Project Newsletter
Year 1

EUCLIDS
childhood life-threatening infectious diseases study

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Meningococcal susceptibility genes associated with macular degeneration

Bacterial infection is the major cause of disability and death in children worldwide. The EUCLIDS project aims to understand the genetic basis underlying susceptibility and outcome to the major childhood infections including meningitis, septicaemia, bone and joint infections due to meningococcus, pneumococcus, staphylococcus aureous, Group A streptococcus and salmonella. The project aims to use existing cohorts of patients with meningococcal disease, those undergoing vaccines against meningococcus, and newly recruited patients with a range of bacterial infections assembled from across Europe.

In the first year of the EUCLIDS programme, we have successfully established patient recruitment at centres across Europe and West Africa. An online database for patient enrolment for use by all sites has been established and the necessary ethical and institutional approvals in all partner institutions have been obtained. Genomic analysis of the Spanish and central European meningococcal cohorts, have been completed at Genome Institute of Singapore (GIS) and analysis of the data is now underway by the bioinformatics teams at Imperial and GIS.

To enable investigation of genes controlling meningococcal disease severity, we have defined phenotypes of differing severity for patients in the UK, Spanish, and Austrian/Dutch GWAS. These phenotypic features of severity are now being analysed in relation to genotype. As the Austrian / Dutch GWAS has been genotyped on a newer version of the Illumina gene chip than was used for the original UK GWAS we have had to impute genotype for all SNPs now available and this will enable all three GWAS's to be analysed in a meta analysis now underway.

The most significant finding in our initial analysis of the three GWAS is the confirmation of the role of Factor H (FH), initially identified in the UK GWAS, in all three cohorts. Furthermore, a novel genetic association of the ABCA4 gene with meningococcal susceptibility has been confirmed in combined analysis of all three cohorts. This finding is particularly exciting as both FH and ABCA4 genes are associated with macular degeneration leading to a novel hypothesis of meningococcal susceptibility.

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EUCLIDS consortium at their annual meeting

Santiago de Compostela, 24-25th October 2012

Determining Factor H's role in childhood bacterial infection

To identify the functional basis on which genetic differences operate, we will undertake gene function analysis and explore identified genes in animal models. The study thus aims to produce a new understanding of the genetic and genomic basis underlying severity and outcome of childhood infection, and to identify novel biomarkers to predict susceptibility and outcome of childhood infection.

A specific focus of the program will be to extend our original observation of the association of genetic variation in the Factor H (FH)region with meningococcal disease susceptibility. Functional and protein studies on the mechanisms through which the FH region controls meningococcal susceptibility is likely to provide a new understanding of host pathogen interaction in meningococcal disease susceptibility.

Work to identify the causal gene variants in the FH region is now underway. The GIS group has developed a sequencing strategy for the FH region which is now being applied to the patient cohorts.

Investigation of gene function of the already identified variants in the FH and FH related protein region has commenced through a programme of work to develop novel reagents including monoclonal antibodies against the FH related proteins which will be used in subsequent studies of binding to meningococcal proteins and functional killing assays. To date the team at AMC have raised monoclonal antibodies to the majority of the FH related proteins, and FH, and further work is in progress to identify specific antibodies to the remaining proteins.

To investigate the role of the FH variants in meningococcal and pneumococcal disease, transgenic mice expressing the human FH protein have been generated and studies exploring the role of these genes in murine models are now beginning.

Understanding childhood responses to vaccination

To understand the genetic basis of protective and persistent immunity following childhood vaccination, a genome-wide association study (GWAS) was undertaken in UK infants undergoing vaccination against meningococcal infection. Genes identified as being important in responding to vaccination will be validated using fine mapping and sequencing approaches.

In the first year of the project the GWAS has been completed ahead of schedule. Currently, the genotyping data are being analysed in relation to functional meningococcal bactericidal activity. Pathway analysis is also underway to allow biological pathways controlling vaccine response to be elucidated. The identification of genes controlling vaccine response, persistence of vaccine protection and reactogenicity is expected to provide new information to facilitate improved vaccine design and strategies for childhood vaccination.

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Project overview

Childhood Life-threatening Infectious Disease Study (EUCLIDS) is a 5-year FP7 project funded by the EU (GA #279182).

We aim to undertake a large-scale genomic study to identify the genes, and biological pathways they control, which determine susceptibility and severity in life-threatening bacterial infections of childhood in Europe and globally.

The project has 8 research work packages :

WP1—Clinical network and biobanking;

WP2—Genome wide association studies of Meningococcal disease;

WP3—Genetic control of the immune response to meningococcal vaccines;

WP4—Identifying functional variation in the DfH region by sequencing;

WP5—Functional analysis of the influence of CfH and CfHR1-5 on meningococcal interactions with complement

WP6—Animal models to resolve CfH function in meningoccoal and pneumococcal infection

WP7—Extreme phenotype cohort genomic analysis for clinical biomarker discover

WP8—Bioinformatics and data management.

See our website for more details: www.euclids-project.eu.

SEVENTH FRAMEWORK PROGRAMME

Workshop report—Santiago de Compostela

EUCLIDS held a successful workshop for clinicians and scientists on the "State-of-the-art approaches for clinical studies of bacterial infectious diseases" in Santiago de Compostela, Spain on the 26th November 2012.

55 attendees joined the workshop discussions, which were led by a panel of international experts and members of the EUCLIDS consortium.

Presentation topics included applied genomics, bioinformations, transcriptomics, molecular genetics, functional genetics and the challenges faced by clinical researchers in The Gambia.

Networking opportunities were enjoyed by everyone during the workshop and at the workshop dinner in the beautiful Hostal de los Reyes Católicos.

The next EUCLID workshop will be held in Graz, Austria in November. More details will be released nearer the time (www.euclids-project.eu/2013).

Consortium Members

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