



PanCanRisk

Personalised Bioinformatics For Global Cancer
Susceptibility Identification & Clinical Management

Personalized bioinformatics for global cancer susceptibility identification and clinical management

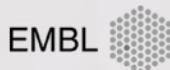
Topic PHC-32-2014

Call Identifier: H2020-PHC-2014-two-stage

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This project has received funding from the European Union's H2020 research and innovation programme under grant agreement No 635290

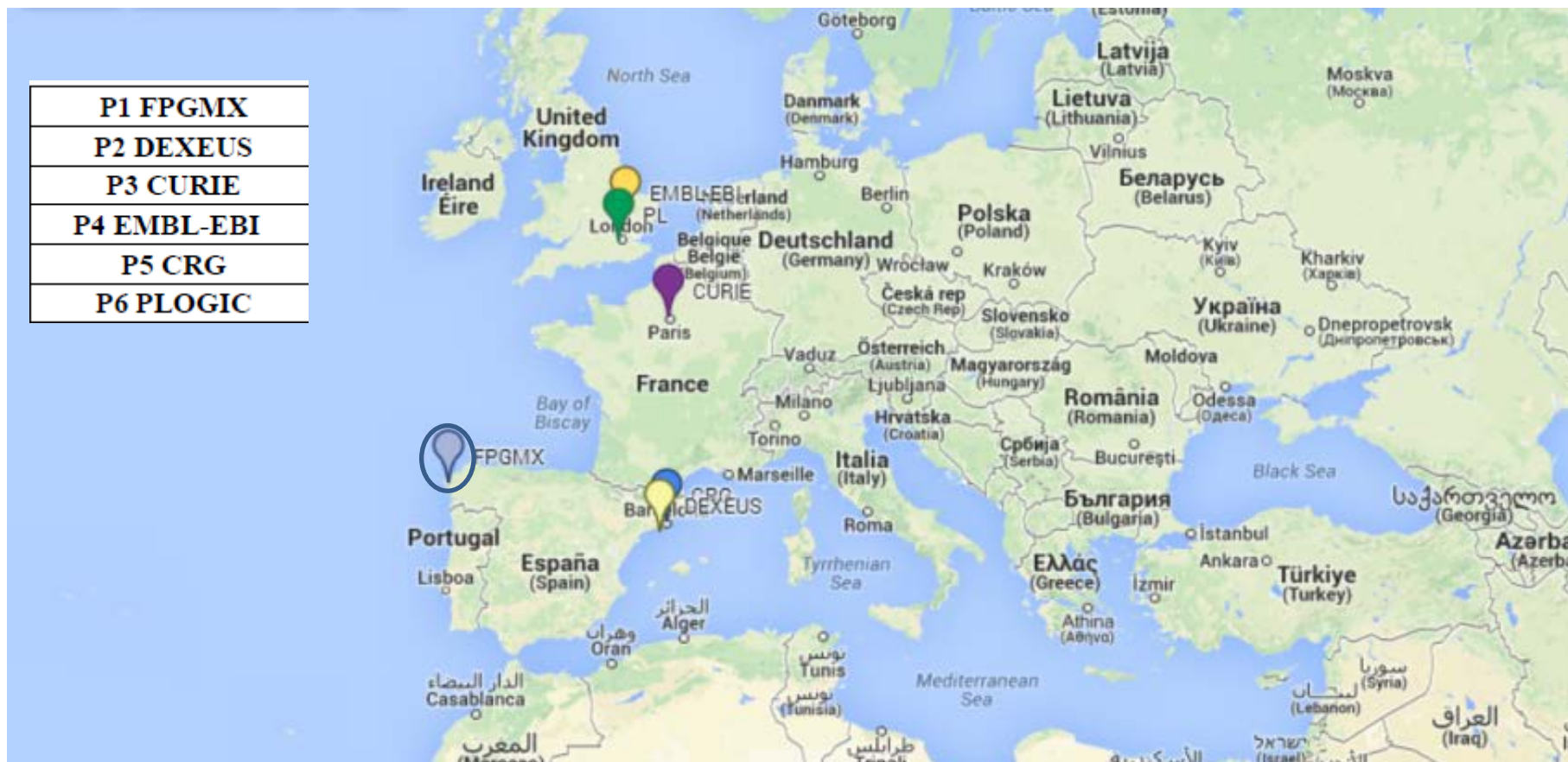


Hypothesis: Patients with common cancer types carry a convergence of rare variants in a reduced number of genes of cancer related pathways

Objectives

- 1/ Discovery and selection of ***potential cancer predisposition genes and variants*** in WGS and WES pan-cancer datasets (ICGC and TCGA) with powerful bioinformatics approaches
- 2/ To scale ***rare variant association studies to pan-cancer data*** of all tumour types, as part of the TCGA/ICGC and PCAWG studies, to identify cancer associated germline mutations
- 3/ To identify ***regulatory risk variants and eQTLs***, integrating germline and somatic mutations and phenotypes, and characterize the ***functionality of risk regulatory variants***
- 4/ To translate ***multi-gene targeted sequencing*** panels of cancer predisposition genes (cancer-risk genes), carrying variants of different levels of penetrance, to cohorts of patients for clinical diagnostic purposes
- 5/ To develop and evaluate ***biomarkers of cancer susceptibility and clinical course*** identified in the context of combination of genetic variants that accumulate in specific genes and pathways to provide high cancer risk

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|--------------------|
| P1 FPGMX |
| P2 DEXEUS |
| P3 CURIE |
| P4 EMBL-EBI |
| P5 CRG |
| P6 PLOGIC |



WP1 - Development of a Computational Platform for Sequencing-Based Cancer Risk Analysis (Ossowski-CRG, Stegle-EBI)

- Implementing a **distributed analysis platform** for the analysis of ICGC/TCGA whole-exome-sequencing cancer samples (eDiVA-Cancer)
- **Cloud-based implementation** of eDiVA-Cancer with secure restricted access and a highly intuitive user interface for use in clinics
- Generate **high-quality variant set** by Pan-cancer-cohort analysis
- Comprehensive **functional annotation** of germline variant set
- Identification of **somatic variants** to facilitate correlation analysis with germline variants
- **Improved methods** for identification of indels and CNV in WES data

WP2- Tools for rare and common variant association analyses in cancer studies

(Estivill-Ossowski, CRG)

- Utilize large-scale cancer cohorts from PCAWG (WGS) and ICGC/TCGA (WES) to dramatically increase the power of sequencing based cancer risk association studies (*Stegle, Ossowski-participating in the development of bioinformatic tools for PCAWG*)
- Develop and test a flexible model for rare variant association analysis that incorporates variant-, gene- and patient-specific characteristics and population effects
- Utilize tissue-specific protein-interaction networks and expression data to group genes for rare variant association tests in order to improve statistical power and biological relevance of associations
- Identification of germline cancer risk variants for validation

WP3-Identification of regulatory variants and eQTLs, integrating germline and somatic mutations (Stegle EBI-Ossowski CRG)

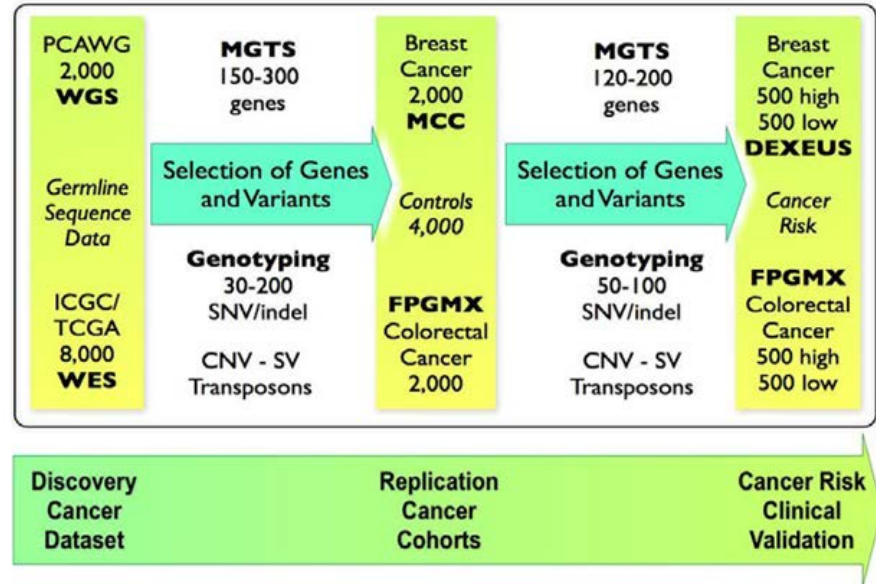
- Derive methods to comprehensively map **regulatory variants**
- Combining evidence from
 - genotype-gene expression relationships (eQTLs)
 - epigenetic information, readouts and marks
- Innovation of new methods and analysis approaches

WP4-Replication and Clinical Validation in cancer and non-cancer cohorts (Carracedo FPGMX, Abuli-Dexeus)

1. *Replication studies by multi-gene targeted sequencing and targeted genotyping* of cancer predisposition genes and variants in breast and colorectal cancer and non-cancer cohorts.
2. *Clinical validation of cancer predisposition genes and variants* in breast and colorectal cancer-risk population cohorts that are screened for breast or colorectal cancer.

Replication studies

4,000 cancer patients
4,000 controls
 Spanish Caucasian origin

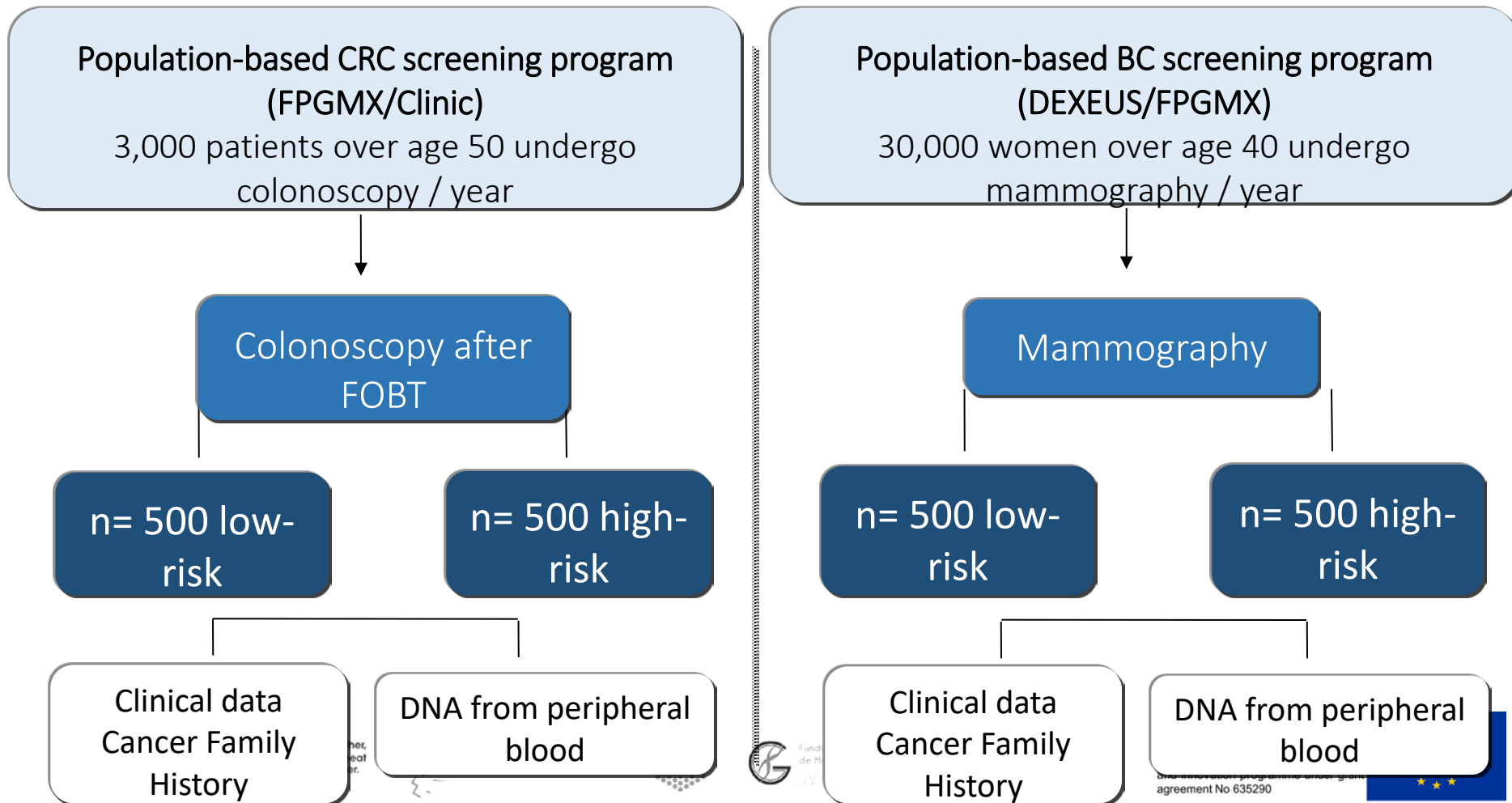


FPGMX cancer cohort
 1,000 BC patients
 1,000 CRC patients
 2,000 controls

MCC-SPAIN cohort
 1,000 BC patients
 1,000 CRC patients
 2,000 controls



Recruitment: *Cancer risk clinical validation studies*



WP5 Functional study of identified risk genes and regulatory variants (Carreira-Curie)

- Generation of knock-in cell clones carrying the variant of interest by genome editing (CRISPR/Cas9)
- Classify variants depending on their gene of origin to define the panel of specific tests to use
- Gene (and protein) expression profile and mutational signature

