**THE MOLECULAR BASIS OF AUTOSOMAL DOMINANT HYPERCHOLESTEROLEMIA: ASSESSMENT IN A LARGE COHORT OF HYPERCHOLESTEROLEMIC CHILDREN**

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Background: Autosomal dominant hypercholesterolemia (ADH) is characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels and premature cardiovascular disease (CVD). Mutations in the genes encoding for the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin 9 (PCSK9) underlie ADH. Nevertheless, a proportion of individuals that exhibit the ADH phenotype do not carry mutations in any of these three genes. Estimates about the percentage of such cases amongst the ADH phenotype vary widely. We therefore investigated a large pediatric population with an unequivocal ADH phenotype to assess the molecular basis of hereditary hypercholesterolemia and define the percentage of individuals with unexplained dyslipidemia.

Methods and results: We enrolled individuals with LDL-C levels above the 95th percentile for age and gender and an autosomal dominant inheritance pattern of hypercholesterolemia from a large referred pediatric cohort of 1430 children. We excluded children with thyroid dysfunction, nephrotic syndrome, autoimmune disease, liver disease, primary biliary cirrhosis, obesity (BMI > 75th percentile for age and gender), as well as children referred via a cascade screening program and those from families with a known molecular diagnosis. Of the 269 children that remained after applying the exclusion criteria, 255 (95%) carried a functional mutation (LDLR 95%; APOB 5%). Conclusion: In the vast majority of children with an ADH phenotype, a causative mutation can be identified, strongly suggesting that most of the large effect genes underlying ADH are known to date.