Genetic Screening for Huntington's Disease

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Huntington's Disease (HD) is a rare neurological disease that affects one in 10,000 people[1]. It is a genetic disorder, caused by a mutation in a sequence of human DNA that is known as the HD gene[1]. This mutation is characterized by several trinucleotide repeats in the genetic sequence, which creates a CAG repeated expansion[2,3]. When the mutant gene is expressed, it produces *huntingtin protein aggregates* in the brain[2,3,4]. These aggregates are known to speed up brain cell death and they play a critical role in the progression of the disease[5].

HD is inherited as an autosomal dominant trait. This means that an individual only needs to receive one copy of the HD gene from an affected parent to express the disorder. Therefore, if one parent expresses the disorder, their offspring have a 50% chance of inheriting it. However, studies have also shown that in 3-5% of the cases, there is no phenotypically affected parent involved[1]. This is because of the meiotic instability of the gene, which causes the size of the CAG expansion to increase as it is passed down from one generation to the next. Studies have found that the expression of Huntington's in an individual is correlated with the size of the CAG expansion: the larger it gets, the higher probability that one will express the disorder, so that while it may not be large enough in a parent's genotype to be expressed phenotypically, their offspring's CAG expansion may be long enough for the disorder to surface[6,7]. In fact, both the age of onset and the severity of the disease are associated with the number of CAG repeats. If an individual has below 26 repeats they will not express the disorder. Between 27-35 repeats the gene may or may not be transmitted to the next generation, but the individual will not have the disorder. From 36-39 repeats, the disorder is more likely to be expressed, and above 40 repeats HD will occur[6].

Huntington's disease is associated with progressive motor disturbances, mental and emotional problems, and cognitive deterioration (loss of the ability to think)[7,8]. Factors such as the severity of symptoms, age of onset, and the rate of clinical progression all contribute to highly variable expressions of the disorder. This can be seen even within affected families[1]. Within this variation, two distinct types of Huntington's exist, the more common adult-onset HD and the relatively rare juvenile type. The most likely age for the initial expression of adult-onset HD is between 35-50 years. Symptoms of the juvenile variant of the disease usually begin before the age of 20, typically during childhood or adolescence, and are usually more severe and progress more rapidly[1,7].The preliminary symptoms of adult-onset HD include irritability, depression, small involuntary movements (chorea), and trouble learning or making decisions. As it progresses, the chorea becomes more pronounced. The patient often has problems walking, speaking, and swallowing, and cognitive abilities continue to decline[1,8]. The duration of this terminal disease is usually 10-30 years in adult-onset cases, while early-onset individuals will live for approximately 8 to 10 years after the disease has surfaced[7].

Scientists have recently identified the HD gene with the help of a number of genetic techniques and are now able to test individuals for it. Such tests are associated with many pressing ethical issues and the impact their results may have on both the tested individual and on society must be taken into consideration when discussing how genetic testing should be regulated.

There are several applications of genetic testing, including predictive testing, carrier testing and prenatal diagnosis. Predictive tests screen for the presence of a disease gene in high risk individuals before they have begun to show any symptoms[9].The most widespread application of genetic testing today is neonatal screening, in which blood samples are tested for abnormal or missing gene products. Although this

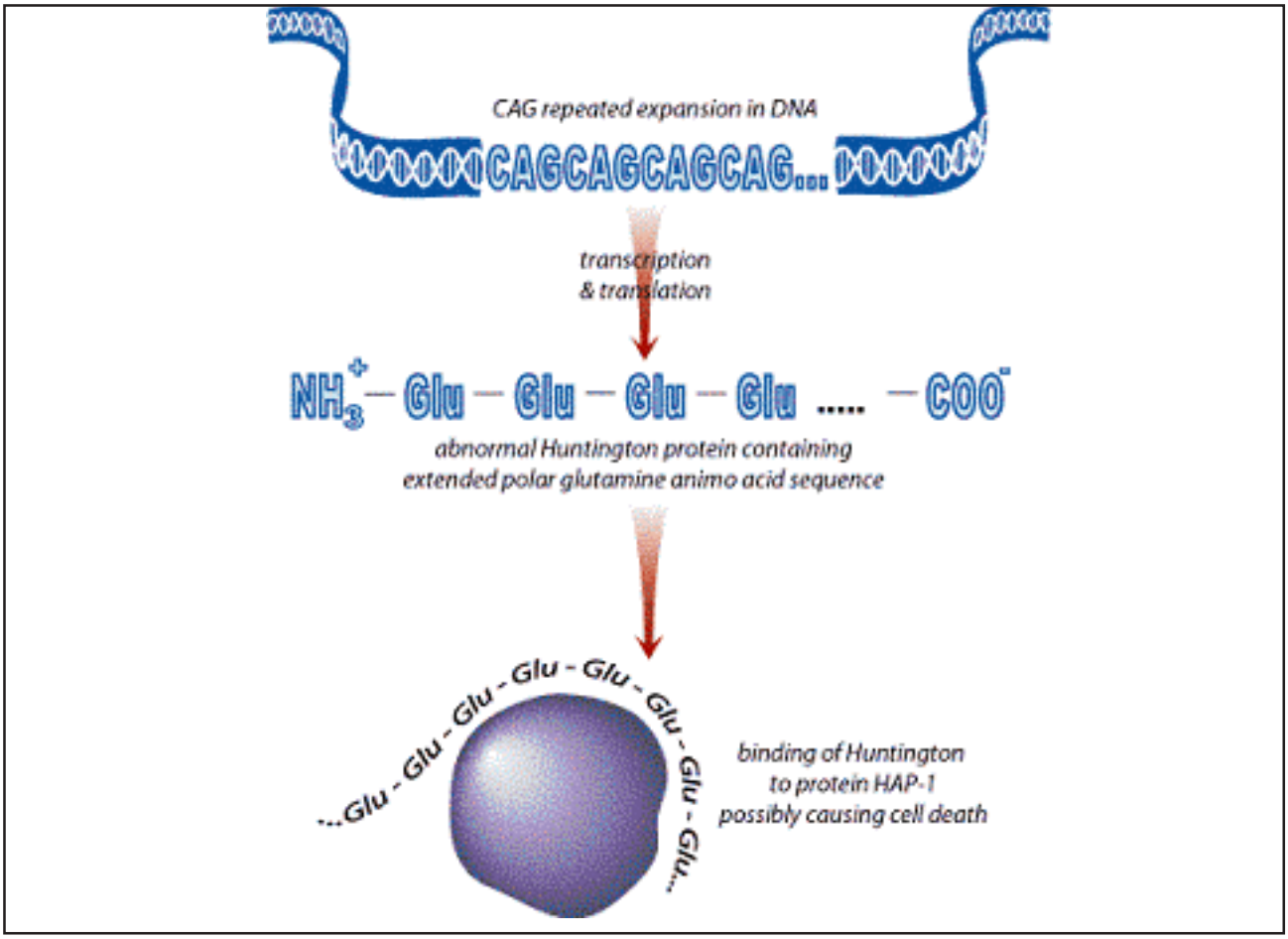

Figure 1. The proposed mechanism for the expression of huntingtin protein aggregates and their possible effect on nerve cells

testing is used for detecting inborn errors of metabolism such as phenylketonuria[9], it could be expanded to screen for the HD gene in infants. Carrier testing is used to identify individuals who might be carrying a genetic disorder (although they may not ever express it), and it is usually used by couples who want to assess the risk of passing it onto their children[10]. Prenatal diagnosis is used to identify genetic disorders in the fetus early on in the pregnancy[9,11]. However, despite the fact that scientists can detect the mutation for HD, the test results only dictate that the individual will eventually express the disorder[9]. It does not tell them when they will start showing the symptoms, what the exact pattern of progression will be, or how it will affect the individuals tested and impact those around them[12].

There are numerous benefits for using genetic testing to screen for the HD gene. Individuals in high-risk families live with troubling uncertainties regarding their own future and the future of their children. Results from tests can provide relief and allow people to make informed decisions[13]. For example, negative test results may provide a tremendous amount of relief for an individual who may no longer need to prepare for the possibility of being afflicted by the disease or passing it on as a carrier. Positive test results can allow the person to prepare for the onset of symptoms and make sound health management decisions, and couples can plan the possibilities of having children accordingly[13]. In such cases, couples may choose to refrain from having children because they don't want to pass the disorder onto their child nor do they want to raise a child that has the disorder[14]. In cases where the couple still wants to have children, prenatal screening would allow them to screen their pregnancies for fetuses that do not carry the HD gene[11,14]. Another option would be to use pre-implantation genetic diagnosis to select for embryos that do not carry the gene. This technique

uses in vitro fertilization to create embryos from the mother's eggs and the father's sperm and then tests them for genetic abnormalities[9]. The analysis results can then be used to select geneticcally healthy embryos for implantation into the mother. Unlike prenatal testing, this method circumvents the moral dilemma a couple may face when deciding whether or not to terminate a pregnancy[14].

In spite of its advantages, genetic testing and selective reproduction bring up numerous ethical questions, not to mention the controversial issue of eugenics. Historically, eugenics has been defined as selectively choosing biological traits that improve the inborn qualities of human beings for future generations[10]. Gillott claims that a major goal of genetic testing is not to improve future generations, but to avoid the birth of a child with a disabling genetic condition. Furthermore, Hoedemakers points out that producing offspring that are free of genetic disorders has potential benefits for the community. These include a reduction of the incidence of the disease and the general improvement of public health[13], which would in turn result in a reduction of health care costs. On the other hand, Hoedemakers also discusses the potential harm that could come from such medical practices. At the community level, it could include discrimination against population groups in which genetic disease is more prevalent, social pressure to participate in genetic screening programs, or a greater tendency to hold parents responsible for the suffering of their offspring[13]. Moreover, there is the issue of screening out individuals who on the one hand may have a genetic disease, but on the other hand may make great contributions to society. As Koch points out, "to eliminate the person who might develop these conditions in midlife or later would be to deprive society at large of people like physicist Stephen Hawking (ALS), former US president Ronald Reagan (Alzheimer's), or singer Woody Guthrie (Huntington's)"[15]. Other ethical questions raised when discussing genetic testing include the termination of fetuses and associated morality of the practice. For the purposes of this paper, the ethical issues of abortion are not discussed.

Aside from its benefits, there are also many possible negative consequences to genetic screening. It may have a considerable psychological impact on the individual being tested[11]. The most immediate effect is the emotion aroused in patients upon receiving their test results. Many individuals who get tested have already seen close relatives fall victim of the disorder, and if their test results are positive, the patient may lapse into depression and despair[11]. According to Koch, there is an increased risk of suicide among those who test positive for HD[15]. Prenatal screening entails a high risk of physical damage to the fetus, which means that healthy fetuses can be damaged or even killed[13]. However, in studies for prenatal testing of Down's syndrome, women who were questioned about these risks stated that test procedure-related miscarriage is justified when weighed against the possibility of having a child with the disorder[15]. Positive test results for children tested can include greater parental concern with negative psychological effects on the child. It can create stress for both parent and child because they are now aware of the fact that they will have to deal with a severe late onset disease in the future, and there can be psychological damage for the child as a result of self-stigmatism, or stigmatism by other family members[13].

Because HD is a familial disease, the results of one individual can have a strong impact on the family and also make significant inferences about the genetic makeup of other family members [12,16,17]. Genetic diagnosis notwithstanding, the emotional impact resulting from tests can produce a definite shift in family dynamics. For example, a patient identified as a carrier of the disease may feel anger, while those who have escaped it may feel overwhelmed with guilt for avoiding a disease that will so harshly affect a close relative[11]. Also, if someone tests positive for the disorder, when there was no previous confirmed diagnosis in the parents, the issue of pressuring other family members to get tested becomes a problem.

According to Kent, even these considerations are still too simplistic. He points out that due to different personalities and dynamics, the issue of the impact of genetic testing among family members can be far more complex:

> *The ideal world notion of important information being sensitively and carefully disclosed in a caring and supportive way does not always hold true. In some situations*

the giving or withholding of information and the manner in which it is done can be an exercise in power or reflection of other aspects of the family context[12].

There are those who hold strong beliefs that for families in which there is a high risk of genetic disease, test results should not be seen as the private property of the tested individual. Rather it should be seen as family information shared by all those to whom it applies[12]. Therefore, regardless of the confidentiality of the test results, physicians might feel obligated to override the patient's wishes and inform other family members of that individual's carrier status in the pursuit of the greater good[12]. However, the disclosure of the results can also infringe on a person's right "not to know"[13]. If an individual has a parent, sibling, or child that has been tested for HD, and they do not want to find out about their own risk, then it could be seen as morally wrong to try to disclose such information.

There is also the issue of privacy and genetic discrimination when considering the use of genetic testing[18]. If an individual is tested for a genetic disease and their test results are accessed by potential employers or insurers, an individual could suffer a number of economic deprivations[9,17,18]. Employers who may wish to know if their employees are susceptible to disorders that can impair work performance may discriminate against individual who test positive for HD, witholding job opportunities from them. Insurance companies could deny HD carriers coverage or use the genetic test results to calculate increased costs of their insurance[13]. Currently in the US "no federal legislation has been passed relating to genetic discrimination in individual insurance coverage or to genetic discrimination in the workplace"[19]. In fact, according to the report done by the Human Genome Project:

States have a patchwork of genetic-information nondiscrimination laws, none of them comprehensive. Existing state laws differ in coverage, protections afforded, and enforcement schemes. Some of the first state laws enacted to address this issue prohibited discrimination against individuals with specific genetic traits or disorders. Other state laws regulate both the use of genetic testing in employment decisions and the disclosure of genetic test results. These state laws generally prohibit employers from requiring workers and applicants to undergo genetic testing as a condition of employment. Some states permit genetic testing when it is requested by the worker or applicant for the purpose of investigating a compensation claim or determining the worker's susceptibility to potentially toxic chemicals in the workplace. These statutes often require the worker to provide informed written consent for such testing, contain specific restrictions governing disclosure, and prevent the employer from taking adverse action against the employee[19].

These problematic issues could change quite dramatically in the future, as research on the active treatment of Huntington's disease is currently quite promising. A major area being explored is in the effectiveness of using cystamine for preventing the accumulation of huntingtin protein aggregates in brain tissue[5,20]. Scientists have found that cystamine boosts neuroprotective proteins (proteins that remove huntingtin from the brain cells) and therefore prevents the associated cellular death in brain tissue[5]. Other research areas are investigating the biochemical pathways involved with the expression of the HD gene[2,21]. Should scientists develop an effective treatment against HD, it could quite possibly require the treatment to begin before the symptoms occur[5]. Therefore, genetic screening could become an essential tool to allow individuals, who are carriers of the gene, to live complete lives without the disease condition of HD and also relieve the issue of their children being adversely affected. Although genetic screening is currently quite controversial, it may prove to be yet another enormous advance in human medicine, used not only for uncovering genetic disorders but also as an aid for pinpointing treatable illnesses in individuals before they start.

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