European populations and the postgenome era

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Genome Era

- Over 160 genomes completely sequenced in databases
- These include human genome

Human Genome Project

- 22 000 protein coding genes (www.wnsembl.org/Homo_sapiens)
- Over 10 million SNPs (> 1% frequency), 7 million catalogued (www.ncbi.nlm.nih.gov/SNP)
- More tahn 1400 genes correlated directly with the disease (www.ncbi.nlm.nih.gov/Entrez)

Until now:

Validate hypothesis by serial application of diverse experimental approaches to one or a few genes proteins.

After genome projects:

Generate hypothesis using one or few parallel high-throughput approaches to obtain data on large group of genes/proteins.

Identification of Mutated Genes

Monogenic Diseases

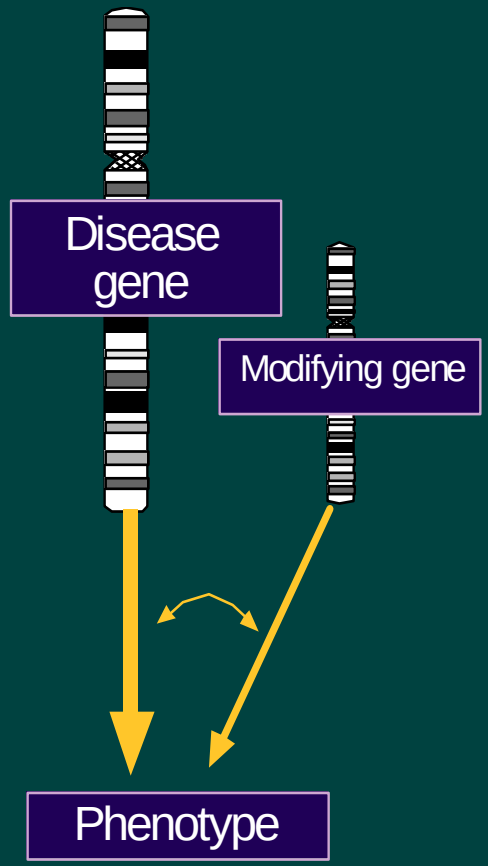
- 1580 disease phenotypes
- 1270 mutated genes

Common Diseases

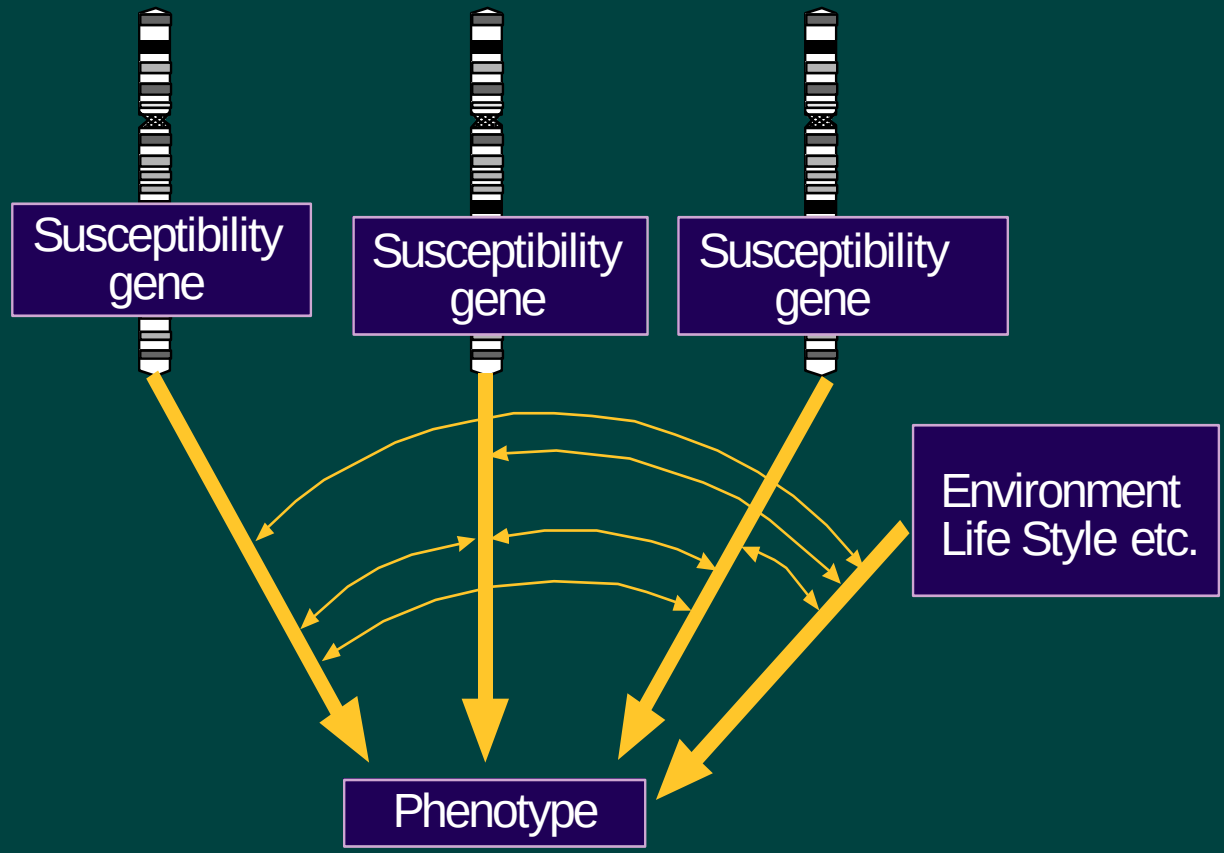
- Mostly rare high impact genes

Genetic Traits

Simplex or monogenic



Complex or multifactorial



Genomics era in Biomedicine

- For the first time in human history we can produce a high-resolution picture of our individual genomes and monitor for changes in diseases
- For the first time the role of genetic and life-style risk factors can be defined
- Special European competitive advantage of in biomedical research can be utilized in this historical era

Ultimately it should be possible

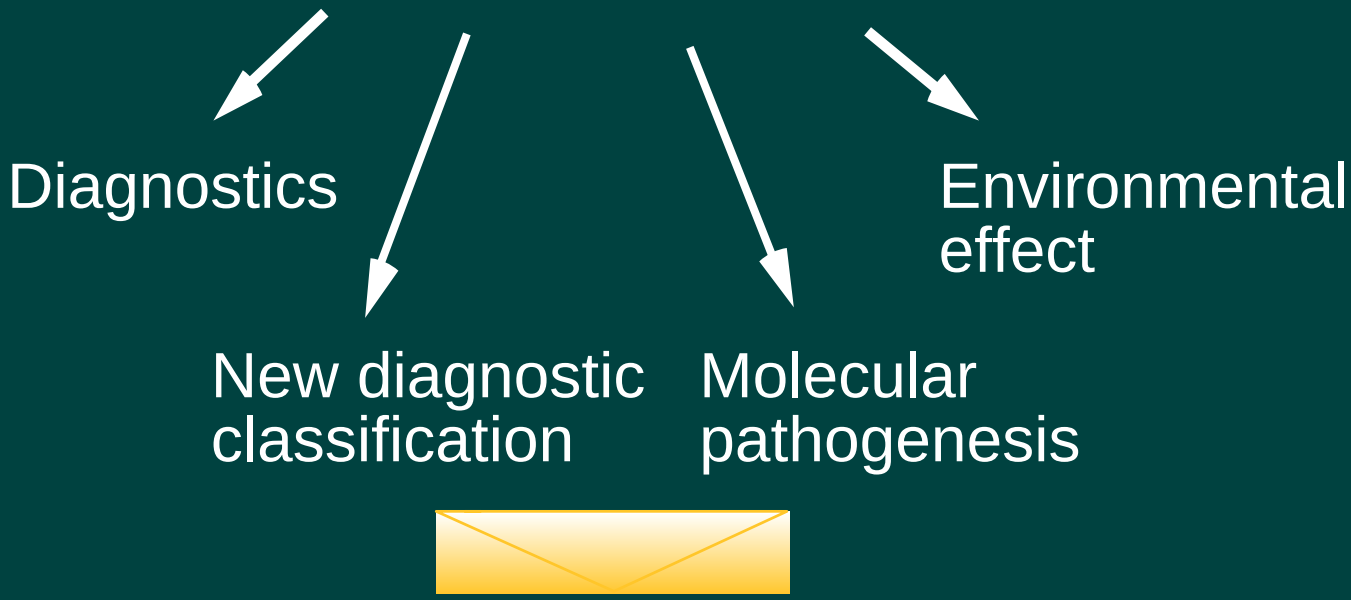
Examine individual's genetic make-up at any position of the sequence

Deduce functional consequences and relate them to other risk factors

Make a well-informed choices of medical actions

Genetic Information

- The basis of modern medicine



European Strengths

Good, equal education

Equal health care

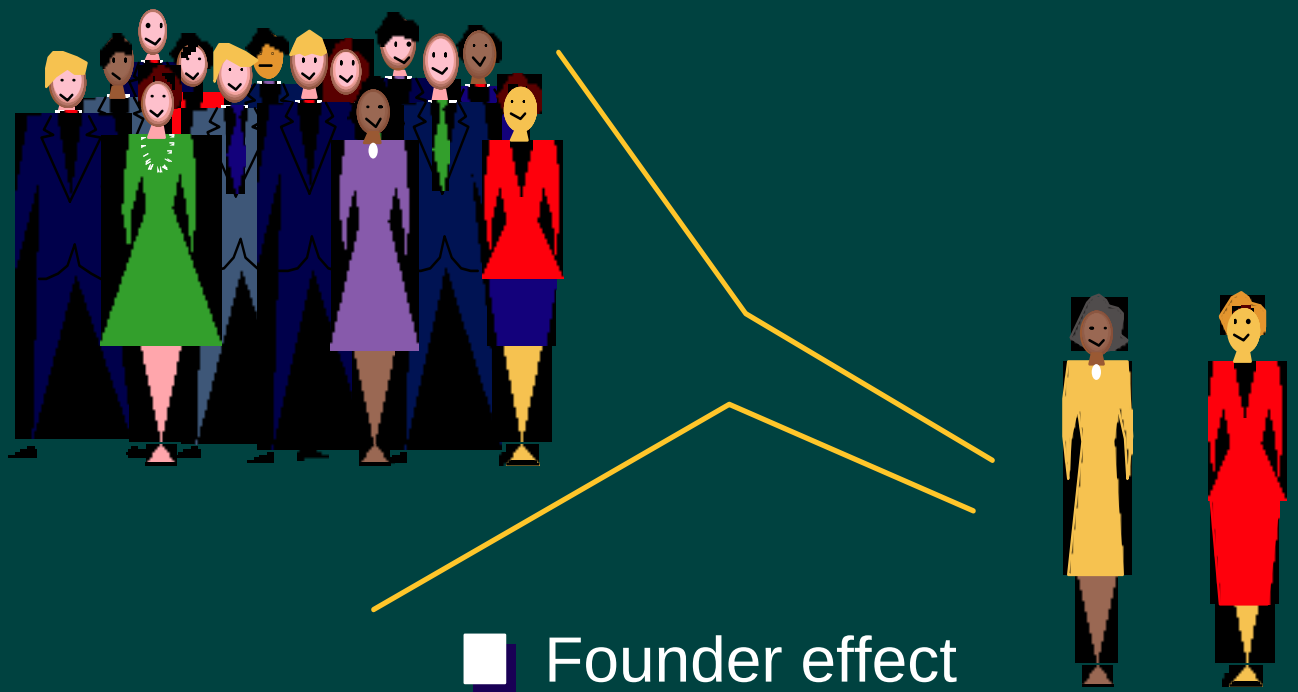
Developed social infrastructure

Developed information technology and networks

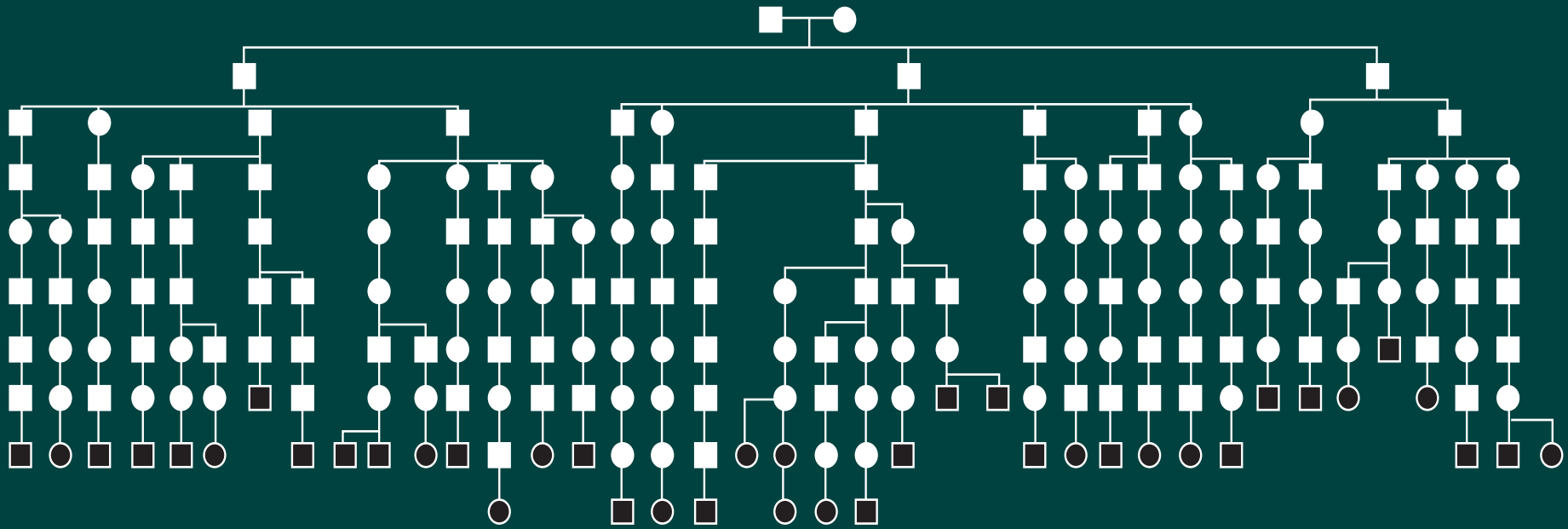
Identification of Complex Disease Genes in Isolated Populations

- Higher degree of genetic homogeneity
  - -Fewer mutations in disease genes
  - -Mutations technically easier to identify (LD)
- Higher degree of environmental homogeneity
  - - Life style,diet, culture
  - - Training of physicians, clinical practice

Population Isolates



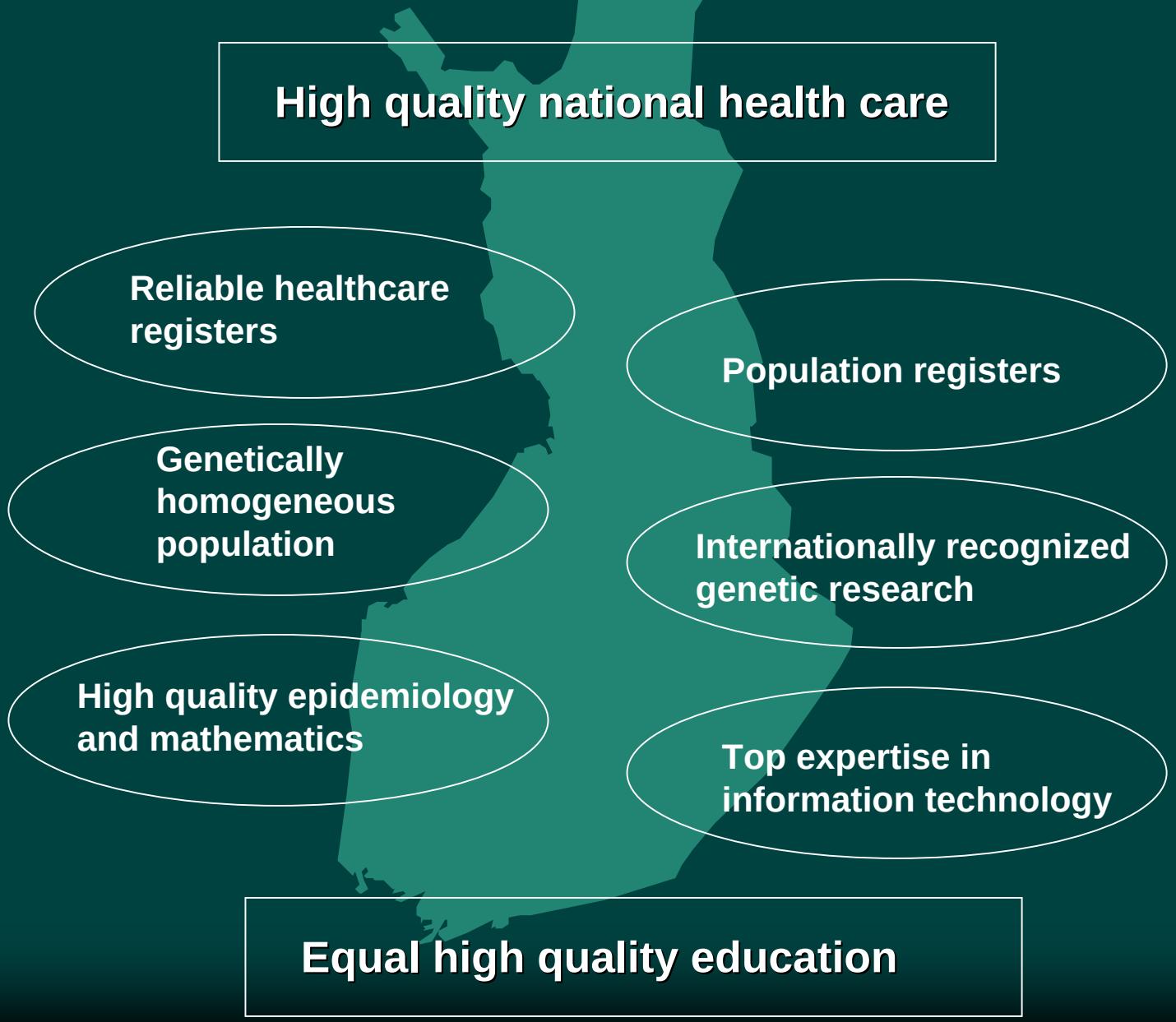
- Founder effect
- Genetic drift
- Isolation



All affected individuals sharing the same ancestor have a high probability to share the same (founder) disease allele

The DNA-region flanking the mutation is also identical, reflecting the appearance of the founder chromosome

Case of Finland



Finland - One of the best characterized populations for disease mutations

Founder Effect

Genetic Drift

Isolation

Regional Expansion

Enrichment of Rare Diseases

Fin-Major mutation

Population records since 1634

Registers of one payer health care system

”Inbred” training of clinicians

Favorable attitudes by public

The Disease Genome of Finns

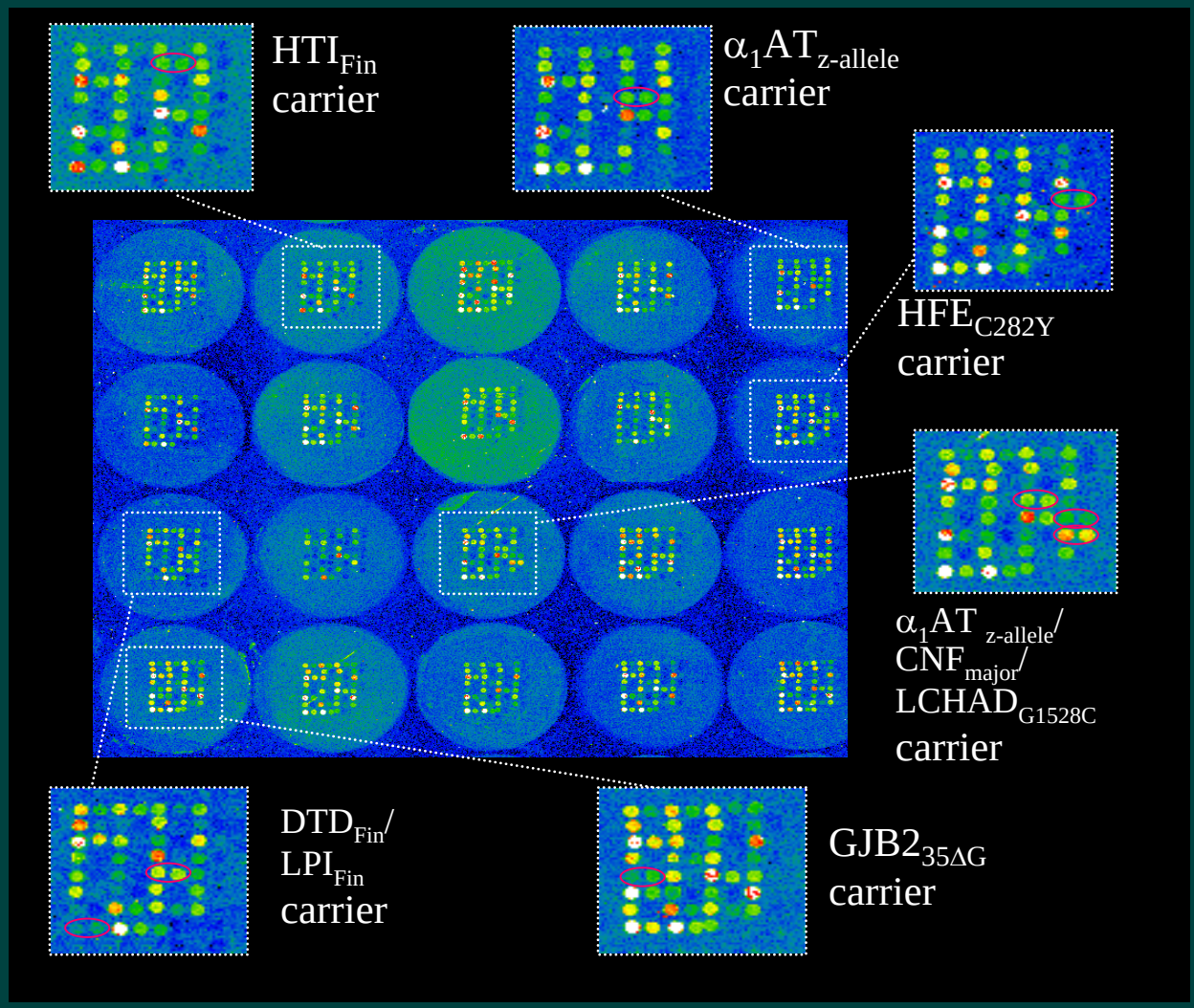
- **GRACILE** (death in infancy)
- **LAAHD** (intrauterine death)
- **FSH-RO** (fertility disturbance)
- **EPMR** (progressive retardation)
- **PEHO** (progressive retardation)
- **TMD** (muscle disease) dominant
- **RAPADILINO** (growth disturbance with malformations)
- **LCCS** (intrauterine death)
- **IOSCA,** OHAHA (progressive retardation)
- **CHS** (progressive retardation)
- **vLINCL** (progressive retardation)
- **HYDROLET** (intrauterine death)
- **SALLA** (progressive retardation)
- **MKS** (intrauterine death)
- **MEB** (severe retardation)
- **TCD, CHM** (eye disease), X -recessive
- **INCL** (progressive retardation)
- **HOGA** (eye disease)
- **DTD** (growth disturbance)
- **JNCL** (progressive retardation)
- **CHH** (growth disturbance)
- **MUL** (growth disturbance)
- **FAF** (eye, nerve and skin disease) dominant
- **USH3** (ear and eye disease)
- **PLOSL** (progressive retardation)
- **AGU** (progressive retardation)
- **CLD** (watery diarrhea)
- **NKH** (severe retardation)
- **LPI** (metabolic disease)
- **CCD** (watery diarrhea)
- **APECED** (autoimmune polyendocrinopathy)
- **RESCH**, RS (eye disease), X- recessive
- **PME** (neurological disease)
- **SMB12** (anemia)
- **CNA2** (eye disease)
- **CNF** (kidney disease)

56... 58... 60... 62... 64... 66... 68... 70... 72... 74... 76... 78... 80... 82... 84 ...86... 88... 90... 92... 94... 96... 98

- **Gene cloned - Mutation known**
- **Localization known**
- **No localization**

Finnish Disease Database

Finland Chip



DNA-Chip for population screening

2400 DNA-samples analyzed for 31 disease mutations on the chip

- Prevalence of recessive mutations
- Regional variations
- Feasibility for large screening programs

Who carries a mutation?

Finnish diseases: 1

Any of 31: 1:2

Finnish: 1:8

Any: 1:3

Finnish diseases 1:10

Any of 31: 1:3

General lessons

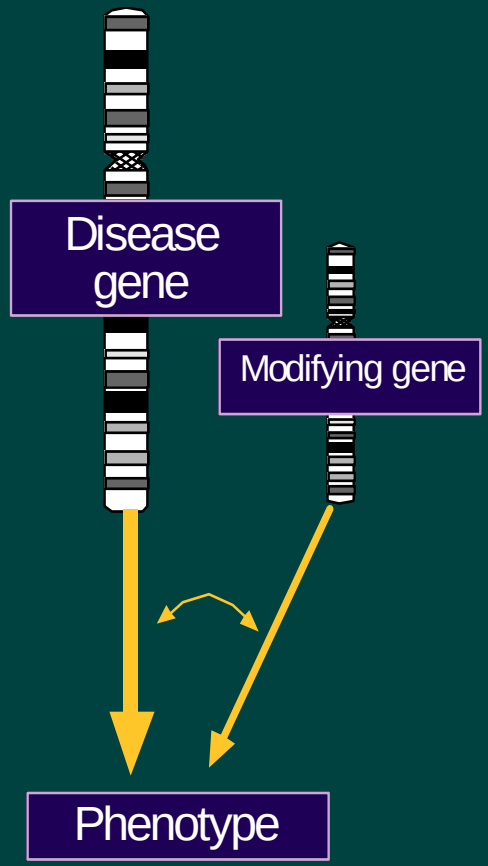
- Disease mutations are common (1:3) when monitoring for only 31 mutations

- If 22 000 mutations would be monitored

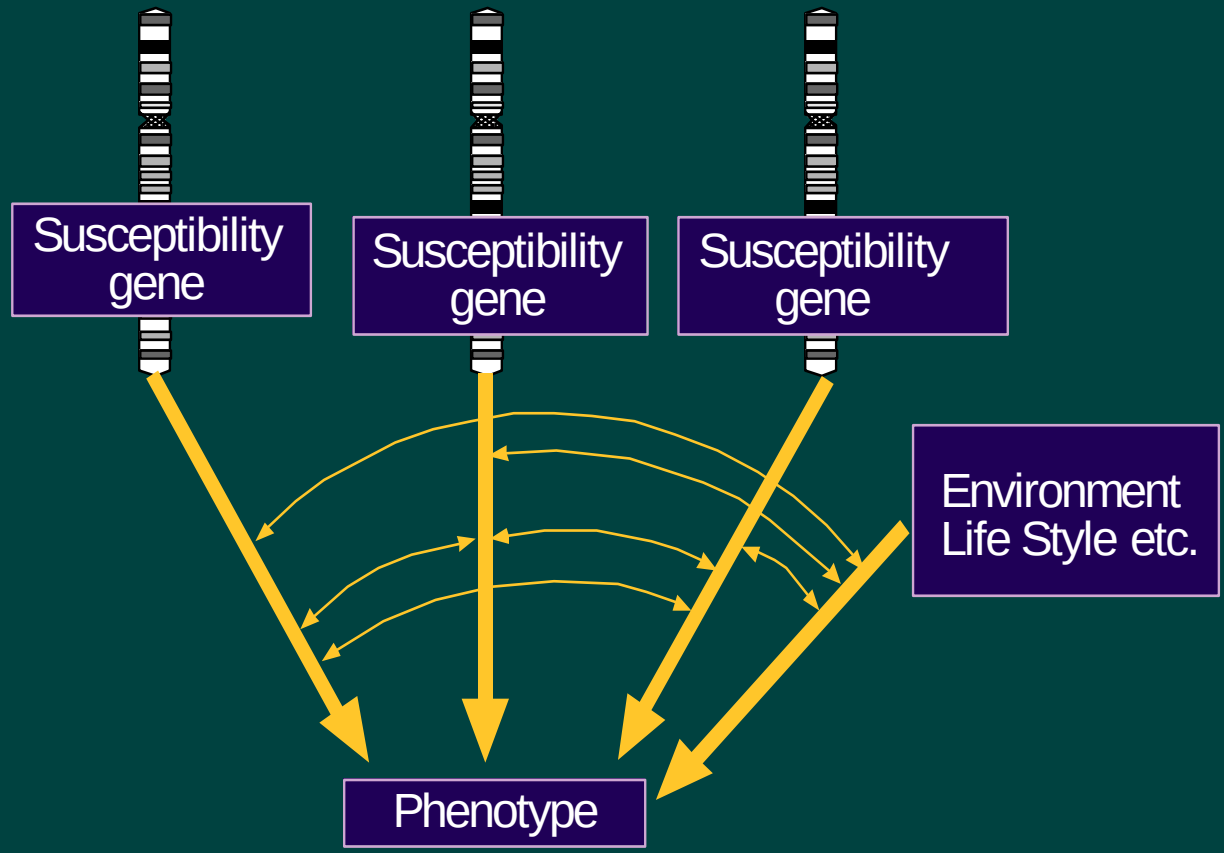
Every individual carries multiple mutations

Genetic Traits

Simplex or monogenic



Complex or multifactorial



Genetics can dramatically help in our understanding of common, complex diseases

Identification of key pathways involved

Find the gene in rare families

Pick the allelic markers

Test them for association in case/control samples

Analyze multiple populations

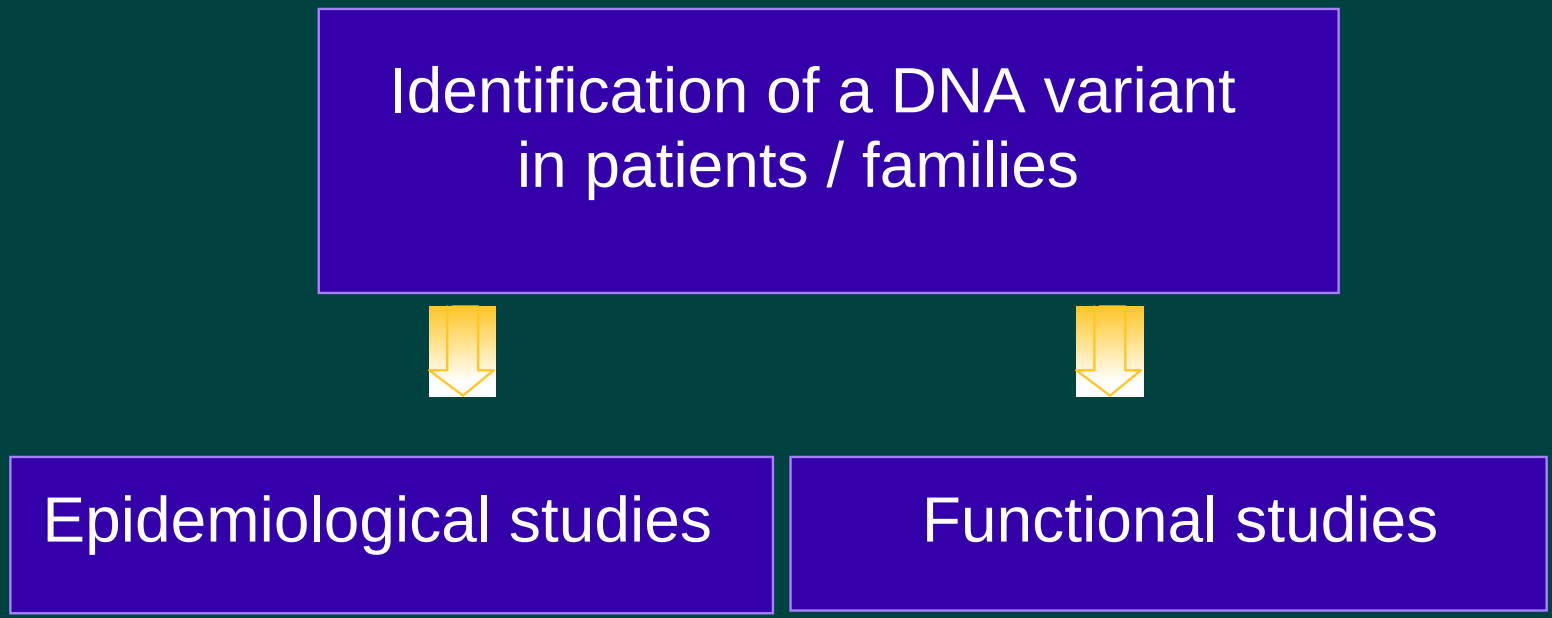
Determine the population attributable fraction and significance in epidemiological cohorts

Common Trait Genome Scans in Finnish study samples

- Multiple sclerosis
- Schizophrenia
- Combined hyperlipidemia
- Low-HDL
- Hypertension
- Osteoarthritis, small joint
- Obesity&BMI
- Stature
- Migraine
- Autism
- Lactose intolerance
- Asthma
- Dyslexia
- Crohn's syndrome & ulcerative coli
- Familial ventricular tachycardia
- Coronary artery disease
- Type II Diabetes
- Pre-eclampsia
- Psoriasis

Most loci replicated in other populat

Complex Diseases



Disease Mutations

Fully penetrant
monogenic disease

Coding region mutations
cSNPs

Partially penetrant
polygenic disease

Non-coding and regulatory
region mutations
rSNPs

Common disease study samples

Multiplex families

Ascertainment bias for rare, high impact genes

To identify defective pathways

Case–control samples

“Mixed bag” of rare and common genes,

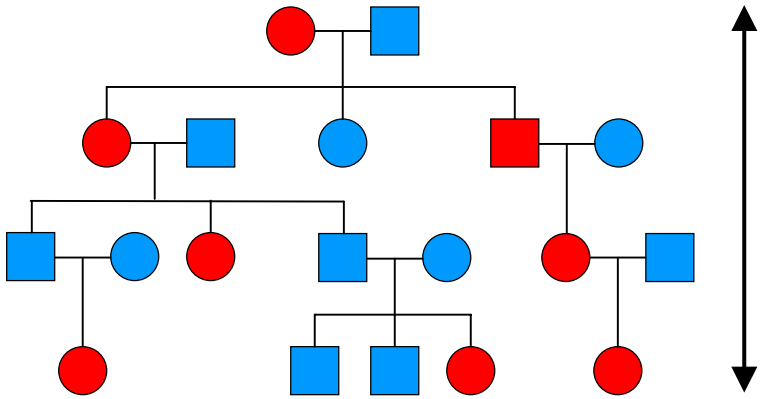
To verify the relevance of variants

Epidemiological cohorts

To define the size of the effect of genetic versus environmental risk factors

Study Designs

1

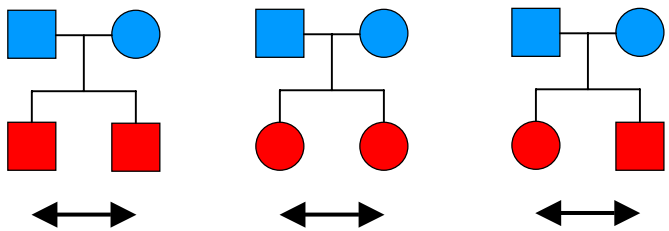


Linkage analysis:

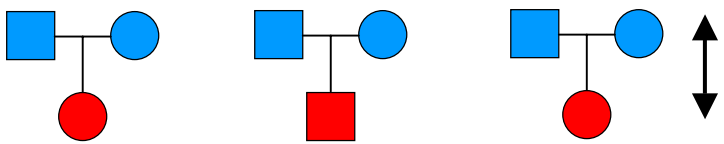
large pedigrees with
several generations

LOD - Scores
AP - Analysis

100

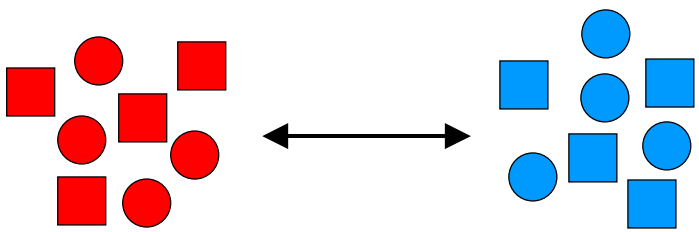


Affected Sib-Pairs
ASP-Analysis



Association analysis
with family controls

1000



Case-control
analysis with
genomic controls

Different study samples meaningful for different aims

For identification of novel genes and metabolic pathways

Families, sibpairs, ascertained for a given trait (disease)

Case control samples

For risk impact estimation

For new diagnostic entities

Epidemiological study samples with excessive amount of health care and life style information

Necessity of large numbers

Current diagnostic classification of diseases does not reflect the molecular background

Disease alleles of common diseases are probably old and have a wide diversity

We need huge ascertained and **non-ascertained** populations samples from several populations to :

1) identify disease predisposing variants

2) verify their significance

LARGE BIOBANKS

- Estonian Genome project (Egeen)
- DeCode (Iceland)
- Carthagen (Canada)
- UK Biobank
- Swedish National Biobank Program (Swegene, Wallenberg Consortium North)
- Genomeutwin cohorts
- NIH Prospective cohort based population study

Biobanks and Finland

Biobank can be a trash bank without detailed clinical and epidemiological data, DNA:s are worth of nothing

Most biobanks will be useful 10-20 years from now

Finland could start from ”the other end”, not from biobanks but from epidemiological data collections

Benefits from epidemiological samples for society materialize relatively soon

Examples of epidemiological study samples in Finland

		Size	Consented DNA-samples
For cardiovascular traits			
FINRISK	92	8000	5600
	97	10000	8700
	02	11000	10 000
For diabetes		6000	2000
For autism		2000	2000
For psychosis		3000	3000
	Total:		~ 32 000

Examples of Finnish Population Cohorts

	Size	Consented DNA-samples
Twin cohort	170 000	27 000
Health 2000 cohort (National health study)	11 500	11 500
Northern Finland		
cohort 66	12 000	11 000
cohort 86	9500	9000
Total:		~ 60 000

Complex Diseases

- Gene-gene interactions
- Protein-protein-interactions
- Genome studies

Environment

Life style

Genetic Predisposition of Common Diseases

A common allele

- modest relative risk
- little familial recurrence
- high population attributable fraction

A rare allele

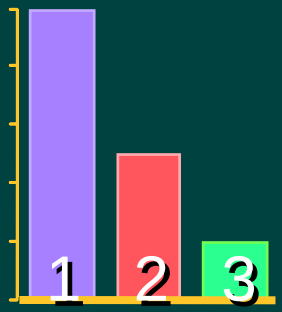
- high relative risk
- much familial recurrence
- low population attributable fraction

Gene 1

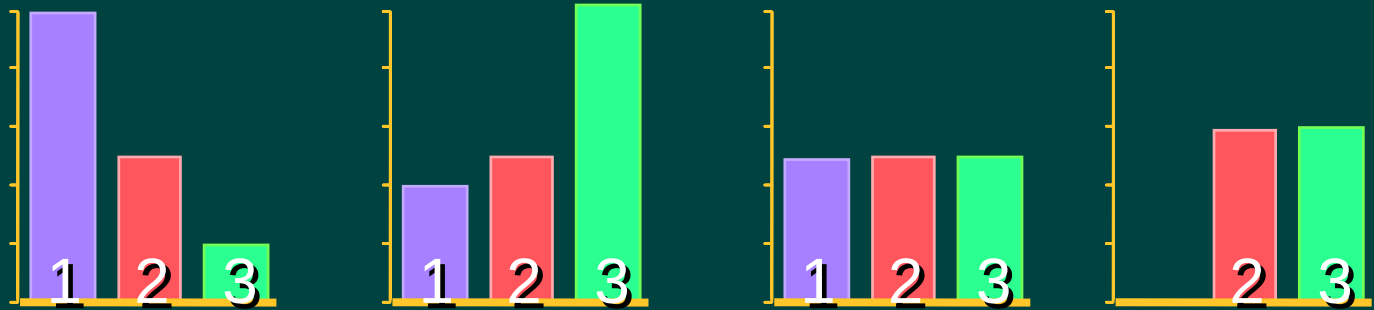
Gene 2

Gene 3

Impact



Risk profile in population



Risk profiles in families

The strength of Finnish epidemiological cohorts

Solid epidemiological criteria have been used to collect the study samples

Excessive amount of life style and health-related data has been collected

Possibility for longitudinal studies

All these features do not exist in current biobanks

European niche in Biomedicine

- Reliable health care infrastructure
- High quality, equal education
- Top level expertise in genetics, epidemiology, clinical medicine and mathematics

Unique possibilities in health care-related genome research and it's rapid implementation in health care

Key issues

- Expertise in epidemiology
- Expertise in clinical medicine
- High quality biological samples collection, storage and database system
- High throughput genotyping and sequencing centers
- Expertise in biocomputational analyses
- Access to multiple different population samples
- Integration of human studies with studies in experimental species
- Attractive environment for top scientists worldwide

Nordic Countries: 24 million

National health care system

Accurate population registers

Reliable healthcare registers

Traditions in genetic research

Some isolated populations

Traditions in epidemiology and mathematics

Expertise in information technology

Equal, high quality education

Nordic Center of Excellence in Disease Genetics: Partners

Stockholm, Sweden
KI

Helsinki, Finland
UH, NPHI, Folkhälsan

Uppsala, Sweden
University of Uppsala

Lund, Malmö, Sweden
Wallenberg Lab.,
Univ. f Lund

Århus, Denmark
Århus University Hosp.

GENOMEUTWIN

(genomeutwin@org)

Genome-wide analyses of European twin and population cohorts to identify genes predisposing to common diseases

GENOMEUTWIN

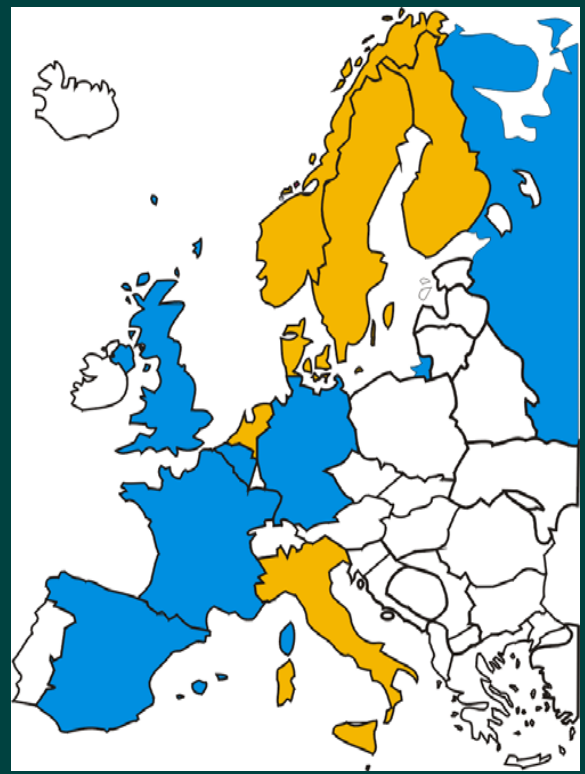
www.genomeutwin.org

One of the large EU Genomics Centers, co-ordinated by Finland

- 8 countries, 800 000 twin pairs
- 13,4M €

To use European twin and populations cohorts fo study genetic and life style risk factors of common traits

- —stature, BMI, CHD, stroke, migraine,



GENOMEUTWIN
research, networking, training

Twin cohorts

Australian twins

Danish twins

Finnish twins

Italian twins

Dutch twins

Norwegian twins

UK twins

Swedish twins

Intellectual core facilities

DNA isolation and genotyping (Uppsala,Helsinki)

Epidemiological expertise (Odense)

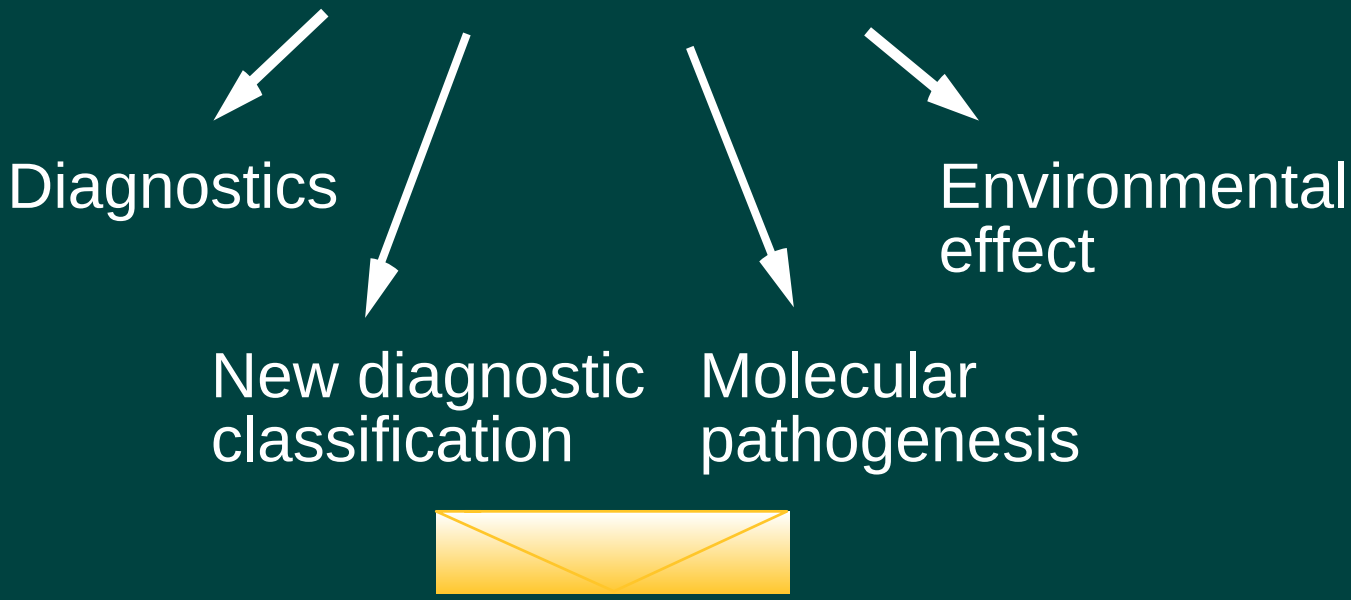
Database expertise (Stockholm)

Biocomputing expertise (Leiden)

Ethical and legal expertise(Oslo)

Genetic Information

- The basis of modern medicine



Genome Information Center