8th International Meeting on Rare Disorders of the RAS-MAPK Pathway
A workshop preceding the ESHG conference in Berlin, 2020

Organisers: Bronwyn Kerr, Marco Tartaglia, Alain Verloes, Martin Zenker.
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Registration limit: 120 participants.
Location: Novotel Berlin am Tiergarten, Str. des 17 Juni 106-108, 10623 Berlin, Germany
Date: Friday, June 05, 2020 – Saturday, June 06, 2020

Note: This event is coupled to the ESHG conference. In case that the ESHG conference is cancelled, this will also lead to cancellation of this satellite event.

Program - Day 1 (Friday, June 05)

900  RASopathies guidelines consensus follow-up meeting:
To promote further the development of international guidelines?
Follow-up of the Milan meeting 2018
(for guidelines consensus group members
and interested participants of the main meeting)
Chair: Bronwyn Kerr and Alain Verloes

900  Details will follow soon

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1200  Lunch Break
Program - Day 1 (Friday, June 05) continued: Main Part of the meeting

12:20 Registration
13:15 Welcome addresses

13:20 **First Session: RASopathy genes and their function in the pathway I**
Chair: Marco Tartaglia

13:20 LZTR1 function in RAS signaling
Raj Sewduth

13:40 LZTR1 loss-of-function at the molecular and organismal level
Pau Castel

14:00 Functional characterization of LZTR1 mutations causing Noonan syndrome
Marialetizia Motta

14:20 Clinical characterization and inheritance patterns of LZTR1-related Noonan syndrome
Julia Brinkmann

14:40 The SHOC2-MRAS-PP1C module in regulating the MAPK pathway
Pablo Rodriguez-Viciana

15:00 The SHOC2-MRAS-PP1C module: its functional dysregulation in RASopathies
Francesca Pantaleoni

15:20 Coffee Break

16:00 **Second Session: RASopathy genes and their function in the pathway II**
Chair: Bruce D Gelb

16:00 RASopathy genetic variation in biobanks
Bruce D Gelb

16:20 SPRED1 mutations: molecular spectrum, functional impact and associated phenotypes
Eric Legius

16:40 RRAS2 mutations: a novel cause of Noonan syndrome
Yline Capri

17:00 RRAS2 mutations: a novel cause of Noonan syndrome
Yoko Aoki

17:25 CDC42, RASA2, FBXW11, ZNF426, YWHAZ, TRAF7: Novel RASopathy genes or not?
Martin Zenker

17:30 Novel gene identification for RASopathies: where are we now?
Marco Tartaglia

17:50 **From the patients’ perspective: The meaning of a confirmed diagnosis.**
Lisa Schoyer (RASopathiesNET) & Marco Roggero (CFC Germany)

18:00 Dinner Buffet

19:40 **Late session: Short reports and clinical cases**
Chair: Marco Tartaglia and Martin Zenker

19:40 – Paternal age and recurrence risk for RASopathies (A. Goriely)

**Short presentations (7 min – 8 presentations maximum) from selected abstracts**
Participants are invited to present their data (case reports and genotype phenotype studies).

20:00 – Severe RRAS mutation associated with tumor development (Zenker group)
20:10 – PPP1CB and the NS-LAH phenotype (E. Leenders)
20:20 – Atypical HRAS mutations: Costello syndrome or not? (A. Verloes)
20:30 – CDC42 links Noonan and Adams-Oliver syndromes (S. Kamphausen)
20:40 – Functional and clinical characterization of a novel PTPN11 mutation cluster (S. Martinelli)
20:50 – Prevalence & molecular spectrum of NF1 mutations in NF1 with congenital heart disease (A. De Luca)
21:00 – Emotion and cognition in Noonan syndrome: Treatment options (E. Wingbermühle & R. Roelofs)
21:10 – … Possible slots for additional short communications
<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>9:00</td>
<td><strong>Fourth Session: New lessons on pathophysiology and management:</strong></td>
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<td><strong>lymphatic, vascular and bleeding issues</strong></td>
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<td>Chair: Armelle Yart</td>
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<td>9:00</td>
<td>Update on lymphatic problems in RASopathies</td>
<td>Sahar Mansour &amp; Kristiana Gordon</td>
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<td>9:20</td>
<td>The patterns and therapeutic options in Noonan syndrome-related lymphedema</td>
<td>Max Itkin</td>
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<td>9:40</td>
<td>Genotype predisposition for lymphatic problems in Noonan syndrome</td>
<td>Christina Lißewski</td>
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<tr>
<td>9:50</td>
<td>Mosaic RASopathies and lymphedema</td>
<td>Kristiana Gordon &amp; Sahar Mansour</td>
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<td>10:00</td>
<td>ARAF mutations and central conduction lymphatic anomaly – a model for RASopathy-related lymphatic anomalies</td>
<td>Hakon Hakonarson</td>
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<td>10:20</td>
<td>RAS/MAPK signaling: a major driver in vascular malformations</td>
<td>Miikka Vikkula</td>
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<td>10:40</td>
<td>New insights into the Noonan syndrome-associated bleeding disorder</td>
<td>Sonia Severin</td>
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<td>11:05</td>
<td><strong>From the patients' perspective:</strong> The impact of lymphedema on health.</td>
<td>Ian Legg (Noonan syndrome, UK)</td>
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<td>11:20</td>
<td><strong>Coffee break</strong></td>
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<td>11:40</td>
<td><strong>Fifth Session: New lessons on pathophysiology and management:</strong></td>
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<td><strong>hypertrophic cardiomyopathy</strong></td>
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<td>Chair: Monika Gos</td>
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<td>11:40</td>
<td>MEK inhibitor treatment in Noonan syndrome-associated cardiomyopathy – an update</td>
<td>Gregor Andelfinger</td>
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<td>11:55</td>
<td>Inhibiting SHP2 function</td>
<td>Lorenzo Stella</td>
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<td>12:10</td>
<td>Infantile HCM – Differences in clinical presentation and outcome between RASopathy-related and sarcomere protein-related HCM</td>
<td>Cordula Wolf</td>
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<td>12:30</td>
<td>Modeling Noonan syndrome in zebrafish</td>
<td>Jeroen den Hertog</td>
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<td>12:45</td>
<td>iPSC-based modeling of RASopathy-related cardiac hypertrophy reveals new mechanisms and therapeutic options</td>
<td>George Kensah &amp; Reza Ahmadian</td>
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<td>13:00</td>
<td>Intrinsic CRISPR repair in a preclinical model of LZTR1-associated cardiomyopathy</td>
<td>Lukas Cyganek</td>
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<td>13:15</td>
<td>The RASponses project in the Netherlands: a way to develop an integrated research agenda</td>
<td>Dagmar Tiemens</td>
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<td>13:30</td>
<td><strong>Closing remarks</strong></td>
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<td>14:00</td>
<td><strong>Meeting of the NSEuroNet consortium</strong></td>
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<td>(for consortium members)</td>
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<td>15:00</td>
<td>Chair: Marco Tartaglia</td>
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Speakers and Chairpersons:

Paolo Alfieri, MD, Department of Neurosciences, Ospedale Pediatrico Bambino Gesù, Rome, Italy
Gregor Andelfinger, MD, PhD, Dept. Pediatrics, University of Montreal and St. Justine Hospital University Centre, Montreal, Canada
Yoko Aoki, MD, PhD, Department of Medical Genetics, Tohoku University School of Medicine, Sendai, Japan
Julia Brinkmann, Institute of Human Genetics, University Hospital of Magdeburg, Germany
Ylne Capri, MD, Department of Genetics, Robert Debré University Hospital, APHP, Paris, France
Pau Castel, PhD, Helen Diller Comprehensive Cancer Center, University of California San Francisco, USA
Lukas Cyganek, PhD, Clinic for Cardiology and Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany
Marije Diender, Department of Pediatrics, Radboud University Medical Center Amalia Children's hospital, Nijmegen, The Netherlands
Jos Draaisma, MD, PhD, Department of Pediatrics, Radboud University Medical Center Amalia Children's hospital, Nijmegen, The Netherlands
Jeroen den Hertog, PhD, Hubrecht Institute - KNAW and University Medical Center Utrecht, Utrecht, The Netherlands
Alessandro De Luca, PhD, Ospedale Casilino della Sofferenza, IRCCS, San Giovanni Rotondo, Italy
Thomas Edouard, MD, PhD, University Hospital Center of Purpan, Toulouse, France
Bruce D. Gelb, MD, PhD, Mindich Child Health and Development Institute, Icahn School of Medicine at Mt. Sinai, New York, NY, USA
Kristiana Gordon, MD, Dermatology & Lymphovascular Medicine, St George’s Healthcare NHS Trust, London, UK
Anne Goriely, PhD, MRC Weatherall Institute of Molecular Medicine (WIMM) University of Oxford, Oxford, UK
Monika Gos, MD, Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland
Karen Gripp, MD, Division of Medical Genetics, A. I. du Pont Hospital for Children/Nemours, Wilmington, DE, USA
Hakon Hakonarson, PhD, Center for Applied Genomics, The Children’s Hospital of Philadelphia, University of Pennsylvania
Max Itkin, MD, PhD, Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
Susanne Kamphausen, MD, Institute of Human Genetics, University Hospital of Magdeburg, Germany
George Kensah, PhD, Department of Thoracic and Cardiovascular Surgery, University of Göttingen, Göttingen, Germany.
Bronwyn Kerr, MD, Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
Christian Kratz, MD, Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany
Erika Leenders, MD, PhD, Dept. Human Genetics and Donders Center for Neuroscience, Radboudumc, Nijmegen, the Netherlands.
Eric Legius, MD, PhD, Center for Human Genetics, KU Leuven, Leuven, Belgium
Ian Legg, President, Noonan Syndrome Association, UK
Christina Liśkiewski, PhD, Institute of Human Genetics, University Hospital of Magdeburg, Germany
Sahar Mansour, MD, SW Thames Regional Genetics Service, St George’s Healthcare NHS Trust, London, UK
Simone Martinelli, PhD, Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy
Laura Mazzanti, MD, Rare Disease Unit, Department of Pediatrics, St. Orsola-Malpighi Hospital, Bologna, Italy
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Francesca Pantaleoni, PhD, Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, Rome, Italy
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Alexandra Scott, MD, Service de Génétique médicale, CHU Ste-Justine, Montréal, Canada
Lisa Schoyer, MFA, President of RASopathiesNET, 244 Taos Road, Altadena, CA, USA
Sonia Severin, PhD, Institut des Maladies Métaboliques et Cardiovasculaires, INSERM/Université Paul Sabatier, Toulouse, France
Raj Sewduth, PhD, VIB-KU Leuven Center for Cancer Biology, VIB, Leuven, Belgium
Lorenzo Stella, PhD, Department of Chemical Science and Technologies, University of Rome Tor Vergata, Rome, Italy
Marco Tartaglia, PhD, Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, Rome, Italy
Dagmar Tiemens, M.Sc., Med. Member of the Dutch Noonan Syndrome Foundation
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Mikka Vikkula, MD, PhD, Human Molecular Genetics, de Duve Institute, University of Louvain, Brussels, Belgium.
Elien Wingbermühle, PhD, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands
Cordula Wolf, MD, Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University of Munich, Munich, Germany.
Armelle Yart, MD, PhD, INSERM UMR1048, Institute of Cardiovascular and Metabolic Diseases, Paul Sabatier University, Toulouse, France
Martin Zenker, MD, Institute of Human Genetics, University Hospital of Magdeburg, Germany
Giuseppe Zampino, MD, Center for Rare Diseases and Congenital Defects, Institute of Pediatrics, Fondazione Polidoclonico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Sponsorship: