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The Implications of Detecting and Diagnosing Fragile-X Premutation Carriers

The author presents an evaluation of the ethics for creating policy around genetic premutation detection. She compares the benefits and consequences of more utilitarian and libertarian approaches regarding patient care when influenced by lenses such as culture and class.

In our world, where designer babies and genetic engineering have become more reality than dream, we are all implicated by the ethical and scientific advancements regarding genetics. With this progress, though, comes controversies on the direction of science. Our growing understanding of the genetic diseases which negatively affect human quality of life enables us to better identify these conditions, but where are the boundaries between human involvement and nature? Is screening going too far to push genetic screening towards the realm of eugenics? Or, are we doing too little to help detect and diagnose problems which change the courses of family trees? The mechanisms behind most genetic conditions are not simple; multiple factors[1] play into the development of a disease and its inheritance. Complex mutations change the way we should look at carrier status and its diagnosis on both scientific and ethical levels. Going forward, general education and deeper dialogue will be needed to determine the path of research and policy for intricate genetic diseases.

One hereditary condition, Fragile-X Syndrome has come to great attention recently, not only as the most prevalent genetic form of mental retardation, but also as a prime example of an unstable nucleotide expansion disorder (Peprah, 2012). Stemming from a mutation in the FMR1 gene, the clinical diagnoses associated with Fragile-X Syndrome (FXS) result from a trinucleotide CGG repeat on the X-chromosome of DNA (Saldarriaga et al., 2014). Mutations in the code for the FMR1 gene lead to underproduction of functional FMRP protein, which normally regulates neural function (Garber et al., 2006). Patients with Fragile-X Syndrome experience varying degrees of mental inhibition starting around 36 months of age (Garber et al., 2006). Generally, males display various forms of social anxiety, repetitive behaviors, language delay, distorted facial features (like protruding ears and long face), and macroorchidism[2] once secondary sex characteristics have developed (Hantash et al., 2011). Females often

[1] Autosomal or sex-linked inheritance and epigenetic variation, to name two
[2] Testicular enlargement

experience less severe symptoms, including attention deficit and personality disorders (Hantash et al., 2011). Fragile-X syndrome has been identified as one of the main causes of autism spectrum disorder (Kazdoba et al., 2014). Affected individuals will often be dependent on others for care throughout adulthood (Smith et al, 2011) (Pembrey et al., 2001).

Figure 1. A young boy with Fragile-X syndrome. Observe the distinctive facial features. http://www.stepwards.com/usmle-content-outline/multisystem-processes-disorders/fragile-x-syndrome/

Although FXS is incredibly debilitating to families, widespread genetic testing for the disease has not been accessible in the past due to the complicated and somewhat mysterious pathway of the FMR1 mutation itself. Individuals express a range of different mutation repetitions in the FMR1 code. The normal range is considered to be less than 55 CGG repeats (Hagerman et al., 2004). Phenotypical symptoms of FXS generally appear when a person has greater than 200 CGG repetitions (Hagerman et al., 2004). Larger gene mutations are associated with more severe symptoms (Kenneson et al., 2001). Individuals, however, who have between 55 and 200 CGG repeats are considered to be premutation carriers (Hagerman et al., 2004). By mechanisms not thoroughly understood, an FMR1 premutation may become a full-fledged mutation (unstable nucleotide expansion) within the process of female oocyte meiosis (Ardui et al., 2016). This means that a mother who is not aware of any history of FXS in her family may have the potential to pass on this disruptive genetic disorder to her children without any prior knowledge of the condition she carries.

New research into the FMR1 premutation, its identification, and its consequences brings the tools to better predict, diagnose, and counsel individuals on FXS. As we seek to understand and build upon this

science, however, we must also be called to consider the direction of genetic research and counseling. After all, approximately 1 in 3335 individuals is affected by FXS in the United States and approximately 1 in 178 women are carriers of the trait (Hantash et al., 2011). Given how widespread carrier status is and how grave a condition Fragile-X syndrome can be, individuals should know their potential risk for bearing a child with the disease. However, genetic testing may not always be available to individuals depending on their insurance. And even if the procedure is covered, many people worry that they will be discriminated against or face higher premiums depending on their results (Fulda et al., 2006). We must think about the health care inequalities that exist within the modern world around genetic testing and look for ways to make medical diagnostics and treatments more universal. And with this, we must also identify the changes needed within general education and public policy to raise awareness of the medical information available to individuals and how it can be interpreted for personal interest. With more shared knowledge and a broader discussion across fields and value systems, we have the chance to build a healthier future and make discoveries that will drastically improve people's quality of life. This review is just the start, a simple invitation to research and debate genetic advancements in the hope of finding a common ground and a warning for the consequences of inadequate medical access.

So far, a few different tests have emerged to identify the Fragile-X syndrome premutation in patients. The various lenses through which scientists can view the disease fuel different approaches for future research. Disease modeling in the Fragile-X knockout mouse already promises to be valuable for testing treatment options and further exploring the mechanisms behind the unstable FMR1 mutation (Kazdoba et al., 2014). In the meantime, researchers are continuing to identify increasingly specific stains to apply to genetic code while it is being amplified during polymerase chain reactions (PCR) (Amancio et al., 2015). When the exact FMR1 sequence is highlighted by a stain, scientists can more efficiently determine the status of a patient's CGG mutation (normal range, premutation, or full mutation). For example, Hantash et al. have shown triplet-primed polymerase chain reaction (TrP-PCR) to be more effective and convenient compared to the previously used Southern Blot test at detecting the FMR1 mutation (Hantash et al., 2011). Localized and inexpensive PCR techniques could be one solution to the problem of class inequalities in diagnostic medicine. Ardui et al. have also looked into single-molecule sequencing for mutation detection and predicted that AGG interruptions within the CGG repeat in FMR1 could play an important role in the mechanisms of FXS (Ardui et al., 2016). Lastly, work by Brasa et al. has uncovered the epigenetic changes around the FMR1 gene that could be used to diagnose and classify Fragile-X syndrome further (Brasa et al., 2016). With broad, extensive research on FXS, there is a stronger chance of finding solutions to its early detection and prevention across diverse populations.

Premutation diagnosis may bear a far greater impact on patient care than a simple warning of carrier status. Just as males and females present with FXS in different ways, male and female premutation carriers have actually been found to present with various clinical problems relating to their FMR1 repetitions (Hagerman et al., 2004). For example, 1 in 400 males hold the FXS premutation, and of these, 33% are affected by fragile-X associated tremor ataxia syndrome (FXTAS) (Hantash et al., 2011). Older men with FXTAS suffer from degenerative neural function and memory loss, as well as other symptoms similar to Parkinson's Disease (Hagerman et al., 2004). Fragile-X associated primary ovarian insufficiency (FXPOI) has about a 20% penetrance among females with the premutation (Hantash et al., 2011). This means that the women will incur premature ovarian failure, leading to early subfertility or infertility (Hantash et al., 2011). Campbell et al. uphold that females with the premutation have a higher risk for other endocrine dysfunction and physical illness (Campbell et al, 2016). Even women at the higher end of the normal range for FMR1 repeats have been shown to experience a sharper decline in ovarian reserve with age compared to other women (Gustin et al., 2015). Not only do these findings support the increased study of the FMR1 premutation and its clinical effects, but so does the promise that with an enhanced understanding of the FMR1 premutation, scientists will be able to apply their knowledge to the study of other unstable nucleotide expansion disorders (eg. Huntington's disease) (Kazdoba et al., 2014) (Peprah, 2012). And so, with greater insight into this and other genetic disorders, physicians should be able to provide better guidance and health care services to their patients, correct?

Not exactly. Inequalities within modern healthcare across class and educational status have hindered progress within the world of personalized medicine. Without inclusive policy shifts and widespread access to scientific resources, genetic testing could be limited to a select few in our society. Researchers are working to develop new lab techniques that are more efficient and therefore more cost effective. This is to be greatly admired and encouraged. However, there remains a deep-set fear across various populations of discrimination from insurance, jobs, and even the government on the basis of genetic testing results (Fulda et al., 2006). Both Egypt and Great Britain have engaged in population-based studies of FXS, and this is certainly one option for the United States to ensure universal testing (Meguid et al., 2014; Pembrey et al., 2001). Although useful for assessing the general state of a country's population, government mandated genetic testing itself holds the potential for harm if this information lands in the wrong hands or becomes some kind of market commodity. If we push for legislation to balance a functional healthcare economy with values for personal privacy and rights, and educate others on these non-discrimination policies as well as the genetic testing options available, we can stop progression to a society where medical information becomes a destructive and classist tool.

When it comes down to a patient's individual care and guidance, his or her physician must weigh the potential benefits and consequences of genetic testing. The counseling that follows walks a fine line between the ethical mindsets of utilitarianism and libertarianism (Fulda et al., 2006). In the utilitarian philosophy, the patient's individual concerns are outweighed by the concerns of the public at large, whereas the more libertarian philosophy values the impact that a decision has on the individual it directly concerns above all (Fulda et al., 2006). In the context of genetic counseling, conflict might arise when a doctor is faced with informing or not informing the family of a patient of a hereditary disease. Family referral can prevent further transmission of the condition, but also could mean disclosing a patient's medical record against his or her will. This same issue came into play as South African researchers looked at the variety of participants in their FMR1 study: for individuals who tested positive for harmful premutation in the gene, a very low proportion of their family members chose to be tested themselves (Essop et al., 2013).

Moral values will probably never be completely universal and this diversity should not be discouraged. Above all the ethical variations, what matters is finding common ground between beliefs for both individual autonomy and the public good. We can ensure that the future of genetic testing is both more accessible and individual by encouraging doctors and researchers who work to better understand Fragile-X syndrome[3] to connect legislators and ethicists who build practical guidelines to scientific applications. Without interdisciplinary collaboration, we risk living in a future where rapidly advancing genetic analysis could be used for discrimination and fuel the ever-growing dichotomy between classes. Medical information need not be accessible to individuals based on financial bracket, but government-funded programs to make genetic testing more universal must also acknowledge some degree of personal privacy.

With the added complexity of the unstable nucleotide expansion behind FXS, the relationship between doctor and patient must also be reassessed. If a patient tests positive for the FMR1 premutation, should a doctor encourage her to refrain from reproduction? This is a private decision, but length of the premutation should perhaps factor into an individual's risk tolerance for pregnancy. Older males would benefit from premutation screening in the case of tremor or memory loss due to FXTAS. Should the patient's family members be informed so they too might be checked? By inviting relatives to be tested for the FMR1 mutation, an individual improves the chances for detection and prevention of Fragile-X tremor ataxia syndrome, Fragile-X primary ovarian insufficiency, and Fragile-X Syndrome. Who should be encouraged to get tested for FMR1 mutations in the first place? With testing not conducted in a population-based format, women wishing to conceive, but especially those experiencing fertility or

[3] As well as other similar unstable nucleotide expansion disorders

endocrine dysfunction, should likely be screened at a doctor's discretion. These are only a few of the questions calling for solutions in the coming years. Both science and ethics will continue to answer them and as informed citizens, we too have a role in making tomorrow's decisions in genetic testing. Our choices will define the ways or lack thereof individuals obtain their medical information based on their social status and moral principles. Communicating with each other, we can all build a healthier future.

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