/8/eaar6637/DC1>

Fig. S1. Amplitude of responses to nonstartle sound stimuli in *Df1/+* mice during PPI assays.

Fig. S2. Elevated expression of α -synuclein and p62 in *Df1/+* mice at 8 months of age.

Fig. S3. Elevated p62 expression in *Df1/+* mice is normalized by CCI-779 administration.

Fig. S4. Increased mTOR activity in *Df1/+* mice is normalized by CCI-779 administration.

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