

Survival Profile for Down Syndrome

Down syndrome is the most common form of inherited intellectual disability. In addition, it is associated with growth deficiency, hypotonia, characteristic craniofacial appearance and developmental anomalies involving the heart and other organ systems. Survival of these patients has changed dramatically over the last several decades primarily because of surgical intervention for cardiac defects. For example, life expectancy increased from 12 years in England in 1949 to recent estimates of over 50 years in western countries. These estimates are based on cross-sectional data because there is little longitudinal information available. Moreover, it is known that adults with Down syndrome are predisposed to a number of disorders including obesity, hypothyroidism, epilepsy, dementia, and Alzheimer's disease; however the impact of these disorders on survival is unknown.

To define the survival profile for those with Down syndrome, Glasson and colleagues assessed survival in 1,332 patients (45% female) born between 1902 and 2000, mostly in Australia. Most patients had had standardized intelligence testing. Death had occurred in 20%. Kaplan-Meier survival probabilities were calculated separately for sex, level of intellectual disability and decade of birth.

The analysis showed that the overall life expectancy for patients with Down syndrome approaches that of the general population in Australia. Seventy-five percent of cases had survived to 50.0 years, 50% to 58.6 years

and 25% to 62.9 years of age. The mean life expectancy for males was greater than females by 3.3 years with the median survival probabilities of 61.1 for males and 57.8 for females. The difference was attributed to a higher incidence of heart defects in females. When examined by decade born, each successive birth group showed increased survival consistent with progressive improvement in medical care. No association was found between level of intellectual disability and survival, which was surprising to the authors because an association had apparently been found in an earlier study.

Approximately 25% of all Down syndrome deaths occurred between the ages of 58 and 63 years. No clear explanation for this was found nor is there any certainty that the trend will continue in patients born more recently. The authors raise the possibility that it could reflect mortality associated with the above mentioned chronic diseases to which adults with Down syndrome are predisposed.

Glasson EJ et al. *Clin Genet* 2002;62:390-393.

Editor's comment: *The information contained in this paper should be very useful to physicians, genetic counselors and others who deal with families concerned about long term survival in Down syndrome.*

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Mutagenesis Does Not Explain Paternal Age Effect in Achondroplasia

Achondroplasia is the prototype of chondrodysplasia in humans. Its major features include short limb dwarfism and a large head with mid-facial hypoplasia. Achondroplasia arises most often as a sporadic event to normal parents and there is a pronounced paternal age effect. It results from activating mutations of Fibroblast Growth Factor Receptor 3 (*FGFR3*), which encodes the transmembrane receptor. *FGFR3* mutations have several unique features including that they arise *de novo* almost exclusively during spermatogenesis and that almost all involve the same G-to-A transition at base pair 1138 (G1138A) of the gene resulting in a glycine to arginine substitution in the transmembrane domain of the receptor. Taken together, these observations have led to the commonly accepted views that *FGFR3* is exceptionally mutagenic and that the paternal age effect reflects replication errors that occur during spermatogenesis. Spermatogenesis continues throughout life and presents many more opportunities for erroneous copying of DNA than does oogenesis in which replication ceases before birth.

Although this explanation makes good sense, there is now evidence that *it is incorrect*.

To test if increased mutagenesis accounted for the paternal age effect in achondroplasia, Tiemann-Boege et al determined the frequency of the common G1138A *FGFR3* mutation in sperm from 118 healthy men ranging in age from 18 to 80 years. They expected to detect a progressive increase in sperm mutation frequency comparable to the increase in number of achondroplasia births to older fathers. However, to their surprise, using a carefully controlled polymerase chain reaction assay, they found only a small increase in the G1138A mutation which by itself could not account for the paternal age effect.

More specifically, they observed that the mutation rate for G1138A averaged about 1 per 11,000 haploid genomes over all ages. Broken down by age, the mutation frequency changed little between the ages of 18 - 40 and 55 - 80 years. It increased about 2-fold between the two age groups, but this was nowhere near