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A Normative Chart for Cognitive Development in 22q11DS: Implications for 22q11DS and Beyond

Elemi Breetvelt[1], *Ania Fiksinski[2], Anne Bassett[3], Jacob Vorstman[4]*

Institution(s): *UMC Utrecht, Utrecht, the Netherlands [1], Centre for Addiction and Mental Health, Toronto, ON, Canada [2], Toronto General Hospital, University Health Network, Toronto, ON, Canada [3], The Hospital for Sick Children, Toronto, ON, Canada [4]*

Background: We have previously reported a modest decline in IQ between 8 and 24 years in 22q11.2DS and that those with negative deviations from this average decline on verbal IQ were at increased risk for schizophrenia. In order to extend these initial findings, we have produced a definitive 22q11DS-specific normative chart for cognitive development using the now considerably larger and quality-controlled dataset of the International Brain and Behavior Consortium (IBBC) on 22q11.2DS. We then reiterated the schizophrenia risk -prediction and calculated the potential advantage of using the norm-chart over using the absolute IQ values. **Methods:** We used cross-sectional and longitudinal IQ data from 1871 individuals with 22q11DS (mean age 15.7, SD 7.4, y; n=330 (17.6%) with schizophrenia). We used polynomial regression, similar to what is used for standardized growth charts, to construct normative charts for Full Scale, Verbal, and Performance IQ (FSIQ, VIQ, PIQ; age-range 6–40 y). We determined the best fit for the data and subsequently focused on longitudinal data to examine whether participants followed their expected trajectory. We re-tested the association between schizophrenia expression and VIQ decline and compared the results based on the norm chart-derived z-scores versus the absolute IQ. **Results:** The 3rd order polynomial regression provided the best fit for the data. In line with previous findings, the 22q11DS population showed declines in FSIQ, VIQ and PIQ. The steepest declines were observed in the youngest, and in the older, age ranges. On average the participants with longitudinal data stayed on or remained close to their trajectory. Consistent with our previous results, individuals who went on to develop schizophrenia showed a negative deviation from their expected trajectory for VIQ. Importantly, the analysis using norm-chart derived Z-scores resulted in a 23-30% reduction of sample size required for sufficient statistical power. **Conclusions:** This study demonstrates the feasibility and potential utility of a normative chart for cognitive development in 22q11DS both for the purposes of research and for clinical settings. For the first time we have evidence that downstream analyses using population-specific normative data can outperform typically used analytical approaches based on standardized, but not population-specific data. We propose that our results may serve as an example for constructing similar normative charts for other genetic disorders.