



Rare Disease Day 2016: Arab Patients' Voices

Every year at the end of February, many people across the world mark Rare Disease Day, which brings together individuals who are affected by rare diseases, or living with affecteds as well as patient organizations, politicians, caregivers, medical professionals, researchers and the pharmaceutical industry. The ultimate aim of this event is to raise awareness and provide information and solidarity to those who are touched by this group of diseases. Generally, the term *Rare Diseases* refers to conditions that affect less than 1 person in 2,000 of the general population. It is important to remember that there are over 6000 rare diseases and at least half of these affect children.

The global theme for this year is *Patient Voice* and its slogan is *Join us in making the voice of rare diseases heard*. The Centre for Arab Genomic Studies (CAGS) has been taking part in this important event for years now and this year is no exception. CAGS' contribution for this year is based on two major sources; namely, the ever-expanding comprehensive genetic database that belongs to the Centre; the CTGA database, which hosts a massive collection of genetic and molecular data from studies on Arab populations. And secondly, accounts from patients' caregivers that shed light onto the experience of being affected by rare diseases. Three stories will be presented below to showcase important aspects of patients' lives and the consequences of having affected individuals in the family.

The field of human genetics is an immensely complicated branch of science, and massive difficulties are faced by patients and doctors along the way of reaching a definitive diagnosis for each specific case. It is quite common for genetic disorders to have a number of nonspecific clinical manifestations, which are shared with many other conditions, even though the underlying genetic defect/s is different. Also, people usually have a relatively large number of genetic "variants of unknown significance" and these have to be carefully filtered in order to obtain the causal variant for the condition in question. Geneticists have to take into consideration the full clinical picture, family history, parents genotyping and other factors in order to get closer to underlying causative mutation/s. Importantly, this process is far from straightforward and in some cases (such as simplex cases) the result is a list of potentially causative



variants that need further investigations. These investigations are expensive and labor-intensive and more importantly they cannot always be done in a clinical setting. Here, clinical and research activities have to unite in order to make progress in this regard. Naturally, the results from this clinically directed research will be utilized routinely afterwards in clinical settings and consequently reduce patients' suffering and time needed for diagnosis. As a matter of fact, supporting this route of scientific/clinical investigation in the context of human genetics is one the main strategies of the Centre for Arab Genomic Studies. The first story, below, is a clear example of the difficulties that can be faced while trying to uncover the true causative variants despite the apparent simplicity of the phenotypical presentation, not in one but in three children from one family!

The story of Mirah, Mayed and Mansour

This is a story of three siblings; Mirah (16 years old) and her two brothers, Mayed (11 y/o) and Mansour (7 y/o). The story began with the eldest of the siblings; Mirah, which was diagnosed prenatally to have abnormal accumulation of fluid in the brain leading to head enlargement. This abnormality can cause convulsion, and mental disability. Few months after Mirah's birth, it was clear that she was not meeting her normal developmental milestones in addition to suffering considerable hearing impairment. Later on, a new problem emerged; Mirah was unable to walk! The family was under constant stress upon later pregnancies because of the fear that there will be more cases with this condition in the family. These fears were not unfounded because "Mayed"; the fourth child and "Mansour"; the last do have somehow similar symptoms to Mirah. These symptoms include motor developmental delay, spastic paraplegia and ataxia, albeit each one of the children has distinctive symptoms that are not present in the rest. This necessitated performing detailed molecular testing to uncover the underlying genetic mutations that cause the abovementioned symptoms. The results of these tests came out for Mirah and are still pending for her brothers. What has transpired already is that Mirah has more than one potentially harmful mutation and it is imperative to get all test results and study the literature for every one of these mutations in order to reach a well-informed diagnosis.

The complexity of the condition did not stop the family from seeking all possible medical help in U.A.E. and abroad. Gradually, patience and persistence are starting to pay off; for Mirah started to walk at the age of seven after going through more than six surgeries and that was a major happy event in the family. Mayed also had undergone more than eight surgical operations and he is making steady progress. The

family had to face a number of serious challenges throughout the past 15 years; from obtaining the best medical diagnoses and treatment to getting the children into the educational system and securing proper rehabilitation and support before it is too late. Additionally, there is considerable pressure from society when it comes to parents of children with special needs, especially when there is more than one affected child in the family. Nevertheless, the State's attitude towards children with special needs is truly admirable, and the level of resources and support directed towards these children is quite high by all standards. Still, families such as that of Mirah and her brother hope for better levels of spreading awareness, medical and social care for children with rare diseases.

Shifa's Story

Shifa is an 11 years old girl from United Arab Emirates and she has the rare condition; *Propionic Acidemia*. This disorder affects nearly 1 in 75,000 individuals around the globe; however, the condition is far more prevalent in the Arabian Peninsula. Prior to Shifa's birth, her mother (Zakiya) had lost three newborn babies, possibly due to this disease, which causes a healthy looking newborn to develop unexplained lethargy, vomiting and poor feeding. At this stage prompt action should be taken or the condition will deteriorate quickly to irreversible damage to the nervous system and death. The condition is usually managed through continuous dietary control in addition to close medical monitoring when the body goes through particular stressful situations (for instance; infections).

Shortly after Shifa was born, she underwent a number of tests and she was diagnosed, consequently, she received extensive care from a specialized medical team in the hope that she will survive and so she did. This care started with installing a feeding tube on baby Shifa so that she could get the correct nutrients for her condition. Zakiya noticed a pronounced improvement in her daughter's health and she attributes that to the care she has been receiving from doctors. Zakiya is particularly grateful to those doctors for being very keen on educating her about Shifa's condition, to the extent that now she feels quite confident with her knowledge about the disorder. Such knowledge, Zakiya stresses, can be a life-saver for a family with similar conditions. On the other hand, day-to-day life is far from easy because Zakya is constantly worried about long-term repercussions of this condition on her daughter's mental abilities. School performance will surely be affected by frequently missing classes because of repeated medical appointments and hospitalization, Zakiya fears. To overcome anxiety, Zakiya focuses on actual adherence to doctors' recommendations in terms of food and supplements so that Shifa can avoid going through episodes whereby her condition deteriorates further.

From her viewpoint, Zakiya believes that, despite the limitless support provided by the State, there is still some room for improvement. Of a particular importance is the issue of spreading more awareness about

this type of disorders, because very few people know about them unlike widespread public attention given to disorders such as thalassemia and cancer. To achieve the latter aim, it is imperative to establish a specialist body (association or society) that directs efforts and resources towards better support and awareness in the context of this disorder. In the same vein, the issue of consanguineous marriage should be strongly highlighted especially in terms of the risks it carries in relation to heritable disorders.

Propionic Acidemia features in the CTGA database in one Phenotypic Record and two Gene Records for PCCA and PCCB genes. Data from 5 Arab countries are displayed and these are U.A.E., Oman, Qatar, Bahrain and Saudi Arabia. According to the phenotypic record, most affected children show different degrees of motor, social and language delay. They also show more serious medical problems, including neutropenia, cardiac abnormalities, periodic thrombocytopenia, hypogammaglobulinemia, developmental retardation, seizures, and coma. Death is likely, if the condition is not intervened with.

The autosomal recessive disorder caused by a deficiency of the propionyl-CoA carboxylase enzyme, which is involved in the normal breakdown of several essential amino acids. The result is branched-chain organic acidemia. According to a study by Al Essa et al. (1998); propionic acidemia is unusually frequent in Saudi Arabia, with a frequency of 1 in 2,000 to 1 in 5,000, which is much higher than the global average. In the same vein, in a study by Al-Shamsi et al. (2014) propionic acidemia was found to be one of the most prevalent Inborn Errors of Metabolism in U.A.E., with a birth prevalence of 2.2-4.9 per 100,000. One novel mutation in the PCCA gene and two different mutations in the PCCB gene were identified among the affecteds by the same study.

The Story of Ahmed and Aya

Ahmed (12 years old) and Aya (9 years old), a brother and sister from Sudan who live with their parents in U.A.E., have a rare condition named: Primary Microcephaly type 2. This condition has a number of manifestations including intellectual disability, delayed development and smallness of the head (microcephaly). The mother of Ahmed and Aya; Najla communicates her experience with a great deal of strength and resolve. The challenges that come with having two affected children are indeed immense; because the two siblings suffer considerable disability and need extensive attention. Furthermore, Aya experienced epilepsy and medical intervention was called for.

None of the abovementioned difficulties were to put Najla off fighting for securing the best possible care for her kids. Fortunately, Ahmed and Aya were completely supported by an excellent team of doctors, who obtained the definitive diagnosis for the condition and managed Aya's epilepsy very well. Najla was

given a full explanation about the condition, and more importantly, she was referred to specialized care providers, in order to increase her chances of attaining maximal development. Currently, both Ahmed and Aya are with Al Noor Training Centre for Children with Special Needs in Dubai and they are making excellent progress there. For example, Ahmed is now capable of speaking clearly and he is no longer dependent on his mother for eating, getting dressed and going to bathroom.

Najla is full of great ideas when it comes to raising the level of community awareness and involvement in the context of caring for children with special needs. She believes that Emirati law provides solid foundation for initiating a publically funded establishment that specializes in providing care for those children. The cost of such care, when provided by private centers and clinics, is beyond the means of families with limited income. Thankfully, Ahmed and Aya are covered by one of the many Emirati charity foundations and thus they can afford the high cost of good quality care they are receiving. Finally, Najla highlights a very important issue in relation to caregivers (often the parents) of sick children suffering from this sort of diseases. It is to do with supporting those caregivers to progress in their own careers/lives in spite of the huge responsibilities that come with have one or more affected children. As a matter of fact, Najla gives an admirable example of what she managed to achieve notwithstanding the difficulties she faces at home. In the beginning, she had to stop her secondary education and give her children full attention but later on she joined Adult Learning Centre in Nad Al Sheba (Dubai), which propelled her to further success. Currently, Najla is a third year student at the Business School at Hamdan Bin Mohammed Smart University, and her studies are funded by a scholarship from the university. As well as doing very well at her studies, Najla, gradually developed the right attitude towards her kids, she truly cherishes the way they are different and is very proud of the great progress they are making with time.

The CTGA database has a phenotypic entry for Autosomal Recessive, Primary Microcephaly 2 and a related entry for its genetic cause (WDR62). As a matter of fact the above-mentioned family – from Sudan – is the only one that features in CTGA. The condition is defined as having a head circumference at least 2 SD below the mean for age, sex, and ethnicity, and it is clinically characterized by primary microcephaly and intellectual disability. Patients usually, but not necessarily, show cortical malformations on neural scans. These malformations include polymicrogyria, pachygyria, hypoplasia of corpus callosum, abnormal/simplified gyral patterning and lissencephaly. Patients show abnormal neurological and behavioral manifestations, including delayed psychomotor development, moderate to severe intellectual disability, impulsivity, and aggression.

The condition is caused by mutations in the WDR62 gene, which is responsible of regulating spindle orientation, centrosome integrity, and progression through mitosis. WDR62 plays an essential role in neuronal proliferation and migration as well as in mother-centriole-dependent centriole duplication. This disorder is extremely rare and Bastaki et al (2015) was the first to report –molecularly and clinically– such a case from the Arab world. The latter report used Whole Exome Sequencing to uncover a novel mutation in WDR62; c.390G>A, in exon 4. The substitution affected the last nucleotide in exon 4, suggesting aberrant splicing.

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Dubai, 23 Feb 2016

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