EUROCleftNet Workshop and Steering Group meeting: 23rd June 2015,

Venue: Gothenburg, Sweden Gothia Towers - Room R26

This **EUROCleftNet Steering Group** meeting and Workshop was designed to coincide with the European Craniofacial Congress and to follow the Annual EUROCAT Registry leaders meeting 17-18 June 2013 in Ispra, Italy.

A detailed, timetabled and budgeted Workplan of EUROCleftnet activities for the last 12 months of the current project has been agreed and this proposal is appended to this Workshop Report. This involves a series of Workshops and Exchange visits, plus ongoing expansion of the Gateway directory of resources.

The WORKSHOP programme was as follows:

SESSION 1: Tuesday, 23rd June : Plenary programme

- **Session 1: INTRODUCTION**
- 9:00 - 9.15 Outline of the aims and objectives of this EUROCleftNet meeting (Peter Mossey)
- 9.15 - 9.30 Gateway update, utility and future plans (Gareth Davies)
- 9.30 - 9.45 Realising the EUROCleftNet objectives over next 12 months through SVEs, Workshops, Conferences – and possibilities for future funding (Peter Mossey)
- 9.45 – 10.00 SVEs to enhance the potential for collaborative research (Carine Carels /Jo Zhou)
- 10.00 -10.15 Maximizing Eastern European Engagement (Gareth / Borut / Youri)
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- **Session 2: REALISING THE EUROCLEFTNET RESEARCH OBJECTIVES**
- 10.30 -11.00 4D imaging - the new measurement paradigm in OFC research (Cilein Kearns)`
- 11.00 - 11.20 OFC outcomes and speech as a KEY outcome measure ? (Anette Lohmander)
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- **Session 3 : PLENARY 1.30 – 1.50 plus WORKSHOPS 2.00 – 3.00**
- 1.30 – 1.50 ECO and CEN : research opportunities (Gareth Davies / Peter Mossey)
- Brief introduction to Workshops:
- 2.00 – 3.00 Translational Research in the field of OFC: Genomics research opportunities: (Preliminary 10 minute presentation). **Chair : Michele Rubini**
- 2.00 – 3.00 Translational Research in the field of OFC: Phenomics research opportunties: (Preliminary 10 minute presentation). **Chair : Ashraf Ayoub**
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- **Session 4 : PLENARY 3.40 –4.30**
- 3.40 - 4.10 Workshop Feedback / Action Plan (15 minutes each)
- 4.10 – 4.30 Plenary Discussion (**Chair: Peter Mossey**)
- 4.30 – 5.00 Steering Group Discussion

All speakers on this plenary programme have offered a copy of their presentation slides and these can therefore be requested by delegates, who will receive a pdf copy by e-mail.

WORKSHOPS AND FUTURE FUNDING OPPORTUNITIES:

Two major themes were selected in the Ferrara meeting in September 2014 based on the expertise of EUROCleftNet personnel being cutting edge in Europe and globally (see below); and a major grant funding opportunity was also identified in Horizon 2020 PHC (Personalised Health Care) and *Marie* **Skłodowska-***Curie actions (*H2020-MSCA-ITN).

1. **Molecular diagnostics approach to risk assessment**: Using all the information at our disposal on the genetics / genomics of orofacial clefting to discuss the possibility of producing a gene-chip utilising the expertise from our existing EUROCleftNet groups particularly Bonn, Nijmegen, Manchester, combined with those who adopt a bioinformatics approach such as Ales Maver and Borut Peterlin, Lublijana, Slovenia.
2. **3D / 4D imaging in OFC diagnostics and outcomes**: The second theme of the conference relates to innovations in imaging for orofacial clefts (and beyond); and Ashraf Ayoub and Yang Ju from Glasgow agreed to lead on this theme, with invitations from a range of European collaborators in France, Italy, Greece and the Netherlands who are interested in making a contribution.

EUROCleftNet will continue to seek grant funding opportunities through the rather dynamic H2020 PHC avenue or a Marie Sklodowska Curie application or both.

PLENARY FEEDBACK after WORKSHOPS

WORKSHOP 1. Genetics / genomics / molecular group Workshop report:

Workshop title:"Translational Research in the field of OFC: Genomics research opportunities".

Since the EuroCleftNet Ferrara meeting in 2014, we have explored H2020 possibilities, but could not find the right call. Marie Curie ITN program could be suitable, but our plan was too premature to write up a good proposal.

The strategies of Marie Curie ITN application of the next call (early 2016) were discussed. We need to focus on increasing career perspective rather than only research. In addition, the amount of money from the ITN program might not be sufficient for collecting patients and for large-scale sequencing work. Furthermore, using cleft chip or alternative MIPS was also discussed. Therefore ITN may be suitable for analyzing existing cohorts, whereas H2020 funding would be necessary for collecting samples and other things.

For any of the upcoming grant opportunities, we need a good plan. The proposal should probably not start with only clefts, but with a much broader context, congenital conditions. Clefts can be used as an indicator of a bigger context i.e. a sentinel birth defect.

Topics that we can include: diagnostics and phenotyping (ns, syn, mms, non-chromosomal); sub-phenotyping that should establish standardized protocols; correlation of genomics and exposomics-phenomics (environmental factors and sub-phenotypes).

We have also discussed biomarkers: metabolites (performing metabolomics studies; retroperspective approach hair growth study, nails, etc). These biomarkers may not explain the genetics directly.

Concrete ideas

The next Marie-Curie ITN proposal will start with a bigger context and cleft studies as an example. It will focus on risks for pregnant women with studies on subphenotyping, biomarkers, omics. The content of the proposal include:

- Phenomics: 3D/4D, microforms, subphenotyping;
- Genetics: syndromic/non-syndromic, cleft-chip/(MIPS?)
- Biomarkers: metabolotomics

Potential title: Maternal and child health: common risk factor approach, with the following as essential elements:

1. For next MSCA or H2020 call Cleft is not a sufficient subject for a grant application but could be an optimal example (a "sentinel") in the frame of a proposal that covers a wider range of health conditions (in the area of Maternal and child's health).
2. MSCA application requires a strong and active participation of non-academic partners (not relegated to a secondary role). We should dedicate the next months for searching and identifying such partners.
3. MSCA application must have a tangible impact in terms of generating new skills, knowledge and innovation, and create career perspectives for early stage researchers. This requires active participation of non-academic units, and wide use of new technologies and innovative procedures.
4. Since it is quite improbable that next H2020 calls will suit to cleft genetics research it is wise to look beyond Europe to search for support. Besides collaborating in application for NIH grants, opportunities to apply in countries as Canada and Australia should be considered.

In the area of Maternal and Child's health – that is very wide - I think that we should focus on 1) a more precise aspect that 2) has a strong impact on health systems and 3) is attractive for private partners. Moreover, 4) cleft could be a major component.

A project facing the problem of exposure to common risk factors during early pregnancy, and aimed 1) to identify gene-environment interactions leading to pregnancy complication or congenital malformations (having cleft as a sentinel) and 2) to establish genotype-tailored measures for prevention could attract private partner collaboration, provide strategies and solutions to national health bodies, and be appealing for EU commission.

WORKSHOP 2. **Research opportunities in 3D/4D imaging**

Workshop Title: "Translational Research in the field of OFC: Phenomics research opportunities"

The workshop provided a unique brain storming opportunity for members of the EUROCleftNET, it was attended by 20 participants representing a wide range of expertise from several countries across Europe. The meeting started by 10 minutes presentation by Prof. Ayoub, the following was the scope of the presentation: The technological advantages and innovation in capturing both the static and dynamic morphology of the face:

- The non-invasive nature of the stereophotogrammetry and its broad clinical applications.
- Demonstration of image capture and analysis of some cleft cases.
- Pilot studies and the validation of the technology.
- Recent publications in peer-reviewed journals
- The previous unsuccessful submission of the project "EuFace 2020"

The discussion afterward focused on the following points:
1. To maximizing the funding opportunity the team should consider other clinical applications for the dynamic recording of facial movements which may include;
a. The neurological disorders which affect the coordination of facial muscle movements
b. Pathological conditions which impact on eye movements
c. Recording of twitches and tremors due to peripheral or central pathology.
2. The cost effectiveness of imaged based 4D recording of the face was debated. It was agreed this has to be highlighted in the next grant submission.
3. Another aspect related to the cost effectiveness was direct introduction of the 4D technology to clinical practice and skipping the need of 3D imaging.
4. It was quite useful to discuss the application of 4D imaging as a training tool for clinicians, non-clinical staff and students.
5. The possibility of utilizing 4D imaging as an educational tool in schools was discussed which will definitely widen the impact and the academic beneficiaries of the technology.
The following potential funding sources for future grant applications: 1. EU funding, 2. NIH, 3. Global Health Care Innovation Initiatives.

We have identified the following three research themes for further discussuion:
1. Morphometrics of phonemics.
2. Health inequality associated with cleft lip & palate and the high mortality rate associated with stigma of the surgically managed cases.
3. "Appearance Matters" a key to improve quality of care.
4. The psychology of facial expressions.
5. Facial functional disabilities and their impact on social interaction

The meeting was concluded by confirming the need to identify a relevant research call, it was agreed that the meeting in Greece at the end of 2015 or early 2016 would be the ideal forum to proceed with the most appropriate funding opportunity.

Our **EUROCleftNet Steering Group meeting** was held during the plenary, with discussion on the following aspects:

1. Progress report from contributing partners
2. **Future EUROCleftNet events**
3. **Building the Eastern European Dimension**
4. Future funding applications
5. **European Cleft Organisation (ECO)**
6. **Psychology of OFC : (COST**)
7. **EUROCAT Central Registry**
8. **Primary prevention initiatives**
9. **Trans Atlantic links &** Global Task Force for OFC

Future EUROCleftNet events: mentioned above are the ongoing SVE program, the cost conference in December and the research grant applications that will be submitted. We are also aware of and in addition there is an opportunity for an EU Workshop on Nursing allied to the CEN standards proposal for neonatal care. In recent correspondence from ESF to the steering group members we have been advised that there is approximately **130,000 Euros** available to spend on research collaborative activities such as short visits and exchanges (through the SVE scheme), workshops and any exchanges that we feel will be of benefit to any aspect of our future OFC research activities.

ECO remains one of the most prolific partners in EUROCleftNet remains the European cleft organisation (ECO) and they have worked effectively in partnership on many fronts. This has been mutually beneficial and two of the significant successors have been the collaborative work on Gateway project and the European standards project (CEN).

COST: Following the December 2014 COST workshop in Kristianstad and the EUROCleftNet led workshop on OFC, and the psychological and psychosocial approach to problems concerning body image and particularly facial appearance; further issues that can be discussed there will be imaging, genetics and cleft surgery and their relative effects on facial appearance.

EUROCAT Central Registry: has been moved to EU Joint Research Center of the in Ispra (near Milan), and EUROCAT is very much interested in collaboration with the EUROCLEFNET. They are organising Registry Leaders Meeting which provides a good opportunity to meet. Perhaps EUROCLEFTNET representives could come and speak about standards of care (and how the effectivness could be monitored by registries?), or about the prevention programme?

Trans-Atlantic links: After the genetics workshop, the plenary discussion with the imaging group gave rise to the idea of grant application being not only restricted to EU grants but also NIH grants. The Global Task Force for OFC originated in Orlando initiated by the European Cleft community, and its aim is global dissemination of research into both treatment and prevention. Chennai Feb 2017 is the next opportunity we will have to discuss.

Attachments:

1. MOSSEY Powerpoint presentation from Gothenburg Workshop
2. EUROCleftNet Sept 2015- June 2016 _ Final Workplan

EUROCleftNet

"ESF Network for Orofacial Clefts Research, Prevention and Treatment"

Pre-Congress Workshop

EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

eurocat
european surveillance of congenital anomalies

EuroCleftNet

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Aims and objectives of this EUROCleftNet meeting

- Update current status of EUROCleftNet
- EUROCleftNet Mid-term report
- Response from ESF
- Recent dialogue re proposed RNP 2015-16 programme
- Explore funding avenues / expand our horizons
- Maintain / strengthen collaborations across Europe

ESF Network for Orofacial Clefts Research, Prevention and Treatment: EUROCleftNet:

This ESF EUROCleftNet Network proposal will build on previous success of collaborative research in the field of non-syndromic OFC (NS-OFC).

This Network aims to deal with the 2 major themes, **treatment** (quality of care) and **prevention** (via genetics and environmental factors), in conjunction with the recently formed European Cleft Organisation (ECO) who have begun to address the health inequalities with particular focus on Eastern Europe.

Professor Peter A Mossey, University of Dundee

EUROCleftNet (2011-2016) aims

Collaborative aims:

- to adopt a multi disciplinary approach
- to be fully inclusive across the EU, including the Eastern European States

in collaboration with ....

- the World Health Organisation (WHO)
- the European Cleft Organisation (ECO)
- All other stakeholders

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european surveillance of congenital anomalies

European Cleft Organisation

EUROCleftNet Successes I

1. Links with other EU research bodies and programmes such as COST (psychological issues concerning facial appearance including cleft lip and palate)
2. Engagement with MEPs in October 2012 at a parliamentary session dedicated to presentation of orofacial clefting issues across Europe; and a subsequent session on rare diseases in November 2013
3. Engagement with potential industrial / commercial partners such as 3dMD, DI3d, Xpand, Slimmer-Zwanger and various charitable organisations
4. Translation of information and research protocols into other languages (7 languages) to facilitate understanding of the Network, and encourage research

EUROCleftNet Successes II

1. Use of the Gateway project to improve the communication and dialogue between cleft researchers across Europe

2. Encouraging research collaborators who were not in original collaboration to join EUROCleftNet steering group as contributing partners, i.e. the University of Ferrara and ALA, Bulgaria.

3. Links with other organisations: WHO, the European Cleft Organisation (ECO), CEN Standards Agency in Brussels.

4. Links with other like-minded research organisations in Europe and beyond e.g. EUROCAT, the International Clearinghouse for Birth Defects surveillance and research (ICBDSR) and engagement with the IADR Global Oral Health Inequalities Research Network (GOHIRN).

EUROCleftNet Success III

1. Pan European directory of resources created through the Gateway project; and this underpinned the recruitment for the EUROCleftNet conference in Bulgaria

2. Dialogue surrounding the development and contribution to the EUROCran Biobank for cleft trio samples

3. Publications arising as a result of inter-centre/multi-disciplinary collaboration (acknowledge ESF)

4. Addressing inequalities in cleft lip and palate care through improving collaboration and research capacity in Eastern Europe

EUROCleftNet Successes IV

1. On-going EuroCleftNet short visits and exchanges dealing with a range of OFC research issues and building research capacity.
2. International research links for Trans-Atlantic collaborative research in OFC with invitation of research collaborator from US to EUROCleftNet conference in Plovdiv.
3. Research grant application submitted to the Marie Curie FP7 programme (and while this did not succeed in attracting funding, it helped form research partnerships which will facilitate future research applications)
4. Engagement with colleagues at International Craniofacial Congress in Orlando in May 2013, involvement in the global Task Force on oral clefts with sharing of the common interest in research on "Prevention" of OFC

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EU Parliament 9th October 2012

European Parliament

- The main messages arising out of the presentations and engagement with MEPs were as follows:

1. Birth Defects affect 1 in 50 births - around 13 million families across Europe
2. across Europe are well documented, but health care and health and soHealth inequalities cial service inequalities remain a major challenge
3. Children with certain birth defects in Eastern Europe are still institutionalised and deprived of their basic human rights
4. Birth defects are emerging as a major cause of both mortality (mainly in the developing world) and morbidity
5. **Europe leads the world in birth defects surveillance and registration, and in many aspects of research in the field of aetiology, treatment and prevention of birth defects**
6. Clinical trials have revealed much more cost effective and less burdensome treatments for birth defects but many of these have not yet been implemented

European Parliament II

- The main messages arising out of the presentations and engagement with MEPs were as follows:

7. There is scope for a massive reduction in health care costs for the treatment of birth defects

8. Genomics research in birth defects in Europe is leading the rest of the world and there is a need to remain at this cutting edge, which requires further funding

9. Patient groups are heavily involved in our birth defects research and make a very meaningful contribution

10. There is a massive swing in the emphasis towards primary prevention in Europe and strategies with respect to lifestyle and behavioural change are being piloted and implemented.

11. We aim to involve non-academic & industrial partnerships across Europe with scientific, educational and translational implications

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Dr Mario Merialdi, Director of Reproductive Health and Research at WHO

- **“In the context of this new global health agenda, prevention and treatment of birth defects and disabilities will represent a major line of action”.**

Steering Group Discussion

- **The steering group AGENDA will include discussion on the following:**
- Discuss recent events / current status of EUROCleftNet
- **Progress reports from contributing partners**
- **Future EUROCleftNet events – publicizing & optomising participation**
- **Building the Eastern European Dimension**
- **Future funding applications: action plans (personalise)**
- **European Cleft Palate and Craniofacial Association (ECPCA)**
- **Psychology of OFC : (COST)**
- **EUROCAT Central Registry**
- **Primary prevention initiatives:**
- **Global Task Force for OFC:**

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Realising the EUROCleftNet objectives over next 12 months through SVEs, Workshops, Conferences – and possibilities for future funding

Detailed EUROCleftNet Workplan 1st September 2015 to 30th June 2016

Proposed Workshops September 2015 – June 2016

1.Nurses Workshop Bucharest / Oct 2015 (Davies)

2.3D/4D Imaging Workshop / Dec 2015 (Ayoub)

3.Psychosocial workshop and future research agenda / COST collaboration Jan/Feb 2016 (Persson)

4.Treatment Outcomes & Standards in Europe workshop / CEN Standards (ECO) March 2016 (Davies / Shaw / Semb)

5.Final EUROCleftNet Conference for Dissemination with Prevention & Genetics Workshops, May / June 2016 (Mossey / Rubini / EUROCAT)

Realising the EUROCleftNet objectives over next 12 months through SVEs, Workshops, Conferences – and possibilities for future funding

Detailed EUROCleftNet Workplan 1st September 2015 to 30th June 2016

Proposed SVE's September 2015 – June 2016

1.Anne Bohmer (GER-UK)

2.Maria Kazakova (BUL-UK)

3.Nedialka Slaninkova (BUL-UK)

4.Paola Franceschelli (IT – NL)

5.Faisal Khan (IT)

Realising the EUROCleftNet objectives over next 12 months through SVEs, Workshops, Conferences – and possibilities for future funding

Detailed EUROCleftNet Workplan 1st September 2015 to 30th June 2016

3. Other proposed Network activities

Gateway Directory of Resources – ongoing development
DNA Trio s biobank / Ferrara/ Rubini

4. Publication Plan

Details of activities related to publications and information dissemination

5. Additional Administrative Support

Intensive administrative activity anticipated during the period of September 2015 and June 2016. We propose to increase administrative support to 2 days a week with an estimated cost of €16660

1. Early Care of Babies Born with Clefts, Bucharest, October 2015

Aim:
This workshop will focus on the nursing care of babies born with clefts and follows the elaboration of a set of recommendations on early cleft care developed by the European Cleft Organisation (ECO) and endorsed by the European Committee for Standardisation (CEN) in Brussels.

Target Audience:
Cleft team leaders/coordinators should ensure this workshop is brought to the attention of the most relevant person in their team/hospital.

Participants will be asked to consider the evidence base and ways of improving best practice through collaborative research.

Where and When:
The workshop will take place on 15 October at one of the Residence Hotels in Bucharest (either Domenii Plaza by Residence, 33 Alexandru Constantinescu st. or Arc de Triomphe hotel, 19 Clucerului st)

1. Early Care of Babies Born with Clefts, Bucharest, October 2015

Programme: Proposed topics will include presentations and practical sessions covering the following areas and the role of future research in the pursuit of evidence based practice will be emphasised:

- Exploration of the role of cleft nursing in different countries
- Measuring and comparing outcomes – research opportunities
- Being heard, being noticed – having an impact in differing medical hierarchies
- Introduction to early cleft care guidelines
- Antenatal support and counselling
- Feeding and nutritional assessments

Psychological effect of a cleft on attachment and bonding and gaps in the evidence base

The impact of additional anomalies e.g. airway obstruction (Pierre Robin) and other conditions

Holistic care and support of the infant and the family and prevention of morbidity

1. Early Care of Babies Born with Clefts, Bucharest, October 2015

Support: EUROCleftNet will fund two night's accommodation with numbers capped at 50 delegates. A limited number of **bursaries** are available giving free access to the workshop and help with travel costs. Preference will be given to applicants from Eastern Europe.

Organising Committee:

Trisha Bannister	Consultant specialist cleft nurse, UK
Kostadinka Bojikova	Specialist cleft nurse Bulgaria
Gareth Davies	Executive Director, ECO, France/Netherlands
Radu Spataru	Cleft Surgeon, Romania
Claudia Malic	Surgeon, Canada / Romania
Peter Mossey	Chair, EUROCleftNet Steering Committee
Nina Lindberg	Specialist Cleft Nurse, Norway
Lisa Smedgard	Specialist cleft nurse, Denmark
Emma Southby	Specialist Cleft Nurse, UK

2. 3D/4D imaging symposium, December 2015

Background: The World Health Organization (WHO) has highlighted the need for quality improvement in patients having craniofacial anomalies. There is also a lack of objective outcome measures of the quality of facial aesthetics and the associated expressions.

Gaps in knowledge: Despite the advanced technique to measure facial animation, there is still insufficient information on the dynamics of facial muscle movement.

State-of-the-art technology: Recently, a non-invasive four dimensional (4D) soft tissue imaging system (Di4D) has been set up in Scotland, it recovers high fidelity facial motion capture data without requiring special illumination, markers or make-up. The objectivity of Di4D capture system is superior to any other system and has the ability to track the dynamic changes in soft tissue movement. The automatic tracking of facial landmarks demonstrated a satisfactory accuracy which would facilitate the analysis of the dynamic motion during facial animations (Al Anzie et al 2013).

2. 3D/4D imaging symposium, December 2015

Challenges & opportunities:

Surgically managed cleft children at the age of 13 are conscious of their facial appearance and may be subjected to bullying due to residual visible lip scar and abnormalities of facial animations.

At this age a decision may be taken to carry out further surgical revisions to deal with the scarred lip. In most of the cases this decision is taken based on the subjective evaluation of the residual dysmorphology by the surgeons, this varies widely among clinicians.

Therefore, it is prudent to have an objective tool to evaluate the magnitude of lip scarring and quantify abnormalities of facial animations to inform the decision making process regarding the need of further corrective procedures and monitor the progress in the surgically managed cleft children. This would be also fine tune the surgical technique of primary surgical repair of cleft lip and palate to minimise the residual dysmorphology.

2. 3D/4D imaging symposium, December 2015

Objectives of the symposium: The main objective of this symposium is to establish a forum of key researchers, leading scientists and experts across Europe in the field of facial imaging and computational biology to underpin the methodological innovation of analysing facial expressions.

The symposium would provide the opportunity to share existing expertise and knowledge on the facial imaging and:-
Highlight the pathway of impacts of this novel approach and identify the groups of beneficiaries of this innovation
Explore existing funding opportunities and research all's that match the scope of the proposed study
Agree on the mechanism of communication and finalise a realistic schedule to submit research grants

…. **think inter-disciplinary and trans-sectoral (e.g. a range of other imaging technologies for a range of conditions)**

2. 3D/4D imaging symposium, December 2015

List of potential participants:

Ashraf Ayoub	UK
Pitas Ioannis	Greece
K. Lyroudia	Greece
David Dunaway	UK
Colin Urquhart	UK
Felicity Mehendale	UK
Mohamed Daoudi	France
Paul Whelan	Ireland
Peter Hammond	UK
Thomas Maal	Netherlands
Stefaan Berge	Netherlands
E Wolvius	Netherlands
Youri Anastassov	Bulgaria
Peter Mossey	UK
Martin Persson	UK
M.J. Koudstaal	Netherlands
Philippe Pellerin	France
Pierre Guerreschi	France
Stephen Morley	UK
Toby Gillgrass	UK
Craig Russell	UK
Balvinder Khambay	UK
Alireza Ghassemi	Germany

3. A Psychosocial Workshop to Design the Next Innovative Research Agenda

Objective: To develop innovative psychosocial research ideas for craniofacial conditions that adhere to the objectives of the Horizon2020 call “Health, demographic change and well-being” or other relevant calls.

Current research in cleft indicates that about 1/3 of this population is not doing so well psychosocially. There is also indication for example that about 30% have additional conditions such as learning disability or ADHD (1), negative educational outcomes (2), are more likely to be unemployed (3), have lower earnings (4) or have poorer health in general in comparison to normal population (5) there is currently a strong need to identify this subgroup in the cleft population that are not doing so well and to understand the cause of this in order to provide adequate care.

Focus on **European Union research priorities** that come from the call for “Societal Challenges”, Successful efforts to prevent, detect early, manage, treat and cure disease, disability, frailty and reduced functionality are underpinned by the fundamental understanding of their determinants and causes, processes and impacts, as well as factors underlying good health and well-being. Improved understanding of health and disease will demand close linkage between fundamental, clinical, epidemiological and socio-economic research.

3. A Psychosocial Workshop to Design the Next Innovative Research Agenda

AIM: Focus (a) on the research priorities for cleft and craniofacial conditions around the EU priorities and (b) involve a range of disciplines including those beyond healthcare.

Suggested list of delegates

Martin Persson	UK
Peter Mossey	UK
Nichola Rumsey	UK
Ashraf Ayoub	UK
Gareth Davies	France
Leva Maulina	Latvia
Henry Svensson	Sweden
Slave Naumouski	Macedonia
Laura Linkevičienė	Lithuania
Nenad Tanaskovic	Bosnia
Predrag Knežević	Croatia
Julija Radojićić	Serbia
Triin Jagomägi	Estonia
Martina Drevensek	Slovenia
Radu Lulian Spataru	Romania
Youri Anastassov	Bulgaria
Nagore Solaeche Prieto	Spain
Kristin Billaud Feragen	Norway
Hakan Agir	Turkey

Date and Venue: Slovenia, Serbia or Macedonia, January or February, 2016 – (1 day)

4. Impact and Research Implications of New Guidelines on the Early Care of Babies Born with Clefts

In March 2015 the European Committee for Standardisation (CEN) approved a set of guidelines in the early care of babies born with clefts. The report, CEN/TC 424*, spearheaded by the European Cleft Organisation and with significant support from EUROCleftNet, was agreed at European level with an overwhelming majority of CEN member bodies voting in its favour.

Gareth Davies, Executive Director of ECO and Chairman of CEN/TC 424 said: *'This document will be helpful to those countries that do not have national guidelines in cleft care and will become a baseline of care against which we can measure service output and standards of care across Europe'.*

EUROCleftNet can assist by ensuring that these guidelines are evidence based, promoted at a high level throughout Europe and used as a means of assessing current levels of care with a view to improving access to excellent cleft care for all babies born with clefts in Europe.

4. Impact and Research Implications of New Guidelines on the Early Care of Babies Born with Clefts

Aims: This workshop will bring together researchers, clinicians, politicians and representatives of national and international standards bodies to discuss the way forward. In particular the workshop will look at:

1) Exploration of the evidence base that underpins the guidelines, and implement, through EUROCleftNet any necessary research to address any identified gaps in evidence
2) Means of dissemination of the guidelines throughout (and beyond) Europe
3) Ways in which the guidelines can be used as a tool for measuring and assessing current levels of care
4) Implementation of the guidelines
5) Methods to evaluate the long term effects on cleft care post implementation

Date and Venue: Brussels, January 2016 (1 day) and possibly back to back with workshop 5 (see below)

***The document is available from the National Members (standards offices) of CEN in 33 European countries.**

4. Impact and Research Implications of New Guidelines on the Early Care of Babies Born with Clefts

Proposed Delegate list:

Peter Mossey	Eurocleftnet
Bill Shaw	EurocleftNet
Sean Kelly	MEP
Vytenis Andriukaitis	European Commissoner for Heatlh
Paula Duarte Gaspar	European Commissioner for health team – health information
Elena Santiago	Director General CEN
Ashok Ganesh	Director Innovation, CEN
Maitane Olabarria	Programme manager sustainability, CEN
Guido de Jongh	NBN – Belgian Standards
Gareth Davies	Chair Technical Committee (TC) CEN 424
Pedro de Cano	TC Spain
Peter Schachner	TC Austria
Youri Anastassov	TC Bulgaria
Emma Southby	TC UK
Radu Spataru	TC Romania
Triin Jagomagi	TC Estonia
Zuzana Oravkinova	TC Slovakia
Rosanna Preston	TC UK and patient voice
Mariette Vermeylen Nujts	TC Belgium and patient voice,
Monika Skoken	MAM Baby Austria – Head of Public Opinion
Martin Persson	COST/ECO
Ysbrand Poortman	Campaigner
Alistair Kent	Campaigner
Michel Grupper	Resurgens/Public Health
Miriam Ryan	ECO
Anton Vorderman	ECO

Date: Jan 2015 and Venue: Brussels ?

5. Improving the Quality of Cleft Lip and Palate Care and Increasing Research Capacity in Europe, March 2016

Background to the proposal: The haphazard nature of European cleft lip and palate clinical services was originally explored in the European Commission Framework IV Biomed Project “Standards of Care for Cleft Lip and Palate in Europe: Eurocleft”, Contract No. BMH4-CT95-0402, 1996-2000.

This work defined international guidelines for minimum standards of care and standardised clinical datasets. At least one representative of every country took part in workpackages leading to the publication of *Policy Statements and Practice Guidelines*

Eurocran, (Framework V, 2000-2004), Contract No. QLG1-CT-2000-01019, included all the European Union States and the Newly Associated States of that period.

In the years since, some restructuring achieved in individual countries, three multinational randomised trials of primary surgical technique have been completed, and TOPS is due to complete recruitment in June 2015.

<u>However in many European countries, services remain fragmented and non-standardised, and few if any prospective clinical studies are underway.</u>

1. Shaw WC, Semb G, Nelson P, Brattstrom V, Molsted K, Prahl-Andersen B, Gundlach KKH. The Eurocleft Project 1996-2000.

5. Improving the Quality of Cleft Lip and Palate Care and Increasing Research Capacity in Europe, March 2016

International Task Force:

Proposal: The workshop will address five topics:

- Review of current guidelines and standards of cleft care
- Barriers and solutions to implementation
- Review of research priorities
- Barriers and solutions to effective European research collaboration
- European contributions to the international task force “Beyond Eurocleft”

Context: Standards of care and associated research represent long-term international challenges for the providers of clinical care and affected families, and this mission will require a strong sense of purpose and continuity in the years ahead.

Ownership of the challenge should rest with the European Association for Cleft Lip and Palate and Related Craniofacial Anomalies (EACCA ???)

The proposal strongly connects with parallel work of the ECO on the political imlementation phase of standards through the European Committee for Standardisation (CEN).

2. Semb G. The Cleft Palate–Craniofacial Journal 51(6) pp. e146–e155 November 2014

5. Improving the Quality of Cleft Lip and Palate Care and Increasing Research Capacity in Europe, March 2016

Proposed Delegate list

Peter Mossey	EuroCleftNet
Bill Shaw	EuroCleftNet
Sean Kelly	MEP
Vytenis Andriukaitis	European Commissoner for Heatlh
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Elena Santiago	Director General CEN
Ashok Ganesh	Director Innovation, CEN
Maitane Olabarria	Programme manager sustainability, CEN
Guido de Jongh	NBN – Belgian Standards)
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Alistair Kent	Campaigner
Michel Grupper	Resurgens/Public Health
Miriam Ryan	ECO
Anton Vorderman	ECO

6. Translating Genetics Research Achievements into Prediction, Prevention, Personalization and Participation, Ferrara, Italy, April 2016

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 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.

Translational research is needed to provide clinicians with safer, more effective, and more powerful tools for both diagnosis and management of patients with clefts.

6. Translating Genetics Research Achievements into Prediction, Prevention, Personalization and Participation, Ferrara, Italy, April 2016

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 the contribute 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.

6. Translating Genetics Research Achievements into Prediction, Prevention, Personalization and Participation, Ferrara, Italy, April 2016

List of delegates (contributors)

Adrianna Mostowska	Poznan University of Medical Sciences, Poznan, Poland
Borut Peterlin	Clinical Institute of Medical Genetics, Ljubliana, Slovenia
Carine Carels	Radboud University of Nijmegen, NL
David R. Fitzpatrick	Western General Hospital, Edinburgh, UK
Elisabeth Mangold	University of Bonn, Germany
Gareth Davis	European Cleft Organization
Greg Elgar	MRC National Institute for Medical Research, London, UK
Jo Zhou	Radboud University of Nijmegen, NL
Julian Little	University of Ottawa, Canada
Peter A. Mossey	University of Dundee, UK
Kerstin Ludwig	University of Bonn, Germany
Martin Persson	University of Bristol, UK
Michael Dixon	University of Manchester, UK
Michele Rubini	University of Ferrara, Italy
Miikka Viccula	de Duve Institute, Université Catholique de Louvain, Bruxelles, Belgium
Tiit Nikopensius	Institute of Molecular and Cell Biology, University of Tartu, Estonia

Date and venue: Dundee, Scotland, UK – May / June 2016

7. Primary prevention of birth defects in Europe – with orofacial clefts (OFC) as a demonstration model - May 2016

This Workshop will invite input from a range of stakeholders whose interests in primary prevention forms a major component of their current work.

High profile among these in Europe are:

1. the initiatives at EUROCAT, ICBDSR, and other international stakeholders such as CDC and MoD

2. the initiative by Prof. Régine Steegers-Theunissen, ErasmusMC, The Netherlands and

3. 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.

7. Primary prevention of birth defects in Europe – with orofacial clefts (OFC) as a demonstration model - May 2016

A. 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-EUROPLAN reccomendations into actions.

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).

7. Primary prevention of birth defects in Europe – with orofacial clefts (OFC) as a demonstration model - May 2016

B. Smarter Medical Care and Eating 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.

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 the mHealth coaching program on nutrition and lifestyle "Smarter Eating with your child"(www.slimmeretenmetjekind.nl) has been developed and launched for parents and caregivers of a healthy child.

Impact: If the platform Smarter Medical Care and Eating of Your Child with Cleft Lip and or Palate proves to be effective it will contribute to significant health gains and savings in health care costs.

7. Primary prevention of birth defects in Europe – with orofacial clefts (OFC) as a demonstration model - May 2016

C. Global Task Force for Prevention of CFA
Launched at the International Craniofacial Congress (ICC) in Orlando in 2013, and will be progressed further via the next ICC in Chennai in 2017.
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.

7. Primary prevention of birth defects in Europe – with orofa clefts (OFC) as a demonstration model - May 2016

Delegates who are expected to attend

ICBDSR x 4 delgates
WHO x 2 delgates
Erasmus MC x 2 delgates

EUROCATx4

Amanda Julie Neville	*Italy*
Maria Loane	*Ireland*
Joan Morris	*UK*
Ester Garne	*Denmark*

Peter Mossey,	University of Dundee, UK
Gurdeep Sagoo	PHG, Cambridge, UK
Domenica Taruscio,	EUROCAT WP7 Primary Prevention leader, Italy
Bernadette Modell	LSHTM, UCL, London, UK
Adrianna Mostowska	Poznan University of Medical Sciences, Poznan, Poland
Borut Peterlin	Clinical Institute of Medical Genetics, Ljubliana, Slovenia
Carine Carels	Radboud University of Nijmegen, NL
Elisabeth Mangold	University of Bonn, Germany
Gareth Davis	European Cleft Organization, France
Julian Little	University of Ottawa, Canada
Kerstin Ludwig	University of Bonn, Germany
Michele Rubini	University of Ferrara, Italy
Tiit Nikopensius	Institute of Molecular & Cell Biology, University of Tartu, Estonia
Youri Anastassov	TC Bulgaria
Radu Spataru	TC Romania
Triin Jagomagi	TC Estonia
Zuzana Oravkinova	TC Slovakia
Rosanna Preston	TC UK and patient voice
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Ysbrand Poortman	Campaigner
Alistair Kent	Campaigner
Michel Grupper	Resurgens/Public Health
Miriam Ryan	ECO

SVE 1 - Germany – UK - September 2015 (4 weel

Applicant: Anne Bohmer, 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 (eg. H3K4me3, H3K27ac) to identify regulatory elements of direct relevance to development of the lip and palate.

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.

SVE2- 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.

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.

- To gain an understanding of previous and ongoing speech and language therapy research at the southwest cleft service.
- To enhance the knowledge about multidisciplinary teamwork and learn how to integrate key aspects into existing provision of care in Plovdiv.
- 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.
- To study how the UK therapists provide appropriate and timely intervention.

To bring this back to improve delivery of cleft care in Bulgaria

SVE3: Nedialka Slaninkova, specialist cleft nurse, Plovdiv cleft team, Bulgaria

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

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

SVE 4 - 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.

SVE 4 - 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

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 Spectometry 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

SVE 5 - Italy - October 15 – March 2016
(6 months Extension)

Applicant: Faisal Khan, Dept. of Anatomy All India Institute of Medical Sciences (A...m 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) SV 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 11b deletion) and computational analyses should be completed shortly. The outcome of thi investigation could possibly be taken by Paola as candidate to investigate with functio 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 not DNA but frozen (and mostly clotted) blood. To obtain good quality DNA from such b quality samples automatic systems are not effective. DNA extraction needs to be done 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

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

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

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.

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.
Pan European directory of resources created through the Gateway project
Translation of information and research protocols into other languages to facilitate understanding and research
Utilisation of the EUROCran DNA Biobank for ongoing research

ECO and CEN : Research opportunities

(Gareth Davies / Peter Mossey)

EUROCleftNet perspective:

EUROCleftNet and ECO share many values in common – one of which is to address the issue of inequality across Europe

Healthcare and equality are both basic human rights, and from the outset we realised that for OFC these were priorities….AND

1. **The EUROCleftNet mid-term conference hosted by Plovdiv in Bulgaria in 2013,**
2. **the support & affiliation of Bulgaria as a EUROCleftNet partner,**
3. **the success of implementing common standards for cleft care via CEN in Brussells, co-led by Bulgaria and**
4. **to date the establishment of several successful SVEs (research exchanges) across Europe**

…are examples of the dissemination and exchange of experiences and expertise.

European Cleft Organisation

CEN focus & issues

- **Focus on early care**
  - Diagnosis (pre and post natal)
  - Referrals
  - Immediate post natal care
  - Feeding
  - Monitoring
  - Parent support
  - Information needs

- **Context of overall care**
  - Inclusion of long term care pathway
  - Cleft team and centre requirements
  - Record keeping and audit
  - National registers – cross border comparisons

The pursuit of research grant funding: Some general observations

Horizon 2020 grant funding is extremely competitive

H2020 calls are becoming increasingly complex, interdisciplinary and trans-sectoral

There is no point in submitting an application for OFC alone – broader topics with tangible IMPACT (health, social, psychological, economic)

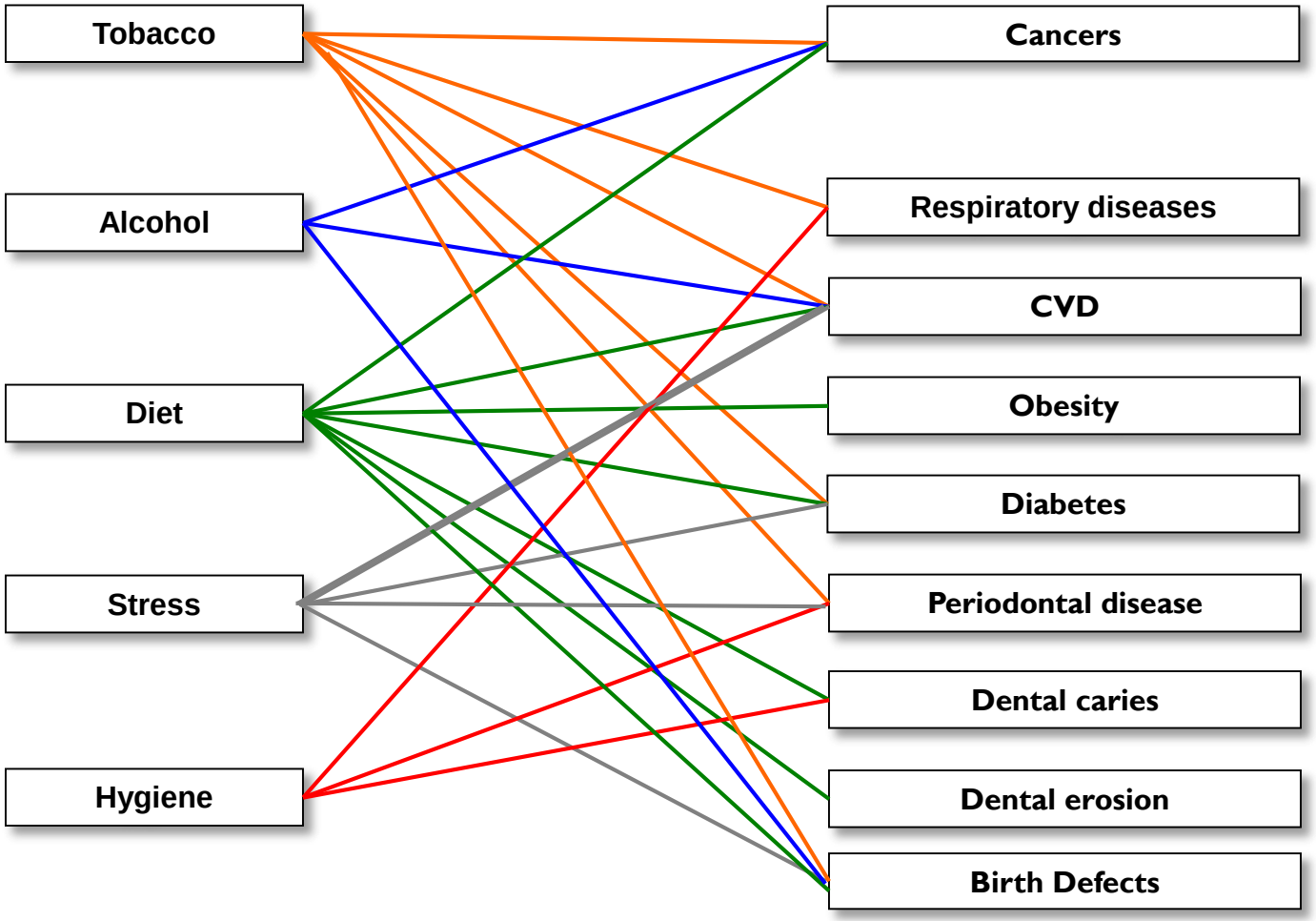
We should look for synergies within our own interests e.g. Can we link psychosocial aspects into other cleft outcomes and other grant applications in our field such as MRI, 3D Face Reader, state of the art sub-phenotyping, 4D animation, videofluoroscopy etc

The canary in the coalmine ?

Could cleft lip and palate be regarded as a sensitive detector of adverse reproductive conditions resulting in higher risk of adverse outcome – across a range of congenital conditions ?

IADR - GOHIRN: Common risk factors in NCDs

World Health Organization



(Grabauskas WHO Regional Office for Europe 1987; Sheiham & Watt, 2000)

Eg OFC

eurocat

european surveillance of congenital anomalies

www.eurocat-network.eu

EUROCAT : surveillance underpinning prevention of congenital anomalies

EUROCAT : surveillance underpinning prevention of congenital anomalies

EUROCleftNet would welcome representation from all stakeholders in Europe (and beyond) for discussion of the drive towards a primary prevention agenda.

eurocat
european surveillance of congenital anomalies

Suggested paticipants

Amanda Julie Neville,
Maria Loane,
Joan Morris
Ester Garne.

Access at: http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions-Reccomendations.pdf

ECO and CEN : Research opportunities

(Gareth Davies / Peter Mossey)

…. So what do we conclude from this ?

Without research we do not have an evidence base for the CEN guidelines that we are advocating

Would even we, who are involved in cleft care be happy to say:

(a) That we are fully aware of the different situations in the different countries

(b) that our cleft care guidelines are fully evidence based and

(c) That we are in a position to move from guidelines to recommendations

ECO and CEN : Research opportunities

(Gareth Davies / Peter Mossey)

… but what has research got to do with it ??

Is it possible to evaluate how well care is being delivered without research ?

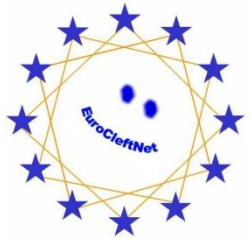
Is it possible to establish whether you are doing the best for the patient without research ?

Is it a good idea to carry out research on things that patients are concerned about ? (patient centered research)

Is it likely that patients are going to be concerned about whether the treatment their child is subjected to is evidence based ?

…. So what do we conclude from this ?

Industrial collaboration in Craniofacial Research



Engage the stakeholders

Lets heed the recommendations of the 63rd WHA. The knowledge & technology to improve the care & prevention of BD in developing countries is available. Networking, internationally and nationally, is needed to harness its capability.

March of Dimes
Saving babies, together

World Alliance of Organizations
for the prevention and treatment of and congenital conditions

WORLD HEALTH ORGANIZATION
GENEVA

CDC
SAFER • HEALTHIER • PEOPLE

NATIONAL INSTITUTES OF HEALTH

IGA
International Genetic Alliance
"Voicing the interests of people affected by genetic diseases"
"Representing Patient and Parent Organisations from Australia, Eastern Europe, Western Europe, Middle East, Gulf States, India, New Zealand, South Africa, South America and North America"

Oral H ies
2010 HO

Prevention of Orofacial Clefts: Does Pregnancy Planning Have a Role?

Cleft Palate–Craniofacial Journal, May 2007, Vol. 44 No. 3
(Peter A. Mossey, B.D.S., Ph.D., F.D.S., R.C.S. (Edin), Janet A. Davies, B.Sc., M.Sc., M.P.H., Julian Little, Ph.D)

ABSTRACT

- ***Objective:*** **To investigate the association between pregnancy planning and orofacial clefts in the United Kingdom.**
- ***Design:*** **Case–control study.** ***Setting:*** **Scotland and the Manchester and Merseyside regions of England.**
- ***Participants:*** **One hundred and ninety-one children born with nonsyndromic orofacial cleft, 1997 to 2000, and 247 controls.**
- ***Results:*** **There was an inverse association between planning for pregnancy and orofacial cleft in the offspring ([OR] = 0.51, 95% confidence interval [CI] 0.33–0.79).**
- ***Conclusions:*** **Planned pregnancies were associated with a lower risk of orofacial clefts.**

Improving the Efficiency of Prevention of ns-OFCs

Personalized Prevention ?

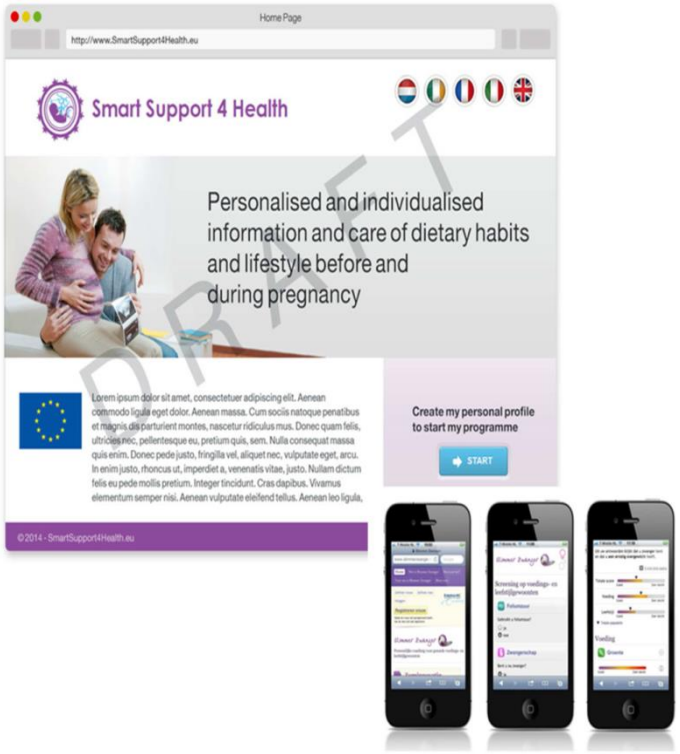
- Risk assessment / genetic counselling
- Optimal dose of Folic acid (detary / supplements) to prevent occurrence and recurrence of specific type of clefts
- Multivitamins (including vitB12, vitB6)
- Ecogenetics (genotype-based prevention strategy)

Scottish Oral Health Research Collaboration

Smart Support 4 Health

Amendable risk factors – the efficacy of personalised coaching ?

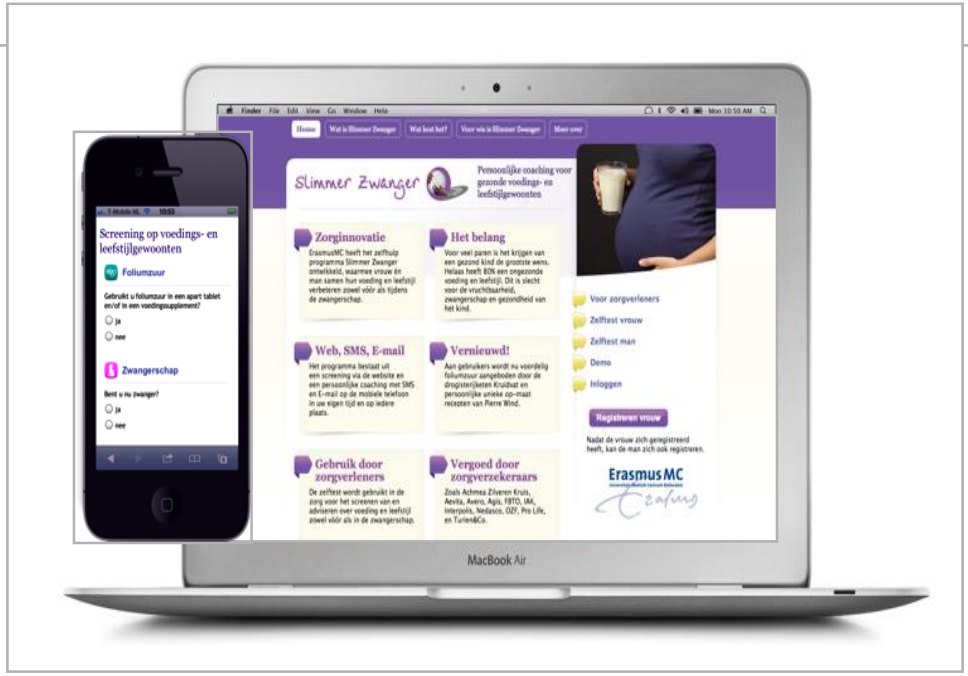
Healthier lifestyle is the way towards primary prevention, and the topic of an application to H2020 in March 2014 “Smart Support 4 Health”



Preconception eHealth tool for tailored nutrition and lifestyle coaching (*launch January 2012)*

https://www.slimmerzwanger.nl/nl/demo-en.php

Parents-to-be and health care givers

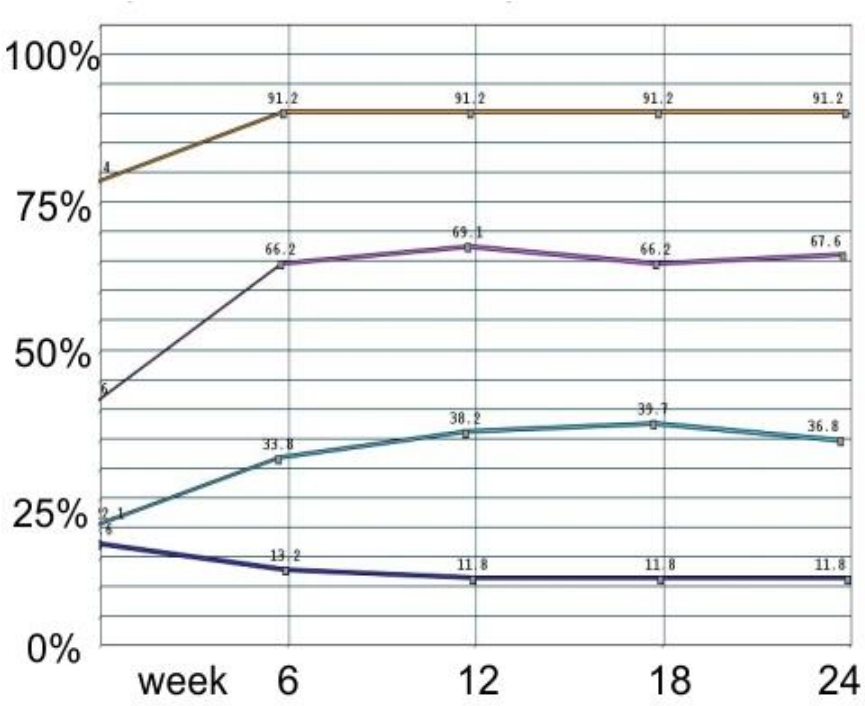


Internet excellent medium to reach the target group anonymously (cheap)
Web-application with email and SMS, at any time and place (smartphone)
Personal screening profile linked to a personal coachingsprogramme
Attitude- Social influence- Efficacy model

Steegers-Theunissen, May 2013

E health / M health “efficacy”

% improvement in nutrition and lifestyle behaviours



- Folic Acid (p = 0.039) **+12%**
- Fruit (p = 0.001) **+25%**
- Vegetables (p = 0.002) **+15%**
- Smoking (p = 0.046) **-6%**

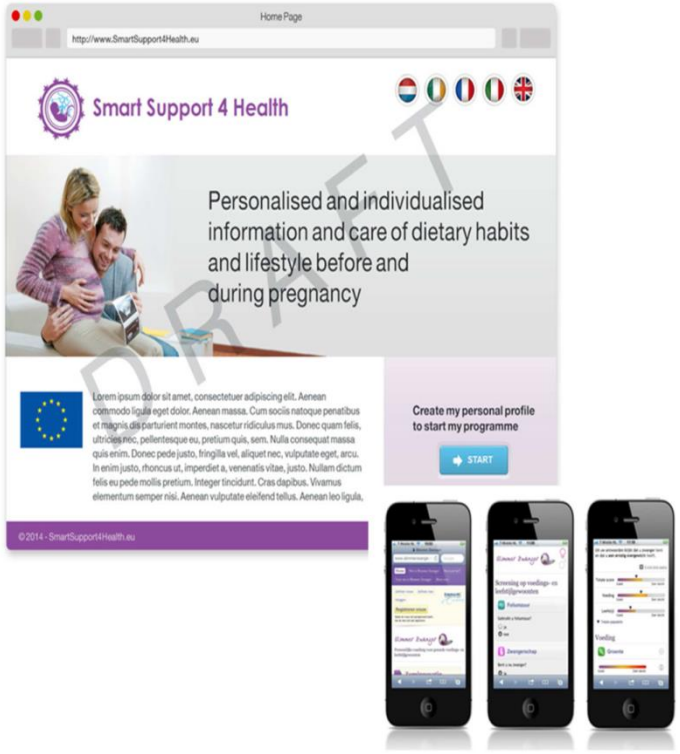
Scottish Oral Health Research Collaboration

One outstanding challenge in OFC research !

Amendable risk factors – but how do we change behaviour ?

Behaviour change is the key to primary prevention, and research needed on methods that reliably change behaviour !

RESEARCH: What are the barriers and facilitators of behaviour change… ??



ESF Network for Orofacial Clefts Research, Prevention and Treatment: EUROCleftNet (2011 – 2016)

Who / what is EUROCleftNet ?

What do we do ?

What have we achieved ?

Projection to the future ?

……from genomics / public health perspectives

Bavero, Italy, June 2015

eurocat
european surveillance of congenital anomalies

Background: The origins – 1990s

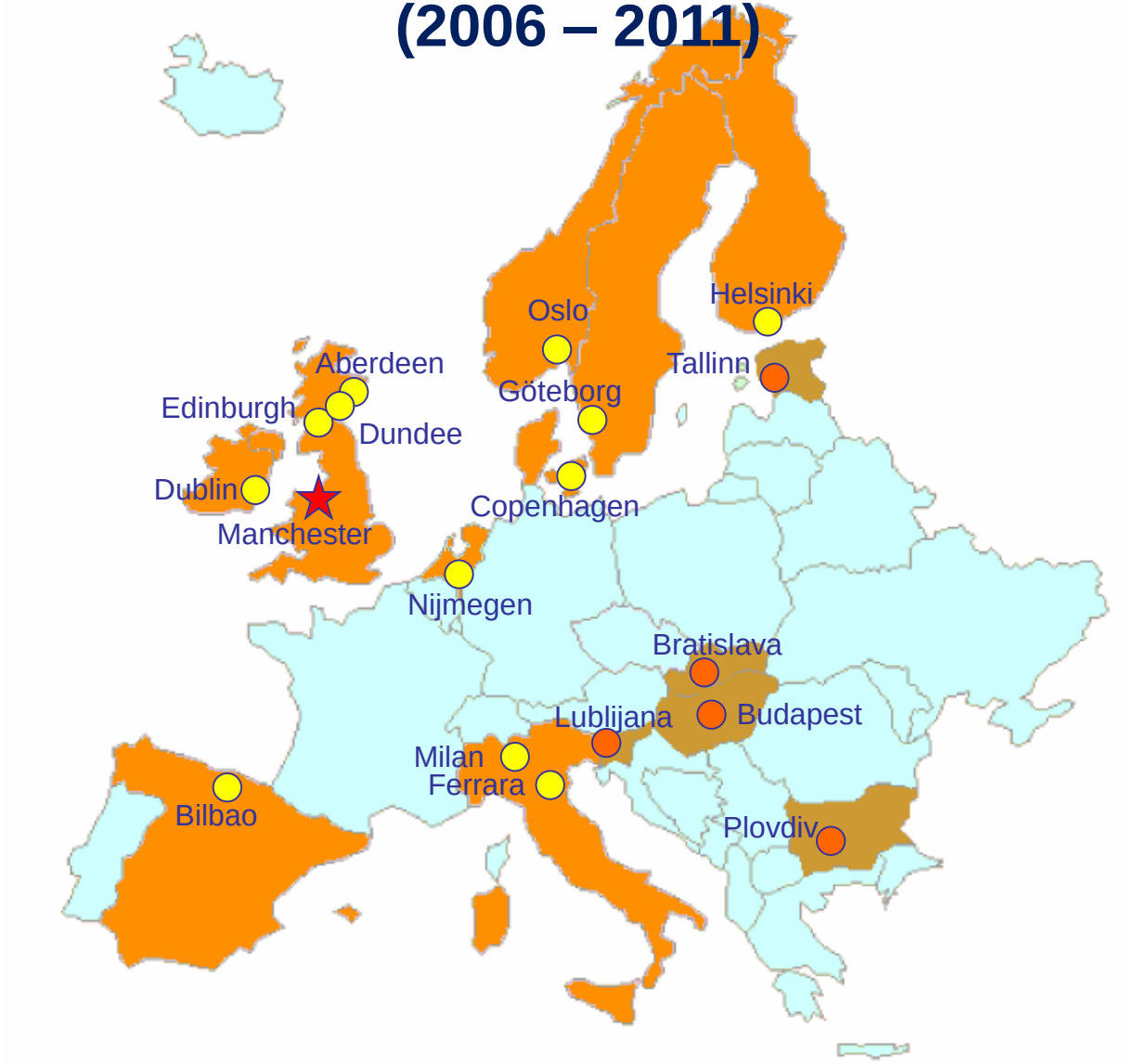
EUROCLEFT

Standards of Care for Cleft Lip & Palate in Europe

A project commissioned by the European Commission


EUROCRAN
European Collaboration on Craniofacial Anomalies

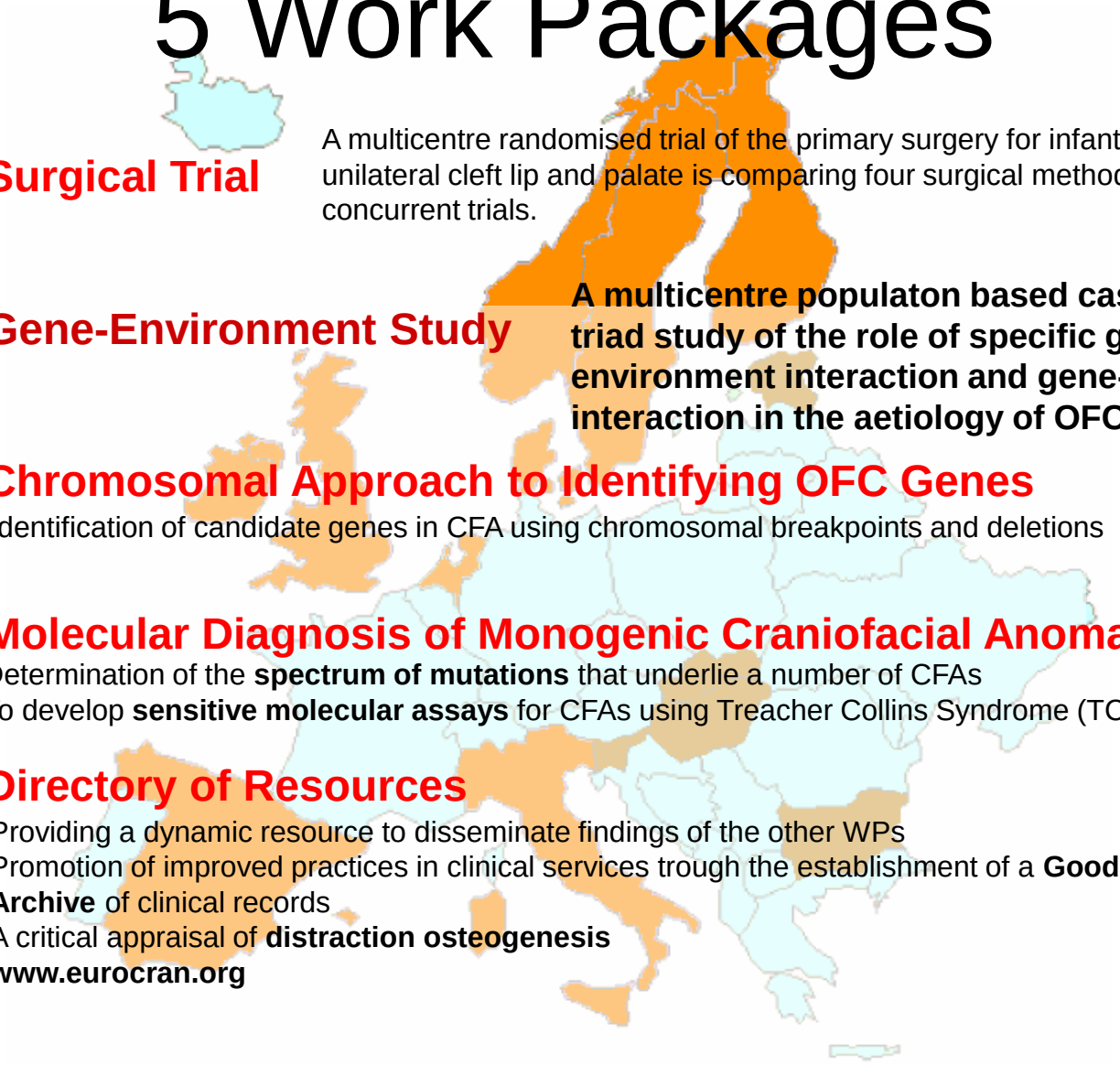
EUROCRAN: 13 western EU countries and 5 NAS (2006 – 2011)



EUROCRAN (2006-2011)

EUROCRAN brought together researchers from a range of clinical and scientific disciplines from 18 (5 NAS) European centres with the shared aim of improving the management and understanding of craniofacial anomalies (CFA).

5 Work Packages



WP1: **Surgical Trial**

A multicentre randomised trial of the primary surgery for infants with complete unilateral cleft lip and palate is comparing four surgical methods in three concurrent trials.

WP2: **Gene-Environment Study**

A multicentre populaton based case-parental triad study of the role of specific genes, gene-environment interaction and gene-gene interaction in the aetiology of OFC

WP3: **Chromosomal Approach to Identifying OFC Genes**

Identification of candidate genes in CFA using chromosomal breakpoints and deletions

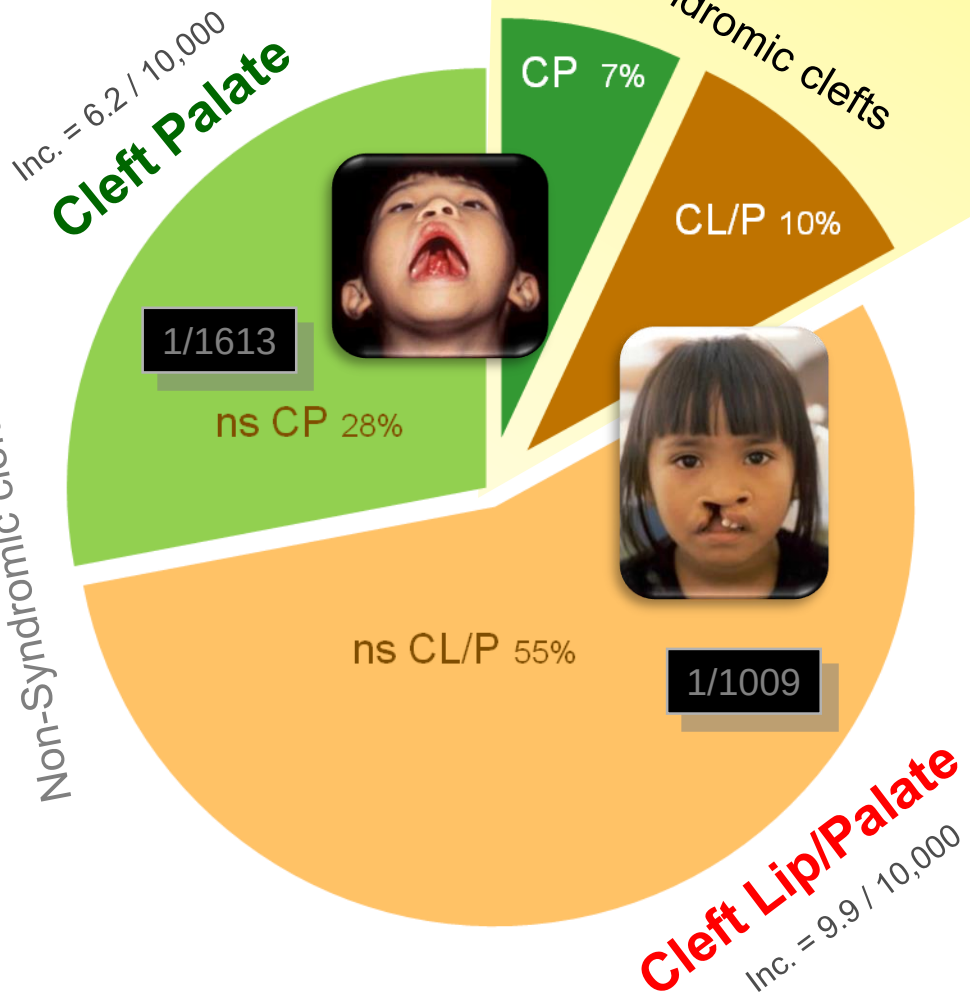
WP4: **Molecular Diagnosis of Monogenic Craniofacial Anomalies**

Determination of the **spectrum of mutations** that underlie a number of CFAs
To develop **sensitive molecular assays** for CFAs using Treacher Collins Syndrome (TCS) as a paradigm

WP5: **Directory of Resources**

Providing a dynamic resource to disseminate findings of the other WPs
Promotion of improved practices in clinical services trough the establishment of a **Good Practice Reference Archive** of clinical records
A critical appraisal of **distraction osteogenesis**
www.eurocran.org

Most OFCs are Non-Syndromic (ns-OFCs)



- Inherited / de novo mutations
- High penetrance
- Monogenic

- Discontinuous traits
- Multifactorial inheritance
- Multiple genes with low penetrance
- Epistatic interactions
- Ecogenetic interactions
- Epigenetics

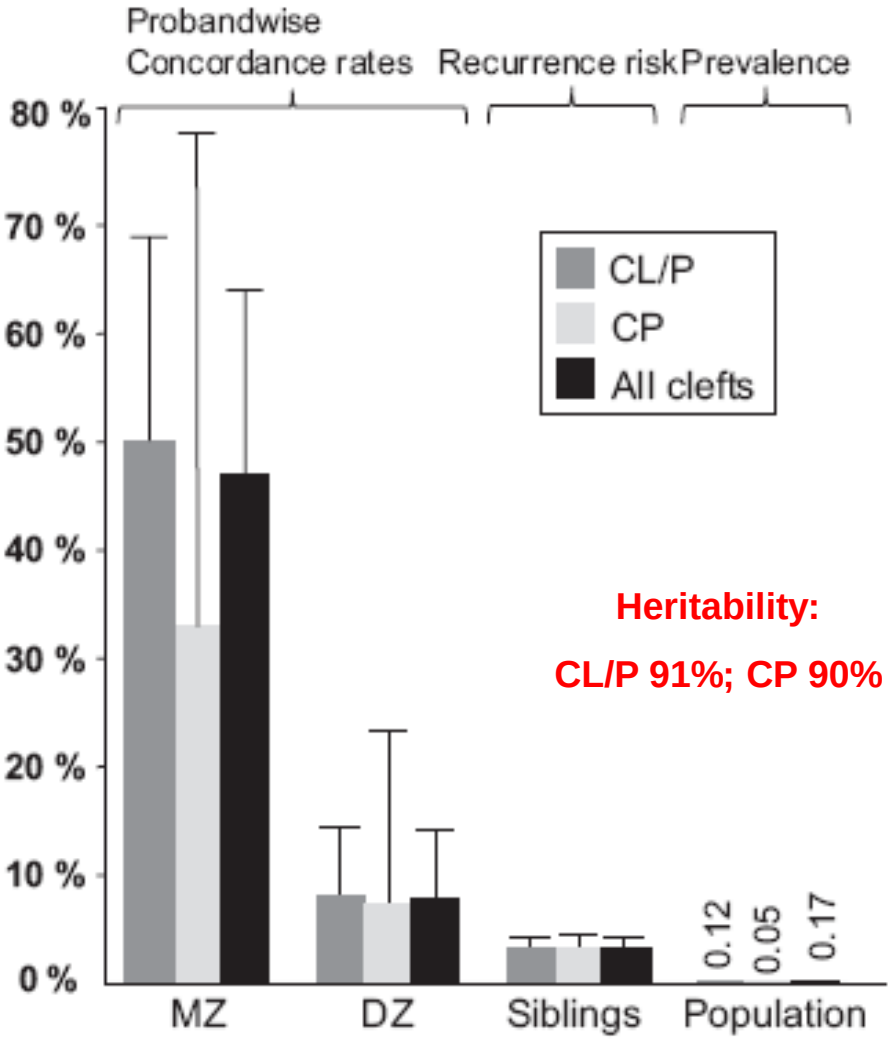
EUROCleftNet – genetics underpinning prevention ?

- **Post GWAS genomic research**

The recent GWAS “phase” of research in the field has spawned a comprehensive list of putative genetic loci, (a) to fine map the cleft loci and identify the functional gene variants (b) embark on epigenetic and functional genomics (c) gene-environment interaction, (d) unravel the epistatic interactions that are part of the aetiology (e) translate genetic findings into clinical practice and prevention strategies.

Expertise in statistical approaches, high troughput genome wide techniques, triad DNA biobank, robust data on phenotyping, diversity of the European populations.

Does ns-OFCs etiology have a genetic component ?



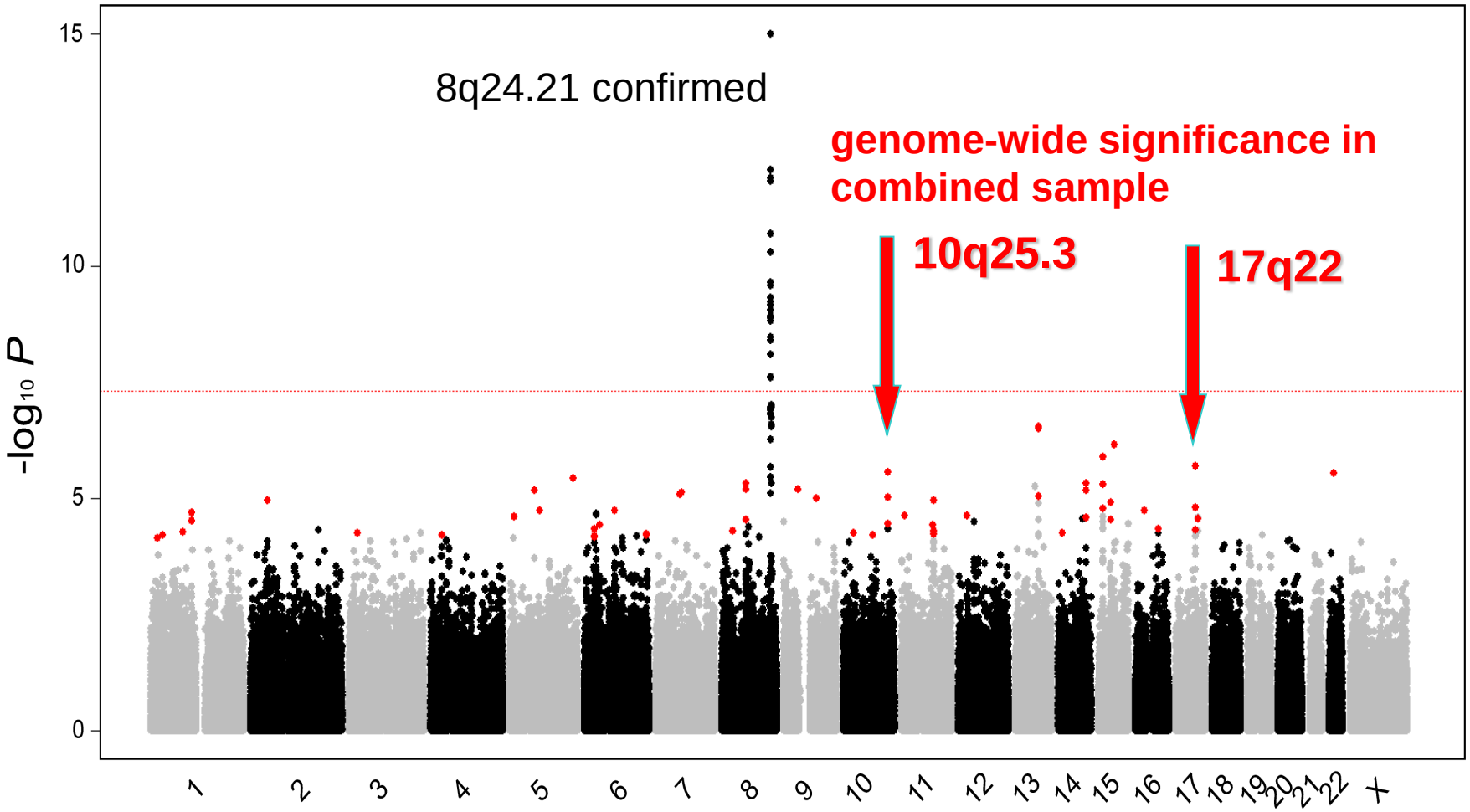
Heritability:

CL/P 91%; CP 90%

207 OFC Twins / 7766 OFC Singletons; 1936-2004, Denmark

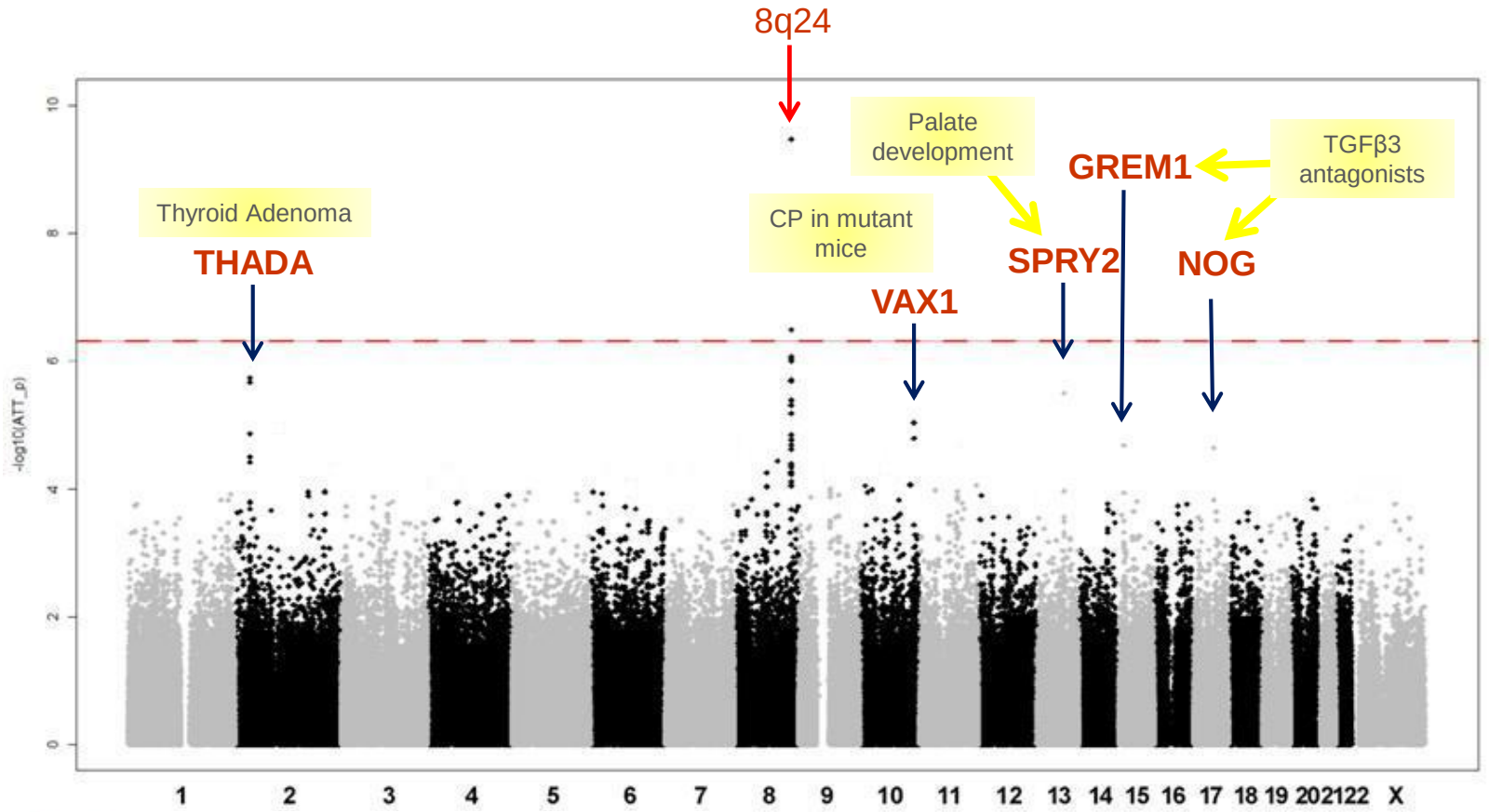
Grosen et al., Epidemiology 22:313-319, 2011

Bonn GWAS – with EUROCRAN trios for replication



Mangold et al., Nat. Genet.2010

GWAS – Functional significance



Manhattan plots of log10(p-values) of Odds Ratio

E. Mangold et al., Nature Genetics 42(1):24-6, 2010

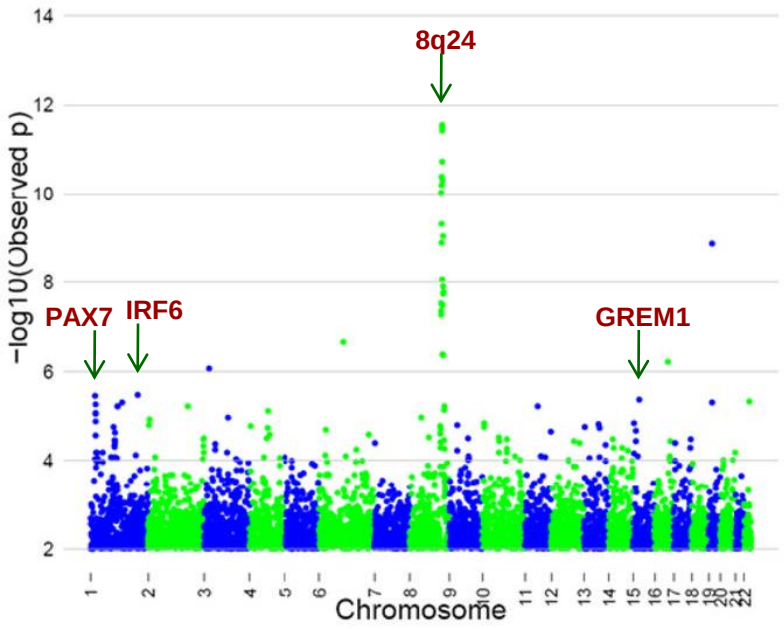
nsCL/P susceptibility genes/loci – before GWAS era

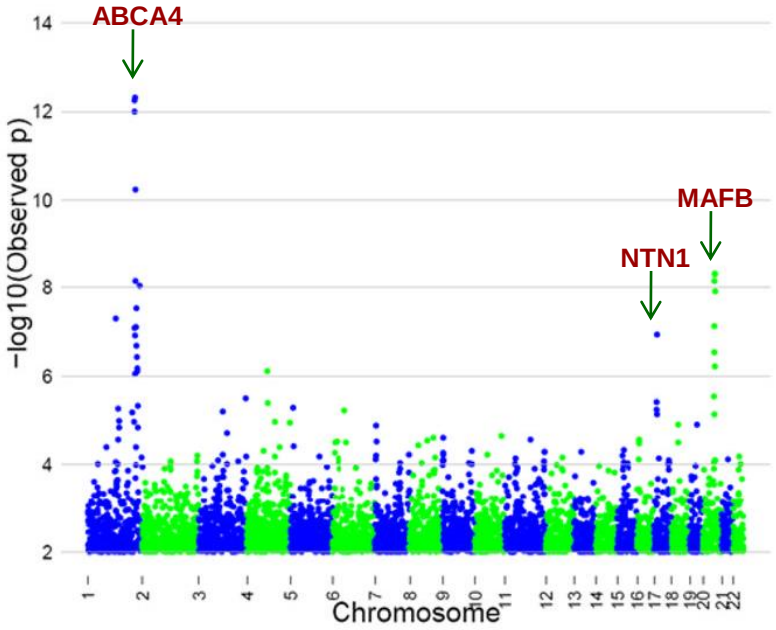
Locus/Gene	Support from
IRF6	Candidate gene study + 1 GWAS + Meta-analysis of linkage studies + many replication studies
FOXE1	Meta-analysis of linkage studies

nsCL/P susceptibility genes/loci known today

Locus/Gene	Support from
1p36	**GWAS meta-analysis**
1p22	1 GWAS + **GWAS meta-analysis**
IRF6	Candidate gene study + 1 GWAS + Meta-analysis of linkage studies + many **replication studies**
2p21	**GWAS meta-analysis**
3p11	**GWAS meta-analysis**
3q12	**GWAS/replication sample**
8q21	**GWAS meta-analysis**
8q24	**4 GWAS + several replication studies + GWAS meta-analysis**
9q22	Meta-analysis of linkage studies, **1 replication**
10q25	**1 GWAS + GWAS meta-analysis + 2 replication studies**
13q31	**GWAS meta-analysis**
15q22	**GWAS meta-analysis**
17q13	**GWAS/replication sample**
17q22	**1 GWAS + GWAS meta-analysis**
20q12	1 GWAS + **GWAS meta-analysis**

Independent GWAS: Europe v Asia

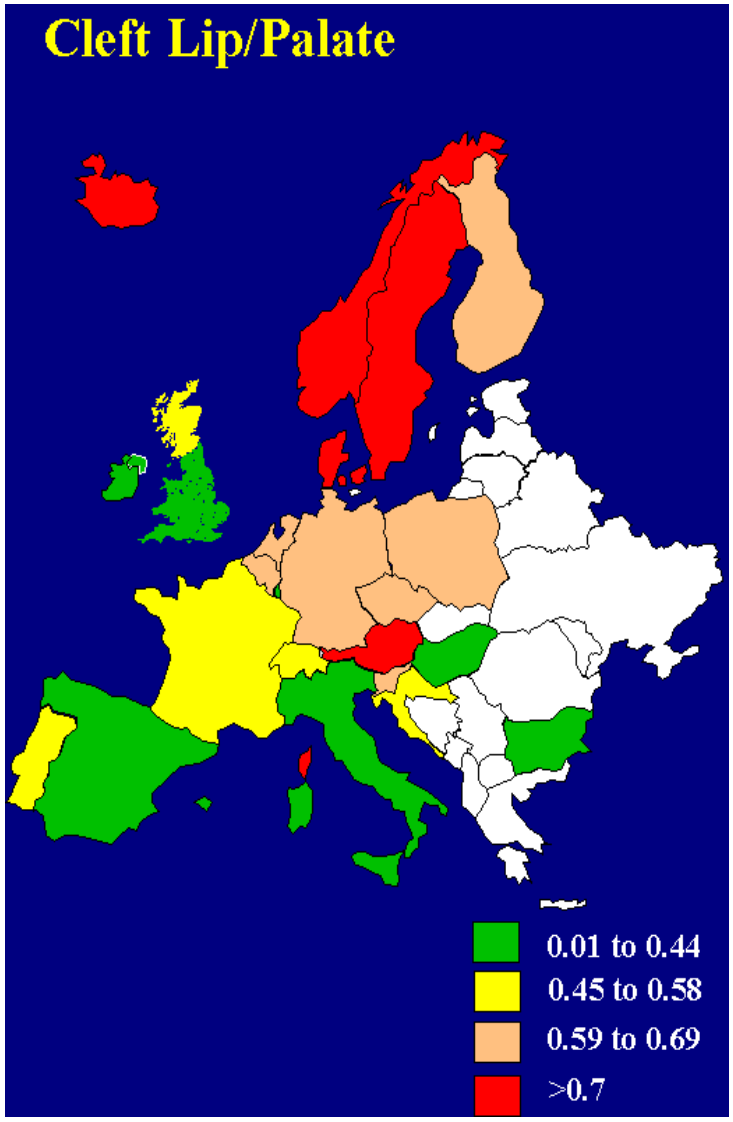


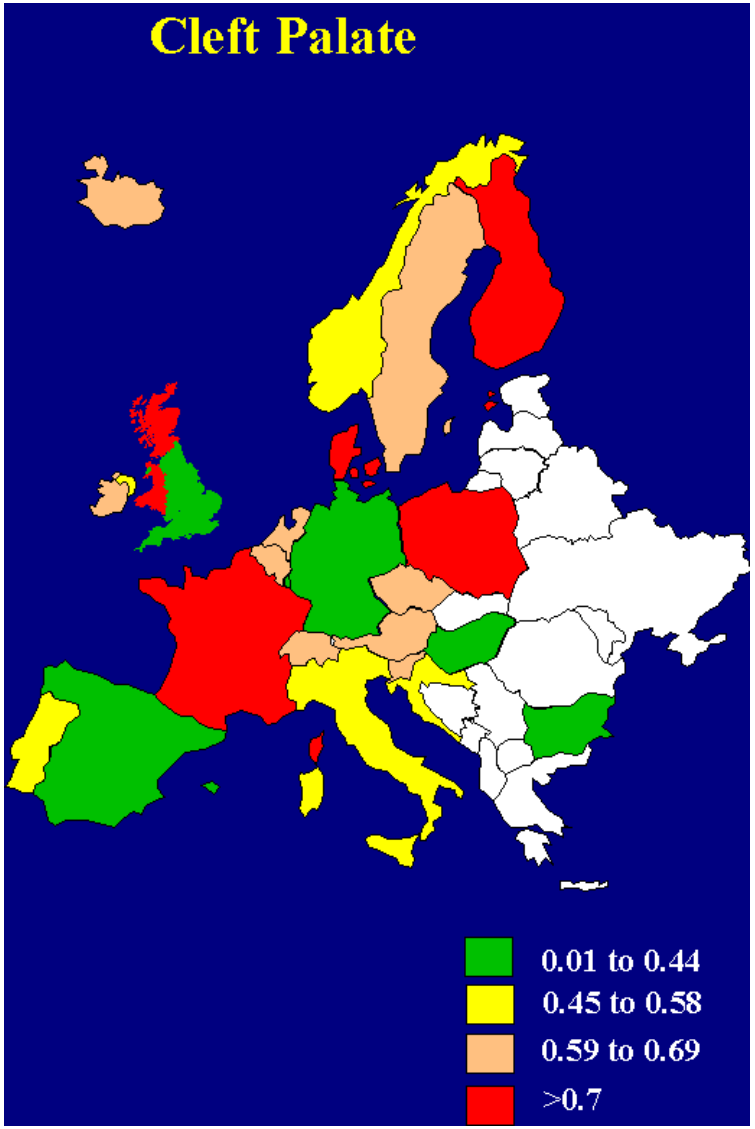


- 8q24.21 is a CL/P risk Locus only for Caucasians
- different CL/P susceptibility genes in different populations

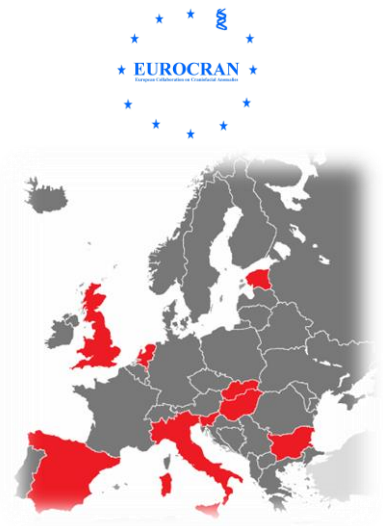
Beaty et al., Nat Genet 2010

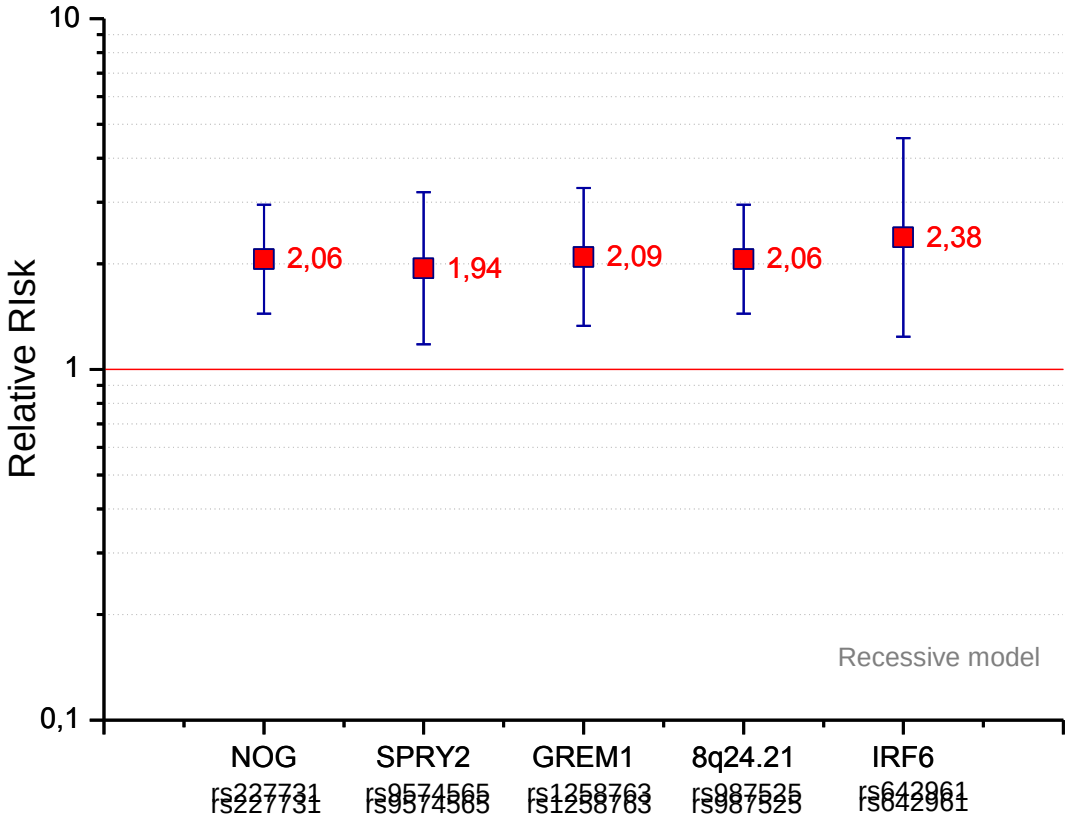
Different susceptibility genes in different populations ?





RISK: Each CL/P-associated SNP provides an increased risk





- Only a part of ns-OFC trait heritability can be explained by common susceptibility variants

Limits of GWAS

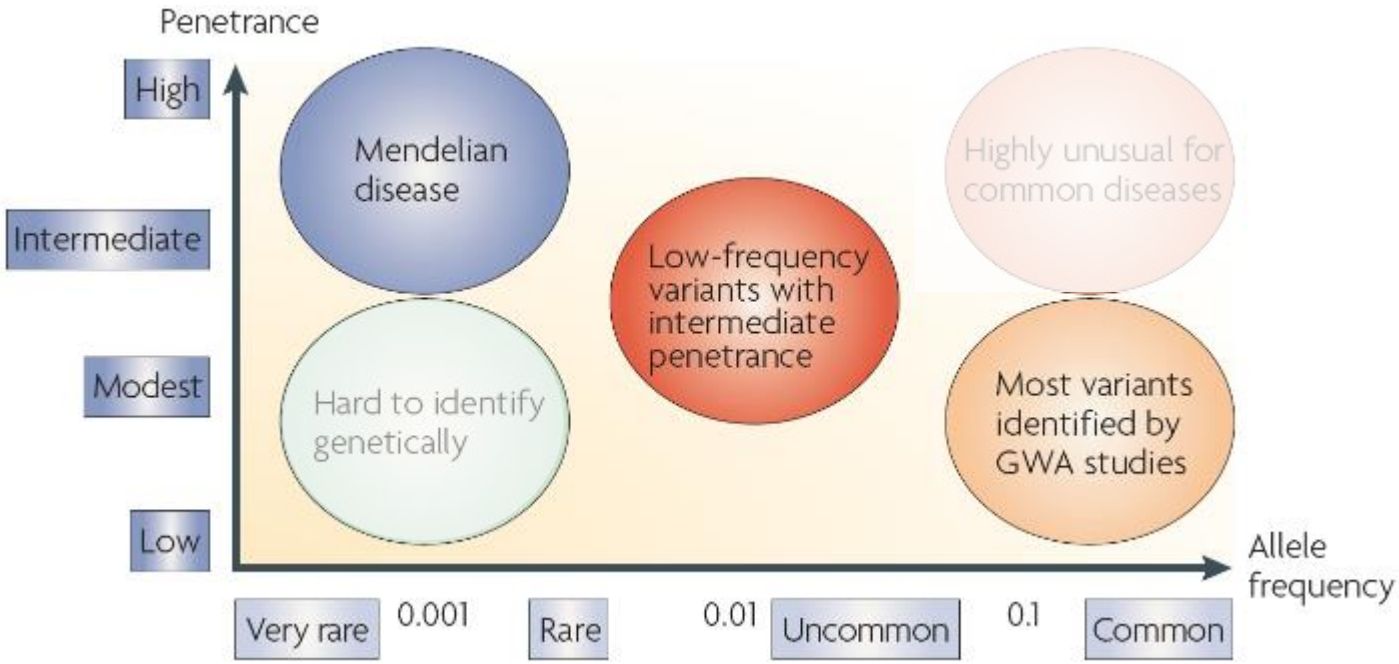
- non-Additivity effects of SNPs identified by GWAS
- Does NOT identify low-fequency variants with intermediate penetrance

Genetic Landscape of ns-OFCs

Genes of Syndromes

Genetic dark matter

Common susceptibility variants



NGS

GWAS

wellcome trust

Genomic approaches

Search for both common and rare variants

GWAS → Common variants & Common variants in LD with rare variants

Rare variants could explains missing heritability for complex traits (Manolio et al 2009)

Rare variants tend to be population specific (Keinan et al., 2012; Tennessen et al., 2012).

Possibility of etiologic rare variants in African population.

WES & Deep targeted sequencing around GWAS signals → Rare variants

“Global burden of cleft lip and palate and global multi-centre initiatives”

- **Where do we go from here ?**

Professor Peter A Mossey
Director, WHO CC

UNIVERSITY OF DUNDEE

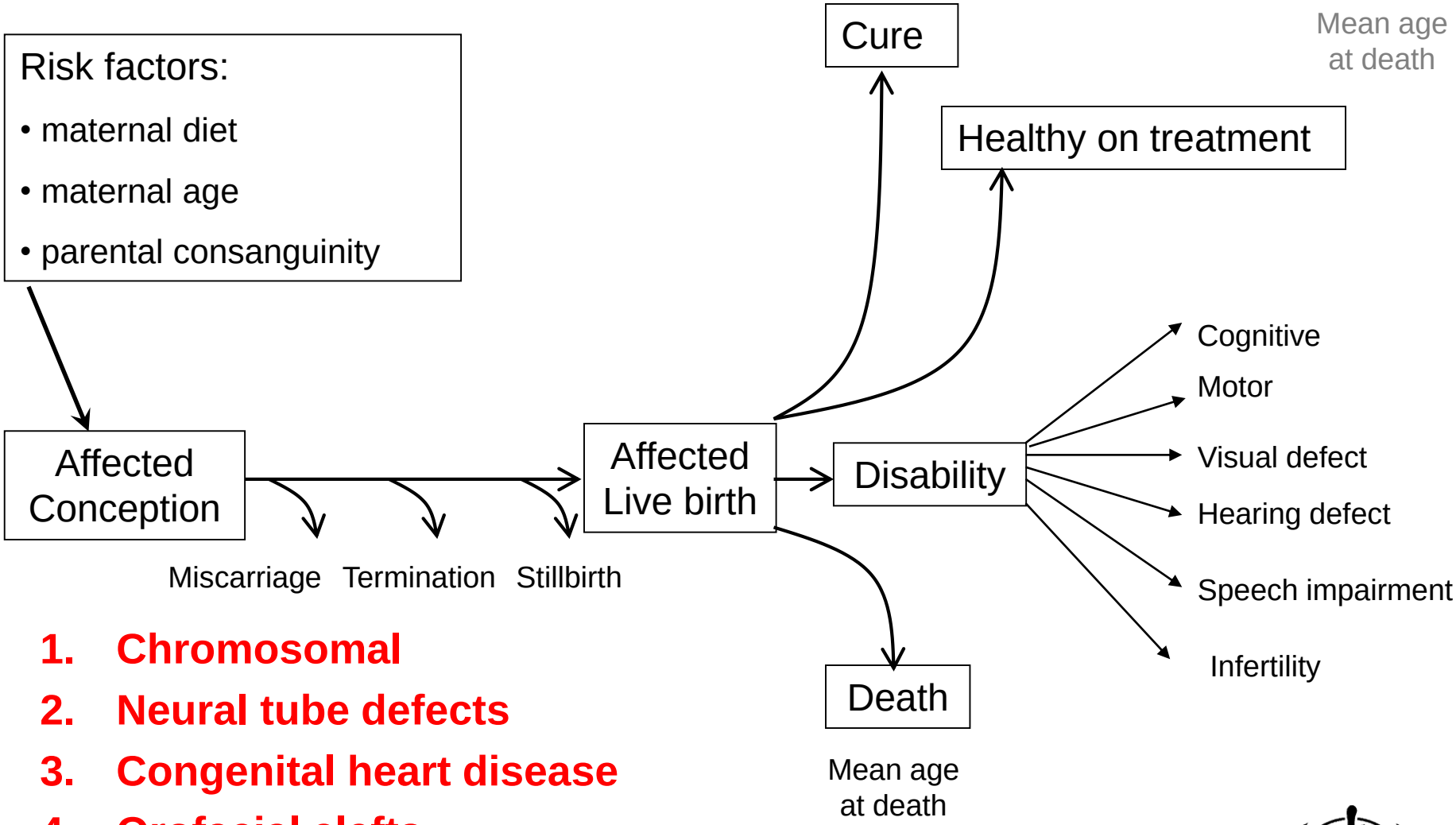
World Health Organisation, 2010

- **SIXTY-THIRD WORLD HEALTH ASSEMBLY A63/10**
- **Provisional agenda item 11.7 1 April 2010**
- **Birth defects: Report by the Secretariat**

- **Recommendation to all member states**

- **Global Burden of Disease (GBD) initiative (2010)**

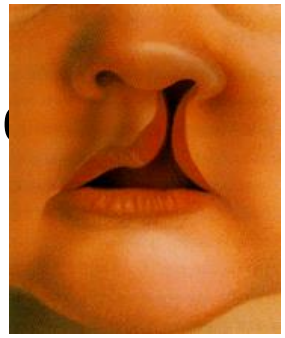
GBD generic schematic for congenital abnormalities (2010)



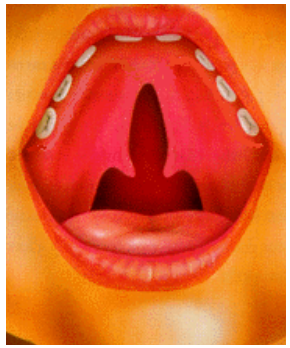
1. **Chromosomal**
2. **Neural tube defects**
3. **Congenital heart disease**
4. **Orofacial clefts**
5. **Structural GU and GI**
6. **"Other"**

WHO - Brussels October 2012

GBD: the overall aim ?



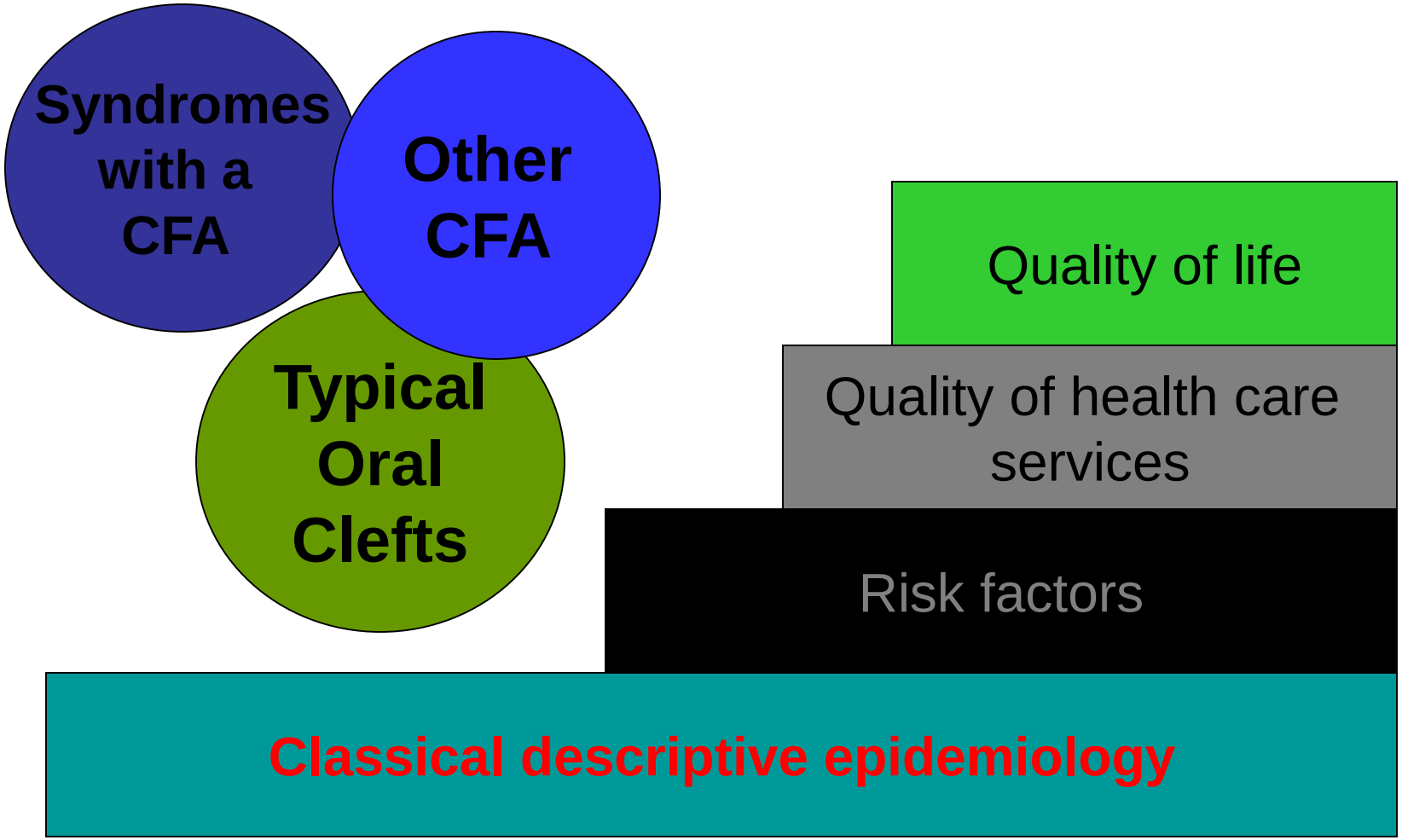
1. Epidemiological characterisation of disease and natural history @ global level
2. Identification of data gaps
3. Accurate definition of morbidity / mortality (including sequelae for each outcome)
4. Estimation of YLDs and DALYs for OFC



- **YLDs = Years Lived with Disability**
- **DALYs = Disability Adjusted Life Years**

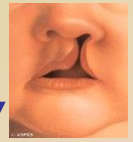
The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.

General philosophy : step by step approach



Slight protective effect of 677TT genotype in mothers, evident only in FA supplemented mothers (significant for CL/P)

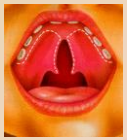
MTHFR 677TT



CL/P

MTHFR 677TT

MTHFD1 1958AA



CPO

Significant reduction of CPO risk in 1958AA mothers supplemented with FA (opposite effect of FA for CL/P)

Folic Acid Supplementation in early pregnancy

FA supplementation does not interact with child MTHFR or MTHFD1 genotype

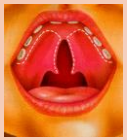
No association of TGFA TaqI with folic acid supplementation

MTHFR 677TT mothers who did not smoke during pregnancy have a reduction in risk of having child with CL/P

MTHFR 677TT

CL/P

MTHFR 677TT



CPO

MTHFR 677TT mothers protects from CPO only among smokers (n.s.)

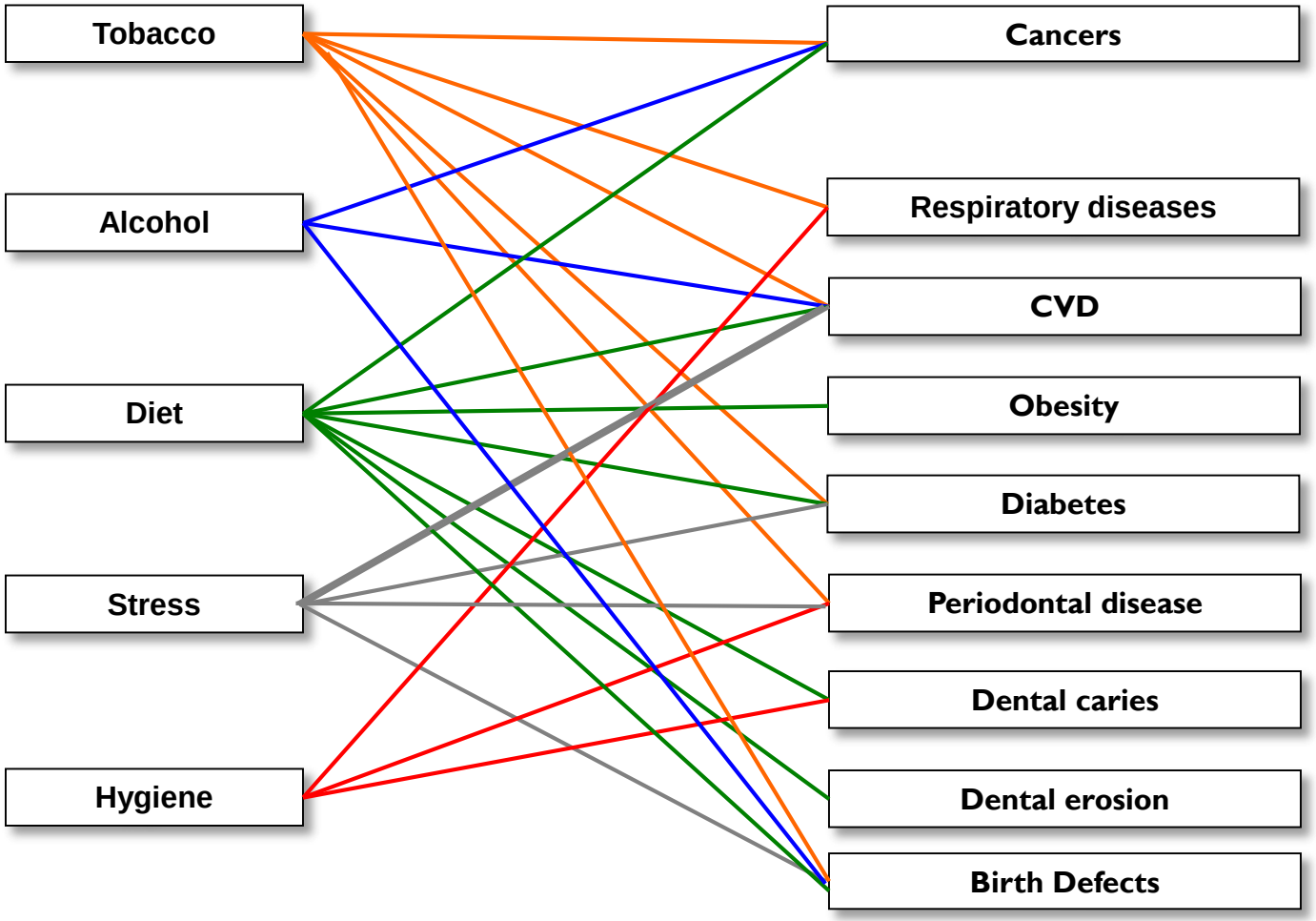
Smoking in early pregnancy

Protection for CL/P in 341CC children is not influenced by smoking during the pregnancy

No interaction between TGFA, MSX1 or SATB2 and smoking

IADR - GOHIRN: Common risk factors in NCDs

World Health Organization



(Grabauskas WHO Regional Office for Europe 1987; Sheiham & Watt, 2000)

Eg OFC

Prevention of Orofacial Clefts: Does Pregnancy Planning Have a Role?

Cleft Palate–Craniofacial Journal, May 2007, Vol. 44 No. 3
(Peter A. Mossey, B.D.S., Ph.D., F.D.S., R.C.S. (Edin), Janet A. Davies, B.Sc., M.Sc., M.P.H., Julian Little, Ph.D)

ABSTRACT

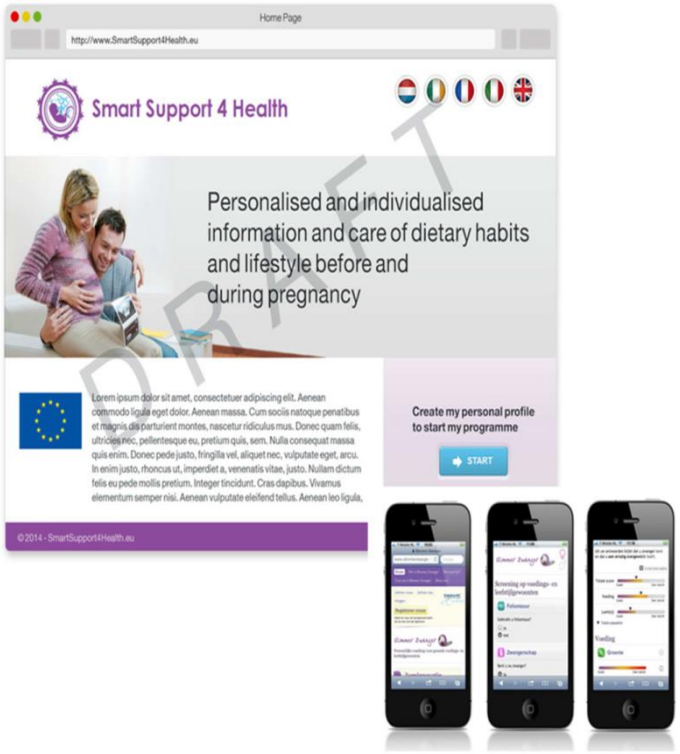
- ***Objective:*** **To investigate the association between pregnancy planning and orofacial clefts in the United Kingdom.**
- ***Design:*** **Case–control study.** ***Setting:*** **Scotland and the Manchester and Merseyside regions of England.**
- ***Participants:*** **One hundred and ninety-one children born with nonsyndromic orofacial cleft, 1997 to 2000, and 247 controls.**
- ***Results:*** **There was an inverse association between planning for pregnancy and orofacial cleft in the offspring ([OR] = 0.51, 95% confidence interval [CI] 0.33–0.79).**
- ***Conclusions:*** **Planned pregnancies were associated with a lower risk of orofacial clefts.**

Scottish Oral Health Research Collaboration

Smart Support 4 Health

Amendable risk factors – the efficacy of personalised coaching ?

Healthier lifestyle is the way towards primary prevention, and the topic of an application to H2020 in March 2014 “Smart Support 4 Health”



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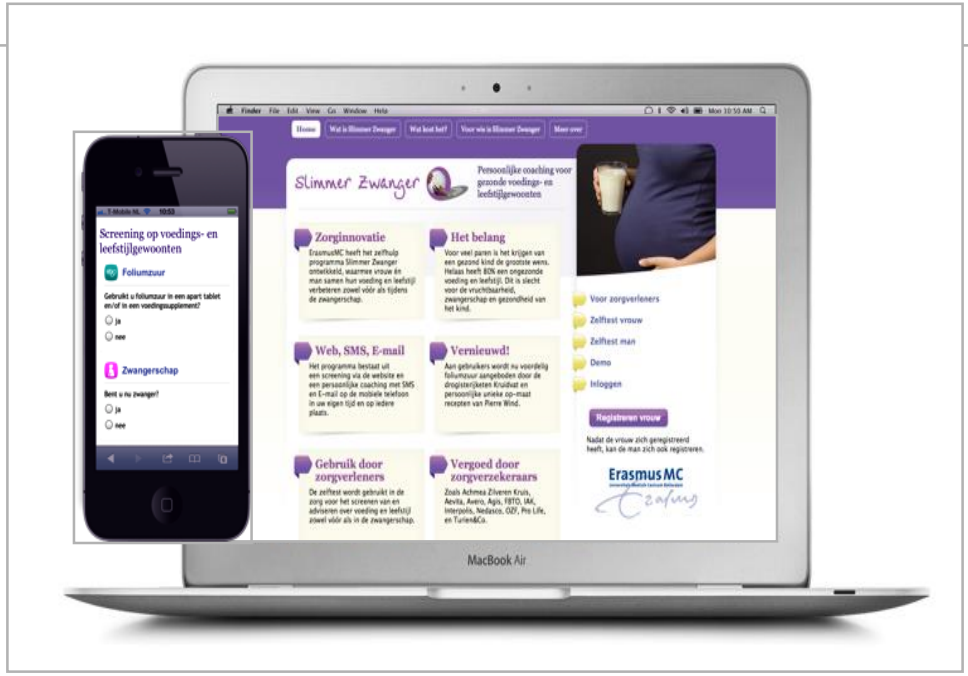
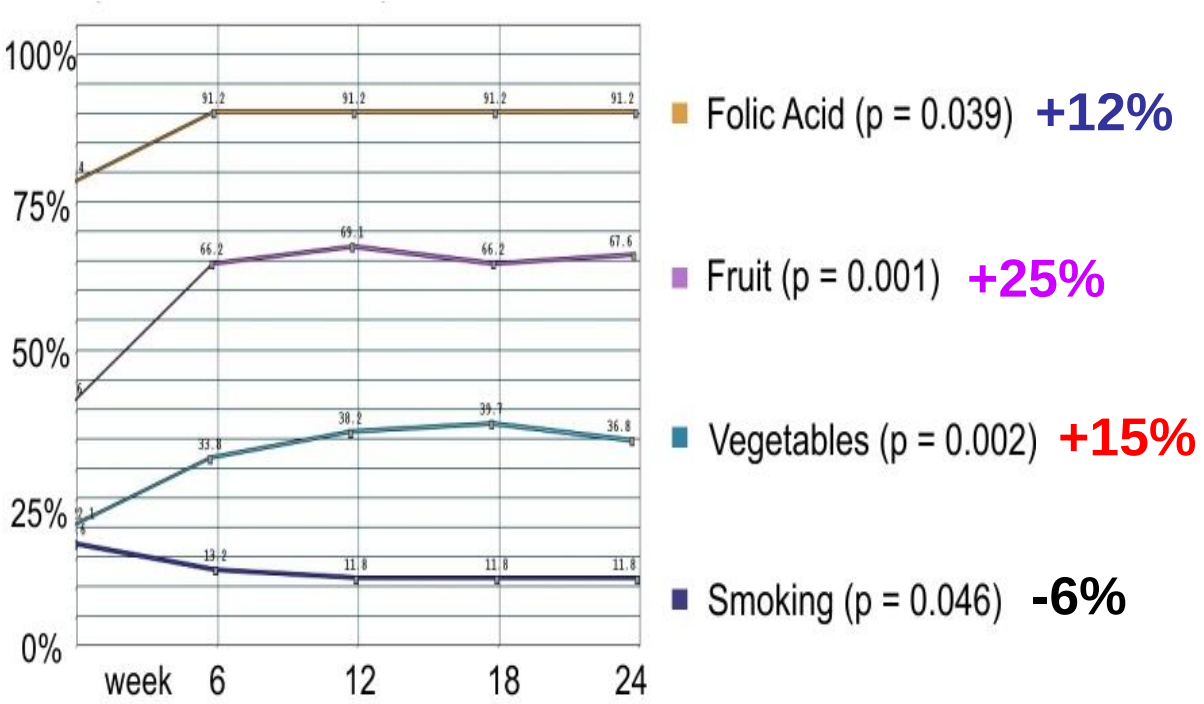


Internet excellent medium to reach the target group anonymously (cheap)
Web-application with email and SMS, at any time and place (smartphone)
Personal screening profile linked to a personal coachingsprogramme
Attitude- Social influence- Efficacy model

Steegers-Theunissen, May 2013

Efficacy

% improvement in nutrition and lifestyle behaviours



Scottish Oral Health Research Collaboration

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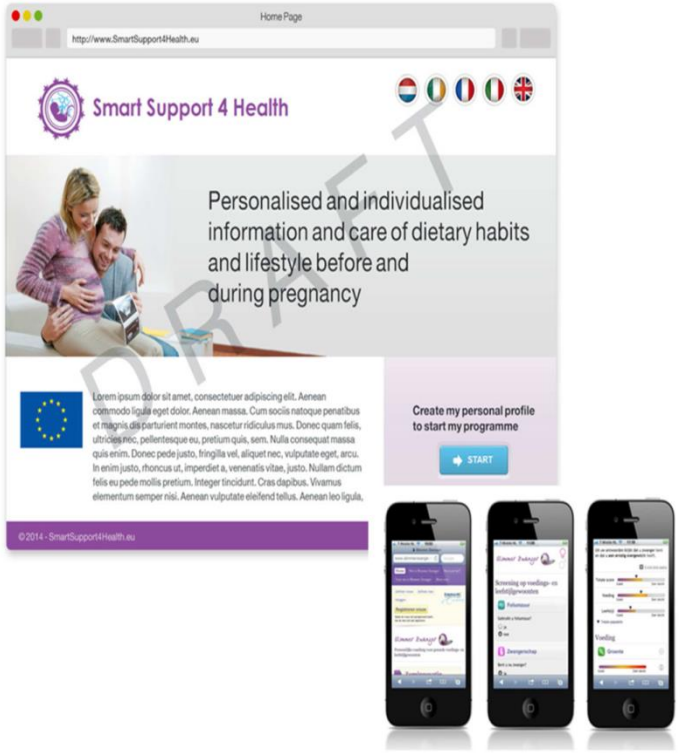


Projected EUROCleftNet Activities over next 12 months

- 1. Nurse Workshop and research issues relating to antenatal /neonatal cleft care, Bucharest, **October 2015** (Organiser: GD / ES)
-
- 2. OFC outcomes including 3D / 4D Imaging and “FaceReader” and underpinning “Facegene”, **December 2015** (Organiser: BS / AA / SK / Yang)
-
- 3. Workshop that facilitates research underpinning the implementation of the CEN standards in Europe, **January 2016** (Organiser: ECO / PM / GD)
-
- 4. Gaps in understanding and future challenges in Psychology & psycosocial research in OFC **March 2016** (Organiser: PM / MP / GR).

- 5. OFC Genetics EUROCleftNet Biobank & Functional variants in OFC, **April 2016** (Organiser: MR / BP)
-
- **6. Prevention Workshop - with environmental factor / behaviour change focus, Dundee May / June 2016 (Organiser: PM / EUROCAT)**

EUROCAT : surveillance underpinning prevention of congenital anomalies

EUROCleftNet would welcome representation from all stakeholders in Europe (and beyond) for discussion of the drive towards a primary prevention agenda.

eurocat
european surveillance of congenital anomalies

Suggested paticipants

Amanda Julie Neville,
Maria Loane,
Joan Morris
Ester Garne.

Access at: http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions-Reccomendations.pdf

eurocat

european surveillance of congenital anomalies

www.eurocat-network.eu

EUROCAT : surveillance underpinning prevention of congenital anomalies

The canary in the coalmine ?

Genetic Susceptibility screening ?

- Develop a panel of OFC gene polymorphisms based on ….
- 1. GWAS
- 2. Syndromic OFC
- 3. Array CGH
- 4. Animal models
- 5. Bioinformatics – developmental / phenotype micoforms etc.
- To be used clinically for screening ?

However we have challenges !

- Common v rare genetic variants
- Occurrence v recurrence
- Geographic / racial heterogeneity
- CLP and CP sub-phenotypes
- From “single” genes to “networks”
- Animal model (CP); Candidate gene studies (CLP)
- GGI, GEI and Epigenetics
- Global collaboration

Gene “networks”

- Many gene loci will have a role in other processes besides those that underlay the phenotype under consideration (**pleiotropy**)
- The effect of genes depends on the **context** of other alleles that are present
- The complexity of relationships among genes may be described as a **network.**

Gene network interactions

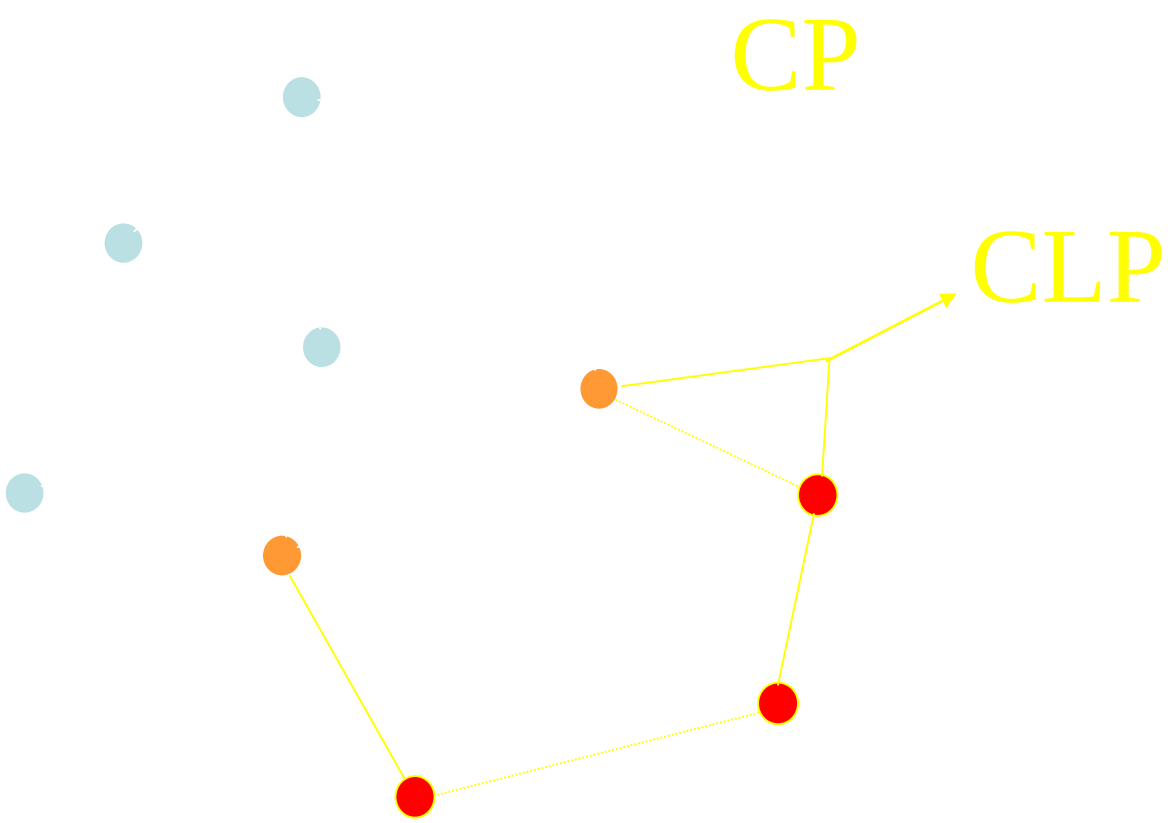
Genetic heterogeneity

It is likely that different families segregate different principal susceptibility genes.

In the majority of cases no susceptibility gene will be mutated in all patients that have the disease.

Risk transmission might be caused by cumulative effects of interchangeable loci or by specific interactions between alleles at two or more loci.

Gene network interactions ?



Detailed EUROCleftNet Workplan 1st September 2015 to 30th June 2016

Part A: Proposed Workshops September 2015 – June 2016

1. Early Care of Babies Born with Clefts, Bucharest Oct 2015 (Davis)
2. 3D/4D Imaging symposium Dec 2015 (Ayoub)
3. A Psychosocial Workshop to Design the Next Innovative Research Agenda (Persson)
4. Impact and Research Implications of New Guidelines on the Early Care of Babies Born with Clefts (Davis) ***joint with*** Improving the Quality of Cleft Lip and Palate Care and Increasing Research Capacity in Europe (Shaw)
5. P4-CLEFT. Translating Genetics Research Achievements into Prediction, Prevention, Personalization and Participation (Rubini) ***joint with*** Primary prevention of birth defects in Europe – with orofacial clefts (OFC) as a demonstration model (Mossey) Final EUROCleftNet Conference with Prevention & Genetics Workshop May/June 16

Part B: Proposed SVE's September 2015 – June 2016

Miriam Figge (UK-NL-DE)
Tereza Petrova (CZ – FR)
Pisani Mosol Karen Alejandra (PE – IT)
Michele Rubini (IT –SL)
Anne Bohmer (GER-UK)
Rita Bassi Andreasi (IT-UK)
Faisal Khan (IT)
Maria Kazakova (BUL-UK)
Nedialka Slaninkova (BUL-UK)
Paola Franceschelli (IT – NL)

Part C: Other proposed Network activities

Gateway Directory of Resources – ongoing development

Part D: Publication Plan & Dissemination

Details of activities related to publications and information dissemination

Part E: Additional Administrative Support

It is expected during the period of September 2015 and June 2016 that additional administrative support will be required to ensure that the proposed workshops and other activities can be fully supported. We propose to increase administrative support to 2 days a week.

Workshop proposal 1

Proposed Title:

Early Care of Babies Born with Clefts, Bucharest, October 2015

Coordinator: Gareth Davis

This workshop will focus on the nursing care of babies born with clefts and follows the elaboration of a set of recommendations on early cleft care developed by the European Cleft Organisation (ECO) and endorsed by the European Committee for Standardisation (CEN) in Brussels.

Target Audience: Health professionals responsible for the planning and coordination of early cleft care, including feeding assessments, development of feeding plans, providing support and counselling to the family, both prenatally and in childhood, and liaising with other health care professionals. In some countries this role is undertaken by a specialist nurse but in others the role may be performed by other trained professionals with relevant skills such as speech and language therapists, feeding specialists, social workers and health visitors. Cleft team leaders/coordinators should ensure this workshop is brought to the attention of the most relevant person in their team/hospital. Participants will be asked to consider the evidence base and ways of improving best practice through collaborative research.

Where and When: The workshop will take place on 15 October at one of the Residence Hotels in Bucharest (either Domenii Plaza by Residence, 33 Alexandru Constantinescu st. or Arc de Triomphe hotel, 19 Clucerului st)

Programme: Proposed topics will include presentations and practical sessions covering the following areas and the role of future research in the pursuit of evidence based practice will be emphasised:

- Exploration of the role of cleft nursing in different countries
- Measuring and comparing outcomes – research opportunities
- Being heard, being noticed – having an impact in differing medical hierarchies
- Introduction to early cleft care guidelines
- Antenatal support and counselling
- Feeding and nutritional assessments
- Psychological effect of a cleft on attachment and bonding and gaps in the evidence base
- The impact of additional anomalies e.g. airway obstruction (Pierre Robin) and other conditions
- Holistic care and support of the infant and the family and prevention of morbidity

Cost: Workshop participants will be expected to pay for their own travel to and from Bucharest. There is no charge for the workshop. A grant from the European Science Foundation means that two night's accommodation will be provided free of charge. We may need to limit numbers so please register early to ensure you have a place.

Bursaries: A limited number of bursaries are available giving free access to the workshop and help with travel costs. Preference will be given to applicants from Eastern Europe. Those wishing to be considered for bursaries should tick the appropriate box in the registration form and attach a Curriculum Vitae together with a short note stating why you should be considered for a bursary place. Bursaries will be awarded by the organising committee and their decision is final.

Organising Committee

- Trisha Bannister — Consultant specialist cleft nurse, UK
- Kostadinka Bojikova — Specialist cleft nurse Bulgaria
- Gareth Davies — Executive Director, European Cleft Organisation, France/Netherlands)
- Radu Spataru — Cleft Surgeon, Romania
- Claudia Malic — Surgeon, Canada/Romania
- Peter Mossey — Chair, EUROCleftNet Steering Committee

- Nina Lindberg Specialist Cleft Nurse, Norway
- Lisa Smedgard Specialist cleft nurse, Denmark
- Emma Southby Specialist Cleft Nurse, UK

Costs based on 50 delegates

European Cleft Organistion	€5000
Bursaries x 18 (€200 per person max.)	€3750
Travel (Speakers x3)	€1250
Total requested from ECO	€5000
European Science Foundation	€10000
Accommodation (2 nights €80 per person)	€8000
Conference Rate (incl. lunch €32 per person)	€1600
Bursaries x 2 (€200 per person max.)	€400
Total requested from ESF	€10000

Workshop proposal 2

Proposed Title:

3D/4D imaging symposium, December 2015

Coordinator: Ashraf Ayoub

Background: The World Health Organization (WHO) has highlighted the need for quality improvement in patients having craniofacial anomalies. There is also a lack of objective outcome measures of the quality of facial aesthetics and the associated expressions.

Gap in knowledge: Despite the advanced technique to measure facial animation, there is still insufficient information on the dynamics of facial muscle movement.

State-of-the-art technology: Recently, a non-invasive four dimensional (4D) soft tissue imaging system (Di4D) has been set up in Scotland, it recovers high fidelity facial motion capture data without requiring special illumination, markers or make-up. The objectivity of Di4D capture system is superior to any other system and has the ability to track the dynamic changes in soft tissue movement. The automatic tracking of facial landmarks demonstrated a satisfactory accuracy which would facilitate the analysis of the dynamic motion during facial animations (Al Anzie et al 2013).

Challenges & opportunities: Surgically managed cleft children at the age of 13 are conscious of their facial appearance and may be subjected to bullying due to residual visible lip scar and abnormalities of facial animations. At this age a decision may be taken to carry out further surgical revisions to deal with the scarred lip. In most of the cases this decision is taken based on the subjective evaluation of the residual dysmorphology by the surgeons, this varies widely among clinicians. Therefore, it is prudent to have an objective too to evaluate the magnitude of lip scarring and quantify abnormalities of facial animations to inform the decision making process regarding the need of further corrective procedures and monitor the progress in the surgically managed cleft children. This would be also fine tune the surgical technique of primary surgical repair of cleft lip and palate to minimise the residual dysmorphology.

Objectives of the symposium: The main objective of this symposium is to establish a forum of key researchers, leading scientists and experts across Europe in the field of facial imaging and computational biology to underpin the methodological innovation of analysing facial expressions.

The symposium would provide the opportunity to share existing expertise and knowledge on the facial imaging and:-

1. Highlight the pathway of impacts of this novel approach and identify the groups of beneficiaries of this innovation
2. Explore existing funding opportunities and research all's that match the scope of the proposed study
3. Agree on the mechanism of communication and finalise a realistic schedule to submit research grants

List of potential participants:

Ashraf Ayoub	UK
Pitas Ioannis	Greece
K. Lyroudia	Greece
David Dunaway	UK
Colin Urquhart	UK
Felicity Mehendale	UK
Mohamed Daoudi	France
Paul Whelan	Ireland
Peter Hammond	UK
Thomas Maal	Netherlands
Stefaan Berge	Netherlands
E Wolvius	Netherlands
Youri Anastassov	Bulgaria
Peter Mossey	UK
Martin Persson	UK
M.J. Koudstaal	Netherlands
Philippe Pellerin	France
Pierre Guerreschi	France
Stephen Morley	UK
Toby Gillgrass	UK
Craig Russell	UK
Balvinder Khambay	UK
Alireza Ghassemi	Germany

Cost

Accommodation x 22	€3000
Meals	€550
Flights	€5450
Transfers	€1000
Total	€10000

Venue: To be finalised

Workshop proposal 3

Proposed Title:

A Psychosocial Workshop to Design the Next Innovative Research Agenda

Coordinator: Martin Persson

Objective: To develop innovative psychosocial research ideas for craniofacial conditions that adhere to the objectives of the Horizon2020 call "Health, demographic change and well-being" or other relevant calls.

Current research in cleft indicates that about 1/3 of this population is not doing so well psychosocially. There is also indication for example that about 30% have additional conditions such as learning disability or ADHD (1), negative educational outcomes (2), are more likely to be unemployed (3), have lower earnings (4) or have a poorer health in general in comparison to normal population (5). There is currently a strong need to identify this subgroup in the cleft

population that are not doing so well and to understand the cause of this in order to provide adequate provision of care.

At the same time European Union has specified research priorities as indicated in the text below that come from the original text of the call for Societal Challenges, the text in bold indicates the possible areas we could focus upon:

Successful efforts to prevent, detect early, manage, treat and cure disease, disability, frailty and reduced functionality are underpinned by the fundamental understanding of their determinants and causes, processes and impacts, as well as factors underlying good health and well-being. Improved understanding of health and disease will demand close linkage between fundamental, clinical, epidemiological and socio-economic research.

Obviously the Horizon 2020 calls are complicated, however they also give us an understanding of what areas the EU priorities and where some of our research agenda should focus upon.

So the 1 day ESF psychosocial workshop should:-

Focus on the design for research priorities for cleft and craniofacial conditions around the EU priorities mentioned above

Focus how we can link in psychosocial aspects into other grant applications in our field such as the Face Reader for example. This is important for all disciplines since the EU wants a multidisciplinary approach in many grant applications.
Feasibility of EU grant applications
Partners' resources
Implication for provision of care
Incorporation of EU priorities

List of delegates

Martin Persson	UK
Peter Mossey	UK
Nichola Rumsey	UK
Ashraf Ayoub	UK
Gareth Davies	France
Leva Maulina	Latvia
Henry Svensson	Sweden
Slave Naumouski	Macedonia
Laura Linkevičienė	Lithuania
Nenad Tanaskovic	Bosnia
Predrag Knežević	Croatia
Julija Radojićić	Serbia
Triin Jagomägi	Estonia
Martina Drevensek	Slovenia
Radu Lulian Spataru	Romania
Youri Anastassov	Bulgaria
Nagore Solaeche Prieto	Spain
Kristin Billaud Feragen	Norway
Hakan Agir	Turkey

Number of delegates: 18 – 20

Date and Venue: Slovenia, Serbia or Macedonia, January or February, 2016 – (1 day)

Costs

Travel	€9700
Accommodation	€4000
Meals	€800
Estimated Venue Cost	€500

Total €15000

References

1. Feragen KB, Stock NM, Rumsey N. Toward a reconsideration of inclusion and exclusion criteria in cleft lip and palate: implications for psychological research. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association. 2014;51(5):569-78.
2. Persson M, Becker M, Svensson H. Academic achievement in individuals with cleft: a population-based register study. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association. 2012;49(2):153-9.
3. Marcusson A, Akerlind I, Paulin G. Quality of life in adults with repaired complete cleft lip and palate. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association. 2001;38(4):379-85.
4. Ramstad T, Ottem E, Shaw WC. Psychosocial adjustment in Norwegian adults who had undergone standardised treatment of complete cleft lip and palate. I. Education, employment and marriage. Scandinavian journal of plastic and reconstructive surgery and hand surgery / Nordisk plastikkirurgisk forening [and] Nordisk klubb for handkirurgi. 1995;29(3):251-7.
5. Christensen K, Juel K, Herskind AM, Murray JC. Long term follow up study of survival associated with cleft lip and palate at birth. Bmj. 2004;328(7453):1405.

Workshop proposal 4 *(Back to Back with Workshop 5)*

Proposed Title:

Impact and Research Implications of New Guidelines on the Early Care of Babies Born with Clefts, Brussels, March 2016

Coordinator: Gareth Davis

In March 2015 the European Committee for Standardisation (CEN) approved a set of guidelines in the early care of babies born with clefts. The report, CEN/TC 424*, spearheaded by the European Cleft Organisation and with significant support from EUROCleftNet, was agreed at European level with an overwhelming majority of CEN member bodies voting in its favour. The process began in 2011 and there has been input from Austria, Belgium, Bulgaria, Estonia, Finland, France, Germany, Lithuania, Spain, Romania and the UK. The final document draws considerably from the EU-funded Eurocleft project (2000) which made recommendations arrived at by consensus amongst health professionals.

Gareth Davies, Executive Director of ECO and Chairman of CEN/TC 424 said:
'This document will be helpful to those countries that do not have national guidelines in cleft care and will become a baseline of care against which we can measure service output and standards of care across Europe'.

EUROCleftNet believes strongly that these guidelines should be evidence based, promoted at a high level throughout Europe and used as a means of assessing current levels of care with a view to improving access to excellent cleft care for all babies born with clefts in Europe.

This workshop will bring together researchers, clinicians, politicians and representatives of national and international standards bodies to discuss the way forward. In particular the workshop will look at:

1) Exploration of the evidence base that underpins the guidelines, and implement, through EUROCleftNet any necessary research to address any identified gaps in evidence
2) Means of dissemination of the guidelines throughout (and beyond) Europe
3) Ways in which the guidelines can be used as a tool for measuring and assessing current levels of care
4) Implementation of the guidelines

5) Methods to evaluate the long term effects on cleft care post implementation

Delegate list:

Peter Mossey	EurocleftNet
Bill Shaw	EurocleftNet
Sean Kelly	MEP
Vytenis Andriukaitis	European Commissoner for Heatlh
Paula Duarte Gaspar	European Commissioner for health team – health information
Elena Santiago	Director General CEN
Ashok Ganesh	Director Innovation, CEN
Maitane Olabarria	Programme manager sustainability, CEN
Guido de Jongh	NBN – Belgian Standards
Gareth Davies	Chair Technical Committee (TC) CEN 424
Pedro de Cano	TC Spain
Peter Schachner	TC Austria
Youri Anastassov	TC Bulgaria
Emma Southby	TC UK
Radu Spataru	TC Romania
Triin Jagomagi	TC Estonia
Zuzana Oravkinova	TC Slovakia
Rosanna Preston	TC UK and patient voice
Mariette Vermeylen Nujts	TC Belgium and patient voice
Monika Skoken	MAM Baby Austria – Head of Public Opinion
Martin Persson	COST/ECO
Ysbrand Poortman	Campaigner
Alistair Kent	Campaigner
Michel Grupper	Resurgens/Public Health
Miriam Ryan	ECO
Anton Vorderman	ECO

Date and Venue: Brussels, March 2016 (1 day) + back to back with workshop 4

Costs

3 nights accommodation:	€6400
Travel	€7500
Venue (Possible CEN)	€1100
Total	€15000

*The document is available from the National Members (standards offices) of CEN in 33 European countries.

Workshop proposal 5 *(Back to Back with Workshop 4)*

Proposed Title:

Improving the Quality of Cleft Lip and Palate Care and Increasing Research Capacity in Europe, March 2016

Coordinator: William Shaw

Background to the proposal: The haphazard nature of European cleft lip and palate clinical services was originally explored in the European Commission Framework IV Project “Standards of Care for Cleft Lip and Palate in Europe: Eurocleft”, Contract No. BMH4-CT95-0402, 1996-2000. This work identified 201 clinical teams responsible for the surgical and related care of children with clefts of the lip and/or palate; completed a survey of clinical protocols in use; and defined international guidelines for minimum standards of care and standardised clinical datasets.

This work was subsumed into Eurocran, a project funded under Framework V, 2000-2004, Contract No. QLG1-CT-2000-01019, and included all the European Union States and the Newly Associated States of that period. At least one representative of every country took part in workpackages leading to the publication of *Policy Statements and Practice Guidelines, Principles Governing Record Taking*, and a *European Register of 201 Cleft Centres.*[1] Workshops on the initiation of *European Multicentred Trials and Prospective Cohort Studies* of cleft surgery were also convened.

In the years since, some restructuring of services was achieved in individual countries, three multinational randomised trials of primary surgical technique have been completed, and one further trial of surgical timing is due to complete recruitment in June 2015. However in many European countries, services remain fragmented and non-standardised, and few if any prospective clinical studies are underway (the four current trials mentioned above are confined to teams in Scandinavia and the UK).

As these are also challenges for other parts of the world an International Task Force was launched at the last conference of the International Confederation of Cleft Lip and Palate and Related Craniofacial Anomalies in 2013[2].

Proposal: The workshop will address five topics:

1. Review of current guidelines and standards of cleft care
2. Barriers and solutions to implementation
3. Review of research priorities
4. Barriers and solutions to effective European research collaboration
5. European contributions to the international task force “Beyond Eurocleft”

Context: Standards of care and associated research represent long-term international challenges for the providers of clinical care and affected families, and this mission will require a strong sense of purpose and continuity in the years ahead. Ownership of the challenge should rest with the European Association for Cleft Lip and Palate and Related Craniofacial Anomalies as the European Chapter of the International Confederation for Cleft Lip and Palate and Related Craniofacial Anomalies, to gain the best chance of an enduring and effective commitment. The proposal strongly connects with parallel work of the European Cleft Organisation on the political imlementation phase of standards through the European Committee for Standardisation (CEN).

1. Shaw WC, Semb G, Nelson P, Brattstrom V, Molsted K, Prahl-Andersen B, Gundlach KKH. The Eurocleft Project 1996-2000.
2. Semb G. The Cleft Palate–Craniofacial Journal 51(6) pp. e146–e155 November 2014

Delegate list

Peter Mossey	EuroCleftNet
Bill Shaw	EuroCleftNet
Sean Kelly	MEP
Vytenis Andriukaitis	European Commissoner for Heatlh
Paula Duarte Gaspar	European Commissioner for health team – health information
Elena Santiago	Director General CEN
Ashok Ganesh	Director Innovation, CEN
Maitane Olabarria	Programme manager sustainability, CEN
Guido de Jongh	NBN – Belgian Standards)
Gareth Davies	Chair Technical Committee (TC) CEN 424
Pedro de Cano	TC Spain
Peter Schachner	TC Austria
Youri Anastassov	TC Bulgaria
Emma Southby	TC UK
Radu Spataru	TC Romania
Triin Jagomagi	TC Estonia
Zuzana Oravkinova	TC Slovakia
Rosanna Preston	TC UK and patient voice
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Monika Skoken	MAM Baby Austria – Head of Public Opinion
Martin Persson	COST/ECO

Ysbrand Poortman	Campaigner
Alistair Kent	Campaigner
Michel Grupper	Resurgens/Public Health
Miriam Ryan	ECO
Anton Vorderman	ECO

Date and Venue: Brussels, Belgium – March 2016 (1 day)

Cost

To be applied with costs for workshop 4

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 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 the contribute 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.

List of delegates (contributors)

Adrianna Mostowska	Poznan University of Medical Sciences, Poznan, Poland
Borut Peterlin	Clinical Institute of Medical Genetics, Ljubliana, Slovenia
Carine Carels	Radboud University of Nijmegen, NL
David R. Fitzpatrick	Western General Hospital, Edinburgh, UK
Elisabeth Mangold	University of Bonn, Germany
Gareth Davis	European Cleft Organization
Greg Elgar	MRC National Institute for Medical Research, London, UK
Jo Zhou	Radboud University of Nijmegen, NL
Julian Little	University of Ottawa, Canada
Peter A. Mossey	University of Dundee, UK
Kerstin Ludwig	University of Bonn, Germany
Martin Persson	University of Bristol, UK
Michael Dixon	University of Manchester, UK
Michele Rubini	University of Ferrara, Italy
Miikka Viccula	de Duve Institute, Université Catholique de Louvain, Bruxelles, Belgium
Tiit Nikopensius	Institute of Molecular and Cell Biology, University of Tartu, Estonia

The overall number of delegates who will attend to the Workshop/Conference could be around 25.

Date and venue: Dundee, Scotland, UK – May / June 2016

Costs

Applied with costs for workshop 7

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 Eating 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 the mHealth coaching program on nutrition and lifestyle "Smarter Eating 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 Eating 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.

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.

Delegates who are expected to attend: The overall number of delegates who will attend to the Conference and Workshops is likely to be around 45. These will include:

ICBDSR x 4 delgates
WHO x 2 delgates
Erasmus MC x 2 delgates

EUROCATx4

Amanda Julie Neville	*Italy*
Maria Loane	*Ireland*
Joan Morris	*UK*
Ester Garne	*Denmark*

Peter Mossey	University of Dundee, UK
Gurdeep Sagoo	PHG, Cambridge, UK
Domenica Taruscio,	EUROCAT WP7 Primary Prevention leader, Italy
Bernadette Modell	LSHTM, UCL, London, UK
Adrianna Mostowska	Poznan University of Medical Sciences, Poznan, Poland
Borut Peterlin	Clinical Institute of Medical Genetics, Ljubliana, Slovenia
Carine Carels	Radboud University of Nijmegen, NL
Elisabeth Mangold	University of Bonn, Germany
Gareth Davis	European Cleft Organization, France
Julian Little	University of Ottawa, Canada
Kerstin Ludwig	University of Bonn, Germany
Michele Rubini	University of Ferrara, Italy
Tiit Nikopensius	Institute of Molecular & Cell Biology, University of Tartu, Estonia
Youri Anastassov	TC Bulgaria
Radu Spataru	TC Romania
Triin Jagomagi	TC Estonia
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Monika Skoken	MAM Baby Austria – Head of Public Opinion
Martin Persson	COST/ECO
Ysbrand Poortman	Campaigner
Alistair Kent	Campaigner
Michel Grupper	Resurgens/Public Health
Miriam Ryan	ECO

Date and venue: Dundee, Scotland, UK – May / June 2016

Cost

Accommodation (2 nights)	€7500
Travel	€6000
Meals	€2000
Venue & Hospitality	€1500
Total	€17000

Short Visits & Exchanges (SVEs)

Application – UK– Netherlands – Germany - September 2015 (Two visits - 3 weeks)

Applicant: Miriam Figge, Unit of Cell and Molecular Biology, Dental School, University of Dundee, DD1 4HN

Visiting: *Dr Carine Carels*, Radboud University, Nijmegen, Netherlands

Short description of the proposed project and the aim of the visit.

Project Aims and Objectives:

Purpose: to learn and use chromatin immunoprecipitation (ChIP) and sequencing (ChIPseq) assays. ChIPseq allows the analysis of DNA-protein interactions, and it is used mainly to investigate how transcription factors influence phenotype-affecting mechanisms (Mundade et al, 2014). This would allow us to establish whether a transcriptionally active SMAD complex binds to the promoter of *HAS2*, initiating transcription. Key Methods: SDS PAGE, Western blotting, ELISA, qPCR, Cell culture and immunocytochemistry.

Methodology:

A series of experiments was designed to enable quantification and assessment of the relationship between transcription and translation of the *HAS2* gene, in response to both reduced and physiologically relevant concentrations of TGFβ3. The catalytic activity of HAS2 was measured, indirectly, by quantifying hyaluronan secretion. The project also focused on signal transduction via activation of the SMAD pathway. Specific antibodies and pathway inhibitors were used to study some of the signal transduction molecules (SMAD2, 3, 4) involved in transmitting the TGFβ3 signal from the cell membrane to the nucleus culminating in transcriptional activity. These experiments focused on the human embryonic palatal mesenchyme line (HEPM), which is of direct relevance.

Techniques:

Expression of the HAS2 enzyme and activation of the SMAD pathway was quantified by Western Blotting and protein localisation by immunocytochemistry. Activity of the HAS2 enzyme was measured indirectly by ELISA of the product HA. Expression of the *HAS2* gene was quantified by qPCR of purified mRNA from cells treated with combinations of TGFβ3 and a specific SMAD2/3 phosphorylation inhibitor.

Proof of Concept:

Resultant data indicated that there was potentially a direct relationship between *HAS2* expression and the SMAD pathway. We therefore designed an additional series of chromatin immunoprecipitation (ChIP) experiments to corroborate this hypothesis. The expertise required to perform these assays was not locally available, we therefore established a collaboration with Prof. Zhou's lab at the Radboud Institute for Molecular Life Sciences, Geert Grooteplein 26/28, Radboud University, Nijmegen.

References:

Mundade,R. et al (2014) ' Role of ChIP-seq in the discovery of transcription factor binding sites, differential gene regulation mechanism, epigenetic marks and beyond', Cell Cycle, vol. 18, pp. 2847-52. doi: 10.4161/15384101.2014.949201

Address/Contact details of Host: Prof. Dr Carine Carels**,** Radboud University, Nijmegen, Netherlands

Proposed starting dates of the visit: 3 weeks in total - 1 week over Easter (06/04/15-10/04/15) and 2 weeks in July (20/07/15-31/07/15)

Estimated travel costs: €1250

Accommodation: €2750

Total grant requested : €4000

Application – Czech Rep– France - September 2015 (8 weeks) In the system 5144

Applicant: **Tereza Petrova,** Dental clinic 3rd Medical Faculty of Charles University, Prague

Visiting: *Professor Benateau,* University Professor - Hospital Practitioner, Manager Maxillofacial surgeon, Caen University Hospital, Caen, France

Short description of the proposed project and the aim of the visit.

The aim of this article is to compare the orthodontic approach to the treatment of the orofacial cleft anomalies in Fakultni nemocnice Kralovske Vinohrady, Prague, Czech Republic and Centre Hospitalier Universitaire, Caen, France.
I would like to start with the description of the orthodontic approach to the orofacial clefts in Prague.

In deciduous and mixed dentition a removable plate appliances with an expansion screw are used. Both the resin base of the appliance and the position of the screw are adapted to the atypical morphology of the palate. An individualised labial arch wire is used in some cases to derotate or straighten the incisors. Sometimes the artificial resin teeth are anchoraged in the basis of the appliance.

In late mixed and permanent dentition the fixed appliance is used. The molar rings are sometimes applied also to the frontal teeth as the dentition of a cleft patient suffers often dysplastic defects and morphological changes of the teeth. Another particularity of a fixed orthodontic appliance in a cleft patient is the atypical form of the expansion arch wires and hyrax appliances. These have to be adapted to the different anatomy of the palate (e.g. oronasial communication or cicatrices).

The bone graft is inserted around the age of eleven when the permanent canine is erupting.

The orthodontic treatment ends with a long retention phase.

Let me describe the therapeutic approach to the orofacial clefts used in Caen.

The orthodontic treatment of a patient with orofacial cleft starts at the age of four with maxillary expansion. This is done with the future intention to close the alveolar cleft using the method of

gingivoperiosteoplasty and bone grafting at the age of five or six. If the lateral incisor is present, the treatment continues with a classical orthodontic alignment. If not, a space maintainer is used and a tooth implant is inserted at the age of fifteen. The technique of mesialisation is used in case of the teeth which present a delay in the eruption.

I would highly appreciate the possibility to see a different therapeutic approach to the orofacial clefts. My specific field of interest is the bilateral complete cleft. The long-term goal of my activities in this field is both to evaluate and improve the facial aesthetics and stability of the orthodontic and surgical treatment of these patients.

I will be seeing cleft patients. I would like to compare the data/results from my actual workplace, but this depends on how much I advance with my actual scientific work (I am trying to collect data about patients with bilateral complete cleft treated in Fakultni nemocnice Kralovske Vinohrady to be able to assess the final aesthetics and stability of orthodontic – surgical treatment). I hope to learn about the effectiveness of the treatment procedures used in CHU Caen and compare it with the effectiveness of the procedures used in Prague.

I have been in contact with Mr Bénatéau Hervé who is the head of the Oral Surgery department in Caen, France. He has offered me a stage in which I could participate as an observer. Each Monday I could see the cleft operations. Each Tuesday I could observe the work of the orthodontists specialised in treating the cleft patients. Each Wednesday I could see an interdisciplinary consultation of the treatment of malformed children including patients to undergo the orthognathic surgery. Furthermore there si an interdsciplinary Friday day with other specialists.
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Address/Contact details of Host:

Professor Benateau
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Caen,
France

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Proposed starting dates of the visit:
14 September 15'– 31 October 15'

Estimated travel costs:
€300

Accommodation:
Total requested for subsistence (€3200)

Total grant requested
€3500

Application – Italy / Peru to Italy - September 2015 (26 weeks)
(in the System # 5135)

Applicant: Pisani Mosol Karen Alejandra, UCSS, Universidad Catolica Sedes Sapientiae, Constellations and Sol de Oro s / n Urb. Sol de Oro. Los Olivos. Lima - Peru

Visiting: *Professor Michele Rubini*, Professor, Università degli studi di Ferrara, Italy

Short description of the proposed project and the aim of the visit.

The main goal of this visit is to create a biobank of lip tissue samples from nsCL/P patients in the frame of EUROCleftNet. Tissue samples will be obtained during surgery operation at the Cleft Lip/Palate Centre of the S. Paolo Hospital of Milan, Italy. Part of samples will be used for genomic DNA (gDNA) extraction, and part will be fixed for tissue section preparations. Occasionally, also

primary cell cultures would be obtained, depending on the quantity of available tissue specimens. All samples will be stored at the EUROCleftNet Biobank site located by the Section of Medical Biochemistry, Molecular Biology and Genetics of the Dept. of Biomedical and Specialty Surgical Sciences of the University of Ferrara.

This collection of lip tissue samples is meant to be an example for other biobank would be an example for other European Cleft Lip/Palate Centres in order to make up a large biobank in the frame of EUROCleftNet, sharing sampling and storing standards and made accessible to all EUROCleftNet members.

Moreover, gDNA samples obtained from lip tissue specimens included will be used for some epigenetic studies. In particular, the level of methylation of specific genomic region near folate genes will be investigated, and compared with methylation level in peripheral blood mononuclear cells from the same patient. The effect of folic acid supplementation during the preconceptional period will be assessed.

Specific aims and work plan this exchange projects will be carried out at two main sites: the CL/P Centre of S. Paolo Hospital in Milan, and the EUROCleftNet Biobank at University of Ferrara. Specific aims will be the following: 1) lip tissue collection and fixation; 2) gDNA extraction and sample biobanking; 3) gDNA methylation analyses.

Lip Tissue sampling (Aim #1) this phase will carried out at Cleft Lip/Palate Centre of the S. Paolo Hospital of Milan, Italy, under the supervision of Dr. Luca Autelitano, Chief of the Craniofacial surgery Unit.

Participation to the study will be dependent upon written informative consent of parents.
Lip tissue samples will be collected at time of first lip surgery operation. Specimens will be dissected in sterile environment. Part will be used for gDNA extraction, and part will be fixed in formalin, embedded in resin. When possible, also primary cell cultures will be established. A blood samples will also be obtained from proband and the two parents, along with information on clinical data and exposure during pregnancy to environmental risk factors.

Lip Tissue biobanking (Aim #2) samples will be transferred to the biobank facility at University of Ferrara. gDNA will be extracted from frozen lip samples of proband and from blood samples of parental trios. gDNA samples will be titrated using fluorescent-dye (pico-green) technology, aliquoted and stored in 2D-barcoded vials (Matrix system) in 96-slots plates suitable for robotic handling. Tissue sections slides will be obtained from formalin-fixed specimens, and slides prepared. Each slide will be bar-coded and stored.

Epigenetic studies (Aim #3) pilot epigenetic study will be carried out focussing on some candidate genes and genomic regions. Methylation of DNA will be tested using bisulfite-modification followed by pyrosequencing. Target region will be LINE sequences and promoters of some genes involved in folate metabolism.

Results will be interpreted considering also the maternal exposure to tobacco smoking during the first three months of pregnancy and the periconceptional supplementation with folic acid, alone or in multivitamins.

Work plan and benefit for EUROCleftNet This project will start on September 1st 2015 and last 6 months.

Tissue sample and blood sample collection will be done at the CL/P Centre of S. Paolo Hospital in Milan under supervision of Dr. Luca Autelitano.

Samples will be transferred to the EUROCleftNet facility at the Dept. of Biomedical and specialty surgical sciences of University of Ferrara, where DNA extraction, titration, aliquoting and storing will be carried out under the supervision of Prof. Michele Rubini.

Periodic updates to the EUROCleftNet co-ordinator, Prof. Peter A. Mossey, University of Dundee, UK will be provided, and EUROCleftNet steering committee kept updated.

This proposed project will provide EUROCleftNet a comprehensive Biobank of nsCL/P tissue samples, including gDNA samples of proband-parents trios, and detailed clinical and exposomic data. Moreover, some preliminary investigation on the role of epigenetics in nsCL/P aetiology will be carried out.

EUROCleftNet members will be kept updated as collection of samples proceeds, and will have full access to use the lip tissue biobank for research purposes.

Description of the proposed work

Lip tissue Biobanking and Epigenetics of Orofacial Clefts

Scientific background Non-syndromic cleft lip with/without cleft palate (nsCL/P) are among the most common birth defects in all populations worldwide. nsCL/Ps are considered multifactorial conditions caused by interactions between genetic factors and the exposure to environmental risk factors. Epigenetic modifications could play a role in the interplay between environmental factors and genotypes could outcome with epigenetic modifications of genomic DNA, and in turn impair the correct fusion of lip prominences during embryogenesis, causing cleft lip.

To date only few studies have been carried out to explore the role of epigenetics in nsCL/P. Our knowledge mainly depends on animal studies, which indicate that altered methylation of specific genomic regions associates with CL/P risk.

Folates have been demonstrated to influence methylation of gDNA, and several studies support the hypothesis that folic acid supplementation during early pregnancy reduces the risk of nsCL/P in humans.

The availability of a collection of lip tissue samples from nsCL/P affected children, along with gDNA samples from proband-parents trios and detailed data on the exposure to environmental factors could allow to study the role of epigenetic modifications in the aetiology of nsCL/P, correlate with folic acid supplementation and eventually provide new insight in the pathogenesis of this congenital malformation.

Besides the scientific value of carrying epigenetics investigations, this project aims to become an examples for other nsCL/P Centres in order to stimulate tissue samples collection from multiple sites across Europe, and ultimately create a shared biobank in the frame of EUROCleftNet.

Dr. Karen Alejandra Pisani is a promising young scientist with skill molecular and cellular biology and some experience in bioinformatics. She is extremely committed to dedicate full time to genetic/epigenetic research on nsCL/P, and to carry her activity under the supervision of Dr. Luca Autelitano (CL/P Centre, Milan) and Prof. Michele Rubini (University of Ferrara).

Address/Contact details of Host:

Michele Rubini
University of Ferrara
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44121 Ferrara FE
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Proposed starting dates of the visit:
1 September 15'– 31 March 16'

Estimated travel costs:
€250

Accommodation:
Total requested for subsistence (€10400)

Application - Italy – Slovenia UK- Netherlands - Germany September 2015 (2 weeks)

Applicant: Michele Rubini, University of Ferrara, Italy

Visiting: ***Slovenia, Dundee / Manchester, Nijmegen, Bonn***

Short description of the proposed project and the aim of the visit.

"This SVE package would be concerned with knowledge transfer related to OFC bio-informatics, and represents a concerted effort that will be carried out by all those who have an interest in identifying the most eligible CLP and CP candidate genes for (a) expression studies and (b) functional genomics.

The cost would cover a series of 1-2 day SVEs from the genetics labs in Ferrara, Slovenia, Dundee / Manchester, Nijmegen, Bonn (with one day trips to latter 2 considered sufficient). Such a dedicated bio-informatics project would contribute to the making of the cleft-chip, especially taking care of data filtering, functional predictions and functional tests, and using tailored software (the generic informatics software would need to be tailored to our own OFC candidate genes).

Total grant requested
€2500

*** Further details to be finalised**

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

Applicant: Anne Bohmer, 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 (eg. 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:

Mike Dixon
Professor of Dental Genetics
Michael Smith Building
Oxford Road
Manchester
M13 9PT

mike.dixon@manchester.ac.uk

Proposed starting dates of the visit:
14 September 15'– 13 October 15'

Estimated travel costs:
€300

Accommodation:
Total requested for subsistence (€1600)

Total grant requested
€1900

Application - Italy – UK - September 2015 (11 days)

Applicant: Rita Bassi Andreasi, Department of Biomedical and Special Surgery Sciences, University of Ferrara, Italy

Visiting: *Professor Peter Mossey*, Professor of Craniofacial Development and Associate Dean of Research*, University of Dundee, United Kingdom*

Short description of the proposed project and the aim of the visit.

Background Recent Genome-Wide Association Studies tracked down around a dozen of loci associated with non-syndromic cleft lip and/or palate (nsCL/P) but so far only few functional variants have been identified in these loci.

The identification of nsCL/P associated gene variants is fundamental in order to detect specific endophenothypes associated with clefting, and unravel the complex molecular mechanisms at the basis of this malformation.

Aim and Experimental Work Predictive analyses carried at University of Ferrara (UniFe) had identified a list of common gene variants in nsCL/P loci putatively affecting binding sites for nuclear factors involved in craniofacial development, and in some of these sites association with nsCL/P has been confirmed by genetic study using a large set of nsCL/P trios. Moreover, collection of lip tissue specimens from nsCL/P patients is ongoing at the S. Paolo Hospital, Milan, IT, and a tissue biobank suitable for gene expression and epigenetic studies is being set up at UniFe.

The purpose of this short visit is to synergize with the research team led by Professor Peter A. Mossey at University of Dundee (UDundee), and share research outcomes and materials obtained at UniFe. As the SVE research programme that Dr. Paola Franceschelli is carrying on at UDundee includes functional studies to validate candidate nsCL/P-associated gene variants, the provision of candidate genetic sites could help much the tracking down of functional nsCL/P variants. Moreover, genomic DNA samples from nsCL/P lip tissue could be used to characterize the functional significance of nsCL/P associated variants at epigenetic level.

Address/Contact details of Host:

Peter Mossey
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DD1 4HR

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Proposed starting dates of the visit:
4 September 15' – 15 September 15'

Estimated travel costs:
€450

Accommodation:
Total requested for subsistence (€935)

Total grant requested
€1385

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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Proposed dates of the visit:
October 15' – March 16'

Estimated travel costs:
€400

Accommodation:
Total requested for subsistence (€10000)

Total request
€10400

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

Address/Contact details of Host:
Anne Roberts
Principal Speech & Language Therapist
South West Cleft Service
Bristol Dental Hospital
Lower Maudlin Street
Bristol
BS1 2LY

Other Team members:
Nigel Mercer, Cleft Surgeon

Proposed starting dates of the visit:
15 November 15'– 22 November 15'

Estimated travel costs:
€400 (includes return flight to London and return train London/Bristol)

Accommodation:
Total requested for subsistence (€595)

Total grant requested
€995

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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Lead specialist cleft nurse
South Thames cleft service
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Westminster Bridge Road
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Other Team members:
Mr Piet Haers – consultant cleft and maxillofacial surgeon

Proposed dates of the visit:
1 February 16'– 14 February 16'

Estimated travel costs:
Around €450 including airport/town connections and visit to northwest cleft team in Manchester

Accommodation:
Total requested for subsistence (€1200)

Total request
€1650

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 Spectometry 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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The Netherlands
NCMLS/FNWI
Geert Grooteplein 25/26
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route 274

Carine.Carels@radboudumc.nl

Other Team members:
Dr. Federica Conte

Proposed dates of the visit:
January 16' – June 16'

Estimated travel costs:
€350
Accommodation:
Total requested for subsistence (€10400)

Total request
€10750

Part C: Other proposed Network activities

Gateway Directory of Resources – ongoing development

Continuation of application 5360

Coordinator: Gareth Davis

The Gateway, http://gateway.ecoonline.org/ has been live since May 2013 year. This is a continuation of the development of a comprehensive online digital library, possibly modeled on the World health Organisation **HINARI** access to health programme.

We hope we can receive input from the ESF while planning this stage as we are aware of the need for forward compatibility and requirements of FuturICT in the context of the complexities of storing and managing big data.

Data management expertise The treatment of cleft lip and palate reflects a multi-disciplinary specialty, and that within EUROCleftNet all disciplines are represented, many within our steering group. Experts in each discipline will ensure the quality of data retrieved from a range of research articles, using state of the art guidelines, and the expertise for providing this in an accessible format on our website will be brought in through the offer of an honorarium

Populating resource directory

1. selection/appointment of country coordinators
2. ongoing dialogue with coordinators
3. data extraction and inputting

For an extension of 7 months the cost is €5089

Part D: Publication Plan & Dissemination: *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 Brussells, 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 **€5000** 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.

Part E: Additional Administrative Support

It is expected during the period of September 2015 and June 2016 that additional administrative support will be required to ensure that the proposed workshops and other activities can be fully supported. We propose to increase administrative support to 2 days a week. Costs for increased level of activity -- one year for 2015, i.e. 9,810€ and 6 months for 2016, i.e. 4,905 €