PgmNr 545: Haploinsufficiency of PRR12 causes a congenital multiple-malformation neurodevelopmental syndrome with a wide phenotypic spectrum.

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De novo heterozygous truncating mutations in the proline rich 12 (PRR12) gene have been reported in three patients with global developmental delay, intellectual disability, eye and vision abnormalities and other features. Consistently, expression pattern of PRR12 supports its role in brain and eye development. However, the disease-association of PRR12 and the disease-causing mechanism have not been well established. In this report, we describe 15 additional unrelated individuals with neurodevelopmental issues who carry 14 rare and damaging variants in PRR12. These variants were found to be de novo in all cases where parental samples were available (n=13). All variants were apparently loss-of-function (7 frameshift, 5 nonsense, 1 splice site), except for one de novo missense variant. In addition, a 3.3 Mb deletion encompassing the entire PRR12 gene, which was a recombination product of a maternal balanced insertion, was identified in one patient. The phenotype varied among the 19 patients with defects in PRR12. The major clinical features were developmental delay (84%), eye and visual abnormalities (68%), cognitive impairment (63%), behavioral problems (58%), and growth retardation (53%). The congenital ophthalmic anomalies included coloboma of the iris, lens, retina and/or optic nerve, microphthalmia, anophthalmia, and cryptophthalmos. The less frequent features included abnormal outer ears (47%), congenital heart defects (37%) and tone abnormalities (37%). Notably, variations in eye anomalies were also observed in the two patients carrying the same p.Lys1092Argfs*131 variant; one patient had a unilateral iris, chorioretinal and optic nerve coloboma with ipsilateral microphthalmia; while the other one only presented with oblong optic nerves and bilateral ptosis. The common features in patients with PRR12 sequence variants, including iris coloboma and intellectual disability, were also observed in the patient with a large
deletion including \textit{PRR12}, supporting that haploinsufficiency of \textit{PRR12} is the disease-causing mechanism. In summary, our studies demonstrated that \textit{PRR12} haploinsufficiency leads to a multi-system neurodevelopmental syndrome with a wide clinical spectrum and variable phenotypic expressivity.