EUROCleftNet Research Conference

Genetics, Environment and Prevention

30th June – 1st July 2016

Apex City Quay Hotel

West Victoria Dock Road, Dundee, Scotland

EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

UNIVERSITY OF DUNDEE

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***Note**: over the course of the conference you may be photographed as a result of your participation in EUROCleftNet conference activities. These photographs may be used when reporting about the event. If you do not want your photograph to be used please advise Bill Slater, Programme Coordinator, University of Dundee (w.j.slater@dundee.ac.uk)*

On behalf of the people and the local council of Dundee it is my privilege and pleasure to warmly welcome delegates to the EUROCleftNet Research Conference.

You will find that like most vibrant major urban areas we are in the process of changing for the future. But, unlike anywhere else that I know of, our geographical setting, the openness and hospitality of our people and the sheer scale of what we are doing will take your breath away! For many years the preparation, literally the ground work, for a new street layout and creation of development sites at Dundee Waterfront has been going on, if not unnoticed then certainly without much fanfare.

That "business as usual" strategy was a deliberate one on our part, but for more than a year now it has been difficult to ignore the major changes going on linking the city centre with our spectacular riverfront setting. Work has started on Kengo Kuma's iconic structure for the V&A Museum of Design Dundee and elsewhere on the Waterfront space is being created for the addition of new restaurants, bars and hotels. Taken together all of that is predicted to create more than 700 new tourism jobs, attract three million extra visitors and generate a further £1bn of spend in the city's visitor economy

But we're not just about the commerce here on the banks of the Tay. I believe that learning, teaching and research are what lies at the soul of this city. The links between the University of Dundee and the city at many different levels are strong and can be traced back to the 19th century. It grew from calls for the extension of liberal education and the advancement of technical instruction in many of the UK's larger industrial communities in the 1860s and 1870s.

Now, with a campus that sits at the heart of Dundee and world class facilities within walking distance of coffee shops, cafes and culture, the university is an integral part of the vibrant city whose name it bears. Students, researchers and staff from all corners of the globe make Dundee their home and enliven every aspect of living here.

Our success in the creative arts has led to us being designated a UNESCO City of Design and further recognition of our achievements has manifested itself in all sorts of other ways, including being named "coolest little city in Britain" by GQ magazine. Perhaps that's why we recently opened up our first scheduled air link with mainland Europe through daily flights to Amsterdam - and when you add that to our flights to London Stansted, air connectivity in the city is really taking off!

In conclusion I would like to put on record how delighted I am that you have chosen Dundee as the location for this gathering of professionals from all over Europe and beyond. I am convinced that we will offer the hospitality, facilities and stimulating environment that you need to have a memorable and successful conference.

With my best wishes.

DUNDEE
ONE CITY, MANY DISCOVERIES

Cllr Bob Duncan, Lord Provost of Dundee

On behalf of the School of Dentistry, University of Dundee, and the EUROCleftNet Research Network, it is a pleasure to welcome you to our conference.

To provide some context, and to supplement the introductions of Professor Peter Mossey and Professor Michele Rubini, you will find details about EUROCleftNet's strategy, successes, the workshop proposals which led to this conference, Short Visits & Exchanges and other useful information throughout this document. Indeed, some of the early career researchers who have been supported by EUROCleftNet Short Visit & Exchange grants will be talking about their projects during Session 3 on Thursday.

I trust there will be ample opportunity for you to engage with fellow delegates - and that our programme will facilitate productive discussion and the exchange of ideas in a stimulating and collaborative environment.

We are extremely grateful for the support of the European Science Foundation who have enabled our Network to achieve so much over the last 5 years, culminating in our conference.

I would also like to extend a special 'thank you' to Dundee & Angus Convention Bureau (DACB) and Dundee City Council for helping to co-fund this event. Conference organisation has been planned in partnership with DACB throughout and, on behalf of all involved, I am truly thankful for their dedicated support.

Bill Slater
EUROCleftNet Programme Coordinator
School of Dentistry
University of Dundee
https://eurocleftnet.org/

EUROCleftNet Strategy

Network for Orofacial Clefts Research, Prevention and Treatment (EUROCleftNet) is a Research Networking Programme funded by the European Science Foundation

Primary objective:

To increase the European capability for cutting edge research aimed at:

(a) improving the quality of care of infants born with cleft lip and palate and address any inequalities across Europe

(b) improve knowledge on risk factors (genetic and environmental) with a view to primary prevention

(c) engage with clinicians, scientists, parents and research users in the strategic planning and conducting of our research.

Steps towards this objective:

- *Development of a strategy for engaging European cleft teams and laboratories in ongoing and new European research collaborations initiative.*
- *Identification and involvement of users in research design and development of outcomes measures for orofacial clefts.*
- *Encourage research initiatives that are aimed towards improving minimum standards of cleft care, universal access to care and equality of care.*
- *Development of a priority list of questions for patient-centred research in the field of orofacial clefts.*

Strategic action points and priorities:

1. To create a Directory of Resources to facilitate research.
2. To continue to promote the concept of collaboration between clinicians and geneticists in research (which underpinned the success of EUROcran).
3. To pursue a portfolio of clinical and genetics research and apply for external funding.
4. To engage with a wide range of stakeholders (including beyond Europe) to ensure that this ESF is able to address orofacial clefting holistically and globally.
5. To communicate and disseminate research findings through local, national and international networks

EUROCleftNet Successes

At the EUROCleftNet mid-term review (MTR) in June 2014 we were asked to list those items that illustrated research progress. The feedback from ESF on this was positive and it was on this basis that the extension to the project was approved.

1. Pan European directory of resources created through the Gateway project
2. Dialogue surrounding the development and contribution to the EUROCran Biobank for cleft trio samples
3. On-going short visits and exchanges (SVE) dealing with a range of research issues
4. Publications arising as a result of inter-centre/multi-disciplinary collaboration
5. Engagement with colleagues in eastern Europe regarding involvement in research in Eastern Europe
6. Addressing inequalities through improving collaboration and research capacity in Eastern Europe
7. Evidence of use of the Gateway project to improve the communication and dialogue between cleft researchers across Europe
8. Links with other organisations: the European Cleft Organisation, CEN Standards Agency in Brussels, research collaborators who were not collaborators originally i.e. the University of Ferrara and ALA, Bulgaria
9. Engagement with MEPs at a parliamentary session in October 2012 dedicated to presentation of orofacial clefting issues across Europe
10. Engagement with industrial partners such as 3dMD, Xpand, Slimmer-Zwanger and charitable organisations
11. Translation of information and research protocols into other languages to facilitate understanding and research
12. Meeting with Scottish Parliament MSPs on Rare Diseases Day and dissemination of EUROCleftNet information
13. Links with like-minded research organisations in Europe and beyond, including international links for collaborative research e.g. Trans-Atlantic collaboration
14. Links with other EU research bodies and programmes such as COST (psychological issues concerning cleft lip and palate)
15. Engagement with colleagues at International meeting in Orlando, involvement in the global Task Force on oral clefts
16. Engagement in the Global Oral Health Inequalities Research Network
17. Research grant application (€5 million EURO) submitted to Horizon 2020 in April 2014

Prior application to the Marie Curie FP7 programme (and plans to submit applications to MC and H2020 again in 2014 and 2015

08:00 – 08:30 Registration (Mezzanine Library)
Tea / Coffee on arrival

All sessions will be held in the Art Gallery on the Mezzanine Level

08:30 – 08:40 **Welcome:** Timothy Newman (Vice-Principal for Research, Knowledge Exchange & Wider Impact, University of Dundee, Scotland)

08:40 – 09:00 **Introduction:** Peter Mossey (University of Dundee, Scotland)
EUROCleftNet - Networking cleft research across Europe

09:00 – 09:10 **Introduction:** Michele Rubini (Medical Genetics Unit - Dept. of Biomedical and Specialty Surgical Sciences, University of Ferrara, Italy)
P4-Cleft: Translating scientific achievement into applications

Thursday 30th June

Session 1 (09:10 – 10:30)
Chairs: Michele Rubini and Peter Mossey
Prediction - identifying cleft loci
(15 minute presentations)

09:10 - 09:25 Elisabeth Mangold (Institute of Human Genetics, University of Bonn, Germany)
Genetic background of nonsyndromic orofacial clefting – Where are we today?

09:25 - 09:40 Elizabeth J. Leslie (University of Pittsburgh, USA)
Taking a genome-wide multiethnic view of orofacial cleft risk

09:40 – 09:55 Adrianna Mostowska (Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poland)
GWAS analysis identifies three novel loci for nsCL/P in the Polish population

09:55 – 10:10 Michael Dixon (University of Manchester, England)
The syndromic / non-syndromic interface in the quest for causative genetic variants

10:10 – 10:30 **Plenary Discussion**

10:30 – 11:00 Break (Mezzanine Library)

Session 2 (11:00 – 12:30)
Chairs: Elisabeth Mangold and
Prediction - identifying cleft-causing variants
(15 minute presentations)

11:00 – 11:15 Azeez Butali (University of Iowa, USA)
Optimising the value of GWAS data by data cleaning and diagnosing more homogeneous subsets

11:15 – 11:30 Lina Moreno (University of Iowa, USA)
A Population-Based Assessment of Effects of Top Candidate Loci for Nonsyndromic Clefting

11:30 – 11:45 Kerstin U. Ludwig (Emmy-Nöther Junior Research group leader, Institute of Human Genetics, University of Bonn, Germany)
Novel insights in orofacial clefting: the power of integrative approaches using clinical and genotype information as well as data from animal models

11:45 – 12:00 Mary L. Marazita (University of Pittsburgh, USA)
Subclinical phenotypic features for genetics research within OFC families

12:00 – 12:15 David R. FitzPatrick (Institute of Genetics & Molecular Medicine, Edinburgh, Scotland)
The clinical and molecular features associated with de novo mutations of SATB2

12:15 – 12:30 **Plenary Discussion**

12:30 – 13:30 LUNCH (Mezzanine Library)

Session 3 (13:30 – 14:45)

Chairs: Peter Mossey and Michele Rubini

Early career researchers discuss their projects

(7 minutes presentations)

1. Faisal Khan (University of Ferrara, Italy)
   Project Title: *Optimising the Cleft case-parent trios DNA bio-bank from EU and advantaged gene-environment interaction studies*

2. Karen A. Pisani (University of Ferrara, Italy)
   Project Title: *Biobank of lip tissue and genomic DNA from nsCL/P cases and pilot epigenetic study*

3. Rita Bassi Andreasi (Medical Genetics Unit – Dept. Of Biomedical and Specialty Surgical Sciences, University of Ferrara, Italy)
   Project Title: *Replication of CNVs studies in patients with syndromic cleft palate*

4. Anne C. Böhmer (Institute of Human Genetics, University of Bonn, Germany)
   Project Title: *Unravelling the complex genetic basis of non-syndromic cleft lip with or without cleft palate – functional follow-up studies at the 13q31 susceptibility locus*

5. Shaho Al Talabani (University of Dundee, Scotland)
   Project Title: *Identification of phenotypic and genotypic markers in the predisposition to OFC through parental microforms*

6. Paola Franceschelli (University of Ferrara, Italy)
   Project Title: *High density genome wide arrays applied to parents of children born with non-syndromic cleft lip and/or palate*

14:15 – 14:45 **Plenary Discussion**

14:45 – 15:15 Break (Mezzanine Library)

Session 4 (15:15 – 17:00)

Chairs: Julian Little and Ron Munger

Personalization - identifying cleft-causing gene-environment interactions

(15 minute presentations)

15:15 – 15:30 George Wehby (University of Iowa, USA)
Genetic Instrumental Variables (Mendelian Randomization): Using Genes to Identify Causal Effects of Environmental Factors

15:30 – 15:45 Julian Little (University of Ottawa, Canada)
Epidemiology of folic acid in mitigating orofacial clefts

15:45 – 16:00 Michele Rubini (Medical Genetics Unit - Dept. of Biomedical and Specialty Surgical Sciences, University of Ferrara, Italy)
Folic acid and nutrigenetics of orofacial clefts

16:00 – 16:15 Adrianna Mostowska (Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poland)
Is there a genetic link between psychological factors such as stress and the risk of OFC?

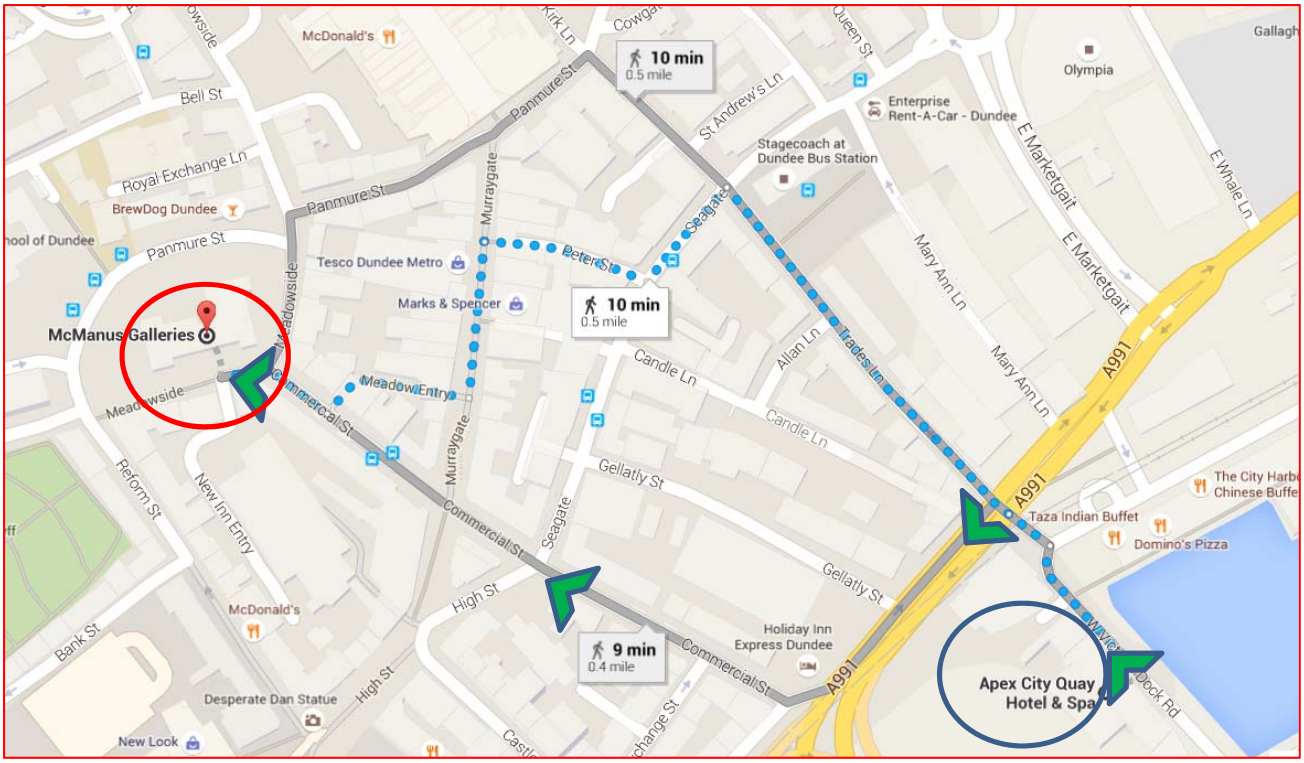
16:15 – 16:30 Heiko Peters (Newcastle University, England)
Functional validation of OFC risk loci using mouse models

16:30 – 17:00 **Plenary Discussion**

19:00 – 23:00 Civic Reception and Evening Meal @
The McManus: Dundee's Art Gallery & Museum
Albert Square, Meadowside, Dundee

Thursday 30th June

Directions from Apex City Quay Hotel to the McManus:
Dundee's Art Gallery and Museum https://goo.gl/maps/H6SJhYssEUq



http://www.mcmanus.co.uk/

Friday 1st July

08:30 – 08:50 **Registration (Mezzanine Library)**
Tea / Coffee on arrival

Session 5 (08:50 – 10:20)
Chairs: Peter Mossey and Régine Steegers-Theunissen
Prevention – monitoring cleft occurrence and recurrence
(20 minute presentations)

08:50 – 09:00 Peter Mossey (University of Dundee, Scotland)
Welcome and Introduction

09:00 – 09:20 Amanda Neville (University of Ferrara, Italy)
The EUROCAT approach to primary prevention

09:20 – 09:40 Ester Garne (Hospital Lillebaelt, Denmark)
Orofacial clefts and fetal medication exposure in the first trimester of pregnancy: what is the risk?

09:40 – 10:00 Régine Steegers-Theunissen (Erasmus MC, the Netherlands)
Novel opportunities for primary and tertiary prevention of (non)syndromic clefting using evidence-based mHealth coaching programs

10:00 – 10:20 **Plenary Discussion**

10:20 – 10:50 **Break (Mezzanine Library)**

Session 6 (10:50 – 12:10)
Chairs: TBC and George Wehby
Prevention – reducing cleft occurrence and recurrence
(20 minute presentations)

10:50 – 11:10 Julian Little (University of Ottawa, Canada)
Environment-specific maternal genetic effects in orofacial clefts

11:10 – 11:30 Ron Munger (Utah State University, USA)
Biomarkers of maternal exposures and metabolic abnormalities and risk of orofacial clefts

11:30 – 11:50 Peter Mossey (University of Dundee, Scotland)
The evidence base for intervention with respect to smoking and consanguinity

11:50 – 12:10 **Plenary Discussion**

12:10 – 13:10 LUNCH (Metro Brasserie)

Session 7 (13:10 – 15:40)

Chairs: Peter Mossey and Bill Slater

Workshop: The future of cleft research

13:10 – 13:30 Cordelia Lennon (University of Dundee, Scotland / Kite Innovation (Europe) Ltd)
European Commission Horizon 2020 (H2020) Health Programme

13:30 – 14:30 Workshops on future collaborations and funding: 3 break out groups, plus possibility of a special interest group
Break out groups will be in either Art Gallery; Venice Room or Barcelona Room

This Workshop will explore the research priorities of international funding agencies, such as National Institute of Health (NIH) / National Institute of Dental and Craniofacial Research (NIDCR), European Commission H2020 and others – and whether there is convergence in other funders for projects that offer opportunities for research of international or global significance in the field of clefts and craniofacial anomalies.

Group (1) Funding priorities and opportunities for collaborative genetic research
Led by: Michele Rubini / Mary L. Marazita / Jonathan Berg

Group (2) Future of OFC clinical and phenomics research networks from global perspective
Led by: Peter Mossey / Bill Shaw / Matthew Darlison

Group (3) Global priorities for research in prevention of OFC
Led by: Julian Little / Ester Garne / Ron Munger

Group (4) Special interest workshop (tbc) as required depending on outcomes from earlier sessions

(continued on next page)

Relevant questions to raise in this workshop are as follows:

1. Are cleft and craniofacial anomalies viewed as an eligible priority for global action?

2. Can we align cleft research with other non-communicable diseases (NCDs) such as diabetes / obesity?

3. Is there an associated health inequalities issue?

4. Can we exploit cleft research alongside the wider issue of reproductive health?

5. What commercial / industrial / economic angles offer research opportunities?

6. Is health economics a significant factor in cleft research?

7. Could non-governmental organisations (NGOs) concerned with cleft care be persuaded that "prevention is better than cure"?

14:30 – 15:00 **Break (Mezzanine Library)**

15:00 – 15:20 **Workshop Feedback (Plenary)**

15:20 – 15:40 **Discussion on Future Planning**

Session 8 (15:40 – 17:00)

Chairs: Bill Shaw and Mary L. Marazita

Participation – Synergies between patients/parents and scientists/clinicians

(15 minute presentations)

15:40 – 15:55 Gareth Davies (European Cleft Organisation)
The role of the European Cleft Organisation (ECO) in supporting best practice and prevention agendas through advocacy, education, and research networking

15:55 – 16:10 Matthew Darlison (University College London, England)
Orofacial Clefts in the Global Context of Congenital Disorders

16:10 – 16:25 Ron Munger (Utah State University, USA)
International Development Goals

16:25 – 16:40 Peter Mossey (University of Dundee, Scotland)
Clefts and craniofacial anomalies: alternative funding strategies in light of global priorities

16:40 – 17:00 Mary L. Marazita (University of Pittsburgh, USA) and Peter Mossey (University of Dundee, Scotland)
Global Task Force for epidemiology, aetiology and prevention

17:00 Close

Speakers – Thursday 30th June

Peter A. Mossey
Professor of Craniofacial Development and Associate Dean for Research, University of Dundee, Scotland

Abstract 1: ***The evidence base for intervention with respect to smoking and consanguinity.*** Meta-analyses reveal that passive smoking and consanguinity ARE both risk factors in OFC. Mossey, P.A.

"*Passive smoking in the etiology of non-syndromic orofacial clefts: a systematic review and meta-analysis*"**.** Sabbagh HJ, Hassan MH, Innes NP, Elkodary HM, Little J, Mossey PA

Data extraction from studies reporting maternal passive smoking and NSOFC was implemented without language restrictions. Risks of bias in the identified studies were assessed and this information was used in sensitivity analyses to explain heterogeneity. Meta-analysis and meta-regression of the extracted data were performed. Egger's test was used to test for small study effects. Fourteen eligible articles were identified. Maternal passive smoking exposure was associated with a twofold increase in risk of NSOFC (odds ratio: 2.11, 95% confidence interval: 1.54–2.89); this was apparent for both cleft lip with and without palate (OR: 2.05, 95% CI: 1.27–3.3) and cleft palate (OR: 2.11, 95% CI: 1.23–3.62).

There was substantial heterogeneity between studies. In the studies that provided data enabling crude and adjusted odd ratios to be compared, adjustment for potential confounders attenuated the magnitude of association to about a 1.5-fold increase in risk.

"*Parental Consanguinity and Nonsyndromic Orofacial Clefts in Children: A Systematic Review and Meta-Analyses*". Sabbagh HJ, Hassan MH, Innes NP, Al Baik A, Mossey PA

Objective: To assess whether individuals born to consanguineous parents had a higher frequency of nonsyndromic orofacial clefts compared with those with no parental consanguinity.

Design: A prespecified plan for a search strategy, inclusion/exclusion criteria, and data extraction from studies reporting consanguinity in relation to nonsyndromic orofacial clefts (NSOFC) was carried out. Papers reporting observational studies with control populations were included, without language restrictions, and these reports were assessed for quality. Sensitivity analyses using subgroups, homogeneity evaluation, and assessment of publication bias were carried out, and meta-analyses of extracted data were performed.

Speakers – Thursday 30th June

Results: Sixteen studies fulfilled the selection criteria and were included in the metaanalyses. There were statistically significant relationships between consanguinity and NSOFC for all 16 studies combined (P = .0003), with odds ratio (OR) = 1.83 and 95% confidence interval (CI) (1.31, 2.54); 10 case-control studies (P = .006), with OR = 2.06 and 95% CI (1.23, 3.46); six cross-sectional studies (P = .03), with OR = 1.34 and 95% CI (1.02, 1.76); first cousins consanguineous marriages (P = .04), with OR = 1.40 and 95% CI (1.01, 1.93); cleft palate alone (P =.01), with OR = 1.89 and 95% CI (1.14, 3.13); and cleft lip with or without cleft palate cases (P = .002), with OR = 1.56 and 95% CI (1.18, 2.07).
Conclusion: Although there was a high level of study heterogeneity, the evidence is consistent in suggesting that consanguinity is a risk factor for NSOFC, with an overall OR of 1.83 (95% CI, 1.31 to 2.54), implying that there was almost twice the risk of a child with NSOFC being born if there was parental consanguinity.

Abstract 2: ***Clefts and craniofacial anomalies: alternative funding strategies in light of global priorities***. We often look to the large funding bodies and stakeholders when seeking guidance on fundable strategies in health. Recent WHO priorities have included non-communicable diseases and disorders, and the Global burden of disease (GBD) is an attempt to quantify the mortality and morbidity is in relation to a range of disorders and diseases. Fortunately a number of the more prevalent birth defects are included in the 2010 WHO recommendations to Member states. The sustainable development goals (SDGs) are a call to action for low income and developing countries, and it is incumbent on the international community to assist with these. The EU Horizon 2020 priorities for funding in health include rare diseases and it is prudent to explore the landscape of Craniofacial disorders including clefts when considering future strategy.

NIH / NIDCR are one of the prime sources of funding for Craniofacial research and post GWAS, there may well be opportunities for cleft research under a recent call on “Genetic sustainability and variability of human structural birth defects”. The NIDCR FY 2015 emphasised a focus on inequalities and the value of a global approach to "apply rigorous, multidisciplinary research approaches to overcome disparities in Dental, Oral and Craniofacial health". This also mentioned the building of a strong evidence base for cost-effective implementation with health economics, cost-effectiveness and cost benefit of health interventions requiring more emphasis with a focus on prevention. Upstream social determinants of health and the common risk factor approach to a number of Do we have the robust evidence base, standardised measuring instruments and costings to be able to make a strong case for craniofacial anomalies and OFC using the health economics and health inequalities agendas?

Speakers – Thursday 30th June

Michele Rubini
Medical Genetics Unit - Dept. of Biomedical and Specialty Surgical Sciences, University of Ferrara, Italy

Abstract 1: ***P4-Cleft: Translating scientific achievement into applications.*** Research into the genetic causes of non-syndromic orofacial cleft (OFC) has recently made great strides and led to the identification of major OFC loci. New research developments are now directed to track down of variants with functional significance, to unravel how exposure to environmental factors interacts with genotype in determining OFC risk, and to identify endophenotypes and epigenomic modifications that can be used for diagnostic and predictive purposes. To better care for children with OFC scientific discoveries must be translated into practical clinical applications. Translational research is needed to provide clinicians with safer, more effective, and more powerful tools for both diagnosis, treatment and management of patients with OFC. However, translational research cannot rely only on the contribution of scientists and clinicians, but strongly needs also active participation of proband's families, and a shift from reactive symptoms-centered medicine to a proactive and patient-centered approach. Prediction, Prevention, Personalization, and Participation are the fundamental components of a proactive approach for CL/P patients (the P4-Cleft approach).

Abstract 2: ***Folic acid and nutrigenetics of orofacial clefts.*** There is evidence that maternal exposure to folate deficiency or to folic acid antagonists during early pregnancy increases the risk of orofacial cleft in the offspring, while supplementation with folic acid in the periconceptional period is generally considered a mild protective factor. Inter-individual differences in the response to folic acid supplementation could be ascribed – at least in part - to common functional variants in genes encoding one-carbon metabolism enzymes or folate transporters, and some evidence supports interaction between folate gene polymorphisms and folic acid supplementation as factor influencing the risk of developing orofacial cleft. Increasing our knowledge on such interactions could potentially lead to developing personalized preventive measures, with higher effectiveness in avoiding cleft recurrence.

Speakers – Thursday 30th June

Elizabeth J. Leslie

Assistant Professor, School of Dental Medicine, University of Pittsburgh, United States of America

Abstract: ***Taking a genome-wide multiethnic view of orofacial cleft risk.*** Orofacial clefts (OFCs) are caused by incomplete fusion of the upper lip and/or palate, resulting in three major subtypes: cleft lip (CL), cleft palate (CP), and CL plus CP (CLP). Combined they represent the most common craniofacial birth defects in humans. OFCs are also noted for the variability of prevalence rates observed around the world. The highest rates of OFCs are found in those of Asian and Amerindian ancestry; individuals with European ancestry have intermediate prevalence rates and individuals with African ancestry are reported to have the lowest rates. As a disorder with complex etiology, multiple genome-wide association studies (GWAS) have been completed in the pursuit of genetic risk factors for OFCs. Although initially performed in cohorts of European ancestry, the last five years have witnessed application of GWAS to diverse populations. One intriguing finding has been the identification of apparently population-specific association results. GWASs of orofacial clefts will be summarized with a particular emphasis on signals with differences in strength between populations. Explanations for the difference in strength of associations will be discussed.

Elisabeth Mangold

MD, Principal Investigator "Genetics of Orofacial Clefting" project, Genetic Counselor, Institute of Human Genetics, University of Bonn, Germany

Abstract: ***Genetic background of nonsyndromic orofacial clefting – Where are we today?*** Nonsyndromic orofacial clefts have a multifactorial etiology, involving both genetic and environmental factors. The first molecular genetic attempts to elucidate the genetic background date back to the late 1980s, and in the early years many candidate genes and loci were studied, however, results of the most of these studies remained inconclusive and had limited overlap. Only in 2008 a candidate gene approach led to a first convincing result: the identification of a causative variant for nonsyndromic cleft lip with/without cleft palate (nsCL/) in the IRF6 promotor region. In 2009 a meta-analysis of linkage data and subsequent fine-mapping gave convincing statistical evidence for the FOXE1 region. The introduction of high-throughput genotyping technologies has enabled genome-wide association studies (GWAS), which have been extremely successful in that they identified multiple common causative loci. The first GWAS was published in 2009 and discovered the 8q24 region as a key susceptibility locus for nsCL/P. Subsequent GWAS in larger samples, meta-analyses of GWAS data, combinations with replication studies and imputation of GWAS data led to identification of many more causative loci for nsCL/P. At the time of writing only 21 susceptibility loci for nsCL/P and one for nonsyndromic cleft palate have been published, and more are yet to come. For some of these loci a sub-phenotype specific effect has been found. Functional studies have identified a causative variant at the NOG locus, and will detect more of them at other loci. In the near future whole-exome and whole-genome sequencing approaches will detect further causative variants, among them rare mutations. A better understanding of the genetic background will pave the way for a better understanding of the underlying biology.

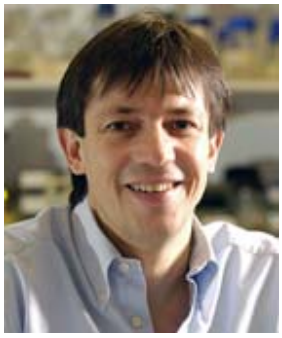
Speakers – Thursday 30th June

Adrianna Mostowska
Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poland

Abstract 1: ***GWAS analysis identifies three novel loci for NSCL/P in the Polish population.*** Non-syndromic cleft lip with or without cleft palate (nsCL/P) is one of the most common congenital anomalies, with a complex and not yet fully elucidated aetiology. Therefore, we conducted a genome-wide association study (GWAS) for nsCL/P in a Polish population-based cohort consisting of 288 oral cleft cases and 576 controls, with a further replication in an additional independent sample. Genome-wide genotyping was performed using Illumina HumanOmniExpressExome-8v1 array enriched for functional exonic markers. We identified three novel loci associated with nsCL/P at 3q29 (rs338217, $p_{comb} = 2.56 \times 10^{-10}$), 6p22.3 (rs9356746, $p_{comb} = 6.31 \times 10^{-6}$) and 12q14.1 (rs7305482, $p_{comb} = 3.61 \times 10^{-9}$). Promising candidate genes at these chromosomal regions include *DLG1* (discs, large homolog 1) and *CDKAL1* (CDK5 regulatory subunit associated protein 1-like 1). In addition, we confirmed the association between the previously reported loci at 1p21.3 (*ARHGAP29*), 8q24.21, 14q22.2 (*GCH1*) and 15q13.3 (*GREM1*) and the risk of nsCL/P. The most significant nucleotide variant in this study was rs17242358 (8q24.21 gene desert) with pcomb = 4.87×10^{-17}. To confirm our GWAS findings further, larger sample size studies in different populations are needed.

Abstract 2: ***Is there a genetic link between psychological factors such as stress and the risk of OFC?*** It has been shown that heightened levels of maternal psychological stress in the periconceptional period may be implicated in the aetiology of non-syndromic cleft lip with or without cleft palate (nsCL/P). However, the differences in stress measurements and a lack of consensus on the definition of maternal stress are reasons that only a small number of researchers are considering the presence of stressful life events during pregnancy as a risk factor in nsCL/P occurrence. In addition, the influence of environmental and genetic factors on each individual's variability in the stress response create additional challenges when investigating the mental/emotional stress as an nsCL/P causal factor. One mechanism by which maternal stressors may cause birth defects is dysregulation of the major stress response system, the hypothalamus-pituitary-adrenal (HPA) axis, leading to increased glucocorticoid production at the adrenals. The emotional state of the mother may also alter the function of the placenta, affecting uterine blood supply and nutrient transfer. In one of our projects, we investigated the association between nucleotide variants of stress related genes and the risk of nsCL/P affected pregnancies. We found that polymorphisms in *SLC6A4* (serotonin transporter) and *TPH2* (tryptophan hyroxylase 2) might be factors increasing the risk of having a baby with this developmental anomaly. The implication of maternal *TPH2* and *SLC6A4* variants in the risk of nsCL/P might be associated not only with the function of serotonin in the brain and regulation of HPA axis reactivity but also with the crucial role of serotonin during foetal development.

Speakers – Thursday 30th June



Michael Dixon
Professor of Dental Genetics, University of Manchester, England

Abstract: ***The syndromic / non-syndromic interface in the quest for causative genetic variants.*** Clefts of the lip and/or palate (CLP) are common birth defects of complex aetiology. CLP affects approximately 1/700 live births, with wide variability across geographic origin, racial and ethnic groups, as well as environmental exposures and socioeconomic status. Historically, CLP has been divided into cleft palate only (CPO) and cleft lip with or without cleft palate (CL/P); this broad sub-division of anatomical defects is consistent with the distinct developmental origins of the lip/primary palate and the secondary palate.

CLP can occur in isolation or, together with additional non-cleft anomalies, as part of a syndrome. Approximately 70% of all cases of CL/P and 50% of cases of CPO are considered to be non-syndromic. The remaining cases are composed of a wide range of malformation syndromes, including over 500 Mendelian syndromes, as well as those arising secondary to chromosomal or teratogenic effects. As syndromic forms of CLP are somewhat more tractable to genetic analysis than their non-syndromic counterparts, extrapolation from syndromic CLP has proven to be useful in the study of non-syndromic CLP.

Azeez Butali
Assistant Professor of Oral Pathology, Radiology and Medicine. University of Iowa, United States of America

Abstract: ***Optimising the value of GWAS data by data cleaning and diagnosing more homogeneous subsets.*** For us to address OFC comprehensively, it is important to understand the causes and to explore strategies for prevention. OFCs are complex traits with genes, environment and stochastic factors contributing to the phenotypic expression in any given individual. To date 6 genome wide association studies (GWAS) for cleft lip with or without cleft palate (CL/P) have been conducted and 18 risk loci identified. All these studies have either been conducted in European populations, Asian populations or both. There is currently no published GWAS for clefts in African only populations. This presentation will discuss findings during data cleaning from the first African only cleft GWAS. The characterization of a homogenous subset is an essential step towards the identification of significant risk loci.

Speakers – Thursday 30th June

Heiko Peters
Reader in Mammalian Genetics, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, England

Abstract: ***Functional validation of OFC risk loci using mouse models.*** The number of newly identified genetic risk loci involved in OFC is rapidly increasing but how they are contributing to OFC in the developing embryo is often unknown. In principle, genetic variants in non-coding regions may point to adverse changes in the timing, the levels, or the region of expression of nearby genes. Genetically modified mice and organ culture experiments can help to distinguish between these possibilities, thereby allowing to study the pathogenic mechanism of de-regulated gene expression affecting craniofacial development. Focusing on specific gene-gene and gene-environment interactions ongoing work will be described that is aimed at defining the pathogenic mechanism of cleft lip and cleft palate formation involving de-regulated expression of Grem1 and Msx1.

Mary L. Marazita
Director, Center for Craniofacial and Dental Genetics; Professor and Vice Chair, Department of Oral Biology, School of Dental Medicine; Professor, Department of Human Genetics, Graduate School of Public Health; Professor, Clinical and Translational Science; Professor, Department of Psychiatry, School of Medicine. University of Pittsburgh, United States of America

Abstract: ***Subclinical phenotypic features for genetics research within OFC families.*** Orofacial cleft (OFC) birth defects exhibit a wide range of phenotypic variability due to the multiple oral and facial structures involved, and the potential for other complexity such as complete versus incomplete defects, unilateral versus bilateral cleft lips, clefts of the hard and/or soft palate. There are also visible microforms such as bifid uvula and notches in the upper lip that are considered very minor manifestations along the spectrum of OFC defects. We hypothesize that there is additional subclinical phenotypic variation within apparently unaffected family members that reflects carrying genetic risk factors, that can help explain reduced penetrance in OFC families, and that might be useful in dissecting genetic heterogeneity. We will present results from GWAS of OFC families and controls, incorporating such subclinical phenotypes.

Speakers – Thursday 30th June

David R. FitzPatrick
Professor, MRC Human Genetics Unit, MRC Institute of Genetics & Molecular Medicine, University of Edinburgh Western General Hospital, Edinburgh, Scotland

Abstract: ***The clinical and molecular features associated with de novo mutations of SATB2.*** We originally identified SATB2 as a gene on 2q33 that caused cleft palate. The advent of new sequencing technologies have allowed many individuals to be screened for causative variants in all genes. I will present clinical, genetic and molecular features associated with de novo mutations (DNM) affecting SATB2 function in 19 unreported cases ascertained on the basis of intellectual disability (ID). Cleft palate was present in less than half of the cases (9/19) although other oral features were common including absent/near absent speech (16/19), drooling (12/19) and dental anomalies (8/19). 11/19 of the DNM were clear loss of function. Eight missense variants were identified and shown to cluster in the first CUT DNA binding domain (6/8). Sibling recurrence due to gonadal mosaicism was seen in one family. A stop-gained mutation in the last exon resulted in production of a truncated protein retaining all three DNA binding domains. The nuclear mobility of the tagged proteins differed significantly between the wild-type with p.Arg389Cys in CUT1 showing increased mobility and both p. Gly515Ser in CUT2 and p.Gln566Lys between CUT2 and HOX showing reduced mobility. The clinical features in the individuals with missense or stop-gain in the last exon were indistinguishable from each other or from cases with LOF mutation. De novo, heterozygous mutations in SATB2 represent one of the commonest genetic causes of syndromic ID. Haploinsufficiency appears to the universal mechanism and where mutant SATB2 protein is produced disturbance of the normal pattern of chromatin association is observed.

Faisal Khan
University of Ferrara, Italy

Abstract: ***Optimising the EUROCRAN DNA trios bio-bank with western EU biobank, and carry on some gene-environment studies.*** Our repository of genomic DNA from cleft cases, or Cleft-bio-bank, is a collection of European Case-parent trios DNA samples/data which is often derived from blood and/or saliva specimens. The maintenance of Cleft-bio-bank preserves the opportunity for future research or genetic testing in order to benefit the case-parent trios and cases community as a whole. Our Cleft-bio-bank includes samples from the EUROCRAN and ITALCLEFT/PENTACLEFT projects, and is an open access research DNA bio-bank in order to supplement EUROCleftNet members. Being a EUROCleftNet membered group, we took advantage of the Cleft-bio-bank and in order, we examined the pool of European trios for frequency of transmission between two TGFA insertion/deletion and susceptibility of developing nsCL/P. Additionally, the test of gene-environment interactions between the two insertion/deletion markers in TGFA and two common maternal exposures (smoking and folic acid supplementation) during pregnancy are factored.

Speakers – Thursday 30th June

Karen A. Pisani
University of Ferrara, Italy

Abstract: ***Biobank of lip tissue and genomic DNA from nsCL/P cases and pilot epigenetic study.*** Epigenetic modifications could play a role in the interaction between environmental factors and genotypes, and some evidence in mice model suggest that altered methylation could impair the correct fusion of lip prominences during embryogenesis, causing cleft lip. To date no studies have been carried out in humans to explore the role of epigenetics in clefting. A collection of tissue samples obtained at time of surgery, along with genomic DNA from case- parents trios and clinical data has been established in Ferrara from 2015. Preliminary results obtained by assaying a global DNA methylation biomarker (LINE-1) are presented.

Rita Bassi Andreasi

Medical Genetics Unit – Dept. Of Biomedical and Specialty Surgical Sciences, University of Ferrara, Italy

Abstract: ***Replication of CNVs studies in patients with syndromic cleft palate.*** Evidence suggests that Copy Number Variations (CNVs) may play a role in the development of cleft palate. A number of deletions or duplications have been detected in patients with syndromic cleft palate, among which those encompassing the 22q11 region are of particular interest. In previous studies, Comparative Genomic Hybridisation array (aCGH) has been used to identify association between CNVs and syndromic cleft palate. In order to confirm findings, we replicated results using a different technique: CytoScan® 750K Array Kit, Affymetrix. We report the results obtained after screening of a group of syndromic cleft palate cases from Glasgow, NHS Greater Glasgow and Clyde.

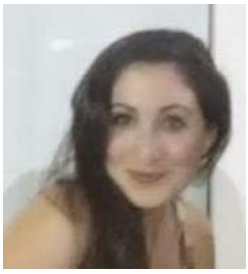
Anne C. Böhmer
Postdoctoral scientist, Institute of Human Genetics, University of Bonn, Germany

Abstract: ***Unravelling the complex genetic basis of non-syndromic cleft lip with or without cleft palate – functional follow-up studies at the 13q31 susceptibility locus.*** Genome-wide association studies (GWAS) have largely contributed to a better understanding of genetic risk regions for complex disorders. The 13q31 locus has been identified as risk locus for non-syndromic cleft lip and cleft palate (nsCLP) in a meta-analysis of single GWAS (Ludwig et al, 2012). Similar to numerous GWAS findings in other traits, the top-associated genetic variants at 13q31 map to a non-coding region. Functional data suggest that regulatory elements at the locus might play a role in the development of the murine face. During my ESF-funded research visit in Michael Dixon's lab I (i) studied regulatory regions at the 13q31 locus and (ii) performed expression analyses of the Sprouty2 gene (SPRY2). The data revealed that (i) the top-associated variants mapped to enhancer elements involved in craniofacial development and (ii) that SPRY2 is expressed in palate forming structures in mouse embryos at stages E11.5 and E13.5. The integration of functional data generated during my research visit and our genetic data from the meta-analysis suggest functional mechanisms underlying the genetic association at 13q31 and generate new hypotheses for further follow-up studies.

Speakers – Thursday 30th June

Shaho Al Talabani
University of Dundee, Scotland

Abstract: ***Identification of phenotypic and genotypic markers in the predisposition to OFC through parental microforms.*** Facial shape, lip prints, orbicularis oral muscle (OOM) status, dental features and the genotype of 81 parents of children with NSOFC were compared to a control group of 73 non-cleft participants of Celtic background. The facial shape and dental features statistically differed between the groups and the OOM defect rate was higher in the parental group in comparison to the controls, however no lip print differences were detected. A candidate gene approach analysis detected some genetic association with case-control status but there were no genotype-phenotype correlations using selected candidate gene polymorphisms.



Paola Franceschelli
University of Ferrara, Italy

Abstract: ***High density genome wide arrays applied to parents of children born with non-syndromic cleft lip and/or palate.*** The complex aetiology of Non-syndromic Orofacial Cleft is still not completely understood, and there is little information about how the genetic risk carried by unaffected relatives can be inherited by children with overt oral clefts. In the present work, aimed to investigate the possible role of cleft candidate genes in unaffected parents, we conducted a case-control association study, using 80 unaffected parents of children with overt orofacial cleft (recruited through clinics in Scotland) and 70 controls (recruited at the University of Dundee, Scotland). Samples were genotyped using high-density genome-wide human arrays (Cytoscan 750K _array, Affymetrix), collecting data from 200,000 SNPs. Considering the small sample set, the association analysis has been restricted to known associated loci and specific candidate regions, to avoid some of the difficulties presented by multiple testing: the Odds Ratio was calculated for 122 SNPs across 30 candidate loci. Among this, 3 SNPs showed a significant inverse association: rs6657063 C>G, an intron variant in ARHGAP29 gene (ORCCC/GG = 0.21, 95%CI: 0.05-0.83, P=0.02), rs3901678 C>A, an intron variant in THADA gene (ORCA-/CC = 0.36, 95%CI: 0.14-0.89, P=0.025), and rs10956463 A>C, located in 8q21.13 (ORAA/CC = 0.31, 95%CI: 0.109-0.902, P=0.02). These preliminary results demonstrate how unaffected relatives present variations in genes thought to be involved in cleft lip and palate development and suggest the possibility of a phenotype-genotype correlation in presence of facial cleft-related subclinical features.

Speakers – Thursday 30th June

Kerstin U. Ludwig
Emmy-Nöther Junior Research group leader, Institute of Human Genetics, University of Bonn, Germany

Abstract: **Novel insights in orofacial clefting: the power of integrative approaches using clinical and genotype information as well as data from animal models.** Despite considerable advances in our understanding of genetic risk loci contributing to nonsyndromic cleft lip with or without cleft palate (nsCL/P), little is known about etiological factors that discriminate between its most common types cleft lip only (nsCLO) and cleft lip and palate (nsCLP). We suggest that the integration of detailed clinical phenotype data, high-resolution genotypes and information obtained from animal models can help to identify novel risk factors for nsCL/P in general, but also provide new insights into nsCL/P subphenotypes. Along these lines, in a recent study, we performed a meta-analysis on three large nsCL/P cohorts and identified strong association between a region on chromosome 15q13, close to the Gremlin-1 (GREM1) gene. In the nsCLP group, relative risks were even higher, and no association was observed in nsCLO. Based on analyses of the murine Grem1 expression pattern during embryonic craniofacial development, the nsCLP patient cohort was further subdivided according to precise clinical data on affected structures. We observed a more than two-fold increase in risk for patients displaying concurrent clefts of both the lip and soft palate but with an intact hard palate. This study identified the first genetic contribution to a rare clinical nsCLP entity which specifically involves clefts of the lip and the soft palate, which develop at different embryological time points.

Julian Little
Professor and Director, School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Canada

Abstract 1: ***Epidemiology of folic acid in mitigating orofacial clefts.*** Two key randomized controlled trials in the 1990's clearly demonstrated that folic acid supplementation in the periconceptional period prevented the first occurrence and recurrence of NTDs by approximately 70%. In Canada, where folic acid fortification of white flour, pasta and some other cereal-based products has been mandatory since November 1998, the prevalence at birth of NTDs has declined by approximately 45%. Fortification has also been implemented in the United States, Argentina, Brazil and Chile. For all types of orofacial clefts (OFC) combined, there was a decrease in prevalence at birth after the introduction of fortification in the United States, but not in the other jurisdictions where fortification was mandated.

Multivitamin supplements are associated with a reduced risk for CL±CP and perhaps CP. In a meta-analysis published in 2008, combined effect estimates indicated risk reductions of 25% and 12% for CL±CP and CP respectively. It is not possible to determine from these studies which of the nutrients in the multivitamins are protective and whether or not other healthy behaviours of multivitamin users

confound these results. Similarly, the effect of dietary or supplemental intake of folic acid on OFCs is uncertain, with one observational study even suggesting an increased risk associated with supplemental intake. The uncertainty was affirmed in a recently updated Cochrane review.
Possible mechanisms involved in putative effects of folic acid supplementation on OFCs have been investigated. These include whether variants of genes thought to be involved in folate metabolism present in the mother or the infant, such as MTHFR, contribute to the risk of OFC. Recent studies also suggest that folic acid may influence the pathogenesis of congenital anomalies through other pathways, including epigenetic mechanisms with possible trans-generational effects. A possible implication of epigenetic mechanisms is that a possible beneficial effect of folic acid fortification in reducing the prevalence at birth of congenital anomalies other than NTDs may take more than one generation to become fully apparent.

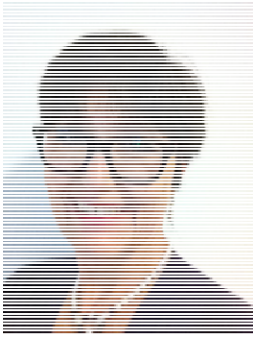
Abstract 2: ***Environment-specific maternal genetic effects in orofacial clefts.*** More than two thirds of CL±CP cases and about half of CP cases occur are non-syndromic, while the other cases are associated with known teratogens, chromosomal anomalies or single-gene syndromes. Non-syndromic OFCs are thought to be caused by genetic and environmental factors and their joint effects. Although the heritability of OFC has been estimated to be high, as yet few genes or loci involved in the etiology of OFC have been identified, either from GWA or candidate gene studies.

The mother can influence her offspring's risk of disease (1) as a genetic donor; (2) through the effect of her genotype on the intrauterine environment directly; (3) indirectly through feto-maternal gene-gene interactions; or (4) through her exposures and associated interactions with her genotype or that of the developing fetus. Several candidate gene studies of OFCs have suggested maternal genetic effects, and in a recent GWAS, several signals of maternal effects almost reached genome-wide significance. Evidence of maternal genetic effects, and of environmental specificity will be discussed, together with challenges in identifying these.

George Wehby
Associate Professor, Health Management and Policy Doctoral Program Director, University of Iowa, United States of America

Abstract: ***Genetic Instrumental Variables (Mendelian Randomization): Using Genes to Identify Causal Effects of Environmental Factors.*** Behavioral risk factors for oral clefts such as smoking, excessive alcohol, and obesity have been suggested in several studies, but previous studies have focused on association estimates and did not provide causal evidence. We examine the effects of maternal smoking, pre-pregnancy weight, and alcohol consumption on the risk of having a child with oral clefts using genetic instrumental variables (Mendelian Randomization). We employ data on a large sample from an international consortium of several population-based case-control and case-cohort studies from the United States and Europe. The presentation will cover study methods and preliminary results.

Speakers – Friday 1st July



Amanda J. Neville
EUROCAT registry leader and JRC EUROCAT joint management committee member; IMER Emilia Romagna birth defects registry; Centre for Epidemiological and Clinical Research, University of Ferrara, Italy - Azienda ospedaliero universitario di Ferrara

Abstract: ***The EUROCAT approach to primary prevention.*** Congenital anomalies (CA) are the paradigm example of rare diseases liable to primary prevention actions due to the multifactorial etiology of many of them, involving a number of environmental factors together with genetic predispositions. Yet despite the preventive potential, lack of attention to an integrated preventive strategy has led to the prevalence of CA remaining relatively stable in recent decades. The 2 European projects, EUROCAT and EUROPLAN, have joined efforts to provide the first science-based and comprehensive set of recommendations for the primary prevention of CA in the European Union. The resulting EUROCAT-EUROPLAN 'Recommendations on Policies to Be Considered for the Primary Prevention of Congenital Anomalies in National Plans and Strategies on Rare Diseases' were issued in 2012 and endorsed by EUCERD (European Union Committee of Experts on Rare Diseases) in 2013. The recommendations exploit interdisciplinary expertise encompassing drugs, diet, lifestyles, maternal health status, and the environment. The recommendations include evidence-based actions aimed at reducing risk factors and at increasing protective factors and behaviours at both individual and population level. Moreover, consideration is given to topics specifically related to CA (e.g. folate status, teratogens) as well as of broad public health impact (e.g. obesity, smoking) which call for specific attention to their relevance in the pre- and periconceptional period.

Ester Garne
Paediatric Department, Hospital Lillebaelt, Kolding, Denmark

Abstract: ***Orofacial clefts and fetal medication exposure in the first trimester of pregnancy: what is the risk?*** In 2006 FDA sent out an alert of increased risk for cleft palate after fetal exposure to lamotrigine in pregnancy. EUROCAT explored this in a large European dataset and was not able to confirm the increased risk. The initial EUROCAT study has now been updated with more years and more exposed pregnancies. The 4-year EUROmediCAT project aimed to build a system for reproductive safety evaluation, to enable the systematic and comprehensive identification of possible adverse effects in pregnancy of medication in humans at the earliest stage post marketing. Four medication groups for chronic maternal diseases were the main focus. Risk of orofacial clefts were evaluated for medications used in asthma, depression, diabetes and epilepsy. Orofacial clefts often came up as a risk from the literature reviews performed in the EUROmediCAT study. Results and impact of the findings will be presented.

Speakers – Friday 1st July

Régine P.M. Steegers-Theunissen
Professor in Periconception Epidemiology, Erasmus MC, the Netherlands

Abstract: ***Novel opportunities for primary and tertiary prevention of (non)syndromic clefting using evidence-based mHealth coaching programs.*** The (non)syndromic clefts (NSC) originate during the first trimester of pregnancy being a largely missed period in antenatal care. Derangements in growth, development and epigenetic programming are involved in the causation of NSC and are largely determined by gene-environmental interactions. The environmental factors also include parental conditions and behaviors such as folic acid supplement use, nutrition, smoking, obesity and non-prescribed medication use. Although most of these personal environmental factors are modifiable, they are extremely difficult to change. Parents–to-be however are most motivated to change poor behaviors when they are aware of the detrimental effects on their (unborn) child. Therefore, these couples should be empowered to use evidence-based and personalized effective tools to improve poor conditions and behaviors. Moreover, these tools should be implemented as instruments to support healthcare professionals in delivering 'nutrition and lifestyle care' in routine patient care. From this background the usability and effectiveness of the mHealth coaching programs (www.SmarterPregnancy.org.uk, www.SlimmerZwanger.nl and www.SlimmerEtenMetJeKind.nl) aiming to change poor behaviors and to improve pregnancy outcome and support healthy eating during the first year of life of the child will be presented as opportunity to customize these tools for the target group of families with enhanced risks of NSC offspring or a child with NSC as well as for their healthcare professionals.

Lina Moreno
Assistant Professor, Department of Orthodontics, College of Dentistry & Dental Clinics, University of Iowa, United States of America

Abstract: ***A Population-Based Assessment of Effects of Top Candidate Loci for Nonsyndromic Clefting.*** Recent GWAS have reported several genes and loci to be associated with non-syndromic oral clefts. However, the generalizability of effect estimates is unclear as the evidence is heavily based on clinic-based samples that may suffer from ascertainment bias. Small samples have also limited the investigations of effects by cleft type and non-syndromic versus syndromic status as well as underlying genetic mechanisms involving maternal gene and parent-of-origin effects. We estimate the effects of main previously reported loci on cleft types in both non-syndromic and syndromic forms using data from a large consortium of population-based case-control and case-cohort studies from the United States and Europe. We examine fetal, maternal gene, and parent-of-origin effects. The presentation will cover study methods and preliminary results.

Speakers – Friday 1st July

Ron Munger
Professor, Department of Nutrition, Dietetics, and Food Sciences, Utah State University, United States of America

Abstract 1: ***Biomarkers of maternal exposures and metabolic abnormalities and risk of orofacial clefts.*** Biomarkers may be useful additions to self-reported data to estimate the magnitude of maternal environmental exposures and to classify mothers according to the type and level of metabolic abnormalities that may be relevant to the risk of having a child with an orofacial cleft (OFC). Prospective collection of biological specimens very early in pregnancy in large cohorts would be helpful, but few ideal studies exist with adequate sample collections. A less ideal but more feasible approach is to conduct case-control studies with careful collection and processing of biological specimens; this approach may be useful when there is relative stability in diets and environmental exposures, when genetic and epigenetic determinants of biomarker levels are important, and for metabolic conditions such as diabetes that tend to be chronic and worsen over time. Two metabolic themes with evidence linking to risk of OFCs include folate-related one-carbon metabolism (1CM) and the cluster of metabolic abnormalities that are precursors to diabetes, known collectively as metabolic syndrome. Our biomarkers studies from the U.S., Philippines, and India provide evidence of the importance of several nutrients involved in 1CM including folate, vitamins B6 and B12, and zinc; the nutritional backgrounds of these populations are very different, hence there are very different patterns of biomarker associations with OFCs. Our studies in Utah indicate that mothers of affected children are less responsive to folic acid intake than controls, that multivitamin supplements are only protective when combined with healthy dietary patterns, and that several genes known to be involved in 1CM may interact with maternal nutrient status to alter risk of OFCs. Obesity and diabetes have been linked to risk of OFCs clefts. Gestational diabetes is far more common than pre-existing diabetes among women of reproductive age and is associated with OFC risk but is tested for and diagnosed in later pregnancy and the mechanisms for OFC formation early in pregnancy are unknown. Our ongoing studies of metabolic syndrome biomarkers in case and control mothers provide evidence that systemic inflammation and altered adipokine levels may be promising biomarkers for mechanistic studies early in pregnancy. Biomarker studies will allow greater understanding of the mechanisms of OFC formation in gene-environment studies and may be important in public health approaches to screen high-risk individuals and populations for targeted nutritional and lifestyle interventions for health promotion and OFC prevention.

Professor Munger's second presentation is on the theme of ***International Development Goals.*** This is during Session 8 (the final Session on Friday 1st July) and will discuss the way forward globally in the funding of clefts in parallel with other disorders.

Speakers – Friday 1st July

Matthew Darlison
Informatics Lead, WHO Collaborating Centre for Community Genetics, UCL Centre for Health Informatics & Multiprofessional Education (CHIME)

Abstract: ***Orofacial Clefts in the Global Context of Congenital Disorders.*** Focussing initially on haemoglobin disorders, work has been ongoing in conjunction with the human genetics programme of the World Health Organisation since the early 1980s to make estimates of the prevalence of a variety of congenital disorders and the associated health burdens.

The most recent round of estimation was initiated by an invitation to the March of Dimes to facilitate inputs to the Global Burden of Disease project, and has now led to the formation of an international working group of experts. The group is led from London by Professors Bernadette Modell (UCL) and Joy Lawn (LSHTM), and aims to estimate baseline birth prevalences, effects of interventions, plus survival and disability to 5 years and beyond, for congenital disorders at the country, WHO region and global levels. Work is ongoing to enable comprehensive publication of data from the Modell Global Database of Constitutional Congenital Disorders (MGDb) online, and estimation methods in a special edition of the Journal of Community Genetics.

Collaborative work is also in progress with the Eastern Mediterranean Regional Office of WHO to support the development of a regional strategy for congenital disorders covering both environmental and "constitutional" causes.

Databases like MGDb help to locate individual disorders, such as orofacial clefts, in a global context in which the priorities are broader: transparency and consensus around epidemiological science as a foundation for sound, evidence-based health policy advocacy and policymaking, leading ultimately to provision of effective, responsive services by knowledgeable and well-supported practitioners.
To achieve this, however, we need community-wide consensus on what we are counting, and how, and on how we attribute various levels of disability.

Since they are easily diagnosed and can be treated surgically with high clinical effectiveness, orofacial clefts represent a point of entry for assessing the effect of paediatric surgery and may thus be in a position to lead the way in defining and developing models for capturing epidemiological data, measuring cost effectiveness and delivering care.

Speakers – Friday 1st July

Gareth Davies
European Cleft Organisation

Abstract: ***The role of the European Cleft Organisation (ECO) in supporting best practice and prevention agendas through advocacy, education, and research networking.*** ECO has adopted a multi-faceted approach in highlighting the challenges of cleft care and promoting prevention. This presentation will explore strategies at various levels. Firstly, as a political lobbying body at European level we aim to engage with, and influence, health agendas at national level. Secondly, we have a track record of using EU instruments to turn knowledge into action by producing and disseminating evidence-based best practice guidelines for health professionals and support groups. Finally we, aim to impact upon the research and prevention agenda through a new role as an accredited European Patient Advocacy Group (ePAG) within the European Reference Network (ERN) for Rare Craniofacial Anomalies and ENT Disorders.

Cordelia Lennon
University of Dundee, Scotland / Kite Innovation (Europe) Ltd

Abstract: ***Horizon 2020 Funding Opportunities: Health, Demographic Change and Wellbeing.*** Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. By coupling research and innovation, Horizon 2020 is helping to achieve this with its emphasis on excellent science, industrial leadership and tackling societal challenges. The goal is to ensure Europe produces world-class science, removes barriers to innovation and makes it easier for the public and private sectors to work together in delivering innovation. The focus of this presentation is on forthcoming funding opportunities in Societal Challenge 1 Health, Demographic Change and Wellbeing

Workshop Proposals (original application)

Workshop proposal 6 (joint with Workshop 7)

Proposed Title: **P4-CLEFT. Translating Genetics Research Achievements into Prediction, Prevention, Personalization and Participation Dundee, May / June 2016**

Coordinator: Michele Rubini / Peter Mossey

Abstract: The scientific knowledge on cleft genetics had increased enormously in the last years, and time is come to turn them into practice.

The P4-CLEFT workshop is aimed to put together the major European scientists and clinicians contributing to cleft research and pave the way for translating knowledge into applications using a proactive approach that make use of the latest biotechnologies and maximizes the role of patient's families' participation.

Aims and Objectives: Research into the genetic causes of non-syndromic Cleft Lip/Palate (CL/P) has recently made great strides and led to the identification of major CL/P loci. New research developments are now directed to track down of variants with functional significance, to unravel how exposure to environmental factors interacts with genotype in determining CL/P risk, and to identify endophenotypes and epigenomic modifications that can be used for diagnostic and predictive purposes.

The amount of knowledge in the field of cleft genetics has grown enormously in the latest years, and time is come to turn it into practice. To better care for children with Cleft Lip/Palate (CL/P) scientific discoveries must be translated into practical clinical applications. Translational research is needed to provide clinicians with safer, more effective, and more powerful tools for both diagnosis and management of patients with clefts.

Today's scientific knowledge on CL/P etiology and the implementation of next-generation sequencing technologies could allow the development of new and innovative tools aimed to help the clinician in the diagnosis of cleft patients and assessing the risk of recurrence. Moreover, the identification of gene-environment interactions and epigenetic modifications could possibly pave the way for the improvement of preventive measures and eventually identify genotype-tailored strategies.

Translational research cannot rely only on the contribution of scientists and clinicians, but strongly needs also active participation of proband's families, and a shift from reactive symptoms-centered medicine to a proactive and patient-centered approach.

The P4-CLEFT Workshop is aimed to gather the major European scientist and clinicians that have recently contributed to the cleft research, and create the better conditions for a multi-disciplinary brainstorming to translate the overall knowledge into practical applications. P4-CLEFT is expected to kick-off the new era of proactive cleft care, based on the use of latest biotechnologies, the tight interplay between scientists and clinicians, and the active participation of patient's families.

Workshop Proposals (original application)

Workshop proposal 7 and Dissemination Conference (joint with Workshop 6)

Proposed Title: **Primary prevention of birth defects in Europe – with orofacial clefts (OFC) as a demonstration model, Dundee, May / June 2016** ***Coordinator: Peter Mossey***

This Workshop will invite input from a range of stakeholders (see invitation list) whose interests in primary prevention forms a major component of their current work. High profile among these in Europe are the initiatives at EUROCAT, ICBDSR, and the initiative by Prof. Régine Steegers-Theunissen, ErasmusMC, The Netherlands and the Global Task Force for Prevention of CFA. These 3 complimentary projects will form the basis of the EUROCleftNet Primary Prevention Workshop in Dundee in May / June 2016.

EUROCAT primary prevention initiative:
The EUROCAT strategy for the future in relation to prevention is clearly stated in the EUROCAT – EUROPLAN: Primary Prevention getting the EUROCAT recommendations into action.

In recent years CA have been identified as one of the major groups of rare diseases in need of cross-border research. In this framework the Public Health Programme 2008-2013 of the European Commission has funded the EUROCAT joint action (2011-2013) which has the key objectives of improving the surveillance and the identification of strategies for primary prevention of CA (http://www.eurocat-network.eu/aboutus/jointactioneurocat). EUROCAT JA task force encompasses 36 associate partners, nine collaborating partners and it is structured into 9 work packages (WP). The National Centre for Rare Diseases of the Istituto Superiore di Sanità coordinates WP7 “Primary Prevention of Congenital Anomalies”. The aim of the WP7 is to establish a shared primary prevention strategy for CA by developing recommendations to be incorporated in EU MS National Plans with the support of the European project for Rare Diseases National Plans Development (EUROPLAN).

Smarter Medical Care and Feeding of Your Child with Cleft Lip and or Palate:
Background: Babies born with cleft lip and or palate have several medical and feeding problems which can impair their growth, development and health during the lifecourse. Because of these problems, they have a lifelong need of special (health) care. The nutrition and lifestyle habits of the parents, in particular during the first years of life, have a significant impact on the feeding and health of their vulnerable babies. So far, individual coaching on medical care, nutrition and lifestyle is a gap in current health care.

Innovation: At the Erasmus MC Prof. dr Régine Steegers-Theunissen, Dept Obstetrics and Gynaecology has led the mHealth coaching program on nutrition and lifestyle "Smarter Feeding with your child” (www.slimmeretenmetjekind.nl) has been developed and launched for parents and caregivers of a healthy child. Here it is our aim to adapt this interactive P4 program on the smart phone for parents of a newborn suffering from a cleft lip and or palate. Empowerment of the parents in changing poor nutrition and lifestyle, and the support in the compliance of medical care, breast- and formula feeding and feeding of their child during the first years of life is our ultimate goal. After translation into the English language and the development of the content and programming of this mHealth platform, it has to be tested on usability and efficacy in a randomized controlled trial. After that it will be ready for implementation in health care.

Impact: If the platform Smarter Medical Care and Feeding of Your Child with Cleft Lip and or Palate proves to be effective in terms of improving nutrition and lifestyle of the parents and growth, development, compliance of medical care, and health of the child, it will contribute to significant health gains and savings in health care costs.
(continued)

Workshop Proposals (original application)

Global Task Force for Prevention of CFA

The Global Task Force initiative was launched at the International Craniofacial Congress (ICC) in Orlando in 2013, and will be progressed further via the next ICC in Chennai in 2017.

Background: The original presentation for the global Task Force 'Beyond Eurocleft' proposed using the European cleft research model to ensure (a) widespread geographic dissemination and (b) succession planning – a new generation of scientists and researchers to be equipped with the skills and the enthusiasm to continue pursuing orofacial cleft (OFC) research.

Major themes in cleft research: The two major themes in OFC research are 1. improving access to and providing best multidisciplinary care for OFC patients and 2. improving knowledge on causation and risk factors. The ultimate goal of such research is to identify possibilities for primary prevention by the following actions:

1. Birth Defects surveillance: the prevalence of OFC and good infrastructure for ascertainment is necessary particularly when preventive interventions are planned

2. Environmental factors: measurement of environmental factors (nutrition, environmental exposures, behavioural factors and medical history) should shift towards biomarkers for precision of measurement.

3. Genetic factors: through GWAS the landscape of genetic predisposition has changed over the last five years. The studies to date suggest that there are different genetic markers predisposing to orofacial clefts in different populations.

4. GEI/GGI/Epigenetics: future studies will concentrate much more on interactions between genetic and environmental factors, interactions between genes in the same or different pathways and epigenetic factors such as DNA methylation and its influence on phenotype.

5. Implementation agenda: the move to more collaborative studies and an implementation agenda have the potential to accelerate the progress of cleft research.

Short Visits & Exchanges (SVEs)

A feature of our Network was our Shorts Visits & Exchanges (SVEs). Short visits were up to 15 days and exchange visits were from 15 days to six months. Planned visits had to be directly relevant to the scope of our Research Networking Programme. A selection of successful applications is provided here:

Application - Germany – UK - September 2015 (4 weeks)

Applicant: Anne Böhmer, Institute of Human Genetics, Department of Genomics, Life & Brain Centre, University of Bonn, Bonn, Germany

Visiting: Professor Mike Dixon, Professor of Dental Genetics, University of Manchester, United Kingdom

Short description of the proposed project and the aim of the visit: Aim of the proposed exchange to the Manchester group are further analyses in order to identify and interpret causative variants in patients with nsCL/P at the specific 13q31 locus. I will perform targeted ChIP-Seq experiments at the 13q31 locus using antibodies against relevant epigenetic marks (e.g. H3K4me3, H3K27ac) to identify regulatory elements of direct relevance to development of the lip and palate. Using the RNA-seq data already generated by the Manchester group will enable gene expression analysis the developing facial processes. I will also link relevant regulatory elements to the genes that they control using a combination of in situ hybridization and chromatin conformation capture analyses. The data that are generated during the project will provide functional targets that can be screened for genetic variation underlying susceptibility to nsCLP using high-throughput sequence analysis upon my return to Germany.

The groups at Manchester and Bonn have been successfully evaluating the genetic background of orofacial clefting for several years.

Address/Contact details of Host:

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Short Visits & Exchanges (SVEs)

Application - Bulgaria – UK - November 2015 (7 days)

Applicant: Maria Kazakova, speech and language therapist, Plovdiv cleft team, Division of Plastic and craniofacial surgery, 'St. George' University Hospital, Plovdiv, Bulgaria.
Visiting: Anne Roberts, Principle speech and language therapist, southwest cleft service, Bristol, United Kingdom
Short description of the proposed project and the aim of the visit.
1) To undertake a comparison of speech results in all types of clefts, operated on in Bulgaria and in Bristol over 5 years of age using each center's databases with video files.
2) To gain an understanding of previous and ongoing speech and language therapy research at the southwest cleft service.
3) To enhance the knowledge about multidisciplinary teamwork and learn how to integrate key aspects into existing provision of care in Plovdiv. The applicant will be able draw upon the highly experienced Swedish team in multidisciplinary approaches - discussions with all members of the team to gain an understanding of assessing the quality of multidisciplinary care and visits to cleft clinics, consultations, speech therapy and surgeries
4) To gain an understanding of how the team at the southwest cleft service Institute monitors and assesses speech and language development from birth to completion of treatment.
5) To study how the UK therapists provide appropriate and timely intervention. Discussions to include:

a) At what age do children start with speech therapy?
b) Methods used in delivering therapy
c) number of patients and frequency of consultations
d) educational resources available e.g. booklets
e) effective working with parents

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Bristol Dental Hospital
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BS1 2LY

Short Visits & Exchanges (SVEs)

Application - Bulgaria – UK - February 2016 (14 days)

Applicant: Nedialka Slaninkova, specialist cleft nurse, Plovdiv cleft team, Division of Plastic and craniofacial surgery, "St. George" University Hospital, Plovdiv, Bulgaria,

Visiting: Emma Southby, lead specialist cleft nurse, south Thames cleft service, St Thomas's Hospital, London, United

Short description of the proposed project and the aim of the visit.
From 2008 a network of feeding specialists exists in Bulgaria. Thanks to a Project of ECO and ALA, several trainings for feeding specialists were organized and a network of 15 feeding specialists with 2 supervisors already exists. A national web based register is functioning from September 2013 and the work of this network is supervised objectively by 2 specialists, Kostadinka Bojikova and Nedialka Slaninkova The experience of Nedialka Slaninkova in the care and feeding of with clefts and Pierre Robin Sequence is already significant, but an exchange of ideas and experiences will be very positive and motivating for her future work. Nedialka is also involved in the organization of multidisciplinary consultation done in every Friday in the Plastic and craniofacial Unit of Plovdiv Medical University. A close look up in the organization of the work of Emma Southby and other UK specialists (some days at another cleft unit, possibly Manchester, are being planned) will permit her to gain new ideas and experience in the management of the nurse network, and develop future training. In particular she would like to be able to plan and to plan comparative retrospective or prospective studies in several areas of scientific interest.

1. Comparison in the referral process between the UK and Bulgaria. In the ways of referral, timing and limitations in each country.
2. Preference and success with the different ways for feeding – type of bottles, parent preferences, success and weight gain.
3. Comparison in cases with Pierre robin sequence treated in Bulgaria and the UK for period of 1 year.
4. Comparison and models for the organization of the multidisciplinary consultation in the UK and Plovdiv.

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Short Visits & Exchanges (SVEs)

Application - Italy – Netherlands – Jan 16 - June 16 (6 months Extension)

Applicant: Paola Franceschelli, PhD student, University of Ferrara, Department of Biomedical and Special Surgery Sciences, Units of Medical Genetics, Italy.
Visiting: Dr Carine Carels**,** Radboud University, Nijmegen, Netherlands

Short description of the proposed project and the aim of the visit.
Aim of the visit: To investigate the molecular and epigenetic mechanisms involved in non-syndromic cleft lip and/or palate development.
Scientific background: Orofacial clefts (OFCs) are common birth defects affecting approximately 1/700 live births worldwide, and exhibit a complex aetiology due to multiple genetic and environmental risk factors. Although gene association studies and genome-wide association studies (GWAS) have identified several strongly associated susceptibility loci, causal variants are still unknown. Moreover, little is known about molecular and epigenetic mechanisms by which the environment adversely influences gene expression.
Specific aims and work plan: This project is in a continuation of the experimental plan that Dr Paola Franceschelli is carrying out in the frame of her 6-months Exchange Visit at the University of Dundee.

In the May-November 2015 project genetic candidate variants for OFCs are selected using a bioinformatics approaches and investigate by functional assay (Electrophoretic Mobility Shift Assay and Chromatin Immunoprecipitation). Outcomes obtained by November 2015 would be the prerequisite for further investigations aimed to 1) explore the complex of nuclear factors acting at level of identified functional variants, and 2) assess epigenetic modifications at somatic level.
The first aim could be carried out interacting with Radboud University of Nijmegen, where another EUROCleftNet-supported researcher (F. Conte) has recently developed applications of Oligonucleotides pull-down followed by Mass Spectrometry technology in the field of cleft research. This technology is expected to provide crucial insight into the actual complex mechanisms at the basis of the increased cleft risk associated with genetic variants.

The second aim would make use of lip tissue samples of patients and apply epigenetic technologies to investigate altered methylation profiles at level of cleft variant sites, end unravel the eventual role of epigenetic modifications in the lack fusion of lip processes during early embryogenesis

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Short Visits & Exchanges (SVEs)

Application - Italy - October 15 – March 2016 (6 months Extension)

Applicant: Faisal Khan, Dept. of Anatomy All India Institute of Medical Sciences (AIIMS) Ansari Nagar, New Delhi

Visiting: Michele Rubini, Università degli studi di Ferrara

Short description of the proposed project and the aim of the visit.
We are preparing a project mainly aimed to complete the rescue of old EUROCRAN samples and therefore maximize the power of that DNA-bank. In his first (ongoing) SVE project, Faisal aims to complete the West-EU biobank, and carry on some gene-environment studies. Actually, he has already explored another variant in TGFA (a 11bp deletion) and computational analyses should be completed shortly. The outcome of this investigation could possibly be taken by Paola as candidate to investigate with functional analyses.

Feisal next project would be the completing the rescue of EUROCRAN DNA collection, taking care of East-EU samples. Unfortunately most of samples rescued from Slovenia are not DNA but frozen (and mostly clotted) blood. To obtain good quality DNA from such bad quality samples automatic systems are not effective. DNA extraction needs to be done using manual procedures, one by one, on order to maximize the quality and quantity of the products. At the end of his second SVE Faisal is expected to provide EUROCleftNet a complete DNA bank. Moreover, in the 6-month period he would carry on some other genetic analyses.

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EUROCleftNet Biobank Management proposal

EUROCleftNet Biobank Management – Michele Rubini

Proposal type: Support to EUROCleftNet data management

Abstract: One of EUROCleftNet priority is to encourage collaboration, standardization and sharing at level of and biobanking DNA samples from cleft families.

To ensure optimal identification of cleft DNA samples and at the same time facilitate automation in handling vials, DNA samples are conveniently stored in 2D-barcoded cryotubes. In order to keep perfect track of each sample and make EUROCleftNet accessing this shared resource, management of cryotubes must be done using appropriate informatics technology and devices.

Aims and Objectives: One of the main aim of EUROCleftNet is to stimulate cooperation between scientists and clinicians across Europe and maximize the sharing of knowledge, expertise, facilities and materials. As agreed at the meeting in Bonn (2012), one of EUROCleftNet priority is to encourage collaboration, standardization and sharing at level of and biobanking DNA samples from cleft families. In particular, EUROCleftNet recommended research teams to agree and share standardized information on cleft patients and standardized cryogenic storing of DNA samples. The global goal of standardization was to link the existing cleft biobanks and establish a comprehensive European biobank network, with shared information, easy access to materials and sample quality suitable for robotic management and ultimate genetic technologies.

To ensure precise identification of every DNA sample and at the same time facilitate automation in handling vials, DNA samples are conveniently stored in 2D-barcoded cryotubes. The use of 2D-barcoded cryotubes has been adopted for storing samples rescued from the EUROCRAN and ITALCLEFT projects. The obtained set of samples - several thousands of cryovials – are organized in 96-tube racks and frozen at -80°C.

To manage this amount of cryotubes and meet the need of keeping track of each position and respond to request of EUROCleftNet researchers to access to each specific samples, an adequate computer equipped with 2D-barcode reader devices and backup system is required. Management software would be developed in order to provide online access to EUROCleftNet members through EUROCleftNet website. This could possibly be extended to include other European DNA banks, ultimately creating a network of cleft biobanks.

Publication plan: *Information dissemination and educational initiatives in the field of OFC*

In the field of birth defects in general and OFC through EUROCleftNet the issue of information dissemination, research networking and collaboration has been of paramount importance, and a central plank on which our success has been built.

Networking and knowledge dissemination for raising of standards has been a major EUROCleftNet programme objective since the project began and the Gateway project has been our flagship project for information dissemination, and has resulted in the most successful ever transfer of research and knowledge across Europe from west to east and vice versa in the field of OFC, resulting in tangible outcomes.

The EUROCleftNet mid-term conference hosted by Plovdiv in Bulgaria in 2013, the affiliation of Bulgaria as a EUROCleftNet partner, the success of implementing common standards for cleft care via CEN in Brussels, and to date the establishment of several successful SVEs (research exchanges) across Europe are examples of the dissemination and exchange of experiences and expertise. All of the future proposed Workshops will aim to have strong and equitable representation in countries from Eastern and Western Europe; and the final EUROCleftNet conference is described as a "dissemination" workshop – with the aim being to ensure that there is a lasting legacy for cleft care by virtue of the knowledge generated and disseminated.

Our mid-term report on the success of our Networking activities included information dissemination and publication of important scientific papers in the field of OFC, and the following will continue.

1. Pan European directory of resources created through the Gateway project
2. Translation of information and research protocols into other languages to facilitate understanding and research
3. Utilisation of the EUROCran DNA Biobank for ongoing research
4. On-going short visits and exchanges (SVE) dealing with a range of research issues
5. Publications arising as a result of inter-centre/multi-disciplinary collaboration
6. Engagement with colleagues in Eastern Europe regarding involvement in research
7. Links with other organisations: the European Cleft Organisation, CEN Standards Agency in Brussels, MEPs, the World Health Organisation and research collaborators and other EU research bodies and programmes such as COST
8. Engagement with industrial partners such as 3dMD, Xpand, Slimmer-Zwanger and charitable organisations (some of which have contributed to the ESF programme)
9. Research grant applications to the H2020, Marie Sladowski Curie programme (and plans to submit applications to MC and H2020 again in 2015, 2016 and beyond)

The steering group therefore anticipate that we will continue to publish EUROCleftNet derived material in the scientific literature as well as the Gateway website and where appropriate social media after June 2016, and a modest amount of funding €5,000 has been allocated for "open access" publications. We will continue to prioritise the prompt publication of our research findings for the benefit, not only of the scientific community, but also the European and global stakeholders in the OFC field and ultimately the infants who have been born with OFC, their parents and their families.

European Cleft Organisation

Founded in 2007, the **European Cleft Organisation (ECO)** is a not-for-profit NGO based in the Netherlands. We strive to ensure all babies born with cleft lip and/or cleft palate have equal access to high quality treatment and care across Europe.

We aim to prevent the abandonment and institutionalization of babies born with clefts – a practice that still occurs in some European countries. We work with local and international bodies, governments, regulators, health-care providers and national parent groups, helping them to achieve more effective outcomes and prevent marginalization. We are a political lobbying body at European level and aim to engage with, and influence, health agendas at national level.

We turn knowledge into action by producing and disseminating evidence-based best practice guidelines for health professionals and support groups. We facilitate learning through local training programmes, international workshops and exchanges of medical personnel. In partnership with other agencies we strive also to address public perception of clefts and counter discrimination in educational and work environments, seeking opportunities, where possible, to develop links with local and national media

Projects and programmes:


Fendlipo

Newsletter of the European Cleft Organisation

Early cleft care guidelines download available

Training in Serbia

Guidelines launched in Brussels

Dr Vesna Knjegnjić, Ministry of Health Republic of Serbia, addresses our meeting in Brussels

- Development of European guidelines in early cleft care (with European Committee for Standardisation (2015, CEN, Brussels) http://europeancleft.org/early-cleft-care-guidelines-now-available-as-a-download/
- Development with EUROCleftNet of web directory for cleft services in Europe (Cleft Gateway) a resource for cleft professionals and patients [**see pages 47-8**]. Currently over 100 centres represented and increasing.
- 8 year programme in Bulgaria, developing a national centre of excellence in cleft care in Plovdiv, working alongside a local partner. Training and developing networks of nurses and speech therapists. Reducing abandonment of babies with clefts.
- Facilitating front line early care training in Latvia, Lithuania, Romania, Serbia, Spain and overseeing development of RomaniaCleft, the first professional cleft association in Romania.
- Partner in 5 EU-funded collaborations - ESF 'EUROCleftNet', COST 'Appearance Matters', Erasmus+ 'When Looks get in the Way', 'Face Value' and 'IHEM' (health education modules).
- Coordinated 2 major European conferences – Plovdiv 2012 (research) Bucharest 2015 (specialist nursing) with funding from EUROCleftNet.

Subscribe to our newsletter on our website at www.europeancleft.org

European Cleft Gateway

European Cleft Gateway - Proposal for multi-language landing page

We are now keen to press ahead with the development of a multi-language 'landing page'.
To further encourage population of the database we are proposing to set up a multi-language internet 'landing page' which will direct people to the Gateway when a search is done for the word 'cleft' in any of 25 European languages. This will serve three purposes:

1) It will ensure patients, clinicians and researchers are rapidly able to use the resources provided by the Gateway
2) There will be an option on the landing page to upload information about cleft centres that are not listed in the directory. These can then be approached directly and asked to complete the online questionnaire.
3) It will further extend the reach of the EUROCleftNet programme throughout Europe

The technical work will be undertaken by Envision who have currently been appointed by the European Cleft Organisation (ECO) to update their own website. We will translate the landing page into the **24 official languages of the European Commission (see below) plus Russian.**

Bulgarian	French	Maltese
Croatian	German	Polish
Czech	Greek	Portuguese
Danish	Hungarian	Romanian
Dutch	Irish	Slovak
English	Italian	Slovene
Estonian	Latvian	Spanish
Finnish	Lithuanian	Swedish

An example of the 'landing page' is on the following page:

European Cleft Gateway

Example 'landing page' for anyone who types 'cleft' into Google in their own language

(text in language x)
Welcome to the European Cleft Gateway - a directory of cleft services throughout Europe developed by the European Cleft Organisation and funded by the European Science Foundation.
If you want to find the nearest hospital that provides treatment for children with clefts and/or undertakes research into cleft treatment and causes, please click on the links below (*direct links to country x details in Gateway*)

Centre 1 (country x)
Centre 2 (country x)
Centre 3 (country x)

The directory is being constantly updated and if you are aware of other hospitals in your country treating children with clefts please provide their contact details here (*link to a SHORT form with a "send" button which will come back to ECO*). We will then contact them and add them to the directory.

The directory also contains details of cleft support groups run by families with children with clefts. In your country we have details of:

Support group 1 (country x)
Support group 2 (country x)

If you know of other groups or support networks and would like to promote their activities via the Gateway and the European Cleft Organisation please provide details here *(link to contact details, activities undertaken, number of members, Facebook details, with a "send' button that will come back to ECO)*

Continue to main pages of European Cleft Organisation for more information about clefts. Choose language: EN/NL/ES/FR

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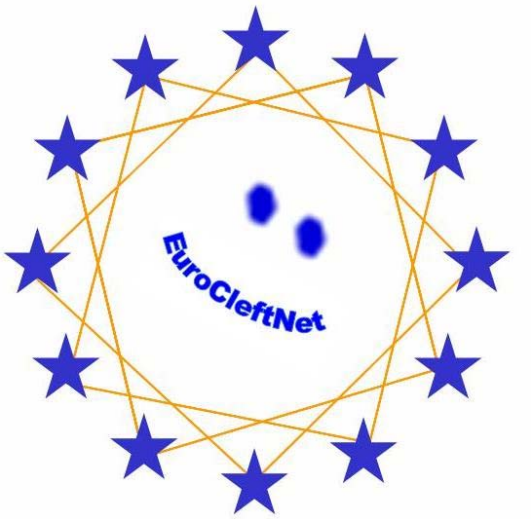
Our Venue

Apex City Quay Hotel & Spa is a contemporary hotel in Dundee, located Quayside near City Centre, Dundee University, and the future home of the V&A Museum of Design. Beyond its status as one of the best hotels in Dundee, the property also provides full Elemis spa treatments at Yu Spa Dundee, and operates the city's premier set of meeting spaces. Offering upscale accommodations, high-end event and meeting spaces, and forward-thinking dining to the edge of Dundee City Quay. The experience starts outside -- where 140-plus free parking spaces add convenience to every stay -- and continues to the friendly front desk staff and the hotel's amenities.


EuroCleftNet