

Dutch Society for Human Genetics
(www.nvhg-nav.nl)

Annual Symposium

1 & 2 October 2018

**Hotel, Sports & Congress Center Papendal,
Arnhem, The Netherlands**



Wij zijn bijzonder erkentelijk voor de
financiële steun van
Stichting Simonsfonds



Logo: Tom de Vries Lentsch
Grafisch ontwerper / fotograaf

Dear colleagues,

Welcome to the annual symposium of the Dutch Society for Human Genetics, the NVHG. This is a joint meeting organized together with the VKGL (Vereniging Klinisch Genetische Laboratoriumdiagnostiek), the VKGN (Vereniging Klinische Genetica Nederland) and the NACGG (Nederlandse Associatie voor Community Genetics en Public Health Genomics).



It's great to work in the field of Human Genetics. Methodologies to interrogate the genome continue to progress at an impressive pace, with huge impact on molecular diagnostics and medicine as a whole. But not restricted to that. There is also a huge impact on uncovering new biological processes and mechanisms of disease, which are opening opportunities for knowledge-based interventions, such as cell therapy strategies, nucleic acids-based protocols and use of small molecules. And the good thing is: these exciting developments will not cease soon. While we can determine the primary exome/genome sequences relatively well, understanding how all of the genetic variation leads to a particular rare genetic disorder is in many cases not straightforward. Understanding the contribution of multiple variants in conjunction to common disorders is a challenge of another magnitude. And this is still only the primary structure of our genome. What about secondary and tertiary structure, epigenetic modifications and environmental effects, such as the microbiome? There is still a lot to be learned about the role of genetic variation in health and disease.

The program for this year's meeting is focused on how we are making progress in these areas. This symposium covers the entire width of pioneering Genetics research conducted by national and international speakers, thereby providing a good overview of current developments in Genetics research.

Next to the plenary sessions, the VKGL and VKGN/NACGG together have organized attractive topical programs. For contrast and reflection, we have invited Sjoerd Repping as special guest speaker on the Monday evening program. He will share his thoughts and very likely challenge you on how emerging reproductive technologies and genetic editing might impact future reproductive choices.

This meeting would not have been possible without the generous support from our sponsors, the Simonsfonds as well as bioscience companies. We thank all of them and encourage all participants to see the representatives at the stands to take note of the products offered by them.

I wish you an inspiring meeting and a great time interacting with your colleagues. Genetics is swinging, so see you on the dance floor.

Hans van Bokhoven

General information

Venue

Hotel, Sports and Congress Center Papendal
Papendallaan 3
6816 VD Arnhem
Nederland
Tel.: +31 26 483 79 11
<https://papendal.com/>
hotel@papendal.nl

Registration

In the Lobby: open on Monday October 1, 2018: 10.00 – 11.00 hrs
open on Tuesday October 2, 2018: 08.30 – 09.30 hrs

Reception and catering

Sydney room

Dinner and party

Sydney room

Abstracts

All abstracts and the full program of the NACGG, VKGN & VKGL sessions are available as downloads via the NVHG website

- Abstracts guest speakers G 01 to G 09
- Abstracts talks T 01 to T 16
- Abstracts posters P 01 to P 22

Posters

Poster boards have a size of 200 cm (height) and 100 cm (width)

Please put up your poster immediately after arrival. Do not forget to remove it at the end of the meeting

Language

The official language of the annual meeting will be English

Accreditation

Accreditation forms are available at the registration desk (GAIA ID number: 332535)

Badges

You are requested to hand in your badge at the end of the symposium

Presentations

You are requested to timely hand in an USB stick with your presentation to the chair of your session

NVHG board and scientific organization

Prof. dr. ir. Hans van Bokhoven (Board - President)

Prof. dr. Johan den Dunnen (Board - Secretary)

Dr. ir. Aimée Paulussen (Board - Treasurer)

Dr. Mieke van Haelst

Prof. dr. Raoul Hennekam

Dr. Lidewij Henneman

Dr. Roland Kuiper

Prof. dr. Richard Sinke

Prof. dr. André Uitterlinden

Dr. Lisenka Vissers

Administrative organization

Els Natzijl-Visser (secretaris@nvhg-nav.nl)

Henny Schurmann (henny.schurmann@mumc.nl)

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October 1 & 2, 2018

The NVHG Annual Symposium 2018 - Dutch Society for Human Genetics
Nederlandse Vereniging voor Humane Genetica (www.nvhg-nav.nl)

Program Monday October 1, 2018

10:00-11:00 Registration
Lobby

10.20-12.30 Opening & Plenary session

Room: Athene B/C

Chair: Hans van Bokhoven

10.20 Opening

10.30-11.10 **Mihai Netea** (Nijmegen, NL) (G 01)

Human Functional Genomics Project: understanding host defense heterogeneity

11.15-11.45 Winner Genetics Retreat – NVHG Graduate meeting 2018;

Mohamed Alimohamed (Groningen, NL) (G 02)

DNA test for translocation detection in acute leukemias using targeted locus amplification

11.50-12.30 **Richard Scott** (London, UK) (G 03)

Lessons from the UK 100,000 Genomes Project

12.30-14.00 Lunch, room: Foyer 1 & 2

Business/private meetings: huishoudelijke vergadering VKGN en VKGL

13:15-14:00 Huishoudelijke vergadering VKGN

Room: Athene A

13.15-14:00 Huishoudelijke vergadering VKGL

Room: Athene B/C

14.00-16.00 **Parallel sessions**

Symposium 1A: VKGL

Room: Athene A

Chair: Marcel Mannens & Dominique Smeets



- 14.00-14.35 **Marielle Alders** (Amsterdam, NL)
Towards genome wide methylation analysis as a diagnostic (functional) test
- 14.35-15.10 **Erik-Jan Dubbink** (Rotterdam, NL)
Classification of solid tumours using DNA methylation profiles
- 15.10-16.00 **Marianne Rots** (Groningen, NL)
Epigenetic editing
-

Symposium 1B: VKGN & NACGG

Theme: Extremes

Room: Athene B/C

Chair: Mieke van Haelst



Extreme phenotypes have always raised the interest of researchers, clinicians and the public. Extreme phenotypes are typically defined as both ends of the spectrum of a continuously measurable trait such as weight or height. Having an extreme phenotype such as massive obesity or excessive height, can have a marked disadvantage, also for health. In a changing environment, however, an extreme phenotype may be more fit (and have an increased survival rate) than all other phenotypes. The systematic collection of (extreme) phenotypes and their correlations with molecular data can be a useful method for studying the etiology of disease. For example, extreme phenotypes in a population can be used to identify rare variants involved in quantitative, complex traits, helping to find the *missing heritability*. In this session we will shed our light on extremes by having three presenters who will address this topic from different perspectives.



- 14.00-14.40 **Liesbeth van Rossum** (Rotterdam, NL)
Extremes in weight: Diagnostics of underlying causes and novel therapeutic solutions
- 14.40-15.20 **Bart Loeys** (Antwerp, BE / Nijmegen, NL)
Extremes in growth: Fibrillin, TGFbeta and BMP at the balance of too short and too long
- 15.20-16.00 **André Uitterlinden** (Rotterdam, NL)
Extremes in the population
-

16.00-17.30 Posters, coffee, tea
Presenters at posters Room: Foyer 1 & 2

17.30-18.30 Room: Athene B/C
Chair: Raoul Hennekam

Sjoerd Repping (Amsterdam, NL) (G 04)

Current and future reproductive technologies: towards genetically perfect children for all?

Evening: (Sydney room)

18.30-19.00 Drinks

19.00-21.00 Dinner

21.00-00.30 Party music Blend It

Program Tuesday October 2, 2018

8.30-9:30 Registration

8.45-10.10 **Plenary session**
Room: Athene B/C
Chair: André Uitterlinden



8.45-09.25 **Stefan Mundlos** (Berlin, Germany) (G 05)
Structural Variations, 3D Genome Organization and their Effect on Gene Regulation

9.30-10.10 **Karen Temple** (Southampton, UK) (G 06)
Imprinting disorders; new phenotypes and new mechanisms

10.20-11.20 **Parallel sessions**

Symposium 2A

Theme: Diagnostic yield of NGS-based testing

Room: Athene B/C

Chair: Lidewij Henneman

10.20-10.35 **Kristin Abbott** (Groningen, NL) (T 01)
NGS expanded carrier screening in the Netherlands: initial implementation results

10.35-10.50 **Jeroen Meekels** (Maastricht, NL) (T 03)
Development of an innovative method for comprehensive preimplantation genetic testing

10.50-11.05 **Cleo van Diemen** (Groningen, NL) (T 05)
Rapid whole exome sequencing as a diagnostic test for fetal multiple congenital anomalies on ultrasound

11.05-11.20 **Lotte Kleinendorst** (Amsterdam, NL) (T 07)
Genetic causes of obesity: diagnostic yield of 18% in a tertiary pediatric obesity cohort

Symposium 2B

Theme: Prioritization and functional follow-up of variants of unknown significance

Room: Athene A

Chair: Lisenka Vissers

- 10.20-10.35 **Laurens van de Wiel** (Nijmegen, NL) (T 02)
Aggregation of population-based genetic variation over protein domain homologues via MetaDome strongly improves diagnostic prediction of missense variants
- 10.35-10.50 **Romy Mesman** (Leiden, NL) (T 04)
Functional characterization of variants of uncertain significance in BRCA2: Fifty shades of BRCA2 deficiency
- 10.50-11.05 **Rick Boonen** (Leiden, NL) (T 06)
Functional Analysis of PALB2 Genetic Variants that Associate with Breast Cancer
- 11.05-11.20 **Britt Mossink** (Nijmegen, NL) (T 08)
The molecular convergence of Kleefstra Syndrome Spectrum

11.20-11.45 Coffee-tea break Room: Foyer 1 & 2

11.45-12.45 Parallel sessions

Symposium 3A

Theme: Genotype-Phenotype correlations and the impact of environment

Room: Athene B/C

Chair: Richard Sinke

- 11.45-12.00 **Lisenka Vissers** (Nijmegen, NL) (T 09)
De novo mutations in CNOT1, a master regulator of gene expression on DNA, RNA, and protein level, cause neurodevelopmental delay
- 12.00-12.15 **Els Vanhoutte** (Maastricht, NL) (T 11)
Filamin-C: genotype-phenotype correlation in patients with cardiomyopathy and/or myopathy
- 12.15-12.30 **Marian Weterman** (Leiden, NL) (T 13)
Hypermorphic and hypomorphic AARS alleles in patients with CMT2N expand clinical and molecular heterogeneities
- 12.30-12.45 **Jakob Goldman** (Nijmegen, NL) (T 15)
Analysis of sibling pairs' de novo mutations suggests limited influence of environmental and familial factors to germline mutation rate
-

Symposium 3B

Theme: Towards personalized treatment of genetic disease

Room: Athene A

Chair: Roland Kuiper

- 11.45-12.00 **Rosanne Ausems** (Nijmegen, NL) (*T 10*)
The Use of Pericytes in a Novel Cell-based Strategy for Correcting the Muscular Phenotype in Myotonic Dystrophy type I
- 12.00-12.15 **Lise van Wijk** (Leiden, NL) (*T 12*)
Functional analysis of BRCAness in female cancers: translation to clinical applications
- 12.15-12.30 **Inge Lakeman** (Leiden, NL) (*T 14*)
Addition of a 161-SNP Polygenic Risk Score to family history-based risk prediction: impact on clinical management recommendations in non-BRCA1/2 breast cancer families
- 12.30-12.45 **Eline van Hugte** (Nijmegen, NL) (*T 16*)
Towards personalized treatment of genetically classified refractory epilepsies using Human Induced Pluripotent Stem Cells (hIPSCs) as an ex-vivo tool
-

- 12.45-14.00 Algemene ledenvergadering NVHG
Room: Athene B/C
- 13.00-14.00 Lunch and posterviewing (room: Foyer 1 & 2)
-

14.00-16.00 Plenary session

Room: Athene B/C

Chairs: Hans van Bokhoven and Mieke van Haelst

- 14.00-14.40 **Edwin Cuppen** (Utrecht, NL) (*G 07*)
National scale tumor whole genome sequencing for personalized cancer treatment in the Netherlands
- 14.40-15.20 **Giuseppe Testa** (Milan, IT) (*G 08*)
Chasing the molecular logic of neurodevelopmental disorders: insights from patient-specific models at single cell resolution
- 15.20-16.00 **NVHG Galjaard lecture – Nine Knoers** (Groningen, NL) (*G 09*)
Towards the Genetics Clinic of the Future: from genetics in kidney diseases to genetics at the heart of healthcare
- 16.00-16.15 **NVHG Awards 2018**; Young Investigator Award, Annual Award, Poster Award
-

16:15 Closure



Special Guest speaker

Monday October 1, 2018 / 17.30 – 18.30 / Room: Athene B/C

Current and future reproductive technologies: towards genetically perfect children for all?

Sjoerd Repping, PhD, professor, director of Centre for Reproductive Medicine, Amsterdam UMC, location AMC/University of Amsterdam (UvA)



Professor Sjoerd Repping is currently the director of the center for reproductive medicine at the Amsterdam UMC, location AMC of the University of Amsterdam.

He obtained his Master Degree in medical biology in Amsterdam in 1998 and obtained his PhD in Medicine and Genetics in 2003 in Amsterdam and at the Whitehead Institute in Boston working on genetic causes of spermatogenic failure.

He became a certified clinical embryologist in 2001 and was lab director from 2005 until 2013. In 2013 he became director of the center.

Furthermore he is director of the Amsterdam Research Institute on Reproduction and Development and member of various

national and international committees.

He has published over 150 papers including papers in NEJM, Nature Genetics and Cell and has supervised over 20 PhD students.

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Special Guest speaker NVHG Galjaard Lecture

Monday October 2, 2018 / 15.20 – 16.00 / Room: Athene B/C

Towards the Genetics Clinic of the Future: from genetics in kidney diseases to genetics at the heart of healthcare

Nine Knoers, PhD, professor, Chair of the Department of Genetics, University Medical Centre Groningen (UMCG), Groningen, The Netherlands



Professor Nine Knoers is currently the chair of the Department of Genetics at the University Medical Centre Groningen.

She received her M.D. (1986) and Ph.D. (cum laude, 1990) from the Catholic University Nijmegen, The Netherlands.

She was trained and certified as Clinical Geneticist at the Radboud University Medical Centre Nijmegen.

From 2011 until 2018, she was chair of the Department of Genetics at the University Medical Centre Utrecht.

She was chair of the Dutch Society of Clinical Genetics (2007-2015) and Member of the Dutch Health Council (2008-2018).

Her research focuses on the identification of genes for inherited renal disorders and on their pathophysiology. Her team has substantially contributed to the elucidation of genes for hereditary kidney diseases.

Professor Knoers is member of several international research consortia on genetic renal disorders and coordinates a Dutch Consortium on renal ciliopathies.

She has published over 250 papers, including papers in Nature Genetics, Science, Lancet and New England Journal of Medicine and has supervised over 25 PhD students.

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The Galjaard lecture is named after Prof. dr. Hans Galjaard, initiated to honour scientists that successfully brought the subject of "Genetics" to the attention of the general public. Previous Awardees are: Gert Matthijs (Leuven, 2012), Gert-Jan van Ommen (Leiden, 2014), Jan Hoeijmakers (Rotterdam, 2016).

Human Functional Genomics Project: understanding host defense heterogeneity

Prof.dr. Mihai G. Netea

Radboudumc, Nijmegen, The Netherlands

Differences in susceptibility to immune-mediated diseases are determined by variability in immune responses. In the Human Functional Genomics Project we assessed the effect of environmental, genetic and non-genetic host factors, as well as microbiota, on the human host defense in humans. Among these factors, age, gender, microbiome, and annual seasonality are important non-genetic factors influencing cytokine production, while 17 independent genetic loci have a strong impact on cytokine responses. The complete dataset has been made publicly available as a comprehensive resource for future studies.

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DNA test for translocation detection in acute leukemias using targeted locus amplification

Mohamed Z.A. Alimohamed

University Medical Center Groningen (UMCG), Groningen, The Netherlands

Mohamed Z. Alimohamed (1), Lennart F. Johansson (1), Eddy N. de Boer (1), Erik Splinter (4), Petra Klous (4), Anneke Bosga (1), Max van Min (4), André B. Mulder (2), Edo Vellenga (3), Richard J. Sinke (1), Rolf H. Sijmons (1), Eva van den Berg (1), Birgit Sikkema-Raddatz (1).

1 Departments of Genetics, 2 Laboratory Medicine, and 3 Hematology, University Medical Center Groningen, Groningen, The Netherlands and 4 Cergentis B.V, Utrecht, The Netherlands

Introduction

Patients with acute leukemias (AL) carry chromosomal abnormalities, affecting their prognosis and treatment. Currently, over 500 different translocations are involved in the disease progression. Traditional diagnostic methods include karyotyping, FISH, array and RT-PCR. However, these methods are laborious and inadequate. Target Locus Amplification (TLA), targeted next generation sequencing technology, based on proximity ligation and enrichment of DNA can overcome these shortcomings.

Methods and Results

Multiplex primer sets covering known break-point regions of 17 most reported genes involved in AL's were designed. TLA was performed on four cell lines carrying translocations detectable by our panel [t(4;11), t(11;19)t(8;13), t(6;9), t(17;19)] in dilution series and sequenced. In this series up to 10% aberrant cells were detected with one additional finding t(9;12), and no false positives.

Bone marrows of 36 patients suspected of AL were taken for routine genetic diagnosis and TLA (consented). Analysis was randomized and blinded, and outcomes were compared. Six samples did not satisfy required quality for analysis. Of 30 patients, our panel confirmed translocations on 16 samples, including cryptic translocation t(12;21). In eleven samples no translocation was detected, concordant to (cyto)genetic findings. Three translocations were missed due to insufficient sequence reads on partner chromosome.

Conclusions

TLA panel showed concordant results for 27 of the 30 successful sequenced samples with no false positives. Therefore, the TLA panel is suited as a first tier screening tool in AL. A prospective study, comparing the diagnostic yield of the TLA panel with current tests, can establish whether it is applicable as a routine procedure.

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Lessons from the UK 100,000 Genomes Project

Dr. Richard Scott

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Current and future reproductive technologies: towards genetically perfect children for all?

Prof.dr. Sjoerd Repping

Amsterdam UMC, location AMC / University of Amsterdam (UvA), Amsterdam, The Netherlands

Developments in reproductive technology go rapidly. Already before Louise Brown, the first ivf child ever to be born, turns 40, one out of thirty children born in the Netherlands is the result of reproductive technology. Even more so, reproductive technologies now allow the analysis of the genetic status of embryos before they are implanted, thereby aiding in the prevention of the transmission of heritable diseases. Preclinically techniques are developed to generate gametes from stem cells and to allow for genetic modification of gametes or early embryos. How far will these techniques go and will they be implemented? Why would we like to use these techniques and who should control this? Will we develop towards a society where everyone can have genetically perfect children whenever they want?

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Structural Variations, 3D Genome Organization and their Effect on Gene Regulation

Prof.dr. Stefan Mundlos

Max Planck Institute for Molecular Genetics, Berlin, Germany
Charité, Universitätsmedizin Berlin, Germany

Recent studies have shown that the genome shows a specific three-dimensional organization in the nucleus which has a major influence on gene regulation. These studies have shown that mammalian genomes are organized in distinctly folded chromatin modules, called topologically associated domains (TADs) that are separated from each other by boundary regions. TADs subdivide the genome into discrete genomic units that restrict the possible contacts enhancers can establish with their target genes. We use a CRISPR/Cas9 based strategy to investigate the effect of human disease-associated structural variations *in vivo* in mice. We show that deletions can result in the fusion of TADs and the re-wiring of enhancer-promoter contacts. At the EPHA4 locus, for example, deletion of parts of the TAD including the boundary result in the activation of the nearby Pax3 gene by Epha4 enhancers and a limb malformation. Furthermore, we analyzed overlapping duplications at the SOX9 locus, that are associated either with a limb malformation (Cooks syndrome), sex reversal, or no abnormality. We show that large duplications spanning a TAD boundary result in the formation of a novel TAD, or neo-TAD. This formation of neo-TADs explains the divergent phenotypes of overlapping duplications at the SOX9 locus. Further, we demonstrate that the increased copy number of cis-regulatory elements is functionally isolated within the neo-TAD and does not affect gene expression of neighboring genes. Moreover, the pathogenicity of duplications depends on the genes and the cis-regulatory information that are incorporated within the neo-TAD. Our results show that duplications including TAD boundary elements can result in the formation of novel genomic units that are functionally and spatially separated from their genomic neighbors. Besides shedding light onto genome biology, our findings provide a framework for interpreting the pathogenic effect of duplications, which are frequently detected in patients with congenital malformations, intellectual disability and cancer.

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Imprinting disorders; new phenotypes and new mechanisms

Prof. Karen Temple

Academic Unit of Human Development and Health, Faculty of Medicine, University of Southampton and Wessex Clinical Genetics Service, University Hospital Southampton, Southampton SO16 6YD, United Kingdom

Human imprinting disorders are congenital disorders of growth, development and metabolism, associated with disturbance of parent of origin-specific DNA methylation at imprinted loci across the genome. Altered imprinted gene dosage in the affected individual is the likely underlying cause of the phenotypic findings but the epigenetic errors affecting expression may be the result of genetic and environmental effects at different times during the development of the oocyte, the sperm or the early embryo. There are eight well recognised imprinting developmental phenotypes in childhood:- Prader Willi, Angelman, Silver Russell, Beckwith Wiedemann, Temple, Kagami Ogata, Transient Neonatal Diabetes and Pseudohypoparathyroidism type 1B syndromes but imprinting errors may also cause nonspecific growth phenotypes and altered timing of puberty.

Some patients with imprinting disorders have multi-locus imprinting disturbance (MLID) and can present with less classical clinical features as more than one imprinted loci is involved. Twinning and IVF may predispose to MLID but causative trans-acting mutations in MLID patients are well recognised e.g. *ZFP57*: (Mackay, Nat Gen, 2008). More recently, mutations in genes essential for the development of the oocyte have been identified in the mother of affected children (Begemann, J Med Genet, 2018). It is likely that patients with imprinting disorders are not being diagnosed because:

- 1) phenotypes do not fit neatly into the classic well-recognised imprinting disorders
- 2) epigenetic testing is not part of routine screening for patients with an unknown diagnosis
- 3) exome analysis focuses on patients and not their parents

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National scale tumor whole genome sequencing for personalized cancer treatment in the Netherlands

Prof.dr. Edwin Cuppen

Center for Personalized Cancer Treatment, Hartwig Medical Foundation and University Medical Center Utrecht, The Netherlands

Next-generation DNA sequencing has boosted the promises of personalising cancer treatment. It has now become possible to routinely sequence the complete genome of a tumor from a patient. While patient stratification based on a limited number of genetic measurements is steadily increasing in routine diagnostics, retrospective systematic analyses of genetic information and treatment outcome are still warranted to improve such stratifications, as significant numbers of selected patients for specific treatments are non-responsive, yet may experience severe treatment side effects. In addition, ineffective treatment contributes significantly to the increasing economical burden of novel cancer treatment drugs on health care costs.

In 2010, we established the Center for Personalized Cancer Treatment (CPCT) to address this challenge and work towards implementation of DNA-guided therapy into routine care in the Netherlands. In all associated hospitals (currently 49), we have implemented trials to collect fresh-frozen biopsies from tumor metastases before patients start treatment with specific targeted drugs and generate whole genome sequencing data in a centralized ISO-accredited sequencing facility based on Illumina X10. Furthermore, we systematically collect clinical and treatment response data from the treating centers and feed back therapy guidance information, to the treating physician. In collaboration with pharma, we have set up a drug-repurposing study that allows for experimental therapy based on molecular indications (off-label drug use). In this setup, both current and future patients may benefit from comprehensive DNA analyses. Currently, more than 3,000 patients have been analysed by whole genome sequencing (tumor average sequencing depth of 114x, control 38x). All data is made available for research aimed at improving cancer patient care.

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Chasing the molecular logic of neurodevelopmental disorders: insights from patient-specific models at single cell resolution

Prof.dr. Giuseppe Testa

Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Director, Laboratory of Stem Cell Epigenetics, European Institute of Oncology (IEO), Milan, Italy

Over the last years my lab has been spearheading the modelling of a particularly informative set of neurodevelopmental disorders caused by point mutations or dosage imbalances in chromatin regulators that operate in inter-related pathways. To this end we harness panels of patient-specific disease-relevant lineages derived by cell reprogramming, including 3D brain organoids that recapitulate salient features of human corticogenesis, to enable a multi-layered genome-wide analysis of the gene expression deficits that are either convergent or divergent across different chromatinopathies. Here I discuss the latest insights from our work, focusing on the single-cell level deconvolution of dosage-dependent alterations in developmental pathways and the integration of our transcriptomic profiles within a cutting-edge meta-analysis of available transcriptomic data. Specifically, the latter allows to empirically assess how far brain organoids can recapitulate human brain development and which protocols of differentiation best suit specific experimental needs. To this end, we have assembled an extensive transcriptome database of human cortical development, combining multiple available published works to be used as a robust standard against which to benchmark the transcriptomes of both early and mature stages organoids, encompassing the most relevant aspects of currently available protocols (patterning versus no patterning, matrigel embedding versus not, and combinations thereof). Our analysis shows that patterned cortical organoids recapitulate faithfully the patterns of expression unfolding in fetal corticogenesis and validate the use of this benchmarking resource for comparative evaluations of brain organoid results deriving from different origins and preparations.

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Towards the Genetics Clinic of the Future: from genetics in kidney diseases to genetics at the heart of healthcare

Prof.dr. Nine Knoers

Department of Genetics, University Medical Centre Groningen (UMCG), Groningen, The Netherlands

Next generation sequencing (NGS) technologies have tremendously revolutionized genomics, with very promising implications for diagnosis, risk prediction, prognosis, prevention and personalized treatment of rare inherited and multigenic complex diseases.

Studies on the yield of NGS techniques in genome diagnostics, health technology assessments, studies on ethical, legal and social issues (ELSI) and investigations on patients' preferences and expectations have indicated that moving towards a "genetics-first" approach in routine clinical practice would be of great benefit to a significant number of patients. For this reason, we and others have initiated projects to build the "Genetics Clinic of the Future" in order to fully utilize the potential of NGS-based genomic medicine.

In this lecture, I will illustrate the potential advantages of a "genetics-first" approach with examples from our studies in nephrogenetics (genetics of congenital and inherited kidney diseases). In addition, I will discuss the projects that have been initiated to build the "Genetics Clinic of the Future" and the first successes, pitfalls and challenges we are encountering in its implementation.

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Abstracts Talks (T)

NVHG – Two Day Annual Meeting 2018

Nr	Name		Title	E-mail
T 01	Abbott	Kristin	NGS expanded carrier screening in the Netherlands: initial implementation results	k.m.abbott@umcg.nl
T 02	van de Wiel	Laurens	Aggregation of population-based genetic variation over protein domain homologues via MetaDome strongly improves diagnostic prediction of missense variants	laurens.vandeWiel@radboudumc.nl
T 03	Meekels	Jeroen	Development of an innovative method for comprehensive preimplantation genetic testing	jeroen.meekels@mumc.nl
T 04	Mesman	Romy	Functional characterization of variants of uncertain significance in BRCA2: Fifty shades of BRCA2 deficiency	r.l.s.mesman@lumc.nl
T 05	van Diemen	Cleo	Rapid whole exome sequencing as a diagnostic test for fetal multiple congenital anomalies on ultrasound	c.c.van.diemen@umcg.nl
T 06	Boonen	Rick	Functional Analysis of PALB2 Genetic Variants that Associate with Breast Cancer	r.a.c.m.boonen@lumc.nl
T 07	Kleinendorst	Lotte	Genetic causes of obesity: diagnostic yield of 18% in a tertiary pediatric obesity cohort	l.kleinendorst@amc.uva.nl
T 08	Mossink	Britt	The molecular convergence of Kleefstra Syndrome Spectrum	britt.mossink@radboudumc.nl
T 09	Vissers	Lisenka	De novo mutations in CNOT1, a master regulator of gene expression on DNA, RNA, and protein level, cause neurodevelopmental delay	lisenka.vissers@radboudumc.nl
T 10	Ausems	Rosanne	The Use of Pericytes in a Novel Cell-based Strategy for Correcting the Muscular Phenotype in Myotonic Dystrophy type I	rosanne.ausems@radboudumc.nl
T 11	Vanhoutte	Els	Filamin-C: genotype-phenotype correlation in patients with cardiomyopathy and/or myopathy	e.vanhoutte@mumc.nl
T 12	van Wijk	Lise	Functional analysis of BRCAness in female cancers: translation to clinical applications	L.M.van_Wijk@lumc.nl
T 13	Weterman	Marian	Hypermorphic and hypomorphic AARS alleles in patients with CMT2N expand clinical and molecular heterogeneities	m.a.j.weterman@lumc.nl
T 14	Lakeman	Inge	Addition of a 161-SNP Polygenic Risk Score to family history-based risk prediction: impact on clinical management recommendations in non-BRCA1/2 breast cancer families	i.m.m.lakeman@lumc.nl
T 15	Goldman	Jakob	Analysis of sibling pairs' de novo mutations suggests limited influence of environmental and familial factors to germline mutation rate	jakob.goldmann@radboudumc.nl
T 16	van Hugte	Eline	Towards personalized treatment of genetically classified refractory epilepsies using Human Induced Pluripotent Stem Cells (hiPSCs) as an ex-vivo tool	eline.vanhugte@radboudumc.nl

Abstracts Posters (P)

NVHG – Two Day Annual Meeting 2018

Nr	Name		Title	E-mail
P 01	Aulchenko	Yurii	WITHDRAWN	
P 02	Brosens	Erwin	High rate of deleterious de novo Copy Number Variations in patients with syndromal Hirschsprung Disease	e.brosens@erasmusmc.nl
P 03	Derks	Kasper	NGS Assurance Spike In for sequencing protocols	kasper.derks@mumc.nl
P 04	Eduardo	Soares	Dissecting human epidermal commitment in healthy and diseased hiPSC models by single-cell RNA-seq	edusoares@gmail.com
P 05	Fokkema	Ivo	Supporting DNA variant interpretation: the LOVDatabases	I.F.A.C.Fokkema@lumc.nl
P 06	Jansen	Sandra	De novo mutations in PPP2CA, the C α subunit of PP2A, cause a neurodevelopmental disorder resembling the phenotype caused by mutations in genes encoding for subunits A and B	sandra.jansen1@radboudumc.nl
P 07	Kant	Benjamin	Mosaic mutation detection using single molecule molecular inversion probes (smMIPs) for autoimmune disorder diagnostics	b.kant@umcutrecht.nl
P 08	Knijnenburg	Jeroen	Precise breakpoint detection of balanced and unbalanced structural variation in whole genome sequencing data using haplotype blocks created by linked-reads	j.knijnenburg@lumc.nl
P 09	Latour	Brooke	WITHDRAWN	
P 10	Mbarek	Hamdi	Genetic influences on fertility: What can we learn about female fertility from genetic studies of twinning	hmbarek@gmail.com
P 11	Nijmeijer	Sebastiaan	Alzheimer's disease biomarkers in cerebrospinal fluid and on amyloid PET in two patients with GRN mutations and early onset dementia.	s.w.nijmeijer@amc.nl
P 12	Polla	Daniel	Identification of a Finnish CRADD founder mutation underlying 'thin' lissencephaly	daniel.lopopolla@radboudumc.nl
P 13	Raaijmakers	Renée	Pericyte-derived iPSCs as a cell-based treatment for the neuromuscular phenotype in Myotonic Dystrophy type 1	renee.raaijmakers@radboudumc.nl
P 14	Reinders	Marieke	Genetic mosaicism in basal cell naevus syndrome	marieke.reinders@mumc.nl
P 15	Van de Beek	Irma	Colorectal polyps and carcinoma in Birt-Hogg-Dubé syndrome	i.beek@vumc.nl
P 16	Van den Heuvel	Lieke	Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy: a 10-years follow-up study	l.m.vandenheuvel@amc.uva.nl
P 17	Van Leersum	Frank	Improving diagnostic yield for filaggrin; hidden mutations in the Dutch population	frank.van.leersum@mumc.nl
P 18	Van Veghel-Plandsoen	Monique	Prenatal diagnosis of Walker-Warburg Syndrome: A case report	m.plandsoen@erasmusmc.nl
P 19	Vanoevelen	Jo M.	Impaired fertility and motor activity in a zebrafish model of classic galactosemia	j.vanoevelen@maastrichtuniversity.nl
P 20	Verberne	Eline	Introducing Next Generation Sequencing in Curaçao: results of the first 11 intellectual disability (ID) panels	e.verberne@vumc.nl
P 21	Verdonschot	Job	Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias.	job.verdonschot@mumc.nl
P 22	Zeidler	Shimriet	Combination therapy in fragile x syndrome; possibilities and pitfalls illustrated by targeting the mglur5 and gaba pathway simultaneously	s.zeidler@erasmusmc.nl









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