

# Genotype-phenotype relationships in children with copy number variants associated with high neuropsychiatric risk: Findings from the Intellectual Disability & Mental Health Assessing the Genomic Impact on Neurodevelopment (IMAGINE-ID) study

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## INTRODUCTION

Several Copy Number Variants (CNVs) have been associated with high risk of development of child and adult neuropsychiatric disorders. (referred to as ND-CNVs hereafter). Although recurrent ND-CNVs are individually rare, collectively pathogenic ND-CNVs have been implicated in ~15% of patients with neurodevelopmental disability. Increasing use of array screening in the assessment of children with neurodevelopmental delay is leading to a rise in the diagnosis of ND-CNVs by medical genetics clinics, yet information on long-term neuropsychiatric prognosis is lacking. There have been limited studies that have contrasted the phenotypes of ND-CNVs across several loci on a range of cognitive and behavioural domains.

## METHODS

**Sample:** 258 children with a ND-CNV recruited via NHS medical genetic clinics (9.7 years (SD=3.1), 65.9% male) and 106 sibling controls (10.9 years (SD=3.0), 51.9% male)

**Deep phenotyping:** we assessed a broad range of behavioural and cognitive traits across psychiatric, neurodevelopmental, psychopathological, cognitive, social, sleep and motor domains, from which **dimensional quantitative** traits were derived.

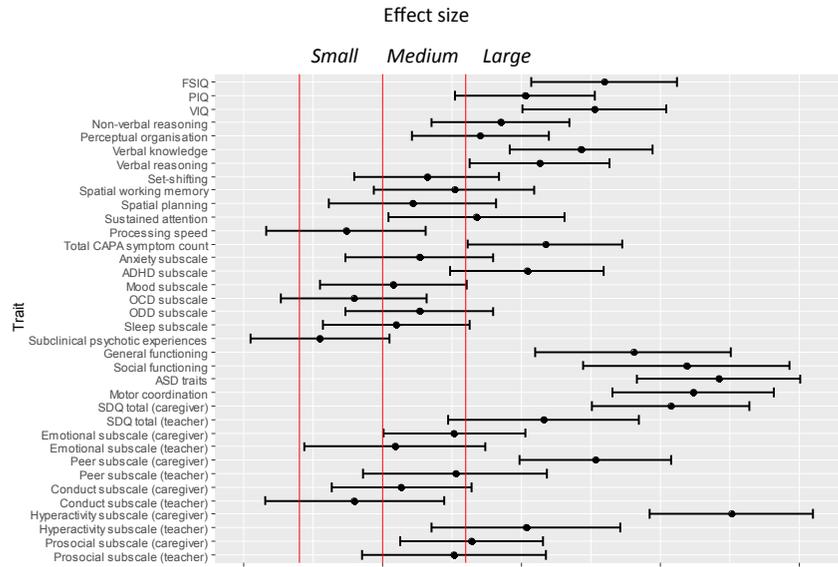
**Multi-informant approach:** caregiver and teacher report as well as direct child assessments

### Specific measures:

- Interviews: Child and Adolescent Psychiatric Assessment
- Cognition: Wechsler Abbreviated Scales of Intelligence, Wisconsin Card Sorting Test, CANTAB
- Questionnaires: Strengths and Difficulties Questionnaire, Developmental Coordination Disorder Questionnaire, Social Communication Questionnaire
- Functioning: children's global assessment scale, social and occupational functioning assessment scales

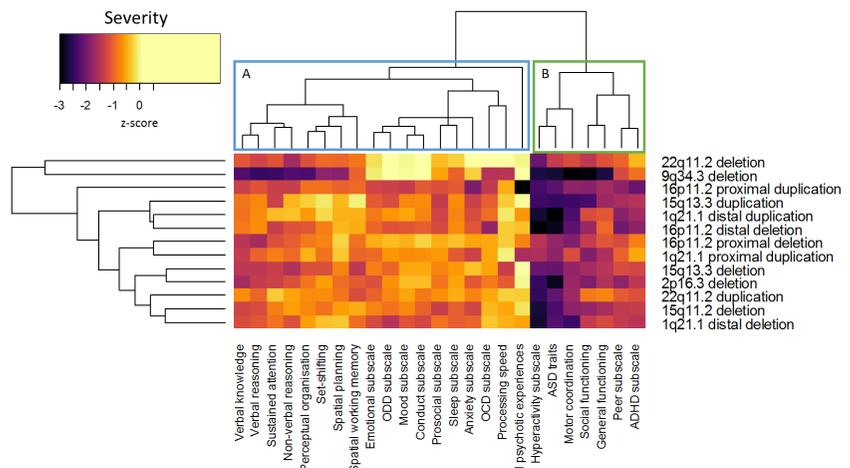
## RESULTS

### 1. Impairments across a range of domains in ND-CNV carriers relative to sibling controls



### 2. Genotype-phenotype relationships within ND-CNV carriers

- Significant profile differences between ND-CNVs, both in terms of qualitative (pattern of deficits) and quantitative (phenotypic severity) differences
- Core cluster of neurodevelopmental deficits strongly impaired across all ND-CNVs, impairment in mental health and cognitive comorbidities variable by ND-CNV
- However genotype only accounts for 5-20% of phenotypic outcome depending on trait - there is great overlap in phenotypic profile across genotypes



## CONCLUSIONS

Children who carry a ND-CNV represent a vulnerable patient group that warrant clinical and educational attention for a broad range of cognitive and behavioural impairments. Although subtle phenotypic differences exist, there are strong commonalities in the neurodevelopmental profile across ND-CNVs. Our findings indicate that genomic risk for neuropsychiatric disorder has pleiotropic effects on multiple processes and neural circuits, and provides important implications for research into genotype-phenotype relationships within psychiatry.