A Darwinian approach to Huntington's disease: Subtle health benefits of a neurological disorder

Benjamin R. Eskenazi, Noah S. Wilson-Rich, Philip T. Starks *

Department of Biology, Tufts University, Medford, MA 02155, USA

Summary Huntington's disease (HD) is a neurodegenerative disorder that, unlike most autosomal dominant disorders, is not being selected against. One explanation for the maintenance of the mutant HD allele is that it is transparent to natural selection because disease symptoms typically occur subsequent to an individual's peak reproductive years. While true, this observation does not explain the population-level increase in HD. The increase in HD is at least partly the result of enhanced fitness: HD+ individuals have more offspring than unaffected relatives. This phenomenon has previously been explained as the result of elevated promiscuity of HD+ individuals. For this to be true, disease symptoms must be expressed during the otherwise asymptomatic peak reproductive years and promiscuity must increase offspring production; however, neither prediction is supported by data. Instead, new data suggest that the mutant HD allele bestows health benefits on its carriers. HD+ individuals show elevated levels of the tumor suppressor protein p53 and experience significantly less cancer than unaffected siblings. We hypothesize that the mutant HD allele elevates carriers' immune activity and thus HD+ individuals are, on average, healthier than HD− individuals during reproductive years. As health and reproductive output are positively related, data suggest a counterintuitive relationship: health benefits may lead to an increased prevalence of Huntington's disease.
© 2007 Elsevier Ltd. All rights reserved.

Background

Huntington's disease (HD) is a debilitating neurodegenerative disorder caused by an abnormal allele on chromosome four. The symptoms of the disease include physical and psychological changes, beginning with the degeneration of the neostriatum, a vital part of the brain with roles in both motor control and cognitive processes [1,2]. This eventually leads to the main diagnostic symptoms of motor function deficit, psychological problems, and cognitive breakdown [3–6]. HD is a late onset disease with an average clinical manifestation at age 41.5 years (SD, ±12 years), an age range of 8–83 years and an average survival of 20 years post diagnosis [7,8]. Disease progression is well defined and often divided into stages of physiological and functional deterioration for classification purposes [7].

The initial study of HD began in the 19th century with the work of George Huntington, but only recently have scientists been able to understand the molecular basis of the disease. The gene associated with HD, IT-15 on chromosome four, is composed of two adjacent trinucleotide repeats of

* Corresponding author. Tel.: +1 617 627 4849; fax: +1 617 627 3805.
  E-mail address: philip.starks@tufts.edu (P.T. Starks).

either CAG or CCG. δ2642, an IT-15 polymorphism, may also contain a GAG trinucleotide repeat and may be attributed to HD causality [9]. A wealth of evidence indicates a strong association between CAG repeat length and the expression of HD, while the association between abnormal CCG and GAG repeats and the disease is less certain and frequently debated [10,11].

HD is classified as a polymorphic triplet disease because its primary mutation at the CAG microsatellite of IT-15, exon 1, is characterized by a marked expansion in length over normal alleles. There is an inverse correlation between the number of repeats and the age of onset of HD [12]. Although HD+ individuals are expected to faithfully pass their allele to affected offspring, studies have found that many HD+ children have longer CAG tracts than do their parents [13], primarily because the CAG allele is transmitted unstably between generations with a tendency towards expansion [14]. There is a sex bias in HD allele stability, with paternal transmission prone to expansion, while maternal transmission tends to be more faithful. Indeed, one study reports that 31% of the gametes of HD+ males contained expanded CAG alleles [15].

A system of disease classification, proposed by the Huntington disease Genetic Testing Working Group [16], allows for the prediction of a patient's phenotype corresponding to microsatellite repeat length. Individuals with 26 or less CAG repeats are considered normal. Those with 27—35 repeats will not be expected to exhibit the disease phenotype, but their allele may be mutable. Individuals with 36—39 repeats fall into the intermediate range and may display the HD phenotype and reduced allele penetrance. Those with 40 or more repeats are HD+ [16]. The disease has been increasing in frequency from an ancestral state of 7—12 repeats in a variety of primate species (no less than eight repeats have been documented in humans), and is predicted to continue spreading in the future [17]. Yet, as an autosomal dominant disorder, HD should generally be selected against [18].

HD, natural selection, and fitness

One obvious reason for the maintenance of Huntington's disease is its late onset, which affords carriers the opportunity to reproduce before the disease unmasks itself. In addition, the tendency towards CAG expansion over contraction has led to numerous events of spontaneous HD in previously unaffected family lines. An estimated 3% of HD cases arise via this route [19], though regional studies have shown that the potential mutation

rate may be as great as 8% of new cases [20]. HD allele frequency and distribution is predicted to be an ongoing process of gradual expansion and ever-increasing disease incidence [17]. Spontaneous mutation is not sufficient to explain all new cases. HD incidence may be increasing because HD+ individuals bearing more offspring than nonaffected individuals.

Several studies comparing HD+ individuals to unaffected siblings indicate that affected individuals have between 1.14 and 1.34 children for every one that an unaffected sibling has [21—25]. Accordingly, it appears that there may be a fitness payoff associated with carrying the HD+ allele that is positively promoted via natural selection. This observation is not novel, and a mechanism leading to heightened reproductive output has previously been suggested. This elevated fertility has been attributed to heightened promiscuity of HD+ individuals as a result of the psychological manifestations of the disease [26]. A current challenge is determining why HD+ individuals have more children than do the HD— population.

HD and promiscuity

A hypothesis for explaining the fertility gap between affected and unaffected individuals posits that promiscuity is the culprit. Dewhurst and colleagues [26] proposed that hypersexuality, combined with a lack of inhibition and a surplus of irresponsible behavior, was leading to increased offspring production. Others latched onto this idea, and the hypothesis evolved into the notion that the lack of motor control and psychological deterioration that accompanies the onset of Huntington's translates into a lack of sexual control and a pattern of indiscriminant mating [27,28]. To the best of our knowledge, this hypothesis has never been critically tested, and the observations on which this claim rests remain unsupported.

The increased promiscuity hypothesis makes at least two critical predictions: first, the HD+ driven behavioral change should occur during peak reproductive years and, as such, should occur during the generally asymptomatic period. This prediction fails because the cognitive and psychological deterioration that may lead to promiscuity is not a function of the mutant allele, but of disease progression and the associated neuronal breakdown. Although deteriorations of the basal ganglia — one of the first signs of cognitive decline — have been noted in HD+ individuals prior to clinical presentation [29], there are no studies linking sexual promiscuity to degeneration in this area of the

brain. While HD+ individuals do frequently lose the ability to discriminate between a good and bad choice, this change in behavior does not manifest until other aspects of the disease are present. Studies show that the risky behavior observed in these individuals is linked to the personality changes that take place *after* the onset of the disease, not during the asymptomatic period [30], during which time executive functions do not appear to be significantly affected [31]. Because the disease is typically expressed later in life, these behavioral changes are not likely to impact reproduction.

Second, increased promiscuity must lead to increased offspring production. This prediction fails because promiscuity does not necessarily increase fitness in mammals [32]. In humans, the use of contraception, the absence of a temporal breeding season, and the limited reproductive period of females provide even more challenges to conceive during a copulatory event than other mammal species. Although additional evidence may be needed to further support the theory that promiscuity and fitness are similarly discordant in humans, the long-held belief that HD+ individuals have a higher fitness than HD− individuals due to the expression of 'deviant' promiscuous behavior appears to be without convincing support.

HD and health

Here, we present an alternative hypothesis: we propose that HD+ is associated with augmented health in carriers, and that this health benefit results in higher offspring production. This hypothesis makes at least two critical predictions.

First, the HD+ individuals must be healthier than HD− controls during peak reproductive years. Doctors working in a Huntington's ward in Copenhagen noticed that their patients rarely died from cancer. Using data in the Danish Huntington Disease Registry (University of Copenhagen), these researchers demonstrated that the rate of cancer in HD+ individuals compared to HD− relatives was approximately 0.6 for all cancers except those of the buccal cavity and pharynx [33].

Second, better health must lead to elevated offspring production. The health and general well-being of an individual are accurate measures of fitness, and healthy people tend to have more children on average compared to less healthy individuals, including siblings [34—36]. Health is also positively associated with social status, which in-turn increases an individual's attractiveness and reproductive success [37]. If cancer rates increase

immune surveillance and vigor, and these correlate with overall health, then the elevated fitness of HD+ individuals can be explained by health benefits of possessing the mutant allele.

HD, p53 and htt

For the elevated health hypothesis to be supported there must be a mechanistic link driving the relationship. We suggest that p53 is a factor in this relationship. The substance p53 is a tumor suppressor protein whose main role in the body is the maintenance of normal cell growth and disruption of the cell cycle in damaged cells [41]. In recent years, research into cancer pathogenesis has concluded that this protein is one of the most important for the regulation of normal cell growth and the prevention of unchecked cellular division. In-depth study of its action has shown that p53 plays essential roles in DNA repair, transcription, genome stability, and apoptosis [42,43]. p53 upregulation has been observed in virally infected cells, and is critical in the antiviral immune response of the body [44]. Normal levels of the protein are implicated in the production of regular, functional T-cells during pathogen-induced immune response [45]. As such, p53 appears to correlate with an individual's ability to mount an effective immune response to cancer and infection, and may be causal in that relationship [46].

How is the HD+ allele related to the production of p53? Although the disease is well studied, the various functions of the protein Huntingtin (htt) are still not clear. htt contains the polyglutamine expansion believed to be causative for HD symptoms and is translated from the IT-15 (exon 1) on chromosome four (i.e., the 'mutant allele'). Each extra CAG trinucleotide in the mutant allele codes for an additional glutamine on the N terminus of htt. It is postulated that the pathology of HD relies heavily on the action of this polyglutamine tail after it is separated from the main protein [47]. Although the pathogenesis of the mutant protein is not well understood, many htt interacting proteins have been identified which may, in-turn, induce the neurodegeneration commonly seen in HD [48]. Of those identified, some are thought to induce apoptosis [49]. Rigamonti and colleagues [50] suggest that the wild type htt protein protects striatal cells (located in the basal ganglia and midbrain which control fine and gross motor skills) from apoptotic stimuli. Others have observed that the mutant protein aggregates with multiple intracellular proteins − including

p53 — *in vitro* and in transgenic mice, forming aggregates in the nucleus of the cell [51—53]. The aggregation between htt and p53 in affected individuals may alter p53-induced transcription within the cell that leads to apoptosis. The transcriptional alterations do not appear to result from an inability to break down p53 after production, and it is speculated that the htt—p53 aggregate masks cellular recognition of the pro-apoptotic protein [54,55]. Thus, the normal rate of cellular apoptosis is accelerated in the striatal neurons of HD+ individuals.

However, since htt is expressed in all cells of the body [56], the pro-immune properties associated with the mutant allele would be expected to function above the basal level of unaffected individuals throughout the entire body. Increased rates of apoptosis may protect the body from neoplastic lesions, providing a positive selective advantage to those with htt. Polyglutamine expansion may interfere with normal htt to regulate growth factor receptor-mediated cellular signaling and biological functions thereby leading to inhibition of cell proliferation, mediated by both epidermal growth factor (EFG) and nerve growth factor (NGF) receptors [57]. In addition, the overproduction of p53 due to the masking effects of htt may compensate for much of the degradation of this protein that is an essential component of the pathogenesis of many viral-induced and genetically mutated neoplasms. These relationships provide mechanistic explanations for the decreased cancer rates observed in HD+, relative to HD−, individuals.

A natural question follows: if elevated p53 is beneficial, why do not all individuals have an increased basal level of p53 in their cells? While elevated p53 seems to suppress cancer growth in HD+ individuals, even for those who smoked for many years prior to their death [37], HD+ individuals suffer a significantly higher incidence of Type II diabetes and Alzheimer's — two diseases with strong autoimmune influence — compared to the general population [58,59]. An increased rate of autoimmune disease is precisely what is predicted in individuals with elevated p53 if the 'normal' level of p53 is optimal. In addition, the beneficial effects of the aberrant polyglutamine tail of htt are constrained to an optimal range of repeat lengths due to the inverse relationship with the age of disease onset. Individuals without a sufficient repeat length will not benefit immunologically, while those with too many repeats will display an early onset Huntington's phenotype that will compress their asymptomatic period and harm their chances of reproductive success.

Future directions

We hypothesize that the HD+ allele provides carriers with a fitness advantage by making them healthier during their reproductive lifespan. Currently, our main evidence is the elevated levels of p53 that occur in HD+ individuals, which may be causal in the significant reduction of cancer relative to the unaffected population [37]. Since cancer is a disease associated with aging, most deaths related to the disease occur in older individuals whose age was a factor in their loss of regulatory function [60]. Although the reduced death rate in HD+ individuals from cancer may explain some increased fertility, the number of cancer deaths prevented by p53 is not likely to be the sole contributing factor.

We believe that the upregulation of p53 indicates other immune system enhancements. This view is supported by the medical literature (see Refs. [45,46]). However, because the notion that an autosomal dominant disease such as Huntington's provides a fitness advantage to carriers is relatively novel, few studies exist that demonstrate a lower incidence of disease in pre-onset HD+ individuals. As such, before our hypothesis can be strongly supported, additional studies must document both the health advantage of HD+ individuals and that an elevated level of p53 is a general correlate for increased immune vigilance and overall health.

While an elevated level of p53 in HD+ individuals is not debated [61,62], the mechanism driving this observation is less clear. Elevated p53 levels could result from an inability to break down p53 after production [54,65]. Alternatively, Sorensen and colleagues [33] propose that the defective protein htt induces or increases the rate of cell apoptosis in certain cells, and thus p53 levels would increase with the increase in apoptosis. An additional hypothesis is that the CAG expansion is recognized by immune factors in the same way they might recognize microbial DNA inserted into the genome [64]. Under this hypothesis, immune activation is produced as an alarm response to a perceived addition of foreign DNA to the genome. Still other researchers believe that htt interacts with another protein, termed Huntingtin interacting protein 1 (HIP-1) in order to induce its apoptotic effect [65]. Clearly, further research into the molecular mechanism of HD pathogenesis is needed.

Finally, it is reasonable to hypothesize that there is an optimal number of CAG repeats for a heterozygous HD+ individual to possess that will provide the desirable health and fitness benefits

without producing untimely early onset of the disease. Individuals with an excessive repeat number (e.g., 46 or above) show early onset of disease and those with relatively few repeats (e.g., 30 and below) may not reap the same health benefit as those with a moderate number of repeats. If this is the case, then CAG repeat expansions will be selected for over time, with a proliferation at the lower end of the repeat range and regulation and selection against the higher end. This prediction has been previously demonstrated in a model of genetic fitness in HD using data on offspring production [66].

Conclusions

Of course, not all diseases need have an adaptive explanation [67]. For example, the genetic basis of late onset diseases may be immune to natural selection [18]. Because symptoms usually express themselves late in life, the genes that cause Huntington's disease are often considered transparent to natural selection — that is, sufferers typically have progressed through their reproductive years prior to onset of disease symptoms. HD is not so easily explained, however, because HD+ individuals have a higher fertility than do both HD− siblings and the HD− population [4].

Our review of the literature indicates that HD+ individuals do indeed have an elevated fertility relative to HD− individuals, and that it is highly unlikely to be attributed to promiscuity — although a direct study on human promiscuity and fitness has yet to be done. Instead, our research indicates that HD+ individuals produce higher levels of cancer suppressing p53, and reap the health benefits associated with a more vigilant immune system. HD+ individuals also suffer from the negative impacts of heightened immune function, as they are more likely than HD− individuals to suffer from autoimmune diseases.

In this light, Huntington's disease may be considered an example of antagonistic pleiotropy. Some genes may be selected for beneficial effects early in life and yet have unselected deleterious effects with age, thereby contributing directly to senescence [68]. For example, the apoE e2 allele is protective against Alzheimer's disease but predisposes to type III hyperlipidemia [69]. Thus, it is possible that certain mutations predisposing to late onset diseases (or generally late onset diseases) may confer certain protective effects.

In recent years, the fields of evolutionary biology and animal behavior have ventured into the realm of modern medicine [18,71−73]. This marriage has shed light on phenomena such as fever and morning sickness (see [74]). So great is the potential benefit of extending biology's unifying principle to medicine that researchers have been calling to add courses in evolution to medical school curricula [75]. In total, our Darwinian approach to Huntington's disease provides a logical framework for examining the selective maintenance — and perhaps even the spread — of the trait, and also provides a direction from which to explore the mechanistic influence on the elevated fertility levels of HD+ individuals.

Acknowledgements

References

[1] Caramins M, Halliday G, McCusker E, Trent RJ. Genetically confirmed clinical Huntington's disease with no observable cell loss. J Neurol Neurosur Psychiat 2003;74: 968−70.

[2] Calabresi P, De Murtas M, Bernardi G. The neostriatum beyond the motor function: experimental and clinical evidence. Neuroscience 1997;78(1):39−60.

[3] Huber SJ, Paulson GW. Memory impairment associated with progression of Huntington's disease. Cortex 1987;23: 275−83.

[4] Harper PS, editor. Huntington's disease. Philadelphia (PA): W.B. Saunders; 1996.

[5] Watt DC, Seller A. A clinico-genetic study of psychiatric disorder in Huntington's chorea. Psychol Med 1993 (Suppl. 23):1−46.

[6] Lovestone S, Hodgson S, Sham P, Differ AM, Levy R. Familial psychiatric presentation of Huntington's disease. J Med Genet 1996;33:128−31.

[7] Mahant N, McCusker EA, Byth K, Graham S, Huntington Study Group. Huntington's disease: clinical correlates of disability and progression. Neurology 2003;61: 1085−92.

[8] Paulsen JS, Hoth KF, Nehl C, Stierman L. Critical periods of suicide risk in Huntington's disease. Am J Psychol 2005;162(4):725−31.

[9] Almqvist E, Spence N, Nichol K, et al. Ancestral differences in the distribution of the delta 2642 glutamic acid polymorphism is associated with varying CAG repeat lengths on normal chromosomes: insights into the genetic evolution of Huntington disease. Hum Mol Genet 1995;4:207−14.

[10] Almqvist E, Elterman D, MacLeod P, Hayden M. High incidence rate and absent family histories in one quarter of patients newly diagnosed with Huntington disease in British Columbia. Clin Genet 2001;60:198−205.

[11] Yapijakis C, Vassilopoulos D, Tzagournisakis M, et al. Linkage disequilibrium between the expanded (CAG)$_n$ repeat and an allele of the adjacent (CCG)$_n$ repeat in Huntington's disease patients of Greek origin. J Hum Genet 1995;3:228—34.

[12] Brinkman RR, Mezei MM, Theilmann J, Almqvist E, Hayden MR. The likelihood of being affected with Huntington disease by a particular age, for a specific CAG size. Am J Hum Genet 1997;60:1202—10.

[13] Trottier Y, Biancalana V, Mandel JL. Instability of CAG repeats in Huntington's disease: relation to parental transmission and age of onset. J Med Genet 1994;31: 377—82.

[14] Leeflang EP, Tavare S, Marjoram P, et al. Analysis of germline mutation spectra at the Huntington's disease locus supports a mitotic mutation mechanism. Hum Mol Genet 1999;8:173—83.

[15] De Rooij KE, De Koning Gans PA, Skraastad MI, et al. Dynamic mutation in Dutch Huntington's disease patients: increased paternal repeat instability extending to within the normal size range. J Med Genet 1993;30: 996—1002.

[16] Huntington Disease Genetic Testing Working Group. Laboratory guidelines for Huntington disease genetic testing. Am J Hum Genet 1998;62(5):1243—7.

[17] Rubinsztein DC, Amos W, Leggo J, et al. Mutational bias provides a model for the evolution of Huntington's disease and predicts a general increase in disease prevalence. Nat Genet 1994;7:525—30.

[18] Nesse RM, Williams GC. Why we get sick: the new science of Darwinian medicine. New York: Times Books; 1994.

[19] Goldberg YP, Kremer B, Andrew SE, et al. Molecular analysis of new mutations causing Huntington disease: intermediate alleles and sex of origin effects. Nat Genet 1993;5:173—9.

[20] Ramos-Arroyo MA, Moreno S, Valiente A. Incidence and mutation rates of Huntington's disease in Spain: experience of 9 years of direct genetic testing. J Neurol Neurosur Psychiat 2005;76(3):337—42.

[21] Marx RN. Huntington's chorea in Minnesota. Adv Neurol 1973;1:237—43.

[22] Shokeir MH. Investigation on Huntington's disease in the Canadian Prairies. II. Fecundity and fitness. Clin Genet 1975;7:349—53.

[23] Stevens DL. Huntington's chorea: a demographic, genetic, and clinical study. MD Thesis, University of London; 1976.

[24] Walker DA, Harper PS, Newcombe RG, Davies K. Huntington's chorea in South Wales: mutation, fertility, and genetic fitness. J Med Genet 1983;20:12—7.

[25] Pridmore SA, Adams GC. The fertility of HD— affected individuals in Tasmania. Aust NZ J Psychiat 1991;25: 262—4.

[26] Dewhurst K, Oliver JE, McKnight AL. Socio-psychiatric consequences of Huntington's disease. Brit J Psychiat 1970;116:255—8.

[27] Postrach F. Juvenile Huntington chorea with persistent sexual deviance: a case report. Psychiat Neurol Med Psychol 1989;41:746—50.

[28] Rich SS, Ovsiew F. Leuprolide acetate for exhibitionism in Huntington's disease. Movement Disord 1994;9:353—7.

[29] Lawrence AD, Hodges JR, Rosser AE, et al. Evidence for specific cognitive deficits in preclinical Huntington's disease. Brain 1998;121(7):1329—41.

[30] Dawson S, Kristjanson LJ, Toye CM, Flett P. Living with Huntington's disease: need for supportive care. Nurs Health Sci 2004;6:123—30.

[31] Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R. Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation. J Neurol 2004;251:935—42.

[32] Wolff JO, Macdonald DW. Promiscuous females protect their offspring. Trends Ecol Evol 2004;19:128—34.

[33] Sorensen SA, Fenger K, Olsen JH. Significantly lower incidence of cancer among patients with Huntington disease: an apoptotic effect of an expanded polyglutamine tract? Cancer 1999;86:1342—6.

[34] Lopreato J, Yu M. Human fertility and fitness optimization. Ethol Sociobiol 1988;9:269—89.

[35] Fananas L, Bertranpetit J. Reproductive rates in families of schizophrenic patients in a case-control study. Acta Psychiat Scand 1995;91:202—4.

[36] McGrath JJ, Hearle J, Jenner L, Plant K, Drummond A, Barkla JM. The fertility and fecundity of patients with psychoses. Acta Psychiat Scand 1999;99:441—6.

[37] Ellis LE, editor. Reproductive and interpersonal aspects of dominance and status. Social stratification and socioeconomic inequality 1994;2:260.

[41] De Laurenzi V, Melino G. Evolution of functions within the p53/p63/p73 family. Ann NY Acad Sci 2000;926:90—100.

[42] Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997;88:323—31.

[43] Choisy-Rossi C, Reisdorf P, Yonish-Rouach E. Mechanisms of p53-induced apoptosis: in search of genes which are regulated during p53-mediated cell death. Toxicol Lett 1998;102—103:491—6.

[44] Takaoka A, Hayakawa S, Yanai H, et al. Integration of interferon-alpha/beta signalling to p53 responses in tumour suppression and antiviral defence. Nature 2003;424: 516—23.

[45] Baek KH, Shin HJ, Yoo JK, et al. p53 deficiency and defective mitotic checkpoint in proliferating T lymphocytes increase chromosomal instability through aberrant exit from mitotic arrest. J Leukocyte Biol 2003;73: 850—61.

[46] Lechpammer M, Lukac J, Lechpammer S, Kovacevic D, Loda M, Kusic Z. Humoral immune response to p53 correlates with clinical course in colorectal cancer patients during adjuvant chemotherapy. Int J Colorectal Dis 2004;19: 114—20.

[47] Leavitt BR, Wellington CL, Hayden MR. Recent insights into the molecular pathogenesis of Huntington disease. Semin Neurol 1999;19:385—95.

[48] Li SH, Li XJ. Huntingtin—protein interactions and the pathogenesis of Huntington's disease. Trends Genet 2004;20:146—54.

[49] Harjes P, Wanker EE. The hunt for Huntingtin function: interaction partners tell many different stories. Trends Biochem Sci 2003;28:425—33.

[50] Rigamonti D, Bauer JH, De-Fraja C, et al. Wild-type Huntingtin protects from apoptosis upstream of caspase-3. J Neurosci 2000;20:3705—13.

[51] Davies SW, Turmaine M, Cozens BA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 1997;90:537—48.

[52] DiFiglia M, Sapp E, Chase KO, et al. Aggregation of Huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 1997;277:1990—3.

[53] Becher MW, Kotzuk JA, Sharp AH, et al. Intranuclear neuronal inclusions in Huntington's disease and dentatorubral and pallidoluysian atrophy — correlation between the density of inclusions and IT-15 CAG triplet repeat length. Neurobiol Dis 1998;4:387—97.

[54] Jana NR, Zemskov EA, Wang GH, Nukina N. Altered proteasomal function due to the expression of polygluta-mine-expanded truncated N-terminal Huntingtin induces apoptosis by capsase activation through mitochondrial cytochrome c release. Hum Mol Genet 2001;10:1049—59.

[55] Wyttenbach A, Carmichael J, Swartz J, et al. Effects of heat shock, heat shock protein 40 (HDJ-2), and proteasome inhibition on protein aggregation in cellular models of Huntington's disease. Proc Natl Acad Sci USA 2000;97: 2898—903.

[56] Ambrose CM, Duyao MP, Barnes G, et al. Structure and expression of the Huntington's disease gene: evidence against simple inactivation due to an expanded CAG repeat. Somat Cell Mol Gen 1994;20:27—38.

[57] Song C, Perides G, Liu YF. Expression of full-length polyglutamine-expanded Huntingtin disrupts growth factor receptor signaling in rat pheochromocytoma (PC12) cells. J Biol Chem 2002;277(8):6703—7.

[58] Farrer LA. Diabetes mellitus in Huntington disease. Clin Genet 1984;27:62—7.

[59] Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med 2004;82:510—29.

[60] Nakachi K, Eguchi H, Imai K. Can teatime increase one's lifetime? Ageing Res Rev 2003;2:1—10.

[61] Trettel F, Rigamonti D, Hilditch-Maguire P, et al. Dominant phenotypes produced by the HD mutation in STHdh(Q111) striatal cells. Hum Mol Genet 2000;9:2799—809.

[62] Bae B-I, Xu H, Igarashi S, et al. p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. Neuron 2005;47(1):29—41.

[64] Steffan JS, Kazantsev A, Spasic-Boskovic O, et al. The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proc Natl Acad Sci USA 2000;97:6763—8.

[65] Hackam AS, Yassa AS, Singaraja R, et al. Huntingtin interacting protein 1 induces apoptosis via a novel caspase-dependent death effector domain. J Biol Chem 2000;275:41299—308.

[66] Frontali M, Sabbadini G, Novelletto A, et al. Genetic fitness in Huntington's disease and spinocerebellar ataxia 1: a population genetics model for CAG repeat expansions. Ann Hum Genet 1996;60:423—35.

[67] Forbes S. Pregnancy sickness and embryo quality. Trends Ecol Evol 2002;17:115—20.

[68] Weinert BT, Timiras PS. Invited review: theories of aging. J Appl Physiol 2003;95(4):1706—16.

[69] Utermann G, Vogelberg KH, Steinmetz A. Polymorphism of apolipoprotein E.II. Genetics of hyperlipoproteinemia type III. Clin Genet 1979;15(1):37—62.

[71] Ewald PW. Evolution of infectious disease. New York: Oxford University Press; 1994.

[72] Stearns SC, editor. Evolution in health and disease. New York: Oxford University Press; 1999.

[73] Trevathan WR, Smith EO, McKenna JJ. Evolutionary med-icine. Cambridge: Oxford University Press; 1999.

[74] Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. Q Rev Biol 2000;75: 113—48.

[75] Nesse RM, Schiffman JD. Evolutionary biology in the medical school curriculum. Bioscience 2003;53:585—7.