NCU – Summative report for 2014

Report submission date: 2015-12-27

Principal investigator: Fredrik Wiklund

Project title: Genetic epidemiology of prostate cancer prognosis

NCU grant received (€): 50.000

Project commencement and completion dates: 2014-01-01—2014-12-31

---

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

The overall aim of this project is to improve our understanding of genetic causes for the survival of prostate cancer patients. To achieve this we intend to perform large-scale genomic assessments in several population-based prostate cancer cohorts from the Nordic countries. Already performed genome-wide assessments of prostate cancer survival will set the basis for our study from which targeted explorations of indicated genomic regions will be performed.

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

Exome sequencing
We have performed a whole exome sequencing project of lethal prostate cancer patients. In total 75 Swedish and 50 Finnish patients that have died due to their disease at a very young age (below 65 years) have been selected for sequencing. Exonic sequences was enriched using a Nimblegen capture kit. The enriched DNA was fragmented, tagged and sequenced using Illumina sequencing allowing for high diploid coverage of the individual exomes. All data has been aligned against a reference genome. Overall the quality of derived data his high with over 80% of the captured regions having a coverage of 20X or higher. Exomic variants from the cases has been contrasted against a large set of population controls available from the Exome Aggregation Consortium (ExAC). Several novel findings has been observed displaying significant association with lethal prostate cancer. Currently validation of significant variants are performed using sanger sequencing as well as independent replication analysis in samples from the Norwegian CONOR cohort.

GWAS of prostate cancer survival
We have performed a GWAS study of prostate cancer survival utilizing the PRACTICAL/iCOGS consortium. In total four variants discovered in the initial screening stage as genome-wide associated with survival was put forward for replication in the CONOR cohort; however, none of the variants was observed to be associated in the replication stage. Recently we have completed an extended GWAS of prostate cancer survival through the PRACTICAL/iCOGS consortium including over 55,000 prostate cancer patients. A large proportion of our Nordic populations are included in this effort. Genotyping is completed and survival association results are expected to be available in spring 2016. This secondary GWAS of prostate cancer survival are several magnitudes larger than previous study and we expect that this effort will enable us to identify genomic regions of importance for aggressive and lethal prostate cancer.

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

So far the current project has not been able to discover inherited genetic determinants for prostate cancer prognosis. However, epidemiological studies support existence of such variants and our exome sequencing effort has revealed a number of promising variants that are being put forward for replication in independent cohorts. In addition, through our secondary, and very much enlarged, GWAS study of prostate cancer survival we believe that many more variants associated with prostate cancer aggressiveness and survival will be revealed in the future.

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

Existence of national population and disease registries coupled to large biological banks make the Nordic countries uniquely positioned for performing population-based genetic epidemiological studies of prostate cancer prognosis. Through pooling existing prostate cancer resources in Norway, Sweden and Finland strong synergy effect is achieved by creating a large Nordic population-based cohort of prostate cancer patients with complete information regarding clinical characteristics, treatment, and disease-specific follow-up. These are necessary prerequisite to successfully identify genetic determinants for prostate cancer prognosis. Our Nordic cooperation are therefore of outermost importance to achieve our aim.

5. Publications resulting from the NCU research grant

Szulkin R, Karlsson R, Whitington T, Aly M, Gronberg H, Eeles RA, Easton DF, Kote-Jarai Z, Al Olama AA, Benlloch S, Muir K, Giles GG, Southey MC, FitzGerald LM, Henderson BE, Schumacher FR, Haiman CA, Sipeky C, Tammela

TL, Nordestgaard BG, Key TJ, Travis RC, Neal DE, Donovan JL, Hamdy FC, Pharoah PD, Pashayan N, Khaw KT, Stanford JL, Thibodeau SN, McDonnell SK, Schaid DJ, Maier C, Vogel W, Luedeke M, Herkommer K, Kibel AS, Cybulski C, Lubiński J, Kluźniak W, Cannon-Albright L, Brenner H, Herrmann V, Holleczek B, Park JY, Sellers TA, Lim HY, Slavov C, Kaneva RP, Mitev VI, Spurdle A, Teixeira MR, Paulo P, Maia S, Pandha H, Michael A, Kierzek A; PRACTICAL consortium, Batra J, Clements JA; Australian Prostate Cancer BioResource, Albanes D, Andriole GL, Berndt SI, Chanock S, Gapstur SM, Giovannucci EL, Hunter DJ, Kraft P, Le Marchand L, Ma J, Mondul AM, Penney KL, Stampfer MJ, Stevens VL, Weinstein SJ, Trichopoulou A, Bueno-de-Mesquita BH, Tjønneland A, Cox DG; BPC3 consortium, Maehle L, Schleutker J, Lindström S, Wiklund F. Genome-wide association study of prostate cancer-specific survival. Cancer Epidemiol Biomarkers Prev. 2015 Nov;24(11):1796-800.