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NEW GENERATION GENOMIC PLATFORMS IN INVESTIGATION OF COMPLEX DISEASES AND BEN

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Abstract

New generation genomic platforms enable us to decipher the complex genetic basis of complex diseases and Balkan Endemic Nephropathy (BEN) at a high-throughput basis. They give valuable information about predisposing Single Nucleotide Polymorphisms (SNPs), Copy Number Variations (CNVs) or Loss of Heterozygosity (LOH) (using SNP-array) and about disease-causing mutations along the whole sequence of candidate-genes (using Next Generation Sequencing). This information could be used for screening of individuals in risk families and moving the main medicine stream to the prevention. They also might have an impact on more effective treatment. Here we discuss these genomic platforms and report some applications of SNP-array technology in a case with familial nephrotic syndrome.

Key words: complex diseases, genome wide association studies, SNP, genomic arrays, next generation sequencing.

Human Genome and Gene Variations

The completion of Human Genome sequencing changed the way we do medicine and is fairly ascribed as one of the greatest achievements of the science. It is one of the huge advances of the world we live in, with the potential to dramatically improve our healthcare and our life. Thousands of people from all continents have been working on the project and it took more than 10 years to reach the finished version of the Human Genome sequence in 2003 [1–3]. An enormous amount of data has been generated since then, providing us with the rationale for a better understanding and management of complex diseases in mainstream medical practice. In effect, the genome is a set of tools enabling physicians to understand the biological and disease variability of their patients. Genomics Data consolidates the knowledge from different studies – sequencing, CGH (Comparative Genomic Hybridization) [4], CpG islands studies [5], Gene expression assays [6], microRNA expression [7], Transcription factors binding [8], and studying of epigenetic events [9]. It integrates the Functional Knowledge Base (gene ontology, interaction networks, biochemical pathways, transcriptional modules and literature concepts) with Analytical Tools (statistical analysis, machine learning and visualization) to the common Genomic portals [10]. They further govern the way to new functional knowledge, new physiological understanding, and new testable hypotheses.

We now use the wide definition that Genomics is "the study of functions and interactions of all the genes in the genome, including their interactions with environmental factors" [11].

The aim of Genomics is to build infrastructure for medical science by:

1. Discovery of genes for predisposition to different diseases, or connected to the efficiency/undesired effects of drugs;
2. Providing useful information about molecular markers that could be used in "evidence-based" drug design;
3. Giving important medical information that could be used for realizing "Personalized Medicine";
4. Prevention of diseases by studying the interplay between genes and environmental factors.

In the light of all these facts, Genomics builds a new, integrative part of medicine – Genomics Medicine, which is predictive, personalized and pre-emptive.

The human Genome consists of a total of 30 billion nucleotides (equivalent to the letters in 100 dictionaries). Once the genome sequence is known, scientific interest is attracted to genomic/genetic variations [12]. The most common of them are SNPs – Single Nucleotide Polymorphisms; one of every 300 bases is different between two individuals. These single base changes could be located in a coding part of a gene and be functional (having an effect on protein function) or they could occur outside the gene or in intron parts and to be non-functional. Genetic variations could make differences in the quantity and/or quality of gene products (proteins) and could be responsible for differences in phenotype, differences in risk for disease, and differences in treatment response. Single Nucleotide Polymorphisms are annotated in a huge common internet database and up to June 2012 more than 185 billion SNPs have been reported and described in humans (http://www.ncbi.nlm.nih.gov/projects/SNP/).

It is important to emphasize that hereditary DNA variations determine:

- normal individual human characteristics;
- different phenotypes between individuals;
- risk for disease;
- specific response to environmental factors.

In Genomic Medicine a predictive role is attributed to these gene variants. Identification of specific SNPs would be not enough for making a diagnosis, but it complements with important information the classification of risk in a given population. Therapy becomes more specific and accurate. They might have high significance at population level for realizing screening programs, which could identify individuals at higher risk of developing disease.

The Concept of Complex Diseases

DNA sequence variations are classified as polymorphisms if the population frequency of the rarest allele is more than 1%. They are called mutations in the case of a less than 1% population frequency; in the last case they are the cause of some genetic disorder. There are several thousand monogenic diseases each of which is caused by a mutation in a single gene. Examples are cystic fibrosis, sickle cell anaemia, osteogenesis imperfecta, phenylketonuria, and Huntington's disease. In each of them the inheritance pattern is strictly determined – dominant or recessive. Genetic risk in the families for monogenic diseases is well defined and stable.

Genetics of monogenic diseases differ considerably from the much more frequent complex diseases, such as hypertonia, diabetes, schizophrenia, coronary heart disease, many forms of cancer, etc. The last are developed under the influence of many gene variants and the environment, which is why they are also called multifactorial disorders. Each individual DNA variation contributes a small proportion of the overall risk of disease. The inheritance pattern is complex; risk is not strict and is determined by epidemiological evidence. Possession of a gene mutation in monogenic disease is already connected to high specific risk and development of the disease, whereas the possession of "low penetrance" susceptibility gene variations confers a small increase in risk for the complex disease.

In the case of complex diseases there are inherited DNA variations, both risk and protective ones; the first increase and the second decrease the overall genetic risk, which is finally formed after considering all existing gene variations. There are also risk and protective environmental factors. Total risk for the development of the disease calculates all gene and environmental factors in combination.

The likelihood of developing a single-gene disorder or a genetically complex disease can be expressed in terms of "absolute risk" or "relative risk" as well. "Absolute risk" is the probability of an individual developing a disease during their life; it is precisely determined in monogenic diseases. "Relative risk" compa-

res the risk in two groups of individuals: carriers of a given gene variant and non-carriers. For example, if the risk in the general population is 5 out of 100 and the given gene variant increases it by 20%, then the "relative risk" is 1.2, which means the risk in the group of carriers is 6 out of 100.

SNPs are most commonly used to track predisposition to the disease [13]. In the normal population, a certain percentage will have one SNP, the rest the other. A higher than expected incidence of a given SNP in a disease group suggests this SNP is associated with the disease.

Genome-Wide Association Approach to Common and Complex Diseases

Genome-Wide association studies (GWASs) compare populations that have a particular disease with control groups without the disease in order to identify genetic differences between the two groups [14]. If particular genetic variants are found to be more frequent in people with a particular disease than the controls, these variants are said to be "associated" with the disease.

Genome-Wide Association Approach can be summarized in the following points:

- Identify all 10 million common SNPs;
- Collect 1,000 cases and 1,000 controls;
- Genotype all DNAs for all SNPs;
- That adds up to 20 billion genotypes.

Table 1 presents the study designs used in GWASs (from ref. 15]. In Figure 1 a simple example shows the principle of this approach.

Table 1

Stydy Designs Used in Genome-wide Association Studies

	Case-Control	Cohort	Trio
Assumptions	Case and control participants are drawn from the same population Case participants are representative of all cases of the disease, or limitations on diagnostic specificity and representativeness are clearly specified Genomic and epidemiologic data are collected similarly in cases and controls Differences in allele frequencies relate to the outcome of interest rather than differences in background population between cases and controls	Participants under study are more representative of the population from which they are drawn Diseases and traits are ascertained similarly in individuals with and without the gene variant	Disease-related alleles are transmitted in excess of 50% to affected offspring from heterozygous parents
Advantages	Short time frame Large numbers of case and control participants can be assembled Optimal epidemiologic design for studying rare diseases	Cases are incident (developing during observation) and free of survival bias Direct measure of risk Fewer biases than case-control studies Continuum of health-related measures available in population samples not selected for presence of disease	Controls for population structure; immune to population stratification Allows checks for Mendelian inheritance patterns in genotyping quality control Logistically simpler for studies of children's conditions Does not require phenotyping of parents
Disadvantages	Prone to a number of biases including population stratification Cases are usually prevalent cases, may exclude fatal or short episodes, or mild or silent cases Overestimate relative risk for common diseases	Large sample size needed for genotyping if incidence is low Expensive and lengthy follow-up Existing consent may be insufficient for GWA genotyping or data sharing Requires variation in trait being studied Poorly suited for studying rare diseases	May be difficult to assemble both parents and offspring, especially in disorders with older ages of onset Highly sensitive to genotyping error

Figure 1 – Principle of SNP Genome – Wide Association studies

GWASs must be replicated in order to define more stringent associations [16, 17]. Normally replication studies are done in three stages. In the first stage genotyping is done for the full set of SNPs in a relatively small population at liberal p-value. The second stage is a screening of a larger population at a more stringent p-value. The optional third stage is done for increased stringency. Following this algorithm, many fewer SNPs are discovered with a much stronger association to a given disease. A genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls, done by The Wellcome Trust Case Control Consortium, discovered SNPs associated to coronary artery disease, Crohn's disease, bipolar disorder, hypertension, rheumatoid arthritis, diabetes type I and type II (NHGRI GWA Catalogue www.genome.gov/GWAStudies published 658 GWA at $p < 5 \times 10^{-8}$).

Balkan Endemic Nephropathy (BEN)

The etiology of BEN remains unclear. Two groups of factors may contribute and may explain the endemic distribution of BEN – environmental agents and hereditary factors. A combination of polymorphic genes with various environmental factors may results in an increased risk of the disease [18].

Many nephrotoxins were incriminated as being causative of BEN but have not been identified:

– lead, copper, bismuth, silicon;
– phenolic compounds, PAH;
– zinc, selenium;
– mycotoxins, ochratoxin A;
– plant toxins – acid from Aristolochia Clematis.

Studies on the possible viral etiology involving:

– West Nile virus;
– Leptospira;
– Picorna virus;
– Herpes simplex;
– Hepatitis B etc.

have failed to reveal a convincing relationship between BEN and these viruses.

The evidence for family inheritance comes from the frequency of the disease. The frequency of the disease is proportional to the degree of relatedness. The risk is two times lower for second-degree (19.29%) than for the first-degree relatives (44.62%) and decreases rapidly for more remote relatives (5.25% for third-degree relatives). The effect of different SNP genotypes on BEN risk has been evaluated in combination. The risk increased when CYP3A5 genotype G6986/A6986 (OR 2.5) is combined with active GSTM1 (OR 3.13), NAT1 genotype rapid/slow (OR 7.95) and null GSTT1 (OR 10.07) [19–21].

SNP array – Methodology and Aplications

The technology for whole genome genotyping on SNP-array we use, known as Infinium, allows genotyping of hundreds of thousands of SNPs on a single BeadChip substrate (glass). It is a direct hybridization of the total whole genome-amplified (WGA) DNA sample on the chip, consisting of 50-mer oligonucleotide probes, bounded to microspheres (beads). Initial WGA step amplifies genomic DNA (which is of a few nanograms) of more than a thousand times, leading to a hundreds of micrograms product. This high concentration of target sample enables effective hybridization on target loci of the microchip. After bounding to loci, enzyme SNP reporting is performed and genotype is generated. The separation of the two steps (bounding to the probes and reporting SNP) allows high specificity. For this purpose, highly specified DNA enzymes are used, such as polymerases and ligases.

In the preparation of microchips, Illumina used data from HapMap Phase I for intelligent selection of specific SNPs, which would provide maximum coverage of the human genome. SNPs were selected with rare allele frequency of less than or equal to 5%. There are also included approximately 7,300 non-synonymous SNPs and approximately 1,500 SNPs tagged to the area of the Major Histocompatibility Complex. A total microchip contains 317,000 SNPs.

The standard protocol includes 3 days' work. The first day begins with amplification of the DNA for 20–24 hours, and the whole genome is amplified approximately 1000 times. On the second day the amplified DNA is fragmented (of about 500 bp). It precipitates with isopropanol, centrifuged and re-suspended in

hybridization solution. In preparation for hybridization, Illumina Beadchips are assembled in a special capillary chamber. Hybridization continues for 16–20 hours and represents a complementary binding of the target genomic DNA samples to oligonucleotide probes, covalently bound to the surface of the spheres. On the third day, the Beadchips are processed for the extension of DNA and staining. Washing is done to remove nonspecific hybridization of DNA targets and blocking to reduce nonspecific background signal and chemical noise. Further, the samples are extended 5'–3' allele-specifically using DNA polymerase that incorporates single-labelled hapten didesoxynucleotide (biotin and DNP), depending on the alleles present in the corresponding target sequence. Incorporation of haptens is converted into a fluorescent signal using multi-immunohistochemical staining, which increases the signal-to-background ratio. Finally Beadchips are covered with a protectant to preserve the stability of fluorescent dyes for long stays at room temperature.

The Beadchips are scanned using a two-colour confocal laser scanner with a resolution of 0.8 microns. The images are recorded automatically, they are extracted and intensities are reported using the Illumina BeadScan software. Files are imported into the Illumina BeadStudio genotyping programme where genotypes are recorded based on a pre-defined cluster file with the information about the position of all the SNPs. BeadStudio software provides a simple and efficient file with genotypes and it is integrated with whole genome association studies, as well as with genome browsers and chromosomal viewers serving analysis for loss of heterozygosity and copy number.

Using this SNP array platform, we have analysed the members of a family with a familial chronic nephrotic syndrome. We detected hereditary copy number polymorphisms, as shown in Figure 2 – the father and the son (who is affected) carry the same duplication of 2q12.3 with the same size and position.

Figure 2 – Hereditary CNV (Copy Number Variation) – duplication of 2q12.3 in the son (left) and the father (right) from a family with familial nephrotic syndrome

During the same SNP-array analysis we have also detected Loss of Heterozygosity (LOH) in the 11p14.3–p13 region only in the affected son (Figure 3). A search in the Genome browser for this region revealed that it contains the gene WT1 which is Wilm's tumour suppressor gene1 [22]. Mutations in this gene are responsible for the Denys-Drash syndrome [23], Meacham syndrome [24] and Frasier syndrome, allelic disorders with similar clinical features. Mutation in the WT1 gene can also cause isolated nephrotic syndrome [25] and isolated Wilms tumour [26].

The major clinical manifestation in WT1 defects are degenerative renal disease, nephron disorder, or early-onset nephropathy with distinctive glomerular lesions. Our patient was affected by severe nephrotic syndrome which progressed to end-stage renal failure within a few months and finally the patient died from the disease at the age of 2 years old. We could assume that autozygosity of a chromosomal fragment containing WT1 is a genetic mechanism for the expression of autosomal recessive mutations. This differs from classical inheritance where both parents should carry mutations with a risk of 25% to produce affected offspring. Here our hypothesis is for non-classical inheritance where the father has WT1 mutation (since from pedigree analysis we figured out that the disease runs in his relatives) which is still not enough to cause disease – the mutant gene is only in one copy. However, the additional LOH in the region comprising WT1 makes the individual with doubled copy of the mutant gene and no wild type gene, thus leading to its expression. Further analyses are needed in order to prove our hypothesis.

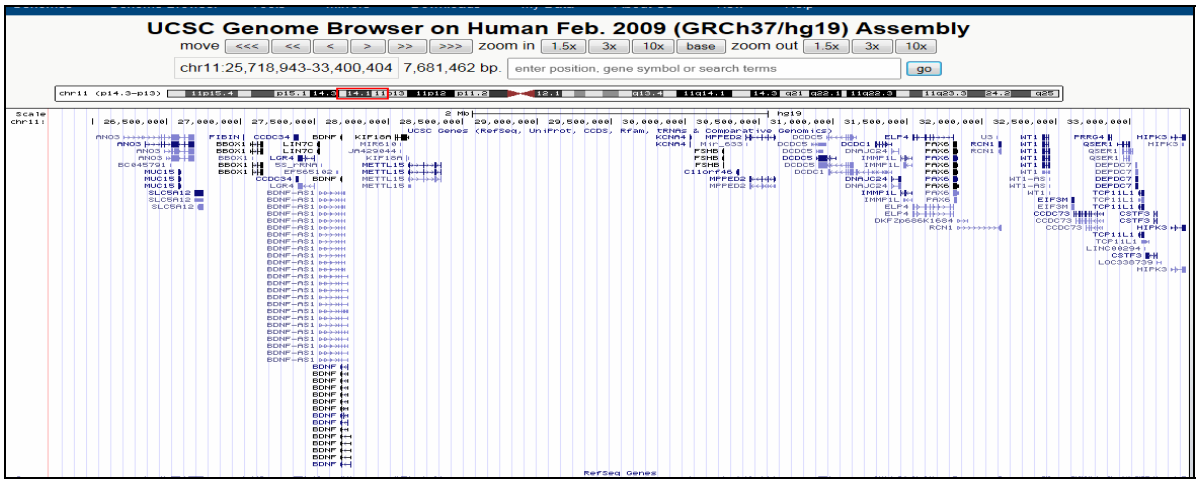
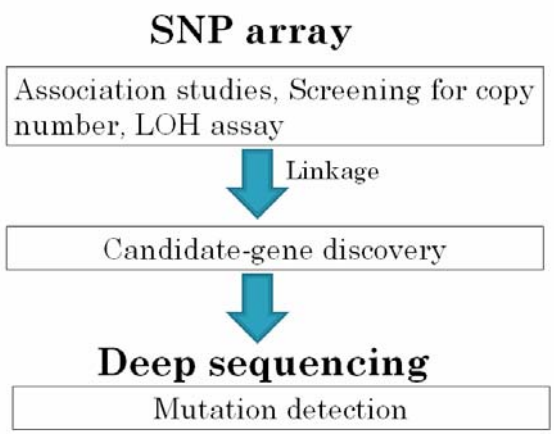


Figure 3 – Detection of LOH in 11p14.3–p13 by SNP-array in a patient with severe nephrotic syndrome (up); the region contains WT1 gene (in red circle, down), which is connected to severe renal diseases

This case shows the power of the SNP-array platform not only for SNP genotyping but also for CNV (copy number variations) and LOH analyses, which shed new light on every clinical case. Thus genomic medicine offers a non-traditional approach in solving diagnostic problems. In opposition to traditional genetics where genotype is directly connected to pheno-

type, now genotyping is followed by interpretation before proceeding to phenotype. It is also mainly oriented to prevention and treatment. With the advances of genomic knowledge we have the tools for discovering the molecular (genetic) basis of a disease. Below is given an example algorithm for the application of new genomic platforms in clinical practice:



The platform of Next Generation Sequencing (NGS)

Using the platforms of NGS we are now able to sequence in one experiment up to 10 Gb sequences (this could be hundreds of genes) for up to 96 samples/patients. This is extremely high-throughput speed, volume and accuracy of analysis, non-comparable to the traditional sequencing methods. The basic principle of NGS technology "sequencing by synthesis" is generating a large number of unique "polonies" (colonies generated by polymerase) that are sequenced simultaneously. These parallel reactions take place on the surface of the "flow-cell" (generally a waterproof glass slide), which provides a large surface area for thousands of parallel reactions.

Targeted next-generation sequencing uses the method of TrueSeq Custom Amplicon (TSCA), in which hundreds of target regions/ amplicons are simultaneously sequenced. For each amplicon to be sequenced a pair of primers is chosen. Annealing of primers to the framented genomic DNA is performed in a 96-well plate (for 96 samples/patients) which is followed by extension and ligation to produce DNA templates consisting of the areas of interest, flanked by universal primer sequences called adapters. DNA templates are then amplified in a test-tube with pre-added index primers differentiating individual samples/patients. The actual sequencing on the flow-cell comes afterwards.

Illumina uses a unique "bridge" amplification that occurs on the surface of the flow-cell. The surface of the flow-cell is covered with single-strand oligonucleotides that are complementary to the adapters from the preparation step. Single-stranded adapter-ligated fragments bind to their counterparts from the surface of the flow-cell and are subjected to reagents for polymerase-based extension. The latter occurs when the free/distal end of the ligated fragment forms a bridge to the complementary oligonucleotide from the surface. Repeated steps of denaturation and extension lead to local amplification of single molecules in millions, all located in a unique place on the surface of the flow-cell. This process is called "cluster amplification". A flow-cell that already contains millions of unique clusters now undergoes automatic cycles of extension and scanning by the genome sequencer. In this way, each DNA fragment is sequenced hundreds of times (which is the number of its copies in the cluster), and that is why the accuracy of the method is extremely high.

The first cycle of sequencing includes incorporation of a single fluorescent nucleotide, followed by scanning the entire flow-cell. These images represent data collected from reading the first base. Any signal above background identifies the physical location of the cluster, and fluorescent emission indicates which of the four bases is incorporated in this position. This cycle is repeated by one base each time producing a series of images, each representing the respective bases in specific clusters. The Reading Guide is based on an algorithm that takes into account the emission color of every cycle. After reading each base the sequence is assembled and compared to a reference sequence, taking into account genetic variations.

In conclusion

New generation genomic platforms enable us to decipher the complex genetic basis of complex diseases and BEN on a high resolution basis, giving valuable information about predisposing SNPs, CNVs or LOH (using SNP-array) and about disease-causing muta-

tions along the whole sequence of candidate-genes (using NGS). This information could be used for screening of individuals in risk families and moving the main medicine stream to prevention. They also might have an impact on more effective treatment.

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Резиме

НОВАТА ГЕНЕРАЦИЈА ГЕНОМСКИ ПЛАТФОРМИ ВО ИСТРАЖУВАЊЕТО КОМПЛЕКСНИ БОЛЕСТИ И БЕН

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Геномската платформа од новата генерација ни овозможува, со висок степен на доверба, да ја дешифрираме комплексната генетска основа на комплексни болести и балканската ендемска нефропатија (БЕН). Овие платформи даваат корисни информации за предиспозирачки СНП (SNP – полиморфизам на единечен нуклеотид), ЦНВ (CNV – варијација во бројот на копии), ЛОХ (LOH – губење на хетерозиготноста) (користејќи SNP-ареи), како и за мутациите што предизвикуваат болести, по должина целата секвенција на гените-кандидати (со употреба на секвенционирање од новата генерација). Оваа информација може да се употреби за скрининг на лица кои се во фамилии со ризик и за придвижување кон главните медицински текови на превенцијата. Исто така, може да има влијание на поефикасниот третман. Овде ги дискутираме овие геномски платформи и даваме извештај за некои од примените на SNP-арејната технологија, во клинички случај со фамилијарен нефротски синдром.

Клучни зборови: комплексни болести, genome wide association studies, SNP, геномски ареи, секвенционирање од новата генерација.