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Short communication

Near East University Genetic Mutation Database (NEU-GD): The first mutation database of Northern Cyprus

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ABSTRACT

The health care system is negatively affected by the genetic disorders that lead to an increasing rate of morbidity and neonatal deaths and affect adults as well. These create a substantial government's psychosocial and economic burden on clinicians, patients and their families with the advancement in the field of genetics. There has been a tremendous increase in the rate in which diseases associated with variant DNA sequences are being sought and identified. The goal behind the creation of Near East University Genetic Mutation Database (NEU-GD) is to map and apprehend the patterns of common genetic diversity in the human genetic makeup in order to accelerate the search for the genetic causes of human disease.

NEU-GD will allow scientists to generate extraordinarily useful information such as allelic variations among population, and description of the genetic blueprint of mutations occurring in human beings.

In this communication we report the construction of the first genetic mutation database for the people belonging to different ethnic groups living in North Cyprus (http://genetics-db.neu.edu.tr/). Therefore NEU-GD can serve as an important tool available online for molecular genetic testing of inherited disorder and persuade for further investigation of novel genetic disorders in North Cyprus population.

1. Introduction

Cyprus is the third biggest island in the Mediterranean Sea situated 75 km to the South of Turkey, 200 km to the North West of Israel/Palestinian Authority zone, 800 km to the South East of the Greek area, and 380 km to the North of Egypt (The Earliest Prehistory of Cyprus: From Colonization to Exploitation, 2001). The demographics of Cyprus are largely distributed into two main ethnic groups, Greek Cypriots and Turkish Cypriots. Turkish Cypriot is Muslims while Greek Cypriot is Orthodox Christian. According to census the population of Cyprus is composed of 60% Greek, 24% Turkish and 16% of other nationalities (2011 census, 2006 North Cyprus data, entire island) (Statistical Service Republic of Cyprus, 2011). Cyprus's position is strategically very significant and situated at the crossroads of great civilizations this area. The island has been administrated by Persians, Assyrian, Hellenistic, Arabs, Roman, Byzantine and Ottomans Empires. After the Ottoman's Rule Cyprus was occupied by the British Empire preceding her freedom in 1960. Therefore, the impact of different civilizations on the current populations in the Island might have resulted in a great mixture of genetic variations also due to genetic drift, migrations, etc. Investigating the genetic variants in a population is highly important and may help investigators to track down the pattern of genetic variation and diversity that exists in a population. Thus with the emergence of population genetics and medical genetics, it has been shown that there has been a geographical variance in mutations for single or multiple genes which is associated with the genetic disorders and that some disease-causing alleles occur more often in people from specific geographical regions. Insight in such allelic variations in a population helps researchers, clinicians and scientist to understand the specific genetic pattern of diseases among different populations belonging to different geographical locations.

After sequencing the whole human genome and identifying its variations between populations and exploring those variations impact on genetic disorder or molecular pathways, the importance of genetic mutation databases has been rising both globally and also specifically for unique populations. Today there are many international and national databases for specific human mutations. One of the first National Mutation Databases (NMDBs) to appear online is the Finnish Disease Heritage (http://www.findis.org) (Sipila and Aula, 2002), Hellenic NMDB

Abbreviations: NEU-GD, Near East University Genetic Mutation Database; NMDBs, National Mutation Databases; FMF, Familial Mediterranean Fever; SNP, Single Nucleotide Polymorphism; HapMap, The International Haplotype Mapping Project; CEPH, The Centre de'Etude du Polymorphism Humain; CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; VDR, Vitamin D Receptor Gene.

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(http://www.goldenhelix.org/hellenic) (Teebi et al., 2002) and recently, the Arab Disease Mutation database (http://www.agddb.org) (Patrinos et al., 2005). A complete detail of the different NMDBs could be found at the Human Genome Variation Society (HGVS) site at http://www.hgvs.org.

To be a part of this network, Near East University Genetic Mutation Database (NEU-GD) contains almost fifty gene regions and one-hundred and fifty different allele variations with their frequencies for Northern Cyprus population. Intrinsically, those variations either have relation to or might contribute to common genetic disease in the East Mediterranean region. Additionally, NEU-GD has several links to other most important genetic databases into its single website to better facilitate to the user.

2. Prevalent genetic disorders in Cyprus

Certain inherited disorders (Thalassemia (Ashiotis et al., 1973; Sozuoz et al., 1988; Baysal et al., 1995), Familial Mediterranean Fever (FMF) (Deltas et al., 2002a; Neocleous et al., 2015), diseases that are related to Vitamin D Receptor Gene (*VDR*) polymorphisms (Yıldırım et al., 2013; Kamel et al., 2014) and the examples of many others) occur at high rates in Cyprus. The inherited autosomal recessive blood disorder, Thalassemia, is well-studied, both in Turkish and Greek Cypriot populations along with the other inherited disorders.

The total population (Turkish Cypriot, Greek Cypriot and the others) of the Island is estimated to be 1,200,000 individuals in 2001 (United Nations, Department of Economic and Social Affairs, Population Division, 2011), out of which one in seven individuals carries mutation in their *β-globin* gene that causes β-Thalassemia and approximately new born one in every 158 is expected to be homozygous (Angastiniotis, 1992). However, since 1985, the screening of Thalassemia is an obligatory process between Thalassemia trait couples; therefore the birth of newborns with a Thalassemia is very rare nowadays.

Another example of frequent disorders in the population of the island is Familial Mediterranean Fever (FMF, OMIM 249100) which is an autosomal recessive inflammatory disorder characterized by attacks of arthritis, fever, peritonitis and erysipelas-like skin lesions (Kastner and Aksentijevich, 2005; Samuels and Ozen, 2000). The prevalence of FMF is most common among Turkish, Arabic, non-Ashkenazi Jewish and Armenian origin (Lightfoot, 1963; Sohar et al., 1967). Mediterranean countries are vastly affected by this disorder including Cyprus (both Turkish and Greek Cypriots), Italy, Spain and Greece (Aldea et al., 2004; Deltas et al., 2002b).

Our mutation database also holds mutation data for other genetic or inherited diseases and provides their allele frequencies in the Northern Cyprus population. As an example, Table 1 shows the allele frequencies of some SNPs (rs224222, rs3743930, rs28940580) that might play a role in the development of FMF (Zamani et al., 2013; Abedi et al., 2013; Cetin et al., 2014; Deniz et al., 2014). According to HapMap (http://hapmap.ncbi.nlm.nih.gov/) and dbSNP data (http://www.ncbi.nlm.nih.gov/SNP/), our primary results showed that the allele frequencies of specific mutations for FMF are different frequencies in CEPH (The Centre de'Etude du Polymorphism Humain) and CEU (Utah residents with Northern and Western European ancestry from the CEPH collection). However, NEU-GD also shows the allele frequencies of some SNPs that have not been determined in either HapMap or dbSNP data (Cetin et al., 2014; Deniz et al., 2014). Thus this database gives an overview over allele frequencies and genotype–phenotype relations of certain allele seen in this specific population. For example rs224222 seems to have a FMF phenotype in Turkish Cypriot and even in the whole Turkish population.

The other benefit of NEU-GD comes up when looking at results from previous studies that have shown a strong connection between Vitamin D Receptor Gene (*VDR*) polymorphisms and diseases such as cancer, asthma, osteoporosis, diabetes, cardiovascular disease (Tizaoui et al., 2014; Gandini et al., 2014; Mohammadi et al., 2014; Roxana et al., 2015; Patrinos and Brookes, 2005). In NEU-GD there is allele frequency of most known and studied four pathogenic *VDR* gene polymorphisms in the Northern Cypriot population. A comparison of these calculated frequencies with frequencies from eleven different populations from HapMap data indicates that the Northern Cypriot population has different and unique allele frequencies compared to its close relatives (Table 2) (Roxana et al., 2015; Patrinos and Brookes, 2005). Therefore, it is expected that Near East University Genetic Mutation Database will provide valued information and great benefit to healthcare institutions and healthcare professionals including clinicians, scientists, genetic counselors, patients and their families to track down the inherited pattern of these diseases and to identify new pathogenic mutations that might have association with the phenotype of the patient.

3. Description of Near East University Genetic Mutation Database

The goal behind the creation of Near East University Genetic Mutation Database is to establish a query interface that is user friendly, and allow both expert and non-expert users to interpret the data. Secondly, matching and valuating identified or new mutations with their pathogenicity found in the clinic (Fig. 1).

Additional property of the database is the data submission part. Users of the NEU-GD such as clinicians and researcher can submit their data or their sample to Near East University Hospital Medical Genetic Laboratory and after getting an approval from our specialist team their submitted data will be shown automatically on the Near East University Genetic Mutation Database. Moreover, if requested by the users, the NEU-GD team can also provide samples to researchers and clinicians around the world.

3.1. How to search the database

There are two main search options of NEU-GD: The basic search that provides the user an easy database search by entering any of the query option that is presented in the advance search and the advanced search which provides the user with an opportunity to refined search option.

The search page has a drop-down menu, which helps the user, especially the general user, to query on the available entries in the database. In the advanced search the options of the drop-down menus are “ethnic group” “population”, and “Gene/Disease Name”. The drop-down menu

Table 1
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SNP no:	Substitution	Changes in amino acid sequence	Allele freq. of CEPH	Allele freq. of CEU	Allele freq. of NEU-GD
rs224222	G>A	R202Q	40% A 60% G	50% A 50% G	35% A 65% G
rs3743930	G>C	E148Q	0% C 100% G	0% C 100% G	25% C 75% G
rs28940580	G>A/C	M680I/A	N/A	N/A	25% C 75% G

Table 2
The table shows the allele frequency of most known and studied four *VDR* gene polymorphisms that found the relationship with many diseases and their comparison with eleven different HapMap populations (http://hapmap.ncbi.nlm.nih.gov/) and Northern Cypriot population (NEU-GD) (HapMap-CEU: Utah residents with Northern and Western European ancestry from the CEPH collection; HapMap-HCB: 45 unrelated Han Chinese in Beijing; HapMap-JPT: Japanese in Tokyo; HapMap-YRI: Yoruban in Ibadan, Nigeria; HapMap-ASW: African ancestry in Southwest USA; HapMap-CHB: Han Chinese in Beijing; HapMap-CHD: Chinese in Metropolitan Denver, Colorado; HapMap-GIH: Gujarati Indians in Houston, Texas; HapMap-LWK: Luhya in Webuye, Kenya; HapMap-MEX: Mexican ancestry in Los Angeles, California; HapMap-MKK: Masai in Kinyawa, Kenya; HapMap-TSI: Tuscans in Italy).

Population	Allele freq. (%) of SNP rs 2228570 (rs10735810) (A/G)	Allele freq. (%) of SNP rs1544410 (G/A)	Allele freq. (%) of SNP rs731236 (T/C)	Allele freq. (%) of SNP rs7975232 (C/A)
NEU-GD	24 A	22 A	40 T	35 A
	76 G	78 G	60 C	65 C
HapMap-CEU	41 A	44 A	44 T	57 A
	59 G	56 G	56 C	42 C
HapMap-HCB	44 A	2 A	1 T	30 A
	56 G	98 G	99 C	70 C
HapMap-JPT	32 A	12 A	12 T	34 A
	68 G	88 G	88 C	66 C
HapMap-YRI	19 A	28 A	29 T	63 A
	81 G	72 G	71 C	37 C
HapMap-ASW	21 A	22 A	22 T	65 A
	79 G	78 G	78 C	35 C
HapMap-CHB	37 A	6 A	6 T	32 A
	63 G	94 G	94 C	68 C
HapMap-CHD	48 A	4 A	4 T	30 A
	52 G	96 G	96 C	70 C
HapMap-GIH	30 A	42 A	30 T	52 A
	70 G	58 G	70 C	48 C
HapMap-LWK	15 A	25 A	27 T	73 A
	85 G	75 G	73 C	27 C
HapMap-MEX	52 A	24 A	26 T	45 A
	48 G	76 G	74 C	55 C
HapMap-MKK	20 A	37 A	43 T	68 A
	80 G	63 G	57 C	33 C
HapMap-TSI	38 A	41 A	41 T	60 A
	62 G	59 G	59 C	40 C

will help the user to narrow down the search and to pinpoint the specific diseases of interest available in the NEU-GD database. Especially for the specialist users options for text search are available in the form of a "basic search". Moreover, researchers that are based around the world can submit their data via direct submission section and they will help the NEU-GD team to expand the database. After submission of the mutation/polymorphism the data can be uploaded easily after careful evaluation by the scientific moderator team. Subsequently the submitted and approved data will be visible on the NEU-GD database.

Moreover, the user guide option provides essential instruction for the user to be able to use the database efficiently. In addition the Near East University Genetic Mutation Database gives a list of website links to other internationally recognized databases and healthcare organizations. Hereby the users can find supplementary information and compare our findings for North Cyprus population with the other population research data.

3.2. How to access the database

Near East University Genetic Mutation Database can be opened on the WWW (World Wide Web) at the URL (http://genetics-db.neu.edu.tr/). It can be opened on all modern present day browsers such as MS-Internet Explorer and Google Chrome. The website address of the database is http://genetics-db.neu.edu.tr.

3.3. Data sources and database content

The mutation/polymorphism data have been assembled from Near East University Medical Genetic Laboratory and Near East University Centre of Excellence Genetic and Cancer Diagnosis-Research Centre. The data contains detected, identified and also new polymorphisms within gene regions that caused significant or non-significant pathogenic diseases such as *β-globin* gene related with Thalassemia disease, *MEFV* gene related with Familial Mediterranean Fever, Vitamin D Receptor Gene (*VDR*) polymorphism data (Tables 1 and 2) and more than 100 other genes and polymorphisms that might cause diseases. Additionally, the NEU-DB is a very new, growing and ongoing database that upgrades itself everyday with increased numbers and new genes or polymorphisms. As a start, we worked with 1500 subjects in total, but for SNP samples there is a variety, such as for four *VDR* gene polymorphisms we studied approximately 330 samples and for FMF disease we studied 200 samples for 11 polymorphisms in *MEFV* gene.

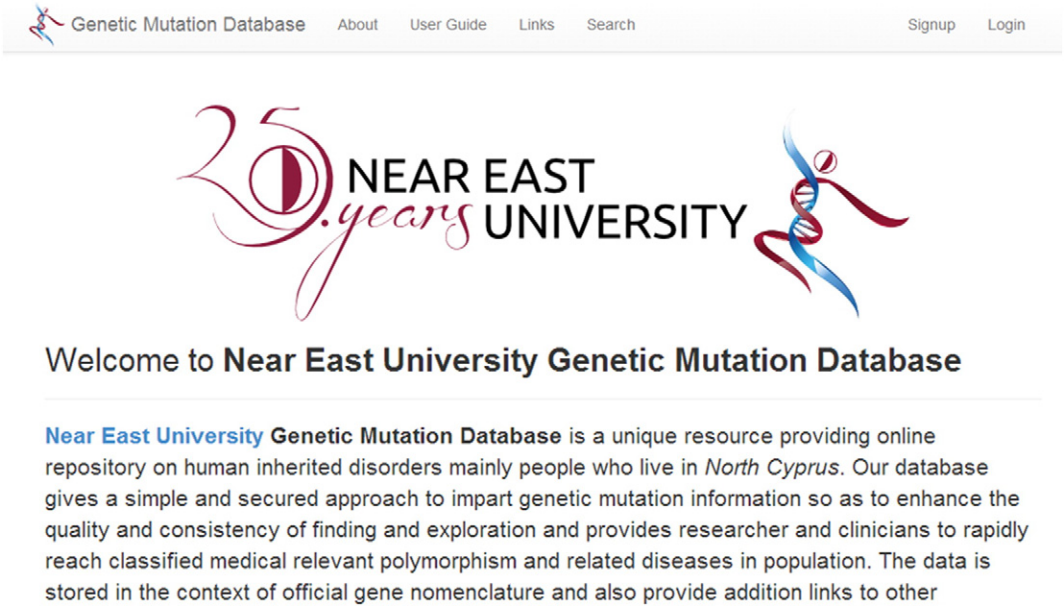

Fig. 1. The homepage of Near East Mutation Database. At the top of the website key features such as information about the database and user guide, the hyperlink to the important pages, search options and finally signup and login sections have been shown.

4. Software details

The back-end of the Software is executed in python 2.7 w/ Flask web framework modules. PostgreSQL has been used as the persistent storage and RDMS at the back end. The interface or the front end is implemented in Html5 and JavaScript w/ Twitter's Bootstrap User Interface Kit.

5. Conclusion and future aims

The tremendous pace of discoveries in molecular genetics has resulted in generation of huge amounts of genetic data. This has resulted in phenomenal advancements in the development of genetic and hereditary databases to catalog and track DNA modifications. National mutation databases are here getting essential for keeping records on national and ethnic DNA information on genetic polymorphisms. These databases should be freely accessible for the researchers and clinicians around the world. Unfortunately to date only few genetic databases have free access. Moreover, a large portion of the national databases is fully up to date due to numerous reasons including constrained corporate or open financing (Patrinos and Brookes, 2005) and due to low updating frequencies. Due to this a fundamental principle of the Near East University Genetic Mutation Database (NEU-GD) is that it will have accurate and up to date data. And the database is welcoming all data submissions around the world.

Genetic polymorphism and mutation research is a new field in North Cyprus and NEU-GD is the first collection of mutation and polymorphism data in Northern Cyprus and also in Turkey. Keeping in mind that the island was a step stone for the distribution of many important civilizations for centuries one future aim of NEU-GD will be to reveal the secret genetic variations that were stored in Northern Cypriots and based on this calculate the frequencies of known or new variations, compare them with genetic variations in other populations and find associations with genetic disorders, thereby using them in the clinic. Our primary results have revealed that the allele frequencies differ between Northern Cypriot population and other close populations such as European, Asian and African. Our studies have therefore supported the notion that the geological location of the island was important for the spread of civilizations resulting in a high degree of gene diversity in the Cyprus population. Thus we conclude that North Cyprus' first genetic mutation database, NEU-GD, will provide data on polymorphisms that will be beneficial for clinicians, researcher, patients and their families, especially researchers and clinicians who are dealing with Turkish Cypriot ethnicity around the world.

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