Supplementary Note

Clinical descriptions of families

(i) Family 1. The male proband (1.III-1) from European descent was referred at age 14 because of scoliosis. He had normal development. Physical evaluation revealed bifid uvula, mild mid-facial hypoplasia with broad nasal bridge, mild pectus excavatum, and joint hyperextensibility. Family history revealed that the maternal grandfather (1.I-2) underwent surgery at age 24 for patent ductus arteriosus and experienced a fatal aortic dissection at age 29. An echocardiogram on the proband showed a dilated aortic root (4.26 cm; Z-score 6.52) and a bicuspid aortic valve. Ophthalmologic evaluation was normal. Karyotyping revealed normal male chromosomes and FISH testing for 22q11 deletion was negative. A subsequent echocardiogram after initiation of beta-blockade showed slowly progressive aortic root enlargement (4.58 cm; Z-score 5.22), mild mitral valve prolapse, and a normal pulmonary artery (2.85 cm; Z-score 0.94). Evaluation of the proband’s mother (1.II-1) revealed a history of scoliosis and spondylolisthesis surgeries. Physical exam was significant for bilateral eye proptosis, hypertelorism, and a wide but not bifid uvula. There was no joint hypermobility or pectus deformity. Echocardiography showed an aortic root of 4.0 cm and mild mitral valve prolapse. Computerized tomography (CT) and magnetic resonance imaging (MRI) scans showed tortuosity of the aorta and branch vessels without evidence of focal aneurysm. She died at age 37 from acute aortic root dissection one week after repeat imaging studies showed a stable aortic dimension of 4.0 cm. This fatal incident prompted a valve-sparing aortic root replacement in the proband. None of the affected family members showed dolichostenomelia, arachnodactyly, myopia, or lens dislocation.
(ii) **Family 2.** The female proband (2.II-1) from European descent has shown normal growth and development. At 1 month of age an echocardiogram revealed an aortic root of 2.1 cm with mild aortic regurgitation. A subsequent echocardiogram at 8 months of age showed an aortic root of 3.1 cm (Z-score 11.2), a dilated pulmonary artery (1.97 cm; Z-score 5.6) and a patent ductus arteriosus. Physical exam revealed bilateral arachnodactyly, fifth finger camptodactyly, a bifid uvula and translucent skin. Her family history was negative for aortic aneurysm or sudden death. The patient underwent valve-sparing aortic root replacement at the age of 16 months. At that time her aortic root had increased to 3.7 cm (Z-score 15) despite beta-blocker treatment. An MRI evaluation confirmed the presence of tortuous vessels. Eye exam was normal. There was no dolichostenomelia, pectus deformity, or scoliosis. Family history was negative for relevant medical problems and both parents had normal echocardiograms and eye examinations.

(iii) **Family 3.** The female African American proband (3.II-1) was diagnosed with a cleft soft palate and lip pits at birth. She had normal motor and cognitive development. At age 6 she presented with an episode of dysphagia. Physical exam was significant for hypertelorism and malar hypoplasia. Mouth inspection revealed a repaired cleft soft palate and a bifid uvula. She also presented with arachnodactyly and fifth finger camptodactyly. The evaluation for dysphagia revealed severe aortic root dilatation without dissection (3.74 cm; Z-score 8.06), the presence of a dilated main pulmonary artery (2.56 cm; Z-score 4.75) and mild mitral valve prolapse. A CT scan revealed a tortuous thoracic aorta that made a
full hairpin turn posterior to the heart and marked tortuosity of aortic branch vessels. Eye examination was normal. There was no dolichostenomelia, pectus deformity, or scoliosis. Family history was negative for relevant medical problems and both parents had normal echocardiograms.

**Family 4.** The male proband (4.II-1) from European descent showed post-axial polydactyly of all extremities except the left foot, bilateral talipes equinovarus and facial features characterized by alternating exotropia, hypertelorism, proptosis, cleft soft palate and bifid uvula, retrognathia, bilateral coronal synostosis, and velvety skin. The neonatal period was complicated by atrioventricular (AV) nodal reentry tachycardia and multiple cardiovascular anomalies including atrial septal defect, dilated ascending aorta, dilated pulmonary artery, tortuous descending aorta, patent and aneurysmal ductus arteriosus, and bicuspid aortic and pulmonary valves. Over time, he developed aneurysms of the renal, superior mesenteric, and left subclavian arteries. Family history was negative for cardiovascular disease or craniofacial anomalies. Imaging of the brain showed Chiari I malformation with hydrocephalus and tortuosity of intracranial vessels. He was also diagnosed with dural ectasia. The patient died at age 9 due to presumed abdominal aortic dissection.

**Family 5.** The male Asian proband (5.II-1) was diagnosed with cryptorchidism and inguinal hernia in early childhood. The clinical course was characterized by kyphoscoliosis, craniosynostosis of metopic and anterior sagittal sutures, hydrocephalus and Arnold-Chiari type I malformation. He developed aortic root and pulmonary artery dilation. His last physical exam at 2 years and 7
months of age was significant for proptosis, hypertelorism, pectus carinatum, dolichostenomelia, arachnodactyly, joint hypermobility and thin skin. The aortic root measured 2.9 cm (Z-score 7.3). The patient died at three years of age due to cerebral bleeding.

**(vi) Family 6.** The male proband (6.I-2) from European descent was diagnosed at the age of 31 years with severe aortic root dilatation (6.0 cm) on a routine echocardiogram and underwent surgical repair. Past medical history was significant for congenital clubfoot repair at the age of 8 years, scoliosis, and strabismus corrected with surgery at the age of 30 years. Clinical examination showed hypertelorism, bifid uvula, blue sclerae, malar hypoplasia, retrognathia, pectus excavatum, scoliosis, flat feet, and translucent skin. His youngest daughter (6.II.2) had a patent ductus arteriosus requiring surgery and progressive dilatation of the aortic root (2.6 cm; Z-score 4.4). Other findings included hypertelorism, malar hypoplasia, retrognathia, blue sclerae, pectus excavatum, flat feet, and translucent skin. His eldest daughter (6.II.1) had right-sided clubfoot requiring surgery. Echocardiogram showed a patent ductus arteriosus and aortic root dilatation (3.6 cm; Z-score 8.4). Other findings included blue sclerae, retrognathia, pectus carinatum deformity, and translucent skin. Radiographic studies of both children reveal generalized osteopenia, wormian bones, bowed long bones, and flattened vertebral bodies.

**(vii) Family 7.** The male Hispanic proband (7.II-1) showed significant aortic root enlargement that progressed rapidly despite medical therapy. He underwent
composite graft repair of the ascending aorta at 14 months of age. He was also diagnosed with pulmonary artery aneurysm. His physical exam showed hypertelorism, strabismus, arched palate with broad uvula, pectus carinatum, kyphoscoliosis, and joint laxity. Family history was negative for relevant medical problems and both parents had normal echocardiograms.

**(viii) Family 8.** The African-American male proband (8.II-1) was diagnosed at birth with craniosynostosis, bilateral clubfeet, camptodactyly, and cleft soft palate. Physical exam showed hypertelorism, retrognathia, finger contractures, arachnodactyly, adducted thumbs and camptodactyly of the toes. Chest X-ray demonstrated thirteen ribs bilaterally. Echocardiography revealed patent ductus arteriosus and an enlarged aortic root (2.51 cm; Z-score 8.0). Ophthalmologic exam showed cataracts and bilateral ptosis. CT-scan of the aorta confirmed marked tortuosity of the descending aorta. Family history was negative for relevant medical problems and both parents had normal echocardiograms.

**(ix) Family 9.** The male proband (9.II-1) from European descent was diagnosed with inguinal hernia and craniosynostosis of the sagittal suture in infancy. Craniosynostosis was surgically repaired at age 4. His physical exam was positive for hypertelorism, retrognathia, bifid uvula, scoliosis, chest deformity, arachnodactyly, camptodactyly, and joint hypermobility. He also developed severe dilatation of the aortic root during childhood. At age 4 his aortic root measured 3 cm (Z-score 7.2). The most recent MRI at age 10 showed arterial tortuosity and an aortic root dimension of 3.9 cm (Z-score 5.7). Eye exam was normal.
(x) Family 10. The male proband (10.II-1) from European descent was diagnosed with aortic root dilatation (3.40 cm; Z-score 6.9) at age 6 after an episode of unconsciousness. Other findings included hypertelorism, joint laxity, retrognathia, translucent skin, and mild scoliosis. He ultimately developed deafness that was attributed to vascular compression by tortuous and dilated cerebral vessels. He also had retinal bleeding in association with aneurysms of the retinal vessels. His aortic root measured 4.8 cm at age 24. His brother (10.II-2) showed marked dilatation and tortuosity of the cerebral vessels, patent ductus arteriosus, atrial septal defect, and dilated pulmonary artery. He underwent aortic root replacement at age 12 with a dimension of 5.2 cm. He demonstrated poor wound healing and has wide and atrophic scars. Other findings included hypertelorism, retrognathia, malar hypoplasia, translucent skin, joint laxity, and mild scoliosis. The father (10.I-2) died suddenly at age 27 years of acute aortic dissection. He had a history of retinal detachments. No further clinical information is available.