Abstract

Neurofibromatosis type 1 (NF1, MIM 162200) is an autosomal dominant disorder affecting about 1 of 3000 live births, involving many cell types and organs, and associated with an increased risk of malignancy, predominantly of the central and peripheral nervous system. Tumour development is caused by inactivation of the *NF1* tumour suppressor gene and subsequent cell cycle deregulation. Mutational analysis of *NF1* is a challenge due to the presence of pseudogenes, large size of the gene, lack of mutational hotspots, and occurrence of a very diverse spectrum of mutations. There is no clear-cut genotype-phenotype correlation allowing accurate prediction of severity of the disorder. Only two mutations have been associated with a particular NF1 phenotype. This PhD thesis is composed of six publications dealing with NF1. Publications 1 and 6 are focused on *NF1* mutation analysis in 67 patients from the Czech Republic. Genotypes and spectra of causal mutations are presented together with phenotypes of the patients and comparison of efficiency of various methods. Sporadic or familial cases with known germline mutation were distinguished by mutational analysis of other family members. This led to a hypothesis that the incidence of sporadic cases could had been overestimated in the past because of overlooked individuals manifesting a milder phenotype within families harbouring a causal NF1 mutation (publication 4). Out of 51 causal mutations 33 were novel and no genotype-phenotype association could be observed. Patients with somatic mosaicism did not show any significant difference as to the NF1 symptoms compared to other NF1 patients. Publications 2 and 5 describe two unusual phenotypes related to NF1. A female patient with mid-aortic syndrome was described in detail in publication 2. Two other case reports presented in publication 5 described idiopathic aqueductal stenosis associated with delayed speech development, Severe speech delay could therefore serve as an indicator of stenosis of the distal aqueduct resulting in hydrocephalus. Publication 3 deals with an unusual mechanism of developing NF1, where mitotic instability of the ring chromosome 17 led to mosaicism for chromosome 17 monosomy and manifestation of the disease. The influence of advanced paternal age on increased risk of new germline mutations in sporadic NF1 patients is studied in publication 4. The analysis of parental age at birth of 103 probands showed that the average age of the parents was significantly increased compared to the general population. A similar trend was also confirmed in publication 6, which was primarily focused on the elaboration and optimization of a diagnostic algorithm for the mutational analysis of the *NF1* gene. The most effective schedule involved RNA-based mutational analysis complemented by the MLPA assay.