THE LAND OF OPPORTUNITIES FOR RESEARCH ON RARE GENETIC NEUROLOGICAL DISORDERS

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Our knowledge about rare genetic neurological disorders is fairly limited, which translates into poor treatment options for them. The very fact the we do not know the prevalence of many such diseases is a testament that we do not invest as much time and funding in research on such diseases as we should. We also ignore the fact that the findings from any study conducted on these rare genetic diseases are not restricted to those particular diseases but rather applies to more common diseases as well. The disease Hereditary Sensory Autonomic Neuropathy II (HSAN II) is an example. Cardinal symptoms of this autosomal recessive neurological disorder include severe loss of pain, temperature and touch sensation since birth[1]. The loss of sensations in these patients can leave even severe injuries, including fractures of bones, unnoticed until they develop severe infections which might lead to amputation of digits and even limbs[1]. The incidence of this disease is not known and there is only symptomatic treatment available for it. Although a few candidate genes have been associated with this disease, the exact gene responsible for HSAN II remains unknown. Few studies have been published on HSAN II, even though research conducted on this disease will not only lead to development of treatment options for this disease but also for other diseases. For example, if we can completely understand the reason for the lack of pain sensation in these patients, we can use this knowledge to develop pain management treatment options for other painful diseases like end stage cancers. Another example of note is simple Autosomal Recessive Optic Atrophy[2]. Patients diagnosed with this disease are normal in every aspect except being completely blind since birth or soon afterwards. The reason for their optic nerve atrophy is not understood and there is also no confirmed mutation associated with this disease. As expected, there is also no available treatment option for it. If more research is conducted on this disease, we can not only develop treatment options for this disease but also for other diseases that require optic nerve regeneration for their cure. The apparent lack of enthusiasm by the scientific community could be due to oversight of rare genetic neurological disorders.However, it is more likely to identify such rare genetic neurological disorders in populations where intra-family marriages are common and chances of passing on a "faulty gene" to the next generation is high. Pakistan is a country where intra-family arranged marriages are very common and much more socially preferred compared to "out of family" marriages, making the genetic pool of this country much denser compared to western countries. Because of this dense genetic pool it is fair to assume that what is 'rare' in western countries is 'not so rare' in Pakistan. Good quality population studies can identify large families in which rare genetic neurological disorders exists. Data collected from them will allow further high impact studies not only on these disorders but also provide evidence for generating new hypothesis that can reshape the very foundations of basic biological sciences. An interesting example of this comes from Uner Tan syndrome. This, probably autosomal recessive disorder, was recently described in a large family belonging to a small village in Turkey. Six out of nineteen siblings-belonging to this family have quadrupedal gait, dysarthric speech, mental retardation, epilepsy and cerebrocerebellar hypoplasia[3]. Genetic mutations and their mechanism of action for the manifestation of this disorder are being actively investigated. Although extremely controversial, this disorder has been proposed as an example of a novel hypothesis, 'reverse evolution'. The transformation from quadrupedal to bipedalism is believed to be the very foundation of the evolution from ape to human[4]. The findings from this and four other families diagnosed with Uner Tan syndrome has not only introduced a new disorder, but also shaken the very foundations of evolutionary biology and attracted a lot of attention from the scientific community. Hence, identification of families with novel rare genetic neurological disorders not only helps in research of that particular disorder but they can also lead to ground breaking discoveries that have impact on other fields of biological sciences. The high incidence of intra-family marriages in Pakistan makes it a 'land of opportunities' to study rare genetic neurological disorders. In order to seize these opportunities we need to conduct epidemiological studies to identify large families with high

prevalence of rare genetic neurological disorders followed by research to identify the genes responsible for these disorders and the mechanism of action of their faulty or absent proteins. Further research can help us to not only develop treatment options for these diseases but also provide findings that may have ground breaking consequences in other aspects of biological sciences. However, it must be realized that Pakistan is a country with poor socio-economic conditions and understandably large investments are not made in the field of scientific research. But the opportunity to study rare genetic disorders in Pakistan should not be wasted. The way to counter this issue is to develop more collaboration with researchers in other countries where funding to support research is not a big problem. We can share knowledge and biological samples and through these collaborations perform high impact research. Therefore, we need to better advertise these opportunities and make it more conducive for other researchers to grab our extended hand. We also need to remove any senseless restrictions on research and make Pakistan, 'the land of opportunities for research on rare genetic diseases', a productive place to conduct research on rare genetic neurological disorders.

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