The cognitive phenotypes of mouse models of 1q21.1, 22q11.2 and 15q13.3 deletion syndromes

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BACKGROUND

The greatest known genetic risk factors for developing schizophrenia includes chromosomal microdeletions at loci 22q11.1, 15q13.3 and 1q21.1[2].

Mice heterozygote for the orthologous chromosomal loci have been generated and made available to partners of the NEWMEDS collaboration. The aim of the current set of experiments was to assess the potential of these mouse models for cognitive translational studies.

To this end, we have characterised the three lines using an extensive battery of assays that depend on neural structures and cognitive domains compromised in CNV patients, schizophrenic patients and alternative CNV mouse models[1,3,4,5,6].

METHOD

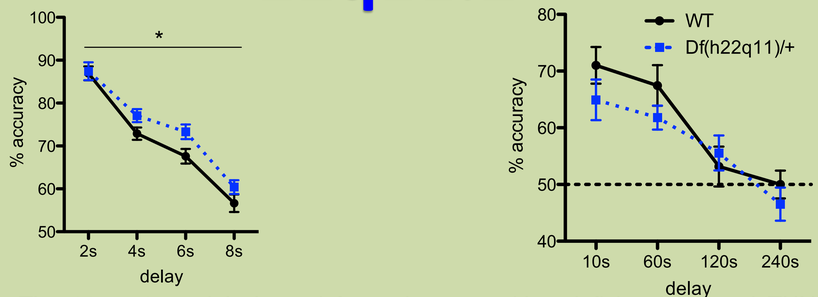
Animals were tested on a battery of touchscreen tasks, operant tasks, maze tasks, and spontaneous learning tasks.

1q21.1. The experiments used 3 cohorts of animals (N = 12-16) tested between 3-20 months of age.

15q13.3. The experiments used 3 cohorts of animals (N = 12-16) tested between 3-20 months of age.

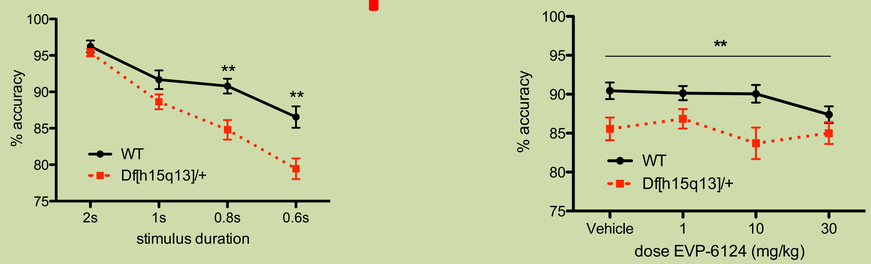
22q11.2. The experiments used 10 cohorts of animals (N = 13-16) tested between 2-16 months of age.

22q11.2



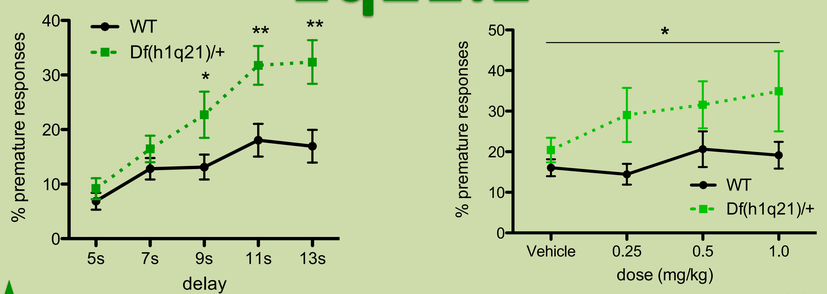
The 22q11.2 model showed few robust cognitive deficits. Improved TUNL spatial working memory (left), and no effect on T-maze delayed spatial alternation (right).

15q13.3



The 15q13.3 mouse model showed an attentional impairment in the 5-CSRTT. The accuracy impairment was replicable and observed in three experiments (left). The accuracy impairment was not attenuated by the partial α7 nicotinic agonist EVP-6124 (right).

1q21.2



The 1q21.1 mouse model showed an impulsive phenotype in the 5-CSRTT when tested on longer delays (left). The effect of genotype was transient as disappeared with repeated testing on longer delays. However, the impulsive phenotype was restored with systemic d-amphetamine (right).

SUMMARY

Model		22q11.2	15q13.3	1q21.1
Deletion		Dgcr2-Hira	Chrna7-Mtmr15	Gpr89-Prkab2
Strain		C57/Bl6NTac	C57/Bl6NTac	C57/Bl6NTac
Behaviour	**Paradigm**			
Memory	Water maze < 20 weeks	×	↓[1]	-
	Water maze > 20 weeks	×	-	-
	Contextual fear conditioning	×	×[1]	-
	TUNL – pattern separation	×	×	×
	Auditory-cue fear conditioning	×		-
	Touchscreen PAL	×	×	×
	Novel object recognition	×	(↓)	×
	Touchscreen discrimination learning			
	'Easy' discrimination	↑	×	×
	'Difficult' discrimination	×	×	×
Working Memory	Y-maze spontaneous alternation	×	×[1]	-
	TUNL – delay challenge	↑	×	×
	Radial arm-maze	×	-	-
	T-maze non-match to sample			
	Acquisition	↓	-	-
	Delay challenge	×	-	-
Executive function	PVT - Premature responses	×	-	-
	5CSRTT - Premature responses	×	×	↓
	Touchscreen extinction learning	×	×	×
	Touchscreen reversal learning			
	'Easy' reversal	↑	×	×
	'Difficult' reversal	×	×	×
Attention	PVT - Reaction time	×	-	-
	PVT - Correct responses	×	-	-
	5-CSRTT - Accuracy	×	↓	×
	5-CSRTT - Omissions	↑	×	×
Motivation	Progressive ratio	×	×	×

Table 1. Cognitive functioning in CNV mouse models. ↓ impaired, ↑ improved, × no effect, - no data.

CONCLUSIONS

The 22q11.2 mouse model display some impairments in tasks of cognition. However, the test battery indicates that the model displays few cognitive impairments sufficiently robust for use in drug discovery. We show that the 15q13.3 model has value for modeling attentional dysfunction and that the 1q21.1 mouse show a transient impulsive phenotype in the 5-CSRTT that can be re-instated through systemic d-amphetamine injections.

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