NCU – Summative report for 2014

Report submission date: 2 Mar 2015

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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 germ cell tumor, hereafter called 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=610,240) 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.

Analysis of the common variants indicates 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.

We put forward 27 SNPs from 15 novel regions and 12 SNPs previously reported, for replication in 710 case-parent triads and 289 cases and 290 controls. Predefined biological pathways and processes, in addition to a custom-built sex determination gene set, were subject to enrichment analyses using Meta-Analysis Gene Set Enrichment of Variant Associations and Improved Gene Set Enrichment Analysis for Genome-wide Association Study. In the combined meta-analysis, we observed genome-wide significant association for rs7501939 on chromosome 17q12 and rs2195987 on chromosome 19p12. The marker rs7501939 on chromosome 17q12 is located in an intron of the HNF1B gene, encoding a member of the homeodomain-containing superfamily of transcription factors.

The sex determination gene set and pathways related to NF-κB, glycerophospholipid and ether lipid metabolism, as well as cancer and apoptosis, was associated with TC. In addition to revealing two new TC susceptibility loci, our results continue to support the notion that genes governing normal germ cell development in utero are implicated in the development of TC.

The association analyses of the coding variants are not yet completed.

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 this cancer form.

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

Kristiansen W, Karlsson R, Rounge T, Whitington T, Andreassen BK, Magnusson PK, Fosså SD, Adami H-O, Turnbull C, Haugen TB, Grotmol T, Wiklund T. Two new loci and gene sets related to sex determination and cancer progression are associated with susceptibility to testicular germ cell tumour. MS provisionally accepted for publication by Hum Mol Genet, December 2014.

These results have also been presented at the 8th Copenhagen Workshop on Carcinoma in situ and Germ Cell Cancer, May 2014; and will be presented at the American Association for Cancer Research Annual Meeting in Philadelphia, April 2015.