Glaucoma is the leading cause of blindness worldwide and the blindness is caused by the degeneration of retinal ganglion cells (RGCs). Although an elevated intraocular pressure (IOP) is widely accepted to be the major risk factor, many patients, especially Japanese, show normal IOP levels (i.e. normal-tension glaucoma, NTG). We have recently discovered a novel NTG model mouse in which astrocytes lack the gene encoding ATP-binding cassette transporter A1 (ABCA1). The NTG mice at a young age (3 months old) showed no RGC damages but showed significant damages of RGCs and visual impairment at middle-age (12 months old). We then investigated molecular mechanisms triggering NTG and focused on optic nerve head (ONH). Excavation of ONH is a common anatomical feature of both hypertensive glaucoma and NTG. We performed RNA-seq and found that a young ONH showed the largest number of gene expression changes. Immunohistochemical analysis showed that ONH astrocytes at a young age already showed reactive gliosis with some tissue remodeling at the periphery. A profile for astrocyte marker genes showed no specific shifts to the neurotoxic phenotype. Gene ontology analysis revealed that remodeling of the extracellular matrix (ECM) was the most relevant biological event in the young ONH. ECM such as collagen IV was highly expressed in the ONH astrocytes. Taken together, our data demonstrated that astrocytes become reactive in the ONH at a young age when RGCs showed no damages. The reactive astrocytes triggered ECM remodeling which would cause excavation of ONH and RGC damages.