Prevalence rates of psychiatric disorders in individuals with NRXN1 deletions compared to idiopathic autism.

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Background

Introduction

- Rare neurodevelopmental copy number variants (ND=CNV) increase the risk of neurological and psychiatric disorders (Chawner et al., 2019).
- Neurexins are pre-synaptic cell adhesion molecules (CAMs) that function in synaptic transmission (Anderson et al., 2015).
- NRXN1 is the largest neurexin gene and is most susceptible to non-recurrent deletions (Castronvo et al., 2019).
- NRXN1 deletions can produce changes in neural signaling pathways and have been linked to disconnections between neural networks (Ching et al., 2019).
- NRXN1 deletions have been identified in phenotypes expressing global delay and speech delay. Furthermore, they have been linked to NDDs including ASD, ID, ADHD and anxiety (Al Shehhi et al., 2019).

Aims

1. Investigate the prevalence of psychiatric conditions in NRXN1 deletion carriers compared to iASD and TD groups using the Developmental and Wellbeing Assessment (DAWBA).
2. Aims to examine and compare differences that may be present between NRXN1 probands and parent carriers.

Project Objectives and Methods

- Participant recruitment: 1.The TCD ASD & NDD NRXN1 del group and 2. AIMS-2-TRIALs Leap Cohort.
- Exclusion criteria are shown in Fig 1.
- Genetic information had also been gathered from both groups to confirm NRXN1 del and iASD status.
- Clinical outcome measures: Development and Wellbeing assessment (DAWBA) and strengths and difficulties questionnaire (SDQ).
- Each group was compared to examine the prevalence of psychiatric conditions.

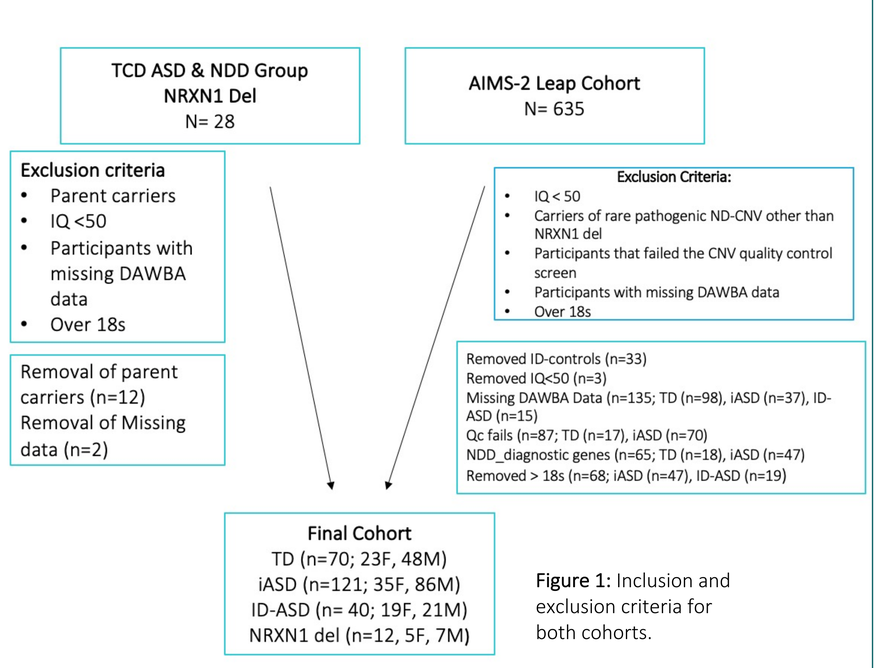


Figure 1: Inclusion and exclusion criteria for both cohorts.

Results

DAWBA diagnosis and SDQ

A.

Psychiatric Disorder	TD <18	iASD <18	ID-ASD <18	NRXN1 Proband	Significance
Any Disorder	4.20%***	50%***	39.40%	41.70%	<0.001[a]
Depression	0.00%	4.20%	6.90%	0%	NS[a] (p=168, FET)
ADHD	1.47% ***	19.83%	10.30%	33.30%	<0.001[a]
Anxiety	2.86% ***	32.23% ***	25.00%	8.30%	<0.001[a]
Behaviour	1.49% ***	32.38% ***	19.23%	33.30%	<0.001[a]
Internalising	2.80% ***	34.71% ***	27.30%	8.30%	<0.001[a]
Externalising	2.86% ***	38.84% ***	21.20%	33.30%	<0.001[a]

a Fischer-Exact Test

B.

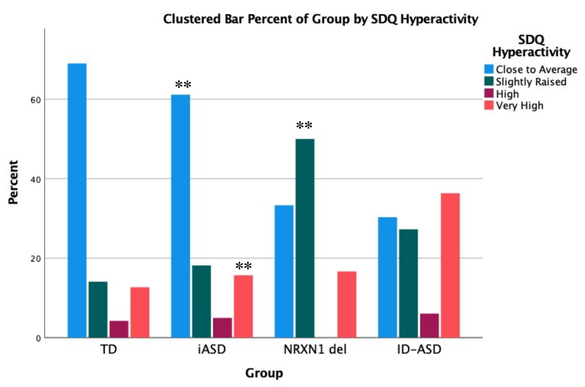


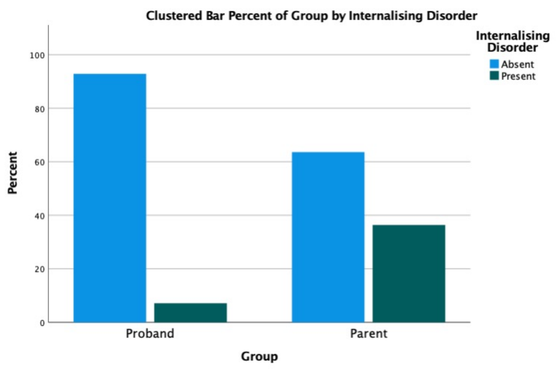
Figure 2: A. The prevalence of psychiatric disorders depicted by % proportions. Statistical significance is represented as p<0.001, ***. **B.** Proportion of individuals for each group split by the fourfold classification based on hyperactivity. NRXN1 del statistically more likely than the other three groups to have a slightly raised hyperactivity score, p<0.005, **.

NRXN1 Parent vs Proband

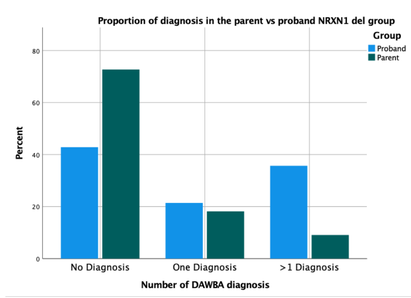
A.

Psychiatric Disorder	NRXN1 Proband	Parent Carriers	Significance
Any Disorder	42.90%	36.40%	NS[a]
Depression	0%%	27.3%%	NS[a]
Anxiety	7.1%%	36.40%	NS[a]
Internalising	7.1%%	36.40%	NS[a]

a Fischer-Exact Test

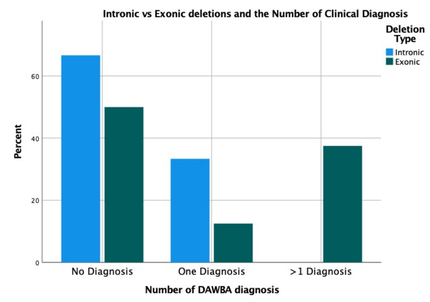


B.



	No Diagnosis	One Diagnosis	>1 Diagnosis	*p*
Parents	72.70%	18.20%	9.10%	NS[a]
Probands	42.90%	21.40%	35.70%	NS[a]

C.



	No Diagnosis	One Diagnosis	>1 Diagnosis	*p*
Intronic	66.70%	33.30%	0%	NS[a]
Exonic	50%	12.50%	37.50%	NS[a]

Figure 3: A. Proportion percentage for each diagnosis. Comparison of internalizing disorders. **B**. Number of Clinical diagnosis plotted against group and **C**. deletion type.

Genetics information

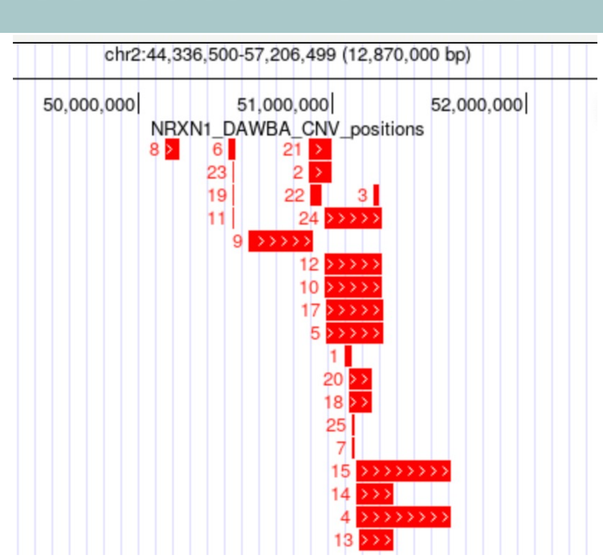


Figure 4: Genetic Information for the NRXN1 del cohort. CNV position, deletion size and start and stop codon are included.

Discussion & Conclusion

- The objective of this study was to compare the prevalence of psychiatric disorders in NRXN1 del individuals compared to ASD, ID-ASD and TD groups.
- 41.7% of NRXN1 probands had a diagnosis of a psychiatric disorder. These rates are comparable to the iASD group (50%) and ID-ASD (39.4%).
- NRXN1 probands had similar prevalence rates to the iASD groups for behavioral disorders (iASD 32.38%, NRXN1 33.3%) and externalizing disorders (iASD 38.84%, NRXN1 33.3%).
- Moreover, DAWBA demonstrated that ADHD, anxiety, behavioral disorder and internalizing and externalizing disorders were significantly more frequent in the iASD group in comparison to the TD-group (p<0.001).
- 50% of NRXN1 probands had a clinical diagnosis of ASD and displayed clinical variability in terms of co-morbid clinical diagnoses.
- The NRXN1 group were more likely to have a slightly raised hyperactivity level than the other three groups based on the SDQ. Similarly, NRXN1 carriers had the highest rates of DAWBA predicted ADHD diagnosis (33.3%) although it did not differ significantly from the other NDD cohorts.
- The similarities between NRXN1 carriers and the ASD group suggest shared vulnerabilities which may suggest similar pathophysiology in neurodevelopment.
- In this way further research is needed to assess the use of NRXN1 del carriers as a genetic model.
- Comparing NRXN1 del probands and parents we found an increased prevalence of internalizing disorders in adult NRXN1 carriers (7.1% in NRXN1 probands vs 27.3% in parents). This may reflect increasing vulnerability to psychiatric disorders over development.
- Exonic deletions were associated with a greater number of comorbidities (> one clinical diagnosis) compared with intronic deletions (37.5% and 0% respectively) supporting the prior observations that they are more penetrant (Cosemans et al., 2019).
- Future research: Focus on comparing NRXN1 del to other synaptic gene conditions.
- Further investigation of phenotypes relative to genetic heterogeneity in NRXN1 deletion carriers in the future will be informative to genetic counselling.

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References:
Al Shehhi, M et al., (2019). https://doi.org/10.1016/j.ejmg.2018.07.015

Anderson, G. et al., (2015). https://doi.org/10.1016/j.cell.2015.06.056

Chawner, S. et al.,(2019). https://doi.org/10.1016/S2215-0366(19)30123-3

Ching, M. et al., (2010). https://doi.org/10.1002/AJMG.B.31063

Cosemans, N et al., (2020). https://doi.org/10.1136/JMEDGENET-2019-106448