



Research Networking Programmes

Short Visit Grant or Exchange Visit Grant

(please tick the relevant box)

Scientific Report

Scientific report (one single document in WORD or PDF file) should be submitted online within one month of the event. It should not exceed eight A4 pages.

Proposal Title: Short visit of Kerstin Ludwig and Elisabeth Mangold (Bonn) to Nijmegen cooperation partners Carine Carels, Jo Zhou, Hans van Bokhoven

Application Reference N°: 6248

1) Purpose of the visit

Goal of this very short visit was to discuss and in detail plan these three projects.

2) Description of the work carried out during the visit

Background

Non-syndromic orofacial clefting is one of the most frequent congenital malformations. Formal genetic and epidemiological studies have shown that the two most common subtypes of non-syndromic orofacial clefting, namely nonsyndromic cleft lip with or without cleft palate (nsCL/P) and cleft palate only (nsCPO), have a multifactorial aetiology in which both genetic and environmental factors contribute to the phenotype. The heritability of nsCL/P has been estimated to be more than 90%.

The groups at Bonn and Nijmegen have been evaluating the genetic background of orofacial clefting for several years (details on expertise see application for this short visit).

One cooperational project between the groups at Nijmegen and Bonn is already ongoing, and two further projects were planned during this short visit:

Project 1 (ongoing)

The causative variants at the loci detected by GWAS and GWAS-meta-analyses, are yet unknown. As most index SNPs in these GWAS studies are localized in the non-coding regions of the genome, we hypothesize that genetic variants in the functional regulatory regions such as p63 binding sites may give rise to the increased risk of nsCL/P or nsCPO.

The Nijmegen group has identified a number of potential p63-mediated regulatory elements that are likely to contribute to nsCL/P and nsCPO. One collaboration project of Nijmegen and Bonn is to continue this research line, to further functionally test these regulatory elements and to test these elements in patient cohorts from the Bonn group.

Project 2 (planned)

Phenotyping is predicted to be key in future approaches to understand the expression of clefting risk genes. One cooperational effort of Nijmegen and Bonn is combining genome-wide SNP data of specific subphenotype samples from their data-set with genome-wide SNP data from the respective Bonn subphenotype-sample in a meta-analysis should result in a strong increase in power.

Project 3 (planned)

Another cooperational effort of Nijmegen and Bonn is to survey the total pathway-specific mutation load in individuals with a given complex disease and compare them with healthy individuals. This project is based on the hypothesis that individual susceptibility to complex diseases may be due in large part to the genome-wide cumulative effects of multiple genetic variants – or genome-wide mutation load – that disproportionately affect the function of specific disease-related pathways in susceptible individuals.

Work carried out during the visit

Project 1 (November 26th):

Presentation (Jo Zhou): presents previous work from the Nijmegen group – many p36 binding sites were discovered that could bear causative variants. The Bonn group had sequenced two p63 binding sites during 2013, no variants that are truly causative for orofacial clefting had been found at these two binding sites.

Discussion:

- How shall we evaluate other p63 binding sites at nsCL/P susceptibility loci?
- Which binding sites shall we sequence?
- Could we establish a top down list for a future sequencing project?

Project 2 (November 26th):

Presentation (Carine Carels): The Nijmegen group has gathered a sample of patients (and parents) with nsCL/P and nsCPO, ethnical background: Netherlands = Central European. There is detailed phenotype information and documentation on exogenous risk factors during pregnancy available. However, no genome wide SNP data are available for these samples yet (no funding).

Discussion: Funding?

Project 3 (November 25th):

Presentation (Martin Oti): The Nijmegen group is aiming at evaluation the degree to which cumulative genome-wide mutation load on disease-associated pathways affects individual susceptibility to complex diseases. Martin has a plan for analyses, but has not tested his methods on a real data set so far.

Discussion:

- What kind of data are useful for Martin Oti?
- Under what circumstances can these data be used? Individual SNP data, case-control data.

3) Description of the main results obtained

Project 1 (November 26th):

- GWAS data from the Bonn group (Ludwig et al., 2012) could be used in order to establish a top down list.
- List of p63 binding sites should be sent to Bonn, there it could be combined with the GWAS data.
- Sanger sequencing (following a top down approach) could be done (number of sequenced regions is depending on financial issues)
- Basically, with NGS all p63 binding sites of interest could be covered.

Project 2 (November 26th):

- Carine Carels will submit another application for this.
- There has been a possibility to submit applications for Netherland-German projects (German-Dutch cooperation grants) at the DFG and NWO in former times, these options will be checked out.

Project 3 (November 25th):

- GWAS data are available in Bonn (published in Mangold et al., 2010) and could be used.

- Data use will be allowed on the basis of a contract between the Bonn and Nijmegen group.

4) Future collaboration with host institution (if applicable)

Project 1 (November 26th):

Martin has already submitted a short visit application to the ESF (2 weeks in early 2014). He wants to come to Bonn.

Project 2 (November 26th):

Depends on funding situation

Project 3 (November 25th):

[See Main results obtained]

5) Projected publications / articles resulting or to result from the grant (*ESF must be acknowledged in publications resulting from the grantee's work in relation with the grant*)

Project 1 (November 26th):

This project is aiming at a publication (manuscript, oral/poster presentation).

Project 2 (November 26th):

If the genotyping is funded high ranking publications could result from this cooperation.

Project 3 (November 25th):

This project is aiming at publication(s) (manuscripts, oral/poster presentations).

6) Other comments (if any)