The Centre for Arab Genomic Studies' Report on Rare Disease Day 2014

There are a number of different definitions for *Rare Diseases* despite being self-explanatory apparently. The National Institutes of Health (NIH) define *rare* or *orphan diseases* as the ones that afflict less than 200,000 Americans. The latter number was established in 1984 to reflect prevalence of 85/100,000, and with the current US population of 317 million the rate becomes 63/100,000. It should be noted that threshold prevalence rates differ from one country to another. In this regard "rare diseases" is somehow a misnomer, because in aggregate rare diseases are not rare at all, as they afflict hundreds of millions of people worldwide. Additionally, this classification encompasses a wide range of heterogeneous disorders that differ from each other in a number of characteristics, including prevalence, clinical progression and etiology.

The first step towards tackling the burden of rare diseases in the community goes through proper characterization of the current picture of these disorders on the local and regional levels. The Centre for Arab Genomic Studies (CAGS) carries out this complex task for all genetic disorders in Arab populations. Both clinical and molecular data are collected by CAGS after being reviewed meticulously. CAGS ensures high quality of its input data through the internationally recognized process of scientific peer-reviewing. Collected data is analyzed and organized to be fed into the Centre's Catalogue of Transmission Genetics in Arabs database (also known as CTGA). The latter has developed qualitatively and quantitatively over the past few years to become the largest ethnic-based database worldwide. Screening CTGA for Rare Diseases in the UAE and other GCC countries yields a great wealth of information that can provide proper guidance for healthcare providers and policymakers.

Of the 7,000 – 8,000 known rare disorders, some are extremely rare conditions with only few diagnosed patients worldwide. Hutchinson-Gilford Progeria Syndrome is a good example of the latter conditions, with only one locally documented case from Abu Dhabi – UAE [1]. This condition is lethal and affected children develop signs and symptoms of premature aging such as wrinkled skin, growth failures and cardiovascular disease. On the other hand, some rare diseases have a much higher numbers of patients, thus making it difficult to keep these disorders within the "rare" category. This distinction between rare and non-rare diseases becomes truly blurred when we move from looking at worldwide prevalence rates to ethnicity-specific contexts. Alkaptonuria is an inborn error of the metabolism of the amino acids tyrosine and phenylalanine. It results from mutations affecting the *HGD* gene that controls an important step in the catalytic degradation of phenylalanine. The accumulation of intermediary products of the abovementioned degradation may lead to arthritis, cardiac problems, and kidney and prostate stones. This rare condition has a very low prevalence worldwide (1/250,000 – 1,000,000). However, this is not the case for every individual country around the world; UAE, for example, is estimated to have a prevalence rate of 35/100,000 for this disorder [2].

The vast majority of rare disorders are either genetic in origin or have a significant genetic component (with recessive or dominant mode of inheritance). Others are caused by erroneous immune reactions or from exposure to certain infectious agents. And many of these disorders still await proper clinical and

molecular characterization. This has proven quite difficult for a considerable number of these conditions, many of which manifest themselves in a number of variable ways. More difficult still is the process of dissecting these phenotypes in order to resolve the issue of causality. Needless to say that these steps are usually done under huge pressure from desperate patients, families and advocacy groups.

Despite the immense importance of the CTGA buildup as a major referential source of information about rare genetic disorders in Arab populations, a massive body of work still needs to be done along the way of handling these conditions. Data from CTGA can be ideally utilized to plan and carry out effective prevention programs, and such data is necessary for providing genetic counseling and diagnostic testing. In the same vein, large scale campaigns are indispensible for reaching out to patients and their families as well as the whole community to raise awareness about these disorders and eliminate collective myths and misconceptions.

The CTGA database lists a wide variety of Rare Disorders with entries from numerous Arab countries; many of these disorders belong to the category of Inborn Errors of Metabolism (IEM). Notable examples of these include Biotinidase deficiency, Phenylketonuria, Alkaptonuria and lysosomal storage disorders. Another group of rare diseases are caused by genetic defects of DNA repair mechanisms; examples include Fanconi anemia and Xeroderma Pigmentosum. A brief account of these disorders in the local context is given below.

Biotinidase deficiency is a multiple enzymatic deficiency, in which the body is unable to use the vitamin Biotin. Biotin is necessary for normal metabolism in humans as it plays an important role in the metabolism of fats and amino acids, aerobic respiration, and cell growth. This deficiency results from a mutation in the Biotinidase gene (*BTD*), in which a number of novel missense mutations were reported in the Emirati population [3, 4]. The prevalence of this condition in the latter population was calculated to be between 2.2–4.9/100,000, which makes it one of the most of prevalent disorders among IEM in UAE.

Various degrees of deficiency affecting the enzyme phenylalanine hydroxylase result in *Phenylketonuria* (PKU). Phenylalanine hydroxylase mediates the conversion of phenylalanine into tyrosine, which is necessary for the production of certain hormones, neurotransmitters, and melanin. If left without management, this disorder leads to the buildup of phenylalanine in the body with major developmental consequences. The latter include mental retardation, hypopigmentation, and psychological problems. A comprehensive survey for birth prevalence of PKU in the UAE between the years 1994 and 2000 yielded the rate of approximately 5/100,000 [5]. Numerous mutations were reported to affect the *PAH* gene, some of which seem to be unique to the UAE [3]. Studies that characterize local patterns of mutations are extremely helpful in devising kits for locally relevant therapeutics and diagnostics.

The CTGA entry for *Alkaptonuria* shows studies from UAE stating widely varying prevalence rates. However the study with the wider geographical coverage and larger sample size report a prevalence of 0.98 per 100,000 or less [2,3].

Lysosomal storage disorders are characterized by a genetic defect in one or more lysosomal components that process various cellular molecules to be either reused by the cell or eventually eliminated from the body. Defects underlying these disorders result in the accumulation of certain substances in a progressive manner, thus interfering with normal cellular activity and possibly resulting in cellular death. There are over fifty distinct types of these disorders, and grouped together, they are relatively common with a prevalence ranging from 12-25/100,000 live births. Individual types of these disorders are much less prevalent, for example UAE prevalence rates of Tay-Sachs and Gaucher diseases were 0.74 and 0.25/100,000 respectively [6,7,8].

A number of rare diseases fall under the category of *defective DNA repair disorders*. These are characterized by having ineffective protection from DNA changes due to constant exposure of the human genome to various sources of damage. *Fanconi anemia* is a good example of this subgroup of rare diseases; it is a recessive condition which can lead to bone marrow failure (aplastic anemia), leukemia, and solid tumors. Many of those affected suffer congenital defects of the skin, arms, head, eyes, and kidneys, as well as developmental disabilities. Upon screening 24,233 consecutive live and stillbirths in Abu Dhabi, UAE, one case of Fanconi anemia was observed in a consanguineous family. This incidence rate may reflect higher UAE incidence compared to the international figure (1/350000 births) [9]. Another one of these disorders is *Xeroderma Pigmentosum* which involves photosensitivity, early aging of the skin and a high incidence of skin malignancy. This disorder has been reported to be unusually frequent among Arab populations, and indeed it has been observed in UAE, Qatar, Tunisia, Palestine and Egypt [10].

References:

1- CTGA entry for "Hutchinson-Gilford Progeria Syndrome".
2- CTGA entry for "Alkaptonuria".
3- Al-Shamsi A, Hertecant JL, Al-Hamad S, Souid AK, Al-Jasmi F. Mutation Spectrum and Birth Prevalence of Inborn Errors of Metabolism among Emiratis: A study from Tawam Hospital Metabolic Center, United Arab Emirates. Sultan Qaboos Univ Med J. 2014 Feb;14(1):e42-9. Epub 2014 Jan 27.
4- CTGA entry for "Biotinidase Deficiency".
5- CTGA entry for "Phenylketonuria".
6- Al-Jasmi FA, Tawfig N, Berniah A, Ali BR, Taleb M, Hertecant JL, Bastaki F, Souid AK. Prevalence and Novel Mutations of Lysosomal Storage Disorders in United Arab Emirates : LSD in UAE. JIMD Rep. 2013;10:1-9. doi: 10.1007/8904_2012_182. Epub 2013 Jan 1.
7- CTGA entry for "Tay-Sachs Disease".
8- CTGA entries for Gaucher Disease.
9- CTGA entry for "Fanconi Anemia".
10- CTGA entries for Xeroderma Pigmentosum.