

REPORT ON THE 52ND EUROPEAN HUMAN GENETICS CONFERENCE, 15–18 JUNE 2019, GOTHENBURG, SWEDEN

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The European Human Genetics Conference is a landmark event in the genetics world. The purpose of annual meetings is threefold: to generate excellent science, to teach human genetics, and to provide an optimal environment for making new contacts and finding new collaborators and friends. ESHG 2019 took place in the beautiful city of Gothenburg, Sweden, from the 15th to the 18th of June. Gothenburg is Sweden's second biggest city located on the west coast at the mouth of the Göta River. The meeting took place in Gothia Towers, part of the Swedish Exhibition & Congress Centre. This year about 3300 participants from 91 countries heard about achievements at the forefront of human genetics. There were 1248 posters, 229 e-posters, 158 talks from submitted abstracts, and 97 invited oral presentations.

We had the opportunity to listen to authorities in genetics such as Dr. Craig Venter, who led the first draft sequence of the human genome. During the Mendel lecture, he spoke about the history of genetics and discussed current research, the primary aim of which should be to realize the full impact of genomics prediction and to have a thorough understanding of DNA and how it codes for the wide range of human phenotypes and abilities. Another outstanding speaker, Prof. Guillaume Canaud, gave a lecture about targeted therapy in patients with overgrowth (CLOVES) syndrome, startling the audience with his achievements and receiving a standing ovation. The drug he used improved disease symptoms in all 19 patients.

There were many other fascinating sessions. During the 3D gene regulation session, we heard a lecture by Dr. Anais Le Nabec from Université de Bretagne Occidentale titled “Characterization of *GJB2* cis-regulatory elements in the *DFNB1* locus”. The authors focused on patients with hearing loss who had one pathogenic variant detected in the *DFNB1* locus. They suggested that in hearing loss other mutations interfere with *GJB2* gene expression. The researchers proposed a model for analyzing mutations affecting the *GJB2* gene regulatory sequence, a model which might allow us to better understand the molecular mechanisms contributing to deafness associated with the *DFNB1* locus and improve the diagnosis of genetic deafness.

Pathogenic variants that affect gene expression or interfere with the splicing process were the topic of many sessions. Analyzing these types of variants is important, especially for recessive diseases. During a lecture by Dr. Mamiko Yamada from Keio University School of Medicine in Japan, “Effectiveness of integrated interpretation of exome and corresponding transcriptome data in detecting splicing

variants of recessive disorders”, we heard that combined analysis of exome and transcriptome data can increase the detection rate of genetically caused disease by up to 20 percent. The Japanese researchers used a novel algorithm by Shiraishi, “SAVNet: Splicing-Associated Variants NET”, to integrate RNA-seq and exome data from cancer tissues, producing impressive results.

Clinicians currently have to face the growing problem of mosaicism. Lectures provided insights into mosaicism in autosomal dominant disorders, in cancer-related genes, and associated with pediatric, neurological, or cardiovascular disorders. Dr. Danil Pineda-Alvarez presented a study in which he identified 1799 mosaic single nucleotide variations (SNVs) and 84 mosaic copy number variations (CNVs) among 245 genes. It was estimated that almost 40 percent of mosaic variants were likely to be, or definitively, pathogenic.

The poster session was divided into 24 parts grouped by topic. From our point of view the most important and interesting poster sessions were: i) sensory disorders (eye, ear, pain); ii) skeletal, connective tissue, ectodermal, and skin disorders; iii) neurogenetic and psychiatric disorders; iv) multiple malformation/anomalies syndromes; and v) new diagnostic approaches, technical aspects, and quality control. The sensory disorders session dealt mainly with studies identifying new variants in genes responsible for non-syndromic hearing loss and with a group of disorders in which one of the symptoms is hearing loss (such as Usher syndrome or Ménière disease). The topic of eye diseases encompassed retinal dystrophies, high myopia, Leber hereditary optic neuropathy, and Fuchs corneal endothelial dystrophy. In sessions related to skeletal, connective tissue, and neurogenetic disorders, many interesting cases were presented, e.g., osteogenesis imperfecta, keratoderma-ichthyosis-deafness syndrome, neurofibromatosis, and pontocerebellar hypoplasia. In the session related to multiple malformation syndromes, presentations covered using whole-genome sequencing for diagnosis, multigene panels, and CRISPR-Cas9 to identify the causes of Alström syndrome, branchio-oculo-facial syndrome, and Noonan syndrome. Swedish scientists described applying family trio analysis to rare syndromes, a valuable tool in obtaining a genetic diagnosis. A session on new diagnostic approaches focused on the preparation, execution, and analysis of genetic studies.

Details were given of exome and whole genome sequencing for rare diseases and of a workflow that can facilitate the correct interpretation of next generation sequencing

results. For patients suffering a complaint with a still-unknown genetic cause, despite extensive genetic testing, a re-interpretation scheme was proposed. To reach an earlier diagnosis and provide important prognostic and follow-up information, it is important to integrate powerful next-generation sequencing technology with comprehensive careful clinical evaluations. We saw posters describing research on the zebrafish model, with research on skeletal ciliopathies, osteoarthritis, spinocerebellar ataxia, and others. Such studies gave us valuable knowledge because this animal model is being introduced into our research at the Department of Genetics, Institute of Physiology and Pathology of Hearing (IPPH).

This year the Department of Genetics at IPPH was represented by Monika Ołdak, Dominika Oziebło, Anna Sarosiak, Agnieszka Madejska, Beata Harasimowicz, and Marcin Leja. During the sensory disorders session (dealing with eyes, ears, and pain), five posters were given. Monika Ołdak presented the genetic basis of autosomal dominant hearing loss in pediatric patients. Dominika Oziebło's poster focused on cochlear implantation outcomes in patients with *DFNB1* locus pathogenic variants. Agnieszka

Madejska presented work showing that the newly discovered *KCNQ4* gene variant is a cause of autosomal dominant hearing loss. Important contribution of *STRC* copy number variations to the development of mild-to-moderate hearing loss was presented by Beata Harasimowicz. Marcin Leja introduced "Novel variants in known genes: results of genetic testing in families with autosomal dominant hearing loss". Anna Sarosiak presented a poster in the Reproductive/Prenatal Genetics session, her topic being "Comprehensive chromosome screening of human first polar bodies and oocytes using four different whole genome amplification methods and single-cell next-generation sequencing".

The closing session was an Award Lecture presented by Cisca Wijmenga, professor of Human Genetics at UMCG in Groningen, Netherlands. Her talk, "We and our second genome: two key players in common complex diseases", focused on the important role of the human microbiome. The main concern is to see if changes in the microbiome cause disease, or whether the microbial changes are a consequence of disease. So far it has been demonstrated that microbial changes are causal for both type 2 diabetes and metabolic traits.