Editorial

New discoveries in the field of ID genomics

Intellectual disability (ID) is a neurodevelopmental disorder described as a substantial limitation in functioning that manifests before the age of 18 years. It is one of the main disabling conditions in the present days and is thought to affect 1–2% of the population. It is a highly heterogeneous disorder, with the majority of cases having a genetic aetiology. The possibilities of specific diagnosis and prevention are dependent on the search for genes associated with this disorder. It is still very difficult to clinically recognise a specific genetic defect in any given patient with ID because of overlapping phenotypic spectra and heterogeneous aetiology, and the genetic background in 60% of these cases remains unexplained.

New developments in genetics and other sciences predict that a very large number of genes underlie our intellectual and emotional abilities. This gives a conservative estimate that about 10% of all human genes are implicated in intellectual function. Since mutation of any one of these genes can give rise to intellectual disability, it can be concluded that they do not operate as a robust network, but rather as links in a chain, the failure of any one of which leads to intellectual disability. It may be extrapolated that between 2,000 and 5,000 genes are needed for intellectual and emotional function (Crabtree, 2013). This is supported by the finding that autosomal recessive mental retardation seems to be very heterogeneous, even within a genetically similar background, indicating that it is due to mutations in many genes (Inlow, Restifo, 2004; Kuss et al., 2011).

Establishing a genetic diagnosis in patients with ID is often complicated, mainly because of extensive genetic and phenotypic heterogeneity. The genetic basis of ID may range from large cytogenetic abnormalities to point mutations and epigenetic alterations. The rare monogenic (single gene or Mendelian) disorders are of substantial interest because identification of their genetic basis provides knowledge about disease mechanisms, the biological pathways affected, and potential therapeutic targets (Ng et al., 2010). The identification of Mendelian disease genes has long been the main focus of human genetics. Based on the estimated 10–12% fraction of X-linked genes associated with ID, the number of autosomal ID genes might be as high as 800–850 (Ropers, 2010), or even 2,000 (Schuurs-Hoeijmakers et al., 2011), many of which are sensitive to dosage imbalances. Nevertheless, for a long period it has been difficult to elucidate the aetiology of intellectual disability. Sequencing a large number of genes was time-consuming and expensive, and most efforts at disease-gene identification involved linkage analysis and positional cloning within large families with a large number of affected individuals. Research was limited by factors such as the availability of only a small number of cases/families, locus heterogeneity, or substantially reduced reproductive fitness, each of which lessens the power of traditional positional cloning strategies and often restricts the analysis to *a priori* identified candidate genes. The rate of the identification of novel genes associated with ID and other neurodevelopmental disorders has recently progressed rapidly due to advances in gene discovery by molecular cytogenetic and molecular genetic techniques (array-CGH and NGS, respectively). Theoretically, it is now possible to identify causal mutations in most individuals with ID regardless of frequency, heterogeneity, and inheritance (Topper et al., 2011). Thus every single patient with an unrecognised clinical condition becomes the main unit in identifying new candidate genes for Mendelian disorders.

During previous research projects that were aimed at improving diagnoses of ID in Lithuanian patients, scientists have collected a cohort of more than 200 patients (trios, i. e. father, mother and affected child) with syndromic and non-syndromic ID and several extended families with more than one affected individual. Molecular karyotyping revealed chromosomal alterations in patients, few of which were unique and contributed to the identification of novel candidate genes for ID.

During the project "Unique Genome Variants in Congenital Neurodevelopmental Disorders: Origin, Genomic Mechanisms, Functional and Clinical Consequences" (Research and Development, a Lithuanian–Swiss cooperative programme), scientists strived to identify the genetic reasons for ID and neurodevelopmental disorders using the most advanced techniques. The results of this investigation are presented in this issue (see Preikšaitienė et al. 'Identification of genetic causes of congenital neurodevelopmental disorders using genome-wide molecular technologies'). Scientists performed a high-resolution (1M) array CGH analysis in search of novel chromosomal alterations. They also sought to identify candidate genes of autosomal recessive, dominant and X-linked forms of ID by performing whole-exome sequencing in members of families with two affected sibs and a subset of trios. The gene expression analysis and the studies of transgenic animal models within this project help to confirm the selected genes as ID genes and expand knowledge about their expression patterns, as well as the functions and interactions of the encoded proteins. The results of this study show the advantages of using different genome-wide technologies for seeking one aim: the identification of the genetic consequences of ID. The research demonstrated that molecular cytogenetic abnormalities might play an important role in the identification of ID genes. The introduction of the array-CGH technique provided a unique possibility to identify novel microdeletion/microduplication syndromes, as well as to expand phenotypes and to elucidate the genomic aetiology of previously well-known conditions (Ciuladaite et al., 2014; Preiksaitiene et al., 2015). Increasing the resolution of array platforms further accelerated the pace of discovery of genes that are implicated in the manifestation of both contiguous genes and monogenic conditions. Exome strategies are successful and identify new Mendelian disease genes in approximately 60% of projects. Improvements in bioinformatics and in sequencing technology will likely increase the success rate even further. Exome sequencing is likely to become the most commonly used tool for Mendelian disease gene identification for the coming years.

The project revealed the identification of single gene disorders that cause non-syndromic and syndromic ID and revealed the expansion of scientific knowledge and molecular diagnostic capability, shedding light on the genes linked with newly identified syndromes.

Vaidutis KUČINSKAS, Prof., PhD, Dr. Habil.