Versican/PG-M is a large chondroitin sulfate (CS) proteoglycan of the extracellular matrix, which contains a core protein of approximately 550 kDa and up to twenty three CS chains. Its core protein consists of two globular domains G1 and G3 at N- and C-termini, respectively, and two CS-attachment domains between them. The N-terminal G1 domain, composed of A, B and B' subdomains, binds to hyaluronan and link protein, and forms a stable complex termed proteoglycan aggregate. Versican/PG-M is transiently expressed in embryonic tissues including heart, aorta, dermis, nervous systems, and cartilage primordium, and may play important roles in adhesion, migration, proliferation, and differentiation of cells. In adult tissues such as heart, blood vessels, and brain, it is constitutively expressed and may serve as a structural macromolecule of the matrix. However, its function in vivo has not been fully understood yet. Here, we generated mice whose versican/PG-M lacks the A subdomain of G1 domain. Although the heterozygote mice (Csgp2+/−) were viable and fertile, exhibiting no obvious phenotypic abnormalities, the homozygotes (Csgp2−/−) were embryonic lethal and showed different levels of phenotype in heart, aorta, and dermis, and survived up to E16.5. At E9.5 (C57B1/6 background) and E16.5 (hybrid of C57Bl/6, 129Sv and Balb/c), all the homozygotes were alive as assessed by their heart-beat. They were small and their heart was dilated compared with wild type and heterozygote (Csgp2+−). The heart was dilated compared with wild type and heterozygote embryos. Histologically, all the atria and ventricles were dilated, the ventricular chambers appeared large, and heart wall was thinner and the cell density was lower than wild type. The outer cardiac membrane was directly attached to the heart wall, whereas some connective tissue and capillaries were present under the membrane in wild type. Mallory-azan staining revealed diminished deposition of collagen fibers in Csgp2−/− heart wall. Immunohistochemically, versican/PG-M was decreased in Csgp2−/− embryonic heart except for the endocardial cushion and valve, whereas hyaluronan was observed in whole heart. By immunostaining with smooth muscle a-actin, smooth muscle cells of Csgp2−/− heart and aorta appeared immature, with wild type Csgp2+/− skin showed loose dermis with less fibers and capillaries. Gap formation in the upper dermis was often observed. Whereas mature collagen fibers were horizontally aligned in the wild type dermis, those of Csgp2−/− dermis appeared immature and disorganized. Further analyses using embryonic fibroblasts of Csgp2−/− revealed impaired matrix formation, although they synthesized both collagens and versican/PG-M. Taken together, these results indicate that versican/PG-M requires the A subdomain of G1 for stable matrix deposition, and that it plays an essential role in cardiovascular and skin development, regulating smooth muscle cell differentiation and collagen fiber formation.