Genetic and Clinical Correlations of Xp21 Muscular Dystrophy

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Summary: We have investigated over 100 patients with Xp21 muscular dystrophy, drawing together the results of detailed clinical, genetic and dystrophin investigations. A spectrum of disease severity was confirmed, with the most homogeneous clinical groups being at either end of the spectrum, represented by the typical Duchenne and Becker phenotypes. The groups in between showed clinical heterogeneity, and variability in the genetic and dystrophin results. While an out-of-frame deletion in association with undetectable dystrophin is most likely to predict the most severe phenotype, and increasing abundance of dystrophin is associated generally with a milder clinical course, no value of dystrophin abundance reliably predicts a particular phenotype. However, deletions of the dystrophin gene involving exons 45–47 and 45–48 especially do seem to be consistently associated with the mildest Becker phenotype. Additional factors must play a role in determining the exact clinical course.

The advances in identifying the gene and protein responsible for Duchenne and Becker muscular dystrophy (DMD and BMD) have provided the potential for precise definition of the diseases at the molecular level. The relationship between the genetic defect, protein abnormality and clinical phenotype can now be explored, leading to the identification of possibly useful prognostic indicators, as well as an enhanced understanding of the function of the gene and its product. We are performing a population-based study of the Xp21 muscular dystrophies aiming to use the information available from the new techniques to reassess the spectrum of the X-linked muscular dystrophies in our area.

The essential question to be addressed in considering the genetic and clinical correlations of these diseases is how mutations in the same gene (Worton and Thompson 1988) give rise to such variation in phenotype. DMD is at the most severe end of the spectrum and has the highest birth incidence. Its rapidly progressive clinical course, with patients losing independent mobility classically before the age of 12 years and dying by their early twenties, is well-known and well-described (Emery 1988). The second category, of intermediate or outlier dystrophy (Brooke et al 1983), is less well defined. It comprises a group of boys who do consistently better
than classical Duchenne patients. They are quoted usually as becoming wheelchair-bound between the ages of 12 and 16 years and their survival is also longer. BMD covers a wide range of severity, classically distinguished only by the fact that patients are not wheelchair-bound by the age of 16 years (Emery and Skinner 1976). Finally, within the separate category of females affected with Xp21 dystrophy—the manifesting carriers—there exists a similar spectrum from severe disease indistinguishable from boys with Duchenne to very mild weakness late in adult life (Moser and Emery 1974).

The unifying feature between all of these conditions is the pattern and progression of muscle involvement, which is relatively specific and predictable (Walton and Gardner-Medwin 1988). Complications such as cardiomyopathy, scoliosis and respiratory failure are almost uniform among Duchenne boys, but are seen in the other groups too. Intellectual impairment may be seen across the board, but is most frequently reported in DMD.

Becker, in his original papers on the milder X-linked form of muscular dystrophy, was sufficiently impressed by its overall resemblance to DMD to suggest even then that the two disorders might be allelic (Becker and Kiener 1955; Becker 1962). Now that this is confirmed (Kingston et al 1984) and as other disorders previously thought to be unrelated are proved to be BMD (Sunohara et al 1990; Gospe et al 1989), there is an understandable tendency to include all the phenotypes under an ‘umbrella’ title such as the Xp21 dystrophies, or the dystrophin-related dystrophies. This conveys correctly the spectrum of disease seen but as a diagnosis to discuss with a patient it lacks any prognostic value and thus would be highly unsatisfactory. We have used clinical assessments that subdivide these disorders yet again in order to attempt to understand their variability.

**CLINICAL ASSESSMENT**

To enhance the definition of our clinical data, we have collected detailed information from over 100 patients with Xp21 muscular dystrophy, in whom the genetic and dystrophin abnormalities are known, whose ages range from 6 months to 88 years.

Patients up to 20 years in our region with muscle disease are almost without exception patients of the paediatric muscle clinic in Newcastle upon Tyne. In 1988, there were 76 patients with DMD and intermediate dystrophy in the region, giving a prevalence of 2.48/100,000 population (Gardner-Medwin and Sharples 1989). Details are available for all of these patients of their speeds, at successive clinic visits, of traversing a set distance, climbing a set of steps and rising from the floor. Accurate documentation is available for the age of losing independent mobility, the length of time calipers were used, and the age of becoming completely wheelchair dependent. From this time regular measurements of forced vital capacity are made. Formal IQ results (Weschler 1974) are available for many patients. Thus comparison is possible between patients on all of these parameters. We constructed a histogram of the age at which this group of patients became wheelchair-bound (or entirely reliant on calipers). This ranged from 7 years 3 months to 14 years 8 months, with a mean of 9.02 years. From the histogram of the ages at losing independent mobility (Figure 1), we designated four subgroups: those wheelchair-bound below the age of 9 (group