ABSTRACT

In rare diseases, parallel studies of consanguineous and non-consanguineous populations facilitate elucidating not only genetic origin of individual conditions, but also their pathophysiology and disease mechanisms. The aim of the dissertation is to compare findings in three pediatric endocrine conditions – congenital hyperinsulinism, monogenic diabetes, and short stature – conducted in a unique cohort of children from a highly consanguineous region of Sulaimani, Kurdistan, Iraq (consanguinity rate 44%) with a non-consanguineous cohort from Prague, Czech Republic. With informed consent, DNA of all probands were primarily analyzed by NGS methods followed by variant selection and verification by a bioinformatic pipeline. In consanguineous individuals, the genetic cause of congenital hyperinsulinism was elucidated in 100%, monogenic diabetes in 74% and short stature in 65% of patients. Homozygous variants were the most prevalent, with the spectrum of causative genes and thus disease mechanisms differing considerably from non-consanguineous individuals. In studies of non-consanguineous patients with growth hormone deficiency and those born small for gestational age, the rate of positive findings were 29% and 42% respectively with largely prevailing monoallelic (dominant) genetic conditions. In addition, this research produced the first ever papers describing large cohorts of children from consanguineous populations with diabetes and short stature. A statistical significance of consanguinity and the occurrence of syndromic diabetes was described. This research highlights the fundamental contribution of studies in consanguineous families to novel insights into disease origin and mechanisms.