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Membership:
Non-Member

Primary Category:
Clinical Genetics

Secondary Category :
Cytogenetics/Microarray

Title:
Predictors of all-cause mortality in adults with 22q11.2 deletion syndrome

Abstract:

Background: We previously reported that adults with 22q11.2 deletion syndrome (22q11.2DS) have an elevated risk of premature death when compared to their unaffected siblings. However, the effect of 22q11.2DS-associated features, such as congenital heart defects (CHD), on mortality is unknown. We hypothesized that in addition to the 22q11.2 deletion, major CHD (defined as CHD of moderate or complex structural complexity) could affect mortality in a large adult sample.

Methods: Our cohort comprised 1265 adults (≥17 years): 290 with 22q11.2DS (135 male (M); median age 29.7, range 17.8-68.6, years), their 444 unaffected siblings (216 M; median age 35.6, range 17.0-83.0, years) and 531 unaffected parents (258 M; median age 58.6, range 17.4-93.0, years), followed for up to 23 years. We compared survival between groups using Kaplan-Meier estimates and Cox regression (hazard ratio (HR) and 95% confidence interval (CI)) to investigate the relationship between mortality and potential predictor variables including major CHD, psychotic illness, and intellectual disability.

Results: Adults with 22q11.2DS had significantly lower survival compared to both unaffected siblings ($p<0.0001$) and parents ($p<0.0001$). The 22q11.2 deletion (HR 10.3, 95% CI 3.2-32.5) and major CHD (HR 4.7, 95% CI 2.1-10.6) were significant predictors of mortality. Amongst adults with 22q11.2DS, major CHD (HR 3.0, 95% CI 1.2-7.5) remained a significant risk predictor of death when controlling for other factors including age at ascertainment. There were 31 (10.7%; 13 M) deaths of individuals with 22q11.2DS at median age 46.4 (range 18.1-68.6) years. The most common causes of death were sudden death, heart failure, and cancer.

Conclusions: Individuals with 22q11.2DS who survive childhood have diminished life expectancy.

Premature mortality is attributable in the main to the 22q11.2 deletion, with major CHD as an additional significant contributor. Median age at death was nearly 5 years older than when examined ~10 years ago in a smaller cohort. A substantial minority of patients outlive both parents. Post mortem studies and further large, longitudinal studies will be critical to help understand the underlying mechanisms involved in the premature death of those with 22q11.2DS, and the potential modifying effects of anticipatory care.