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The Impact of Parental IQ on the Variable Penetrance of Intellectual Impairment in 22q11DS

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Background: The 22q11.2 deletion syndrome (22q11DS) is associated with a range of phenotypes, including neurodevelopmental disorders. Similar to other pathogenic copy number variants (CNVs), the proportion of individuals who express any single associated phenotype is far from 100%. A major research goal is to identify factors that modify the penetrance of individual phenotypes in the presence of the 22q11.2 deletion. The current study is part of an ongoing genotyping and deep phenotyping study of probands and parents. Here, we investigated whether the variable penetrance of intellectual impairment in individuals with 22q11DS is modulated by the intellectual level of their unaffected parents. **Methods:** To date, we have studied 42 individuals (21 males (50%), mean age 26.7 (SD 8.9) y) with de novo 22q11.2 deletions. We used the Wechsler Abbreviated Scale of Intelligence–II to obtain Full Scale, Verbal, and Performance IQ (FSIQ, VIQ, and PIQ). In 31 families we obtained IQ data for both parents and used the mean parental IQ for analyses; for 11 other probands we used individual maternal or paternal IQ. We tested the association between parental and proband IQ using Pearson's correlation and accounted for the effects of schizophrenia expression, age, and sex using a linear regression model. **Results:** The mean FSIQ in probands was 72.6 (SD 16.8) and 101.6 (SD 15.1) in parents. We found a significant correlation of moderate effect size between intellectual functioning in probands and parents, for FSIQ, VIQ, and PIQ (Pearson's R = 0.524, 0.536, and 0.492, respectively; $p<0.0001$ for all three). The strength of the association with proband IQ was similar for either maternal or paternal IQ only. The linear regression model for proband IQ was significant ($p<0.0001$) and revealed that a higher parental IQ was related to higher proband IQ ($p<0.0001$) after accounting for other factors such as schizophrenia. **Conclusions:** The results suggest that the variable penetrance of intellectual impairment in individuals with 22q11DS is to a significant extent related to parental intellectual functioning. This is consistent with previous findings in a 22q11DS population that used parental educational attainment as a proxy for IQ, and largely consistent with findings reported for other CNVs. Our results indicate that the 22q11.2 deletion provides a "first hit" that has a major impact on IQ, but that other familial background effects, e.g. genetic and environmental factors, modulate the degree to which IQ is affected.