

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.*

William Horton, MD

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

the increased frequency of achondroplasia births in older fathers.

The authors addressed in considerable depth various possible explanations for their findings. Several involve experimental biases or artifacts. For example, fathers of children with sporadic achondroplasia may constitute a subgroup of men with distinct mutation properties that differ from the sperm donor population. There may be unappreciated ascertainment biases with regard to the makeup of donor population or in previous studies. Despite extensive controls, there could have been underreporting of mutations in the PCR assay. These studies may have led to overestimating the magnitude of the paternal age effect.

Two of the possibilities deserve special attention. The first is that there may be an age-dependent increase in germ-line permutations at the G1138A site that are neither converted to a full mutation or repaired before fertilization. One candidate lesion would be an unrepaired G/T mismatch resulting from deamination of 5-methyl cytosine. The cytosine at position 1138 is known to be highly methylated in sperm and therefore a candidate for such a premutation, which might go undetected under conditions of PCR.

Another possibility is that the G1138A mutation gives a selective advantage to sperm that carry it. The authors acknowledge the highly speculative nature of this possibility, but point out that FGFR3 is expressed and presumably active in mature sperm cells. They also caution that invoking this possibility must include an explanation of how a potential selective advantage would increase with age.

Tiemann-Boege et al. *PNAS* 99 2002;14952-57.

Hurst LD, Ellegren H. *Nature* 2002;420:365-66.

Editor's comment: *Many observations over the last several years have led to the dogma that FGFR3, especially the site where achondroplasia mutations arise, is extraordinarily mutable during spermatogenesis and that this mutability increases dramatically with age. The idea that DNA is prone to replication or mitotic errors, that there are many more opportunities for such errors to occur during spermatogenesis compared to oogenesis, and these can somehow accumulate with age has been conceptually appealing and is easy to explain during counseling. However, the results reported here cast serious doubt on its validity. Assuming they hold up, which seems highly likely given the considerable lengths to which the authors went to control their experiments and validate their results, the dogma will need to change.*

The notion of genetic premutation in achondroplasia is not new. It was proposed by John Opitz and others long before mutations of FGFR3 were discovered. It never gained much momentum, probably because it lacked experimental data with regard to a specific locus or mutation; however, the paper by Tiemann-Boege et al may add new life to this concept.

The possibility that sperm which harbor activating mutations of FGFR3 have a selective advantage for motility, fertilization or the like, is intriguing. Of note is that activating FGFR3 mutations found in the achondroplasia family of disorders have been detected in several types of cancer, including multiple myeloma and bladder, breast and colon carcinoma. The mechanisms through which the mutations contribute to neoplasia are not well understood. However, they may well give the cancer cells a competitive advantage over the normal cells.

William Horton, MD

Is Insulin-Like Growth Factor-1 Monitoring Useful in Assessing the Response to Growth Hormone of Growth Hormone-Deficient Children?

In order to assess the relationship between insulin-like growth factor-1 (IGF-1) and the growth hormone (GH) dose utilized to treat GH-deficient children, the IGF-1 response was compared with the changes noticed in height-standard deviation scores (H-SDS) and height velocity during treatment.

The study was carried out in 24 prepubertal GH-deficient patients with a mean age of 10.5 ± 1.8 years and a mean bone age of 8.4 ± 2.1 years. H-SDS for chronological age and bone age before therapy were -2.6 ± 0.8 and -1.2 ± 0.8 , whereas height velocity was -1.1 ± 1.5 cm. Serum IGF-1 and insulin-like-growth factor binding protein-3 (IGFBP-3) levels were measured before, after 6 months and 12 months of GH treatment,

and correlated with the GH dose. IGF-1 increased significantly during the first six months of therapy, but did not increase any further at twelve months, despite the use of higher GH dosages (0.14 vs. 0.1 IU/kg/day), whereas IGFBP-3 increased at both 6 and 12 months. There was no correlation between GH dose and IGF-1 and IGFBP-3 levels. Height velocity as well as height for chronological age and bone age were significantly greater after one year of treatment with GH. The authors concluded that the increment in IGF-1 during therapy did not correlate with the interval height increase and was found to be less useful than height increments in adjusting the GH dose needed to treat prepubertal GH-deficient children.