Neuroscience Campus Amsterdam

The Genome of the Netherlands (GoNL)

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Introduction

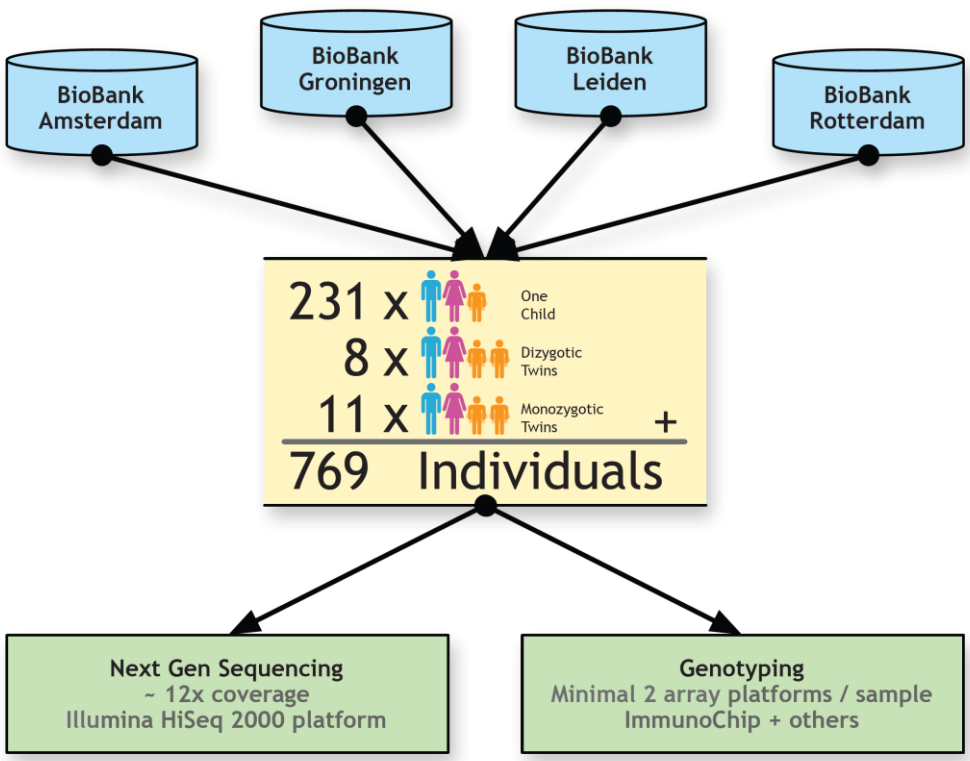
Within the Netherlands a national network of biobanks has been established (BBMRI-NL) as a national node of the European Biobanking and Biomolecular Research Infrastructure BBMRI.

Here, we describe the Genome of the Netherlands (GoNL), one of the projects within BBMRI-NL. GoNL is a whole-genome sequencing project in a sample from all provinces in the Netherlands, which aims to reveal most of the genetic variants within the Dutch population.

Sequencing was done on blood-derived DNA from uncultured cells and accomplished coverage was 14-15x. The family-based design represents a unique resource to assess the frequency of regional variants, accurately reconstruct haplotypes by family based phasing, characterize short indels and complex structural variants, and establish the rate of *de novo* mutational events.

GoNL will also serve as a reference panel for imputation in Dutch and other cohorts to refine association signals and uncover population-specific variants.

GoNL will create a catalog of human genetic variation in this sample, uniquely characterized with respect to micro-geographic location The resource will be made available to the research and medical community.

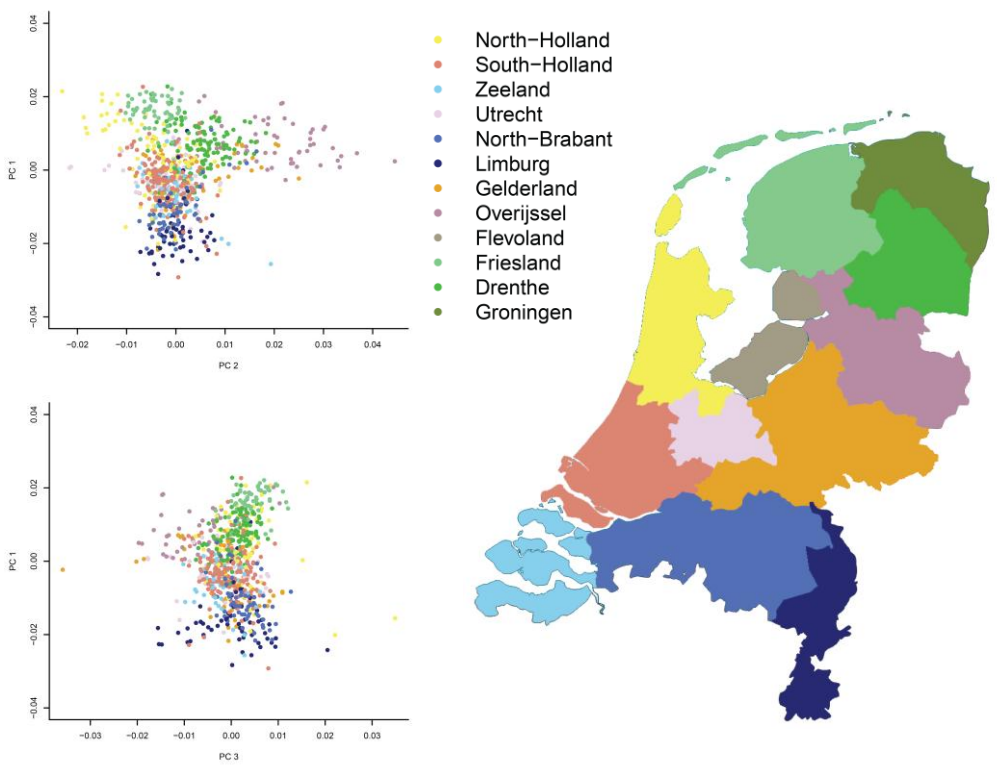


Sequencing

A coverage of 12x in both parents and the offspring was chosen. This design gives 500 haplotypes at reasonable depth (i.e. those transmitted to the children) and 500 haplotypes at half of that depth (i.e. those not transmitted to the children). This dataset should significantly contribute to existing information, since, for example, the 1000 Genomes Project has a 4x coverage. Paired-end sequencing on the Illumina HiSeq2000 platform was done at Beijing Genomics Institute (BGI). The raw reads were analyzed following 1000G best practices, in collaboration with the Broad Institute and BGI. When reads were aligned against build 37 of the human genome coverage was, as expected, randomly Poisson distributed over the genome with a coverage peak in between 14 – 15x.

Genomic Structure of the Netherlands

To describe the regional genomic differences in the genetic make-up across the Netherlands, Principal Component Analysis (PCA) was run using the EIGENSOFT package. The PCA was first run on 4,441 unrelated Dutch individuals from the Netherlands Twin Registry (NTR) typed on the Affymetrix Human Genome-Wide SNP 6.0 Array (130,248 SNPs with minimized LD). Three PCs correlated significantly with geographic location and distinguished between: (PC1) the North and South of the Netherlands; (PC2) between the East and West; and (PC3) between the middle-band of the Netherlands and the rest of the country. When projecting these PCs on the GoNL individuals, for whom we have the province of the current living address available, it is clear from the Figure below that PCs capture the geographical variation this dataset as well.



Phenotypes

All participants are part of active biobanks. As the participants come from prospective studies, a wealth of additional phenotypes is available. These include risk factors for morbidity and mortality, information on lifestyle and medication that have been assessed by the biobanks. As part of BBMRI-NL the data will be enriched with metabolomics data (NMR, mass spectrometry), whole-genome epigenetic (450K Illumina methylation arrays) and RNA-sequencing. Data on morbidity are collected by record linkage projects in the Netherlands with databases such as PALGA, NKR and others. These data are becoming available or will be generated as part of additional BBRMI-NL projects.

Conclusions

GoNL will be an excellent starting point to enrich GWAS samples across Dutch biobanks with more functional DNA variation and with the BBMRI-NL infrastructure there is an excellent basis to further explain the functional consequences of disease-associated variants.

More info can be found on: **www.nlgenome.nl.**

BBMRI•NL

Nederlands Tweelingen Register

VUmc VU University Medical Center Amsterdam

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