Two Patients with the Heterozygous R189H Mutation in ACTA2 and Complex Congenital Heart Defects expands the Cardiac Phenotype of Multisystemic Smooth Muscle Dysfunction Syndrome


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De novo heterozygous mutations changing R179 to histidine, leucine or cysteine in the ACTA2 gene are associated with Multisystemic Smooth Muscle Dysfunction Syndrome (MSMDS). Characteristic hallmarks of this condition, caused only by these specific ACTA2 mutations, are congenital mydriasis (mid-dilated, non-reactive pupils, figure 1), a large persistent ductus arteriosus (PDA), aortic aneurysms evolving during childhood, and cerebrovascular anomalies. We describe two patients, a 3-day-old newborn and a 26-year-old woman, with this unique mutation in association with a huge PDA and an aorto-pulmonary window. In addition, one showed a coarctation of the aortic arch and the other a complete interruption of the aortic arch type A; thereby expanding the spectrum of cardiac congenital heart defect of this syndrome. Each patient displayed a huge PDA and an extra-cardiovascular phenotype consistent with MSMDS. These observations exemplify that a functional alpha 2 smooth muscle actin is necessary for proper cardiovascular organ development, and demonstrate that a very exceptional congenital heart defect (aortopulmonary window) can be caused by a mutation in a gene encoding a contractile protein of vascular smooth muscle cells.

Figure 1: Digital images of the iris of patient 1 showing a persistent extensive pupillary membrane with multiple wisks. The iris stroma appears hypoplastic, the pupil being only partially dilated.