NEONATAL MARFAN SYNDROME AND RESPIRATORY DISEASE

J. C. S. Dean1, D. J. Lloyd2, G. F. Cole2
1 Department of Medical Genetics; 2 Neonatal Unit; 3 Department of Medical Paediatrics, Aberdeen Royal Hospitals NHS Trust, Foresterhill, Aberdeen, Scotland, UK

Neonatal Marfan syndrome is a severe form of the disease usually associated with cardiac valvular regurgitation and aortic dilatation resulting in death in the first year of life. In addition to the usual skeletal and ocular features, flexion contractures, crumpled ears, redundant skin and a progeroid facial appearance are not uncommon. The disease may be associated with mutations in exons 23–32 of the fibrillin gene and with deficient decorin production.

We describe a patient with neonatal Marfan syndrome presenting as a newborn with anchondactyly, joint laxity, abdominal wall laxity, sunken eyes giving a progeroid facial appearance and blue sclerae. Iridodonesis was noted at 2 months of age. There were initial feeding difficulties and later concerns about poor muscle tone. At 6 months of age, she developed a respiratory infection complicated by recurrent pneumothorax. Emphysematous bullae were noted on chest X-ray. The aortic root was dilated. She died from respiratory failure 7 days from the onset of symptoms.

Aim of the case report: The Marfan syndrome has a wide variability in expression. Symptoms in adults and older children are well known but may differ from the neonatal Marfan syndrome in which serious problems lead to early disability and death, especially cardiac valve insufficiency and pulmonary emphysema.

A full-term newborn girl of a mother with classical Marfan syndrome and a father with skeletal findings of Marfan syndrome, was admitted one day after birth because of a large diaphragmatic hernia. She was noted to have a large diaphragmatic hernia and emphysema of the lungs. She was reoperated on at 1 month of age due to recurrent pneumothorax. She was discharged home at 2 months of age and was doing well at 6 months of age.

Grants. The National Marfan Foundation, US

49 P

IN VITRO EXPRESSION OF THE NEONATAL MARFAN MUTATIONS

T. Rantamäki1, L. Karttunen1, C. M. Kielty2, L. Peltonen1
1 Department of Human Molecular Genetics, National Public Health Institute, Helsinki, Finland; 2 School of Biological Sciences, University of Manchester, UK

Neonatal Marfan syndrome (nMFS) represents the most severe, neonatally lethal form of different Marfan syndrome (MFS) phenotypes. Several mutations in nMFS have been detected in the fibrillin-1 gene (FBN1). These mutations appear to have clustered in a distinct region of FBN1, exons 24–32. These exons code for a part of the longest stretch of consecutive EGF-like (epidermal growth factor like) motifs in fibrillin polypeptide.

We have constructed a FBN1 minigene to study the consequences of different nMFS mutations by in vitro expression. This construct contains exons 24–32 of FBN1 cDNA inserted into a SV-Poly expression vector together with a signal sequence derived from a lysosomal enzyme, aspartylglucosaminidase. Several nMFS as well as a couple of classical MFS mutations were introduced into this minigene using an in vitro mutagenesis kit. For transient transfection COS-1 cells are transfected with different minigenes, then pulse-labeled, and medium, cells and ECM are harvested at different time-points. Polypeptides are immunoprecipitated with a polyclonal antibody and then analyzed on SDS-PAGE and fluorography. So far, all the minigenes have been shown to be expressed and the polypeptides secreted into the medium. Some variation in the processing of different polypeptides is seen. In some cases the polypeptides have also been detected in ECM. We have also set up a stable cell line in CHO cells that expresses the wild type minigene. By rotary shadowing electron microscopy we could demonstrate that these cells produce fibrillin 'mini-fibers' that are seen as short linear fibrillar structures in cell layers.

Grants. The National Marfan Foundation, US

50 P

NEONATAL MARFAN SYNDROME: A CASE REPORT

S. de Knecht1, J. L. Yntema2, B. Hamel3, J. R. M. Cruysberg4
1 Paediatric Heart Center and 2 Paediatric Pulmonology, Dept. of Paediatrics; 3 Dept. of Human Genetics; 4 Dept. of Ophthalmology, University of Nijmegen, The Netherlands

Aim of the case report: The Marfan syndrome has a wide variability in expression. Symptoms in adults and older children are well known but may differ from the neonatal Marfan syndrome in which serious problems lead to early disability and death, especially cardiac valve insufficiency and pulmonary emphysema.

A full-term newborn girl of a mother with classical Marfan syndrome and a father with skeletal findings of Marfan syndrome, was admitted one day after birth because of a large diaphragmatic hernia which was reoperated on at 1 month of age due to recurrent pneumothorax. She was discharged home at 2 months of age and was doing well at 6 months of age.

Grants. The National Marfan Foundation, US
homology among them. MFAP1 is a 439 amino acid, highly acidic and as a group they have been designated microfibril associ­
TGF-p-binding proteins (LTBPs), which share structural domains.

q2L MFAP2, previously designated MAGP, is a 183 amino acid protein whose human gene is located near the FBN1 locus, 15ql5-

Microfibrils having a diameter of 10-12 nm are widely distributed in many tissues of the body, often but not always in association with elastin. Characterization of the microfibrils remains incom­
plete, but recent findings have suggested that the proteins compos­
ing the microfibrils can be grouped into two classes: (1) large ones > 150 kDa and (2) small ones < 50 kDa. The large class contains two closely related gene families, the fibrillins (FBNs) and latent TGF-β-binding proteins (LTBPs), which share structural domains, including epidermal growth factor and 8-cysteine motifs. Presently, > 150 kDa and (2) small ones < 50 kDa. The large class contains two closely related gene families, the fibrillins (FBNs) and latent TGF-β-binding proteins (LTBPs), which share structural domains, including epidermal growth factor and 8-cysteine motifs. Presently, two distinct FBNs and three LTBPs are known. Phylogenetic analy­
sis suggests that these two gene families have evolved from a com­
tion ancestral gene. The small class of proteins is more heteroge­
neous and as a group they have been designated microfibril associ­
ated proteins (MFAPs). Sequence analysis has not revealed any homology among them. MFAP1 is a 439 amino acid, highly acidic protein whose human gene is located near the FBN1 locus, 15q15-
q21. MFAP2, previously designated MAGP, is a 183 amino acid protein with a wide tissue distribution, whose human gene locus is 1p36.1-p35. MFAP3 is a 362 amino acid protein whose human gene is near the FBN2 locus, 5q21-q31. It is not known whether the linkage of these two MFAPs near FBN loci has any functional sig­
nificance or is merely coincidental. Several other glycoproteins including emilin and a 36 kDa protein have been localized to the microfibrils. While it is likely that the FBNs provide the basic scaffolding of the microfibrils, the function of the other proteins is unclear. They may stabilize the microfibril structure, interact with other matrix components as has been demonstrated for MFAP2 and elastin and thereby act as nucleation sites in fiber formation, or serve as cytokine storage depots as has been suggested for the LTBPs.

Grants. NIH grants AR20553 & AR41474.

52

FBN2 MUTATIONS IN PATIENTS WITH CONGENITAL CONTRACTURAL ARACHNODACTYLY AND RELATED PHENOTYPES

D. M. Mjilewiez1, E. S. Park1, C. M. Aults2, R. C. M. Hennelkan3, H. Zhang1, F. Ramirez2, E. A. Putnam1

Univ. of Texas Houston Medial School; 2Univ. of Amsterdam; 3Mount Sinai School of Medicine New York New York, USA

Congenital contractual arachnodactyly (CCA) or Beals syndrome is an autosomal dominant condition phenotypically related to the Marfan syndrome (MFS). We have recently established that CCA results from mutations in FBN2, a gene that encodes fibrillin-2 found in 10-12 nm microfibrils. The previously characterized mu­
tations in unrelated patients were C1252Y in exon 29 and C1433S in exon 33. We have subsequently characterized novel FBN2 mu­
tations in three unrelated CCA patients. We identified an exon 29 splicing error in two affected siblings with unaffected parents. The splicing defect is due to an A to G transition at the −15 position in the 3′ splice site of intron 28. The affected siblings were heterozy­
gous for the mutation. Analysis of the parents' DNA revealed that the father was a mosaic with the mutation present in his hair bulb and buccal cells, but not in white blood cells; presumably, the father was also a germline mosaic. Another unrelated CCA patient was heterozygous for a mutation resulting in 11092T in exon 25. This mutation is not predicted to alter the secondary structure of the EGF-like domain encoded by exon 25, but does in­
troduce a novel glycosylation site into the domain, suggesting a unique pathogenesis due to this particular mutation. A third puta­
tive mutation in exon 24 (G1056D) was identified in a CCA fam­
ily. We have also identified a family with features of CCA, as well as a characteristic facies with hypertelorism, a broad forehead and flat facial profile. The phenotype segregates with FBN2 (LOD score > 3). These results indicate that FBN2 mutations producing CCA are private. The predicted effects of many of the FBN2 mu­
tations on fibrillin-2 are similar to those of FBN1 mutations. All the currently characterized FBN2 mutations occur in a region of the gene equivalent to the location of FBN1 mutations that produce the severe, neonatal MFS phenotype. Finally, our data suggest that FBN2 mutations result in conditions related to CCA.

53

ABERRANT SPLICING OF FIBRILLIN-2 IN A FAMILY WITH CONGENITAL CONTRACTURAL ARACHNODACTYLY

C. L. Maslen1, D. Babcock1, M. Raghunath2, B. Steinmann1

1Oregon Health Sciences University, Portland, Oregon, USA; 2University of Münster, D-48149 Münster, Germany; 3University Children’s Hospital, CH-8032 Zürich, Switzerland

Congenital Contractural Arachnodactyly (CCA) is an autosomal dominant disorder that is phenotypically similar to, but genetically distinct from Marfan syndrome. Genetic linkage analysis implic­
ted the fibrillin-2 gene (FBN2) as the CCA locus. Mutation analysis of single CCA patients indicate that defects in FBN2 may be responsible for that disorder. However, co-segregation of a mu­
tant allele with the disease phenotype has not been established. We have investigated the primary cause of CCA in a large, well char­
acterized kindred with four generations comprising 18 affected in­
dividuals. Previous studies showed linkage of the CCA phenotype