007: Do proximal nested 22q11.2 deletions have a modified adult phenotype?

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Background: There is evidence that individuals with proximal nested (A-B/A-C) 22q11.2 microdeletions have on average slightly higher IQ and slightly greater adult height than the majority with full extent (A-D) deletions. However, there is a paucity of evidence with respect to qualitative differences in expression. **Methods:** In a well-phenotyped cohort of 472 adults with 22q11.2 deletion syndrome having known deletion extent (i.e., after excluding 20 individuals without deletion extent data), we compared major phenotypes and other features of the n=50 with A-B/A-C deletions (25 female; median age 29.9 years) to the n=422 with A-D deletions (222 female, median age 33.6 years). **Results:** There were no significant between-group differences in age, sex, psychotic illness, moderate to severe intellectual disability, major congenital cardiac disease or mortality. However, the relative risk of developing hypothyroidism was significantly lower in the presence of an A-B/A-C deletion than for an A-D deletion (RR 0.25, 95% CI 0.08 to 0.77, p=0.015). Also, the relative risk of being in the highest IQ group was about twice that for the nested deletion than the full deletion group (RR 2.46, 95% CI 1.47 to 4.13, p=0.0007). Notably, for 12 (24%) individuals in the nested deletion group, the deletion was inherited or transmitted, and for a further 5 (10%) an additional variant was called on the microarray. **Conclusion:** The results suggest that, for individuals with a "typical" 22q11.2 deletion, the deletion extent can have clinically relevant effects on long-term outcomes. There are potential implications for genetic counselling, with further support for the utility of clinical genome-wide microarray, including for the many individuals with only targeted (FISH) 22q11.2 deletion detection. The results also indicate that studies of disease (e.g., autoimmune) mechanisms will require consideration of 22q11.2 deletion extent.