Neurofibromatosis Type 1: From Gene to Population and Cancer

Elina Uusitalo
Institute of Biomedicine, University of Turku, Turku, Finland. E-mail: epjoki@utu.fi.

Elina Uusitalo, MSci, University of Turku and Turku University Hospital, Turku, Finland, defended her PhD thesis on March 23rd, 2018. The opponent was Professor Professor Eric Legius, from Department of Human Genetics, KU Leuven, Belgium and custos was Professor Veli-Matti Kähäri. The thesis was supervised by Dr. Sirkku Peltonen and Professor Juha Peltonen. The thesis can be found at: http://urn.fi/URN:ISBN:978-951-29-7156-5.

Neurofibromatosis type 1 (NF1) is an autosomal dominant syndrome caused by mutations in the large and complex NF1 tumor suppressor gene on chromosome 17. NF1 is the most frequent hereditary tumor predisposition syndrome. The diagnosis of NF1 is usually based on clinical findings, such as tumors of the peripheral nervous system called neurofibromas and hyperpigmentary abnormalities such as café-au-lait pigment spots. This thesis investigated the molecular diagnostics, epidemiology, and cancer biology associated with the NF1 cancer syndrome.

In this thesis, a new method for NF1 molecular diagnostics exploiting nextgeneration sequencing was developed. This is important, because mutation analysis is currently not available for every patient, and in the majority of the patients, the diagnosis is still merely based on clinical manifestations. A national NF1 cohort of 1,404 patients was used in this thesis, and a retrospective register-based total population study was carried out to evaluate the epidemiology and cancer incidence of NF1 in Finland. The results revealed that NF1 incidence is higher than previously accepted. The results with a birth incidence of 1/2,000 challenge the generally accepted NF1 incidence of ~1/3,000. The NF1 cancer incidence was studied with data from the Finnish Cancer Registry. A five-fold increase in cancer incidence was observed, which is the highest cancer incidence reported so far. In addition, cancers in the NF1 patients have a worse prognosis than the corresponding cancers in the general population. In NF1 patients the risk for breast cancer is also elevated, particularly under the age of 40. NF1-related breast cancer has poor prognosis, which is not solely explained by occurrence at young age or by histopathological type. Our results suggest that NF1 mutations are an independent factor contributing to low survival of patients with breast cancer. Active surveillance of NF1 patients and awareness of the NF1-related cancer risk are needed for early detection of the tumors and improved prognosis.

The following conclusions were made on the basis of the results of the present study:

Elina Uusitalo, MSc (second from right) from University of Turku defended her PhD thesis on March 23rd, 2018. The opponent was Professor Eric Legius (right) from KU Leuven, Belgium. The thesis work was supervised by Docent Sirkku Peltonen (left) and Professor Juha Peltonen (second from left).

- Sequence capture methodology combined with high-throughput sequencing is applicable to NF1 mutation analysis.
- NF1 incidence is higher than previously reported being 1/2,000. NF1 also causes significant mortality, which is largely explained by malignant neoplasms at a relatively young age.
- NF1 cancer incidence is higher than previously reported. We observed a five-fold increase in cancer incidence in the NF1 population, which is the highest cancer incidence reported so far. Cancers of the NF1 patients have worse prognosis than the corresponding cancers in the general population. Active surveillance of the patients is needed to detect the tumors early and to improve the prognosis.
- The risk for breast cancer in NF1 is elevated, particularly under age 40. NF1-related breast cancer has poor prognosis, which is not solely explained by occurrence at young age or by histopathological type. Awareness of the NF1-related breast cancer risk should be raised.

List of original publications

1. Uusitalo E, Hammais A, Palonen E, MäkeläV-V, Kallionpää R, Eeva-Mari Jouhilahti, et al. Neurofibromatosis type 1 gene mutation analysis using sequence capture and high-throughput sequencing. Acta Derm Venereol 2014; 94: 663–666.
2. Uusitalo E, Leppävirta J, Koffert A, Suominen S, Vahtera J, Vahlberg T , et al. Incidence and mortality of neurofibromatosis. A total population study in Finland. J Invest Dermatol 2015; 135: 904–906.
3. Uusitalo E, Rantanen M, Kallionpää RA, Pöyhönen M, Leppävirta J, Ylä-Outinen H, et al. Distinctive cancer associations in patients with neurofibromatosis type 1. J Clin Oncol 2016; 34: 1978–1786.
4. Uusitalo E, Kallionpää RA, Kurki S, Rantanen M, Pitkäniemi J, Kronqvist P, et al. Breast cancer in neurofibromatosis type 1: overrepresentation of unfavourable prognostic factors. Br J Cancer 2017; 116: 211–217.
