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PEX1 p.G844D +/+ NMRI mouse: a robust pre-clinical model for mild Zellweger spectrum disorder

Zellweger spectrum disorders (ZSD) form a clinical spectrum of diseases due to a peroxisome biogenesis disorder attributable to mutations in PEX genes. ZSD has an incidence of 1:50.000 live-births. Characteristically elevated levels of phytanic, pristanic, pipecolic, and very long-chain fatty acids, and abnormal bile acid intermediates are observed in the plasma of affected children. Clinical presentation ranges from liver failure and death in infancy to chronic liver disease, neurodevelopmental delay, deafness and blindness among those who survive beyond the first decade of life (mild ZSD). No routine treatment has been shown to arrest or reverse the natural history of this terrible disease. Yet, we previously demonstrated the benefit of liver transplantation or hepatocyte transplantation (HT) on biochemical and clinical outcome in 4 patients with mild ZSD. The aim of this study was to validate a mouse model homozygous for the PEX1 p.G844D hypomorphic mutation as a pre-clinical model for mild ZSD treatment evaluation. We started a colony using 6 PEX1 p.G844D +/- C57BL/6N mice from Jackson Laboratory; +/+ mice (ZSD) are sterile and die within one month. We backcrossed three times the mutation in a NMRI background to get larger litters and more robust homozygous mice. Mice growth and food intake were regularly quantified. We measured mice glycemia before and after a 6 hours fasting test. Mice livers collected at 2 months of age were weighted, fixed, paraffin embedded and stained with periodic-acid Schiff (PAS) ± diastase (as a proxy for glycogen content). ZSD mice exhibited (1) a severe growth retardation associated to an increased food intake/g body weight, (2) lower fed blood glucose levels and (3) a worse fasting resistance. PAS staining on liver sections was severely reduced in fed ZSD mice meaning a low glycogen content. This could be one explanation for their reduced fasting resistance. Scarce peroxisomal ghosts where shown in ZSD mice livers by immunofluorescence staining of the 70-kDa peroxisome membrane protein (PMP70). All the above mentioned classical ZSD metabolites were elevated in ZSD mice compared to their WT siblings. In conclusion, PEX1 p.G844D +/+ NMRI mice are a good and robust pre-clinical model recapitulating liver involvement and growth retardation of mild ZSD. We are currently evaluating HT as a potential therapeutic approach in this model.