NCU – Summative report for 2013

Report submission date: 20 Feb 2014

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Project title: Norwegian-Swedish genome wide association study of testicular cancer with special focus on coding regions

NCU grant received (€): 30,000 EUR

Project commencement and completion dates: 1 Jan 2013 – 31 Dec 2014

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1. Briefly describe the project in a language understandable to non-scientists (max. 100 words)

Risk factors for testicular cancer (TC) are largely unknown, although genetic components and conditions during pregnancy are known to play a role. Recent large genome wide association (GWA) studies in England and USA, have shown that polymorphisms in genes regulating primordial germ cell development, telomerase activity, and sex-determination, are involved. These findings need replication in the Scandinavian populations to shed light on the high incidence rate of TC in our area. In the present study, a large Norwegian-Swedish population of TC patients, their parents and population controls, will be included in a GWA study, using a microchip with both common and rare (coding) genetic variants.

2. Summarize the major findings of the project (max. 400 words)

In the initial screening stage (completed spring 2013), both common single nucleotide polymorphisms (SNPs, n=760,000) as well as coding variants (n=250,000) have been explored among 1,450 TC cases recruited in Norway and Sweden. As population controls, 7,000 and 6,000 Swedish individuals, recruited in a twin study and in a study of schizophrenia, respectively, were used.

Preliminary results from analysis of the common variants, indicate that the well-established TC-associated genes (TERT, SPRY4, BAK1, DMRT1 and KITLG), as well as markers in most of the recently published 12 loci covering 16 genes, were significantly associated with TC. In addition, markers in 15 new regions covering 18-23 genes were associated with TC (P-value $< 10^{-5}$). In these regions, representative markers were taken forward to the replication stage. 831 complete TC triads (case and both parents), recruited in Norway and Sweden,

and a Norwegian case-control population of 300 + 300 subjects, were used for replication of the initial findings. Analysis of the replication data, revealed that two of the 15 regions still remained significantly associated with TC at the genome wide level (P-value < 10^{-5}).

3. Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer (max. 150 words)

Genetic epidemiological studies suggest that TC has a sizeable genetic basis. Identification of the genetic factors that predispose to TC may enable us to identify men at elevated risk of TC before the cancer arises, allowing targeted screening and possible prophylactic interventions for this genetically predisposed subgroup. Enhanced understanding of the genetic basis of TC may also offer new insights into the biology of the disease, which could be helpful in optimizing treatment. Genome-wide association studies have since 2009 identified markers at several loci which together account for approximately 22% of the genetic risk of TC and offer novel biological insights into testicular germ-cell oncogenesis. The large sample size and statistical power of our study, enabled us to reveal additional risk loci for TC, which thus contribute to a deeper understanding of the aetiology of TC.

4. Outline how Nordic cooperation has added value to this project (max. 100 words)

The project takes advantage of combining the populations of Sweden and Norway, which both have complete cancer registration. This enables us to conduct a study with a large study population and excellent power to detect risk alleles. Of particular value was the fruitful collaboration of Norwegian and Swedish experts in various fields, such as testicular cancer epidemiology, molecular biology of male reproduction and biostatistics. Another advantage of this cooperation, is the possibility of investigating why the incidence rate of testicular cancer in Sweden is only about half of that in Norway.

5. Publications resulting from the NCU research grant

Manuscript in preparation for submission to European Urology:

Kristiansen W, Karlsson R, Andreassen KE, Aschim EL, Magnusson PKE, Adami HO, Haugen TB, Grotmol T, Wiklund F. Norwegian-Swedish genome wide association study reveals two new susceptibility loci for testicular cancer.

These results will be presented at the 8th Copenhagen Workshop on Carcinoma in situ and Germ Cell Cancer to be held in May 2014.