University of Split

School of Medicine

Split, May 15 – May 16, 2017

GENETIC ANALYSIS OF THYROID AND PARATHYROID FUNCTION

WORKSHOP PROCEEDINGS

Main organizer: Professor Tatijana Zemunik, M.D., Ph.D.
University of Split
School of Medicine
Project:"Identification of new genetic loci implicated in regulation of thyroid and parathyroid function" (No.1498); HRZZ/MEFST

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Hrvatska zaklada za znanost

SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET

University of Split

School of Medicine

Split, May 15 – May 16, 2017

Workshop:

GENETIC ANALYSIS OF THYROID AND PARATHYROID FUNCTION

Venue: Lecture room **B102** and Computer room **A428**

Main organizer: Professor Tatijana Zemunik, M.D., Ph.D.
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SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET

Monday, May 15th, 2017

Topic: **Genome-wide association studies**
Venue: Lecture room **B102**

10:00 - 10.30 Professor Caroline Hayward, Ph.D. "GWAS analysis: Past, Present and Future"
10:45 – 11:05 Assistant Professor Maja Barbalić, Ph.D.: "Clinical relevance of GWAS findings"
11:20 – 11:40 Associated Professor Ozren Polašek, M.D. Ph.D. "How to build a biobank"
12:00 lunch break (in front of the lecture room B102)

Venue: Computer room **A428**
13:00 – 13:45 Marijana Popović, Ph.D.:"The technology behind genome-wide association studies"
14:00 – 16:00 Luka Brčić, M.Sc.: "Genome-wide quality control procedures and imputation"

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Tuesday, May 16th, 2017

Topic: **Thyroid and parathyroid function**
Venue: Lecture room **B102**

10:00 - 10.30 Professor Tatijana Zemunik, M.D., Ph.D. "What do we know about genetic susceptibility of thyroid and parathyroid function in general population?"
10:45 – 11:05 Associated Professor Vesna Boraska Perica, Ph.D. „Genome-wide association analysis of Hashimoto thyroiditis"
11:20 – 11:40 Dubravka Brdar, M.D. "Physiology and autoimmune diseases of thyroid gland"
12:00 lunch break (in front of the lecture room B102)

Venue: Computer room **A428**
13:00 – 14:30 Antonela Matana, M.Sc.: "Statistical methods for genome-wide association studies"
14:45 – 16:15 Ivana Gunjača, M.Sc: "Post GWAS: Database searching"

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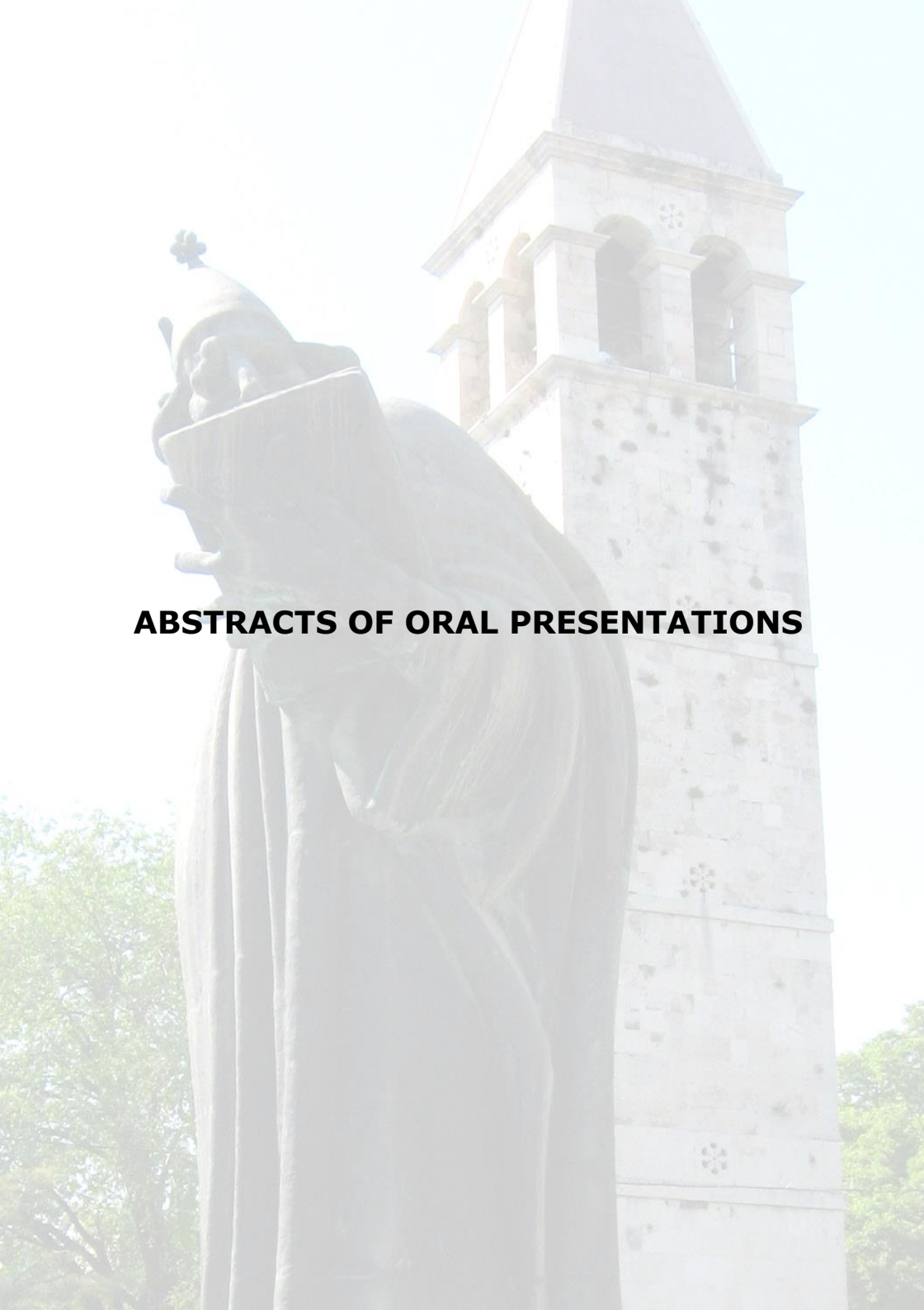

ABSTRACTS OF ORAL PRESENTATIONS

GWAS analysis: Past, Present and Future

Hayward Caroline
MRC Human Genetics Unit, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom

The past 10 years have seen many scientific and biological discoveries made through genome-wide association studies (GWAS). These studies are aimed at detecting variants at genomic loci that are associated with either quantitative traits and/or complex traits in populations. Over the years there have been great advances and improvements in both data quality and software efficiency enabling analysis of large cohorts using the millions of genotypes generated using imputation and sequence methodologies. The future of GWAS studies may become more limited as whole genome sequence becomes more common and leads to more "personalised" medicine. Observations on the past successes and future directions will be considered and discussed.

Clinical relevance of GWAS findings

Barbalić Maja
Department of Medical Biology, University of Split, School of Medicine, Split, Croatia

Genome-wide association studies (GWAS) have been one of the most exciting and the most fruitful scientific endeavours in human genetics. Ever since the first GWAS in 2005, there have been more than 2500 publications published with more than 20,000 unique SNP-trait associations. Despite this high number of discovered associations, GWAS variants have in most cases explained just a small proportion of trait heritability, which raises the question of GWAS utility in risk prediction. GWAS is a hypothesis free approach for underlying pathology so its findings have been useful in identifying new pathogenic pathways with some of them having a potential clinical use. However, given the amount of GWAS discoveries, clinical application of those discoveries has been largely lacking. This presentation will give an overview of the results gained by GWAS as well the clinical potential of such findings.

How to build a biobank

Polašek Ozren
Department of Public Health, University of Split, School of Medicine Split, Split, Croatia

Biobank development has been one of the most progressive fields of the entire biomedical research over the past decade. However, it is not a simple collection of the samples, as the study design, adherence to the inclusion and exclusion criteria and quality of the collection process can have substantial effects on the outcome. One of the critical steps in biobank development is population selection, which needs to reflect the main analytic approach. In case of the 10,001 Dalmatians, the approach was based on isolated populations, which were previously and repeatedly shown to exhibit reduced genetic and environmental diversity. This presentation will provide a quick overview of the 10,001 Dalmatians development, but also an example of the AMANHI biobank, maternal-newborn-paternal biobank in Tanzania, Bangladesh and Pakistan, which is developed by the World Health Organization.

What do we know about genetic susceptibility of thyroid and parathyroid function in general population?

Matana Antonela[1], Torlak Vesela[2], Brdar Dubravka[2], Popović Marijana[1], Gunjača Ivana[1], Lozić Bernarda[3], Punda Ante[2], Polašek Ozren[4], Boraska Perica Vesna[1], Barbalić Maja[1], Hayward Caroline[5], Zemunik Tatijana[1]
[1]Department of Medical Biology, University of Split, School of Medicine, Split, Croatia,
[2]Department of Nuclear Medicine, University Hospital Split, Split, Croatia,
[3]Department of Pediatrics, University Hospital Split, Split, Croatia,
[4]Department of Public Health, University of Split, School of Medicine Split, Split, Croatia,
[5]MRC Human Genetics Unit, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom

Thyroid gland, through secretion of its hormones, regulates metabolism, growth and maturation of all human tissues. The parathyroid glands play a central role in the regulation of calcium metabolism. Circulating concentrations of thyroid and parathyroid hormones and antibodies are under prominent genetic control and influence of environmental factors. However, genetic variants underlying their function are not fully established. Majority of thyroid hormones and antibodies have been underrepresented in the genome wide association studies (GWAS) or have not yet been investigated. There are ten published GWAS of thyroid stimulating hormone (TSH), four of free thyroxine (fT4), one of free triiodothyronine (fT3), and two of

thyroid peroxidase antibody (TPOAb) in general population. First GWA study of parathyroid hormone (PTH) has been published recently. The overall goal of our project is to explore genetic and environmental factors underlying thyroid and parathyroid functions by studying the most comprehensive set of thyroid and parathyroid hormones/antibodies measured in the plasma of general population. The first objective of the project is genome-wide association analysis of seven thyroid and parathyroid hormones/antibodies (fT3, fT4, TSH, Tg, TPOAb, TgAb, PTH) in three independent cohorts of Split, Korcula and Vis (3.000 participants from "10.001 Dalmatian" project) followed by meta-analyses of genome-wide association results. Second and third objectives of our project are determination of gene-environment interaction of associated genetic variants with selected environmental factors, and determination of phenotype-phenotype correlation using the measurements of thyroid and parathyroid hormones/antibodies and selected environmental factors. Results of the project have a potential to improve the clinical practice by leading to novel preventive measures, inventing more effective treatments and creating personalized medicine based on individual genetic profiles. Results will also point to a specific set of risk and protective environmental factors important for thyroid and parathyroid function.

Genome-wide association analysis of Hashimoto thyroiditis

Brčić Luka[1], Barić Ana[2], Gračan Sanda[2], Kaličanin Dean[1], Gunjača Ivana[1], Torlak Lovrić Vesela[2], Brekalo Marko[2], Šimunac Marta[2], Polašek Ozren[3], Zemunik Tatijana[1], Barbalić Maja[1], Punda Ante[2], Boraska Perica Vesna[1]

[1]Department of Medical Biology, University of Split, School of Medicine, Split, Croatia
[2]Department of Nuclear Medicine, University Hospital Split, Split, Croatia
[3]Department of Public Health, University of Split, School of Medicine, Split, Croatia

Hashimoto thyroiditis (HT) is the most common autoimmune disease and the most common endocrine disorder. It is characterized by chronic inflammation of the thyroid gland that may disrupt thyroid function and lead to hypothyroidism. Both, genetic and environmental factors, are thought to play a role in disease development and manifestation; however these factors have not been systematically investigated. Our research is focused on investigation of genetic and environmental factors underlying HT. As part of the Croatian Foundation for Science Installation grant "Genome-wide association analysis of Hashimoto's thyroiditis" we formed a biobank of biological samples from patients with HT who were extensively phenotyped and genome-wide scanned using Illumina Infinuim HumanCoreExome genotyping platform. Diagnosis of HT cases was based on clinical

examination, measurement of thyroid hormones/ antibodies and ultrasound examination. Our first goal is to identify genetic variants that are associated with HT through genome-wide association analysis using 430 HT cases and 430 existing controls (from the "10,000 Dalmatians" study). Our second long-term goal is to identify environmental factors by systematic analysis of all measured phenotypes such as medical status, nutrition, biochemical parameters and antibodies to food antigens. Our preliminary results identified association of one genetic variant at genome-wide significance level and several other genetic variants with suggestive associations ($P<10^{-5}$). Identified genetic variants are currently being *de novo* genotyped in independent replication cohort of 200 HT cases and 200 controls. This is timely planned study that aims to generate new knowledge that will advance our understanding of the genetic basis and underlying biological mechanisms of HT. This knowledge will be beneficial in guiding the development of new prevention, diagnostic and therapeutic methods.

Physiology and autoimmune diseases of thyroid gland

Brdar Dubravka
Department of Nuclear Medicine, University Hospital Split, Split, Croatia

Thyroid gland is an endocrine gland which synthesizes, stores and excretes thyroid hormones (T3 and T4). Basic functional unit of the thyroid gland is the follicle which contains colloid lined with epithelial cells. The main component of colloid is thyroglobulin which contents thyroid hormones. In healthy adults thyroid gland weighs 15-20g. Synthesis of thyroid gland hormones begins with transport of iodide in thyrocyte, followed by oxidation (to elemental iodine I2), organification (creating MIT and DIT), bonding MIT and DIT in T3 and T4 on thyroglobulin molecule. Finally, with process of proteolysis T3 and T4 are released. Function of thyroid gland is controlled by pituitary which releases TSH and by hypothalamus which releases TRH. In bloodstream T3 and T4 are tied with TBG, TBPA and HSA proteins. Daily production of T4 is approximately 130 nmol (100microg), and T3 around 50 nmol (33,5 microg). 90% of T3 generates by conversion of T4; 20% in thyroid gland itself, and 80% in peripheral tissues. Three enzymes catalyze deiodination of T3 and T4 (deiodinase type 1, 2 and 3). Thyroid gland hormones target receptors in cell nucleus. Outcome of activation is regulation of growth, development and metabolism.
In group of autoimmune thyroid diseases there are autoimmune thyroiditis (Hashimoto) and Graves'

disease. Pathological characteristics of Hashimoto thyroiditis are lymphocytic infiltration, loss of follicular epithelium and fibrosis. There is also high concentration of thyroid antibodies: anti-thyroid peroxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-Tg). Graves' disease in 80-100% is caused by TSH receptor stimulating antibodies (TS-Ab). The annual incidence of Hashimoto thyroiditis worldwide is estimated to be 0,3-1,5 cases per 1000 persons. Worldwide prevalence of Graves' disease is about 0,4-2% in women and 0,1% in men. Anti-TPO antibodies are positive: in 90-95% patients with thyroiditis, in 80% patients with Graves' disease and in 15-20% patients with non-autoimmune thyroid disorder. Anti-Tg antibodies are positive: in 70-80 % patients with thyroiditis, in 30-40 % patients with Graves' disease and 10-15 % patients with non-autoimmune thyroid disorder. ATD is a result of combination both genetic and nongenetic reasons, such as sex hormones, iodide intake, infection.

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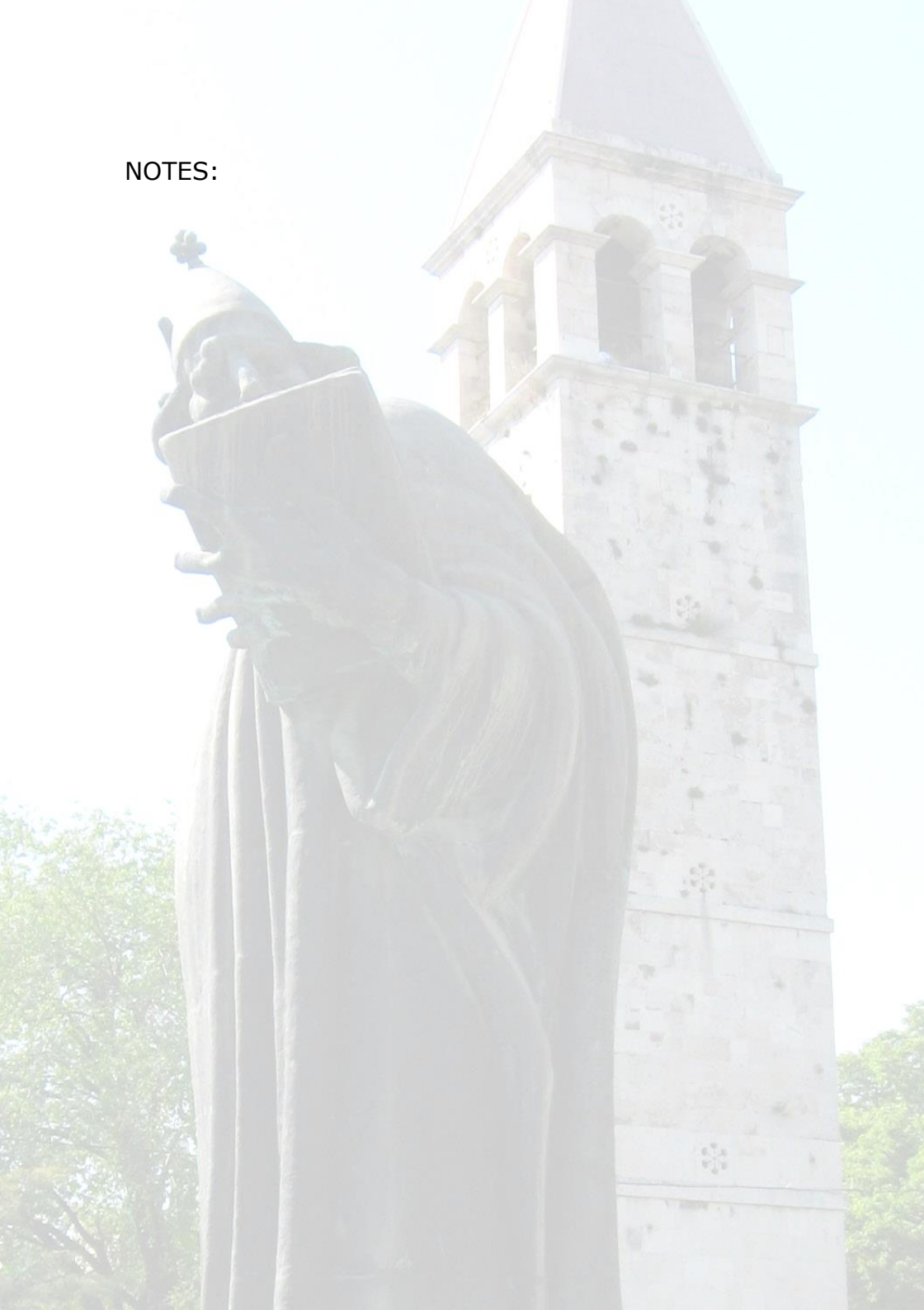

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