Weill Cornell Medicine-Qatar

Research sheds new light on brain disorder

Doha – January 18, 2017: A study by researchers at Weill Cornell Medicine-Qatar (WCM-Q) has revealed the genetic cause of a neurological disorder and the implications it has for marriage.

The research examined the genetics behind cerebellar ataxia, a congenital malformation of the brain whereby the total volume of the cerebellum – a part of the brain that regulates muscle activity at the back of the skull - is diminished. This can result in the sufferer having problems walking, poor coordination and a tendency to be a 'late developer' as a child. Cerebellar ataxia can also be associated with poor muscle tone, lack of coordination and learning disabilities.

However, because cerebellar ataxia is often an inherited disease, it could have major implications for the consanguineous marriages that are common in Qatar. When the mutated gene that causes the disorder is expressed in a recessive manner, both parents have to have the same recessive gene for some of their children to be affected. Because genes are inherited, it is much more likely that people within an extended family carry the same genes. Therefore, a consanguineous marriage within a family who carry the mutated recessive gene is much more likely to lead to cerebellar ataxia in the children of that marriage. The implications of such a marriage should, therefore, be carefully thought about and genetic screening considered.

Collaborating investigators from Weill Cornell Medicine-Qatar, Weill Cornell Medicine in New York and Hamad Medical Corporation have now discovered an unusual recessive mutation that leads to cerebellar ataxia. Their results were recently published in the *Annals of Neurology,* a highly influential journal in the field. The study**,** entitled 'Mutation in non-coding RNA, RNU12 causes early-onset cerebellar ataxia', was carried out by a team of doctors and scientists including lead researcher Dr. Alice Abdel Aleem, WCM-Q's assistant research professor of neuroscience, and assistant research professor of neurology, along with Dr. Elizabeth Ross, the Nathan E. Cumming professor of neurology and neuroscience, and chair of the Neuroscience Graduate Program at WCM in New York; Dr. Mahmoud Fawzy Elsaid, senior consultant pediatric neurologist in the Department of Pediatrics at Hamad General Hospital; and Dr. Tawfeg Ben-Omran, senior consultant and head of clinical and metabolic genetics at Hamad General Hospital

Dr. Abdel Aleem explained that this particular family study was launched after a young woman visited her clinician with symptoms of cerebellar ataxia. Her brother was also found to have the disorder and the researchers asked if they, and their extended family, would take part in research to examine the genetic cause.

Blood samples were taken from two branches of the family and DNA, RNA and protein was extracted. The data was then analysed by the study research team and the WCM-Q Bioinformatics Core. After looking at the entire genome, a rare variation in the DNA sequence of non-protein coding ribonucleic acid (RNA) called RNU12 was found. This RNU12 variant was associated with affected family members, following the inheritance pattern expected of a recessive gene. Laboratory investigations carried out by Dr. Nader Chalhoub, a post-doctoral associate at WCM-Q, confirmed that the variant impacts the expression and function of RNU12. This is an exciting finding, since most disease-associated mutations

identified to date involve the small fraction of the genome that encodes proteins. The non-coding regions that regulate how the genetic blueprint is read by our cells pose a new frontier of genetic investigation that has been challenging to explore.

Dr. Abdel Aleem said: “The study will open a new window for screening for cerebellar ataxia. It also shows geneticists how important it is to conduct research on all parts of the genome - both protein-coding and non-coding – when looking for causes of disease.

“At the national level, because many families here are consanguineous, family members may have the same genetic defect. Therefore, the implications of marriage in such cases should be considered carefully. Genetic counselors can be very helpful in this regard.

“It is also important to raise community awareness about the pivotal role of families who engage in approved genetic studies. This mutation could not have been identified without the participation of both healthy and affected family members.”

However, although the research identified the mutation, it did not identify which of the gene(s) that are regulated by RNU12, and so are affected by RNU12 mutation, are directly responsible for the cerebellar ataxia. That is the subject of further study by Dr. Ross at Weill Cornell’s parent campus in New York. In collaboration with Dr. Aleem's laboratory, Dr. Ross' group will produce and study experimental animal models that are engineered to carry the same mutation as was found in the study family.

"This will allow us to follow in the lab the gene expression patterns that affect the development and aging of the brain – in particular the cerebellum – when two copies of the RNU12 mutation are present,” said Dr. Ross. “We can use this information to probe the pathway downstream of RNU12 that is so important for normal brain development. In this way, we hope to find effective targets for treatment that may slow or even prevent cerebellar ataxia in individuals with RNU12, and perhaps other gene, mutations."

Dr. Khaled Machaca, associate dean of research at WCM-Q, praised the work and its focus on conditions of concern to Qatar. Dr. Machaca said: “It is extremely gratifying to see research that is funded nationally by QNRF reap such important discoveries about conditions that are affecting the health and wellbeing of Qatari families and that these discoveries may usher in personalized medicine approaches for local people. When it comes to issues related to family planning in particular, scientific advances can be greatly beneficial in helping to help ease the emotional stress on the family and the high medical expenses on the system, especially for chronic conditions such as cerebellar ataxia.”

This research was made possible by Qatar National Research Fund’s (QNRF) NPRP grant 4-099-3-039, the Qatar Foundation Biomedical research program, and the Teebi Project.

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Photos Captions:
Photo1: Dr. Alice Abdel Aleem, WCM-Q’s assistant research professor of neuroscience, and assistant research professor of neurology

Photo2: Dr. Alice Abdel Aleem and her team

About Weill Cornell Medicine - Qatar

Weill Cornell Medicine - Qatar is a partnership between Cornell University and Qatar Foundation. It offers a comprehensive six-year medical program leading to the Cornell University M.D. degree with teaching by Cornell and Weill Cornell faculty and by physicians at Hamad Medical Corporation (HMC) and Aspetar Orthopedic and Sports Medicine Hospital who hold Weill Cornell appointments. Through its biomedical research program, WCM-Q is building a sustainable research community in Qatar while advancing basic science and clinical research. Through its medical college, WCM-Q seeks to provide the finest education possible for medical students, to improve health care both now and for future generations, and to provide high quality health care to the Qatari population.

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