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PANCREAS PATHOLOGY OF HUMAN *ARX*-NULL MUTATION: CONSIDERATION OF PANCREAS ENDOCRINE CELLS DIFFERENTIATION

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Aristaless-related homeobox gene (*ARX*) mutation leads to several neurological disorders including X-linked lissencephaly with abnormal genitalia (XLAG), West syndrome and Partington syndrome, with XLAG being the most severe form. Although some of the brain pathology of XLAG has already been described, the crucial extra-brain symptoms are severe growth retardation, transient hyperglycemia and intractable diarrhea. Since ARX expresses in the islets of Langerhans during the embryonic stage, these visceral phenotypes may be related to a loss of ARX function, which develops endocrine cells in the pancreas. We investigated the abnormal pancreatic development of XLAG patients with *ARX*-null mutation. We performed immunohistochemistry of XLAG pancreases, using the antibodies against glucagon, insulin, somatostatin, pancreatic polypeptide, ghrelin, Brn4, Nkx2.2, Mash1, Pdx1, amylase and pancreatic lipase. As the results, the glucagon- and pancreatic polypeptide-producing cells were found to be completely deficient in the islets of Langerhans. We also discovered marked interstitial fibrosis, small exocrine cells with loss of amylase-producing cells and an enlargement of the central lumen of the glandular acini. These pathological findings indicate that ARX contributes not only to endocrine development, but also to exocrine development of the human pancreas, and its deficiency may lead to the severe phenotypes of XLAG patients.

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FREE THYROXINE LEVELS IN THE INITIAL FOUR WEEKS OF LIFE IN EXTREME PRETERM INFANTS AFFECT BRAIN GROWTH

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Background: Low blood thyroid hormone concentrations in the first few weeks of life in extremely preterm infants may be linked with poor neurodevelopment. We conducted a multi-centre randomised controlled trial of thyroid hormone supplementation in babies under 28 weeks´ gestation.

Methods: 78 infants received levothyroxine supplementation and 75 received placebo. There was no difference in overall outcome. A post hoc subgroup analysis was undertaken. FreeT4 (FT4) plasma levels were measured longitudinally during the initial 4 weeks after birth. Two subgroups with average FT4 values in the lowest and highest quartiles were created for each trial arm. Univariate and multivariable analyses comparing the lowest and highest quartiles of FT4 within each trial arm were undertaken. Width of subarachnoid space at 36 weeks corrected for postmenstrual age was used as a measure of brain volume.

Results: Among placebo infants, univariate analyses showed that the lowest quartile of FT4 was associated with larger subarachnoid space (smaller brain volume) [95%CI=0.05(0.002,0.09)]. These infants also had higher mortality, lower gestational age and lower birth weight compared with those in the highest quartile. In the thyroxine group, there was no significant difference in subarachnoid space between the lower and higher quartiles.

Conclusion: Van Wassanaer (2002) reported that low FT4 levels in the first 4 weeks of birth were associated with worse neurodevelopmental