

A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution?

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The incidence of mental disability is 30% higher in males than in females. We have examined entries in the OMIM database that are associated with mental disability and for several other common defects. Our findings indicate that compared with the autosomes, the X chromosome contains a significantly higher number of genes that, when mutated, cause mental impairment. We propose that these genes are involved in the development of cognitive abilities and thus exert a large X-chromosome effect on general intelligence in humans. We discuss these conclusions with regard to the conservation of the vertebrate X-chromosomal linkage group and to human evolution.

According to US census figures from 1890 (Ref. 1), more males than females were mentally disabled. In 1938, Penrose² also noted an excess of males among mentally impaired individuals; these original observations have been confirmed several times^{3,4}. Since 1984, biannual workshops have registered all newly identified X-chromosomal syndromes associated with mental disability⁵. In the last update, 202 such syndromes are listed⁶. At the same time, an unlimited Online Mendelian Inheritance in Man database (OMIM; <http://www.ncbi.nlm.nih.gov/omim/> update January 2001) whole-genome query with the term 'mental retardation' yielded a total of 958 entries. This implies that ~21.1% of all mental disability traits map to the X chromosome, although the new sequence data of the human genome show that only 3.75% of all genes are located on the X chromosome⁷. Hence, the density of genes that, when mutated, interfere with mental performance seems to be nearly sixfold higher on the X chromosome than on the autosomes.

When evaluating the association of mental disability and X-chromosomal genes, two possible sources of bias that would exaggerate the number of genes have to be considered. The first source of bias is that a single gene can be responsible for different

entries in the OMIM database because of imprecise mapping information. Furthermore, some genes have allelic heterogeneity, leading to several different entries. This is most obvious in the case of the X-chromosomal genes *ATRX*, *L1CAM*, *MECP2* and *PLP1*. In our evaluation, we counted the different allelic forms of the same gene only once. The second problem concerns a possible ascertainment bias; owing to the preferential expression of X-linked disorders in hemizygous males, the X chromosome has become an obvious focus for mapping and identifying genes for mental disability.

To avoid the first source of bias, we queried the OMIM database separately for the X chromosome and each autosome, with 'mental retardation' as a search term, but the search was limited to conditions with identified genes solely. In Table 1, the total number of identified genes per chromosome, according to OMIM, is shown together with the number of identified genes that, when mutated, cause mental impairment. Indeed, the frequency of genes affecting mental performance is 3.5 times higher on the X chromosome than on autosomes.

To circumvent an ascertainment bias for X-chromosomal linkage, we performed additional queries with search terms for several other common defect phenotypes: polydactyly, cleft palate, facial dysplasia, skeletal dysplasia and growth retardation. This type of query was not limited to entries with identified genes solely, but to entries where the mode of inheritance is proven (i.e. with an asterisk as a prefix). In Table 2, the results of these queries are shown in comparison with the results of the query with 'mental retardation'. It is evident that there is an X-chromosomal ascertainment bias of common defect phenotypes, which is relatively constant (2.14–2.76 higher for X chromosomal linkage; mean, 2.35). If a correction factor of 2.35 is introduced to eliminate the ascertainment bias for X-chromosomal linkage, mental impairment is still 3.1 times more-frequently associated with X-chromosomal genes than with autosomes (Table 2). Therefore, the higher incidence of X-linked genes associated with mental disability (referred to here as MRX genes) is beyond doubt.

Assuming that these MRX genes are responsible for the development of general intelligence or cognitive abilities ('g' according to Plomin⁸), we can draw several conclusions concerning evolutionary mechanisms.

Human X-chromosomal mental disability genes are evolutionarily conserved

In Table 3, we list non-syndromal MRX genes that, when mutated, lead to mental impairment as the only symptom. We propose that these genes have had a major impact on the rapid development of cognitive abilities during human evolution. As human beings, we are convinced that human evolution must be something special. Therefore, we are very interested to understand these ostensibly human-specific genes.

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Table 1. Number and relative frequency of genes associated with mental retardation^a

Chromosome	Number of genes ^b	Genes associated with mental retardation ^c	Percentage of genes associated with mental retardation ^c
1	658	20	3.04
2	406	8	1.97
3	336	9	2.69
4	258	10	3.88
5	283	6	2.12
6	397	12	3.02
7	308	8	2.60
8	222	7	3.15
9	255	8	3.14
10	230	6	2.61
11	418	8	1.91
12	351	11	3.13
13	109	5	4.59
14	206	8	3.88
15	175	5	2.86
16	251	11	4.38
17	403	9	2.23
18	96	2	2.08
19	438	9	2.05
20	147	7	4.76
21	90	4	4.44
22	146	7	4.79
All autosomes	6182	180	2.91
X	406	41	10.1
Y	23	0	0

^aThe data are based on the Online Mendelian Inheritance in Man (OMIM) database statistics from 28 January 2001.

^bThe total number of mapped and identified genes is given.

^cThe number and relative frequency of genes that, when mutated, lead to a disease including mental disability as a symptom. The relative frequency of such mental retardation genes on the X chromosome was analysed by two-way contingency tables (Statview5.0, SAS-Institute, and SYSTAT9.0, SPSS Inc.). When the X chromosome was compared with the sum of all autosomes, the frequency of genes associated with mental disability was three times higher on the X chromosome (odds ratio, OR = 3.7, Fisher's exact test $P < 0.00001$). An identical result was obtained tabulating all single chromosomes (Pearson $\chi^2 = 73.5$; $df = 22$; $P < 0.00001$), with all the significance coming from the X chromosome. This is evident when comparing with the result of the autosomes only (Pearson $\chi^2 = 14.7$; $df = 21$; $P > 0.8$).

However, as indicated in Table 3, organisms that are very distantly related to humans have orthologs of these MRX genes. In evolutionary terms these MRX genes are conserved. They are engaged in basic cellular mechanisms, such as mRNA stabilization, cytoskeleton organization and signalling cascades. Furthermore, they belong to the X-chromosomal linkage group, which is the most conserved gene assembly in vertebrates^{9,10}. More than 300 million years ago, the mammalian sex chromosomes developed from a pair of chromosomes that was not obviously different from other chromosome pairs¹¹. The special selection process active during evolution and speciation must have forced genes that were fortuitously associated with the X chromosome to develop an extended functional spectrum.

Female mate-choice has shaped the human mind

The observation of an excess of genes responsible for cognitive abilities on the X chromosome is reminiscent of an earlier observation that described an excess of sex- and reproduction-related genes on the human X chromosome¹². This phenomenon has been described as 'the large X-chromosome effect'^{13,14}. We propose a large X-chromosome effect for general cognitive abilities in humans. It is reasonable to define the evolution of enhanced cognitive abilities as a specifically human trait. A large X-chromosome effect influencing the development of a specific character (fertility or cognitive ability) implies that this character is selected for in the species. Even Darwin made a sharp distinction between natural and sexual selection. Sexual selection leads to the development of specific secondary sexual, and mostly male, characteristics (e.g. peacocks' tails or elks' antlers) that increase female preference for the individual as a mate. As such, this male characteristic need not increase the chances of survival of the individual male, but it promotes a higher mating frequency.

In 1930, Fisher¹⁵ reintroduced the discussion on sexual selection. He suggested co-evolution between the development of a male characteristic and the development of female preference for that characteristic. Eventually, this would lead to a run-away process and to the development of exaggerated secondary sexual ornaments in the male. In the systems mentioned above, two different genetic systems are involved: a morphological male trait and a female perception system to appreciate that trait in the male. Lande and Arnold¹⁶ described a model in which the male sexual characteristic and the female mating preference develop jointly in the same genetic system. This model describes the male sexual characteristic not as a morphological trait, but as a specific behavioural trait. In such system, there is positive feedback in both sexes on the same genes responsible for secondary sexual character development. This interaction leads to acceleration of a specific trait development, making it much faster than Fisher's run-away process.

Human evolution and the astoundingly fast development of human brain function have been driven by such a positive feedback process in both sexes on the same genetic system. This is reflected by a threefold increase in brain volume in the past 2.5 million years. But this is not all. Usually, the development of a sexual characteristic is balanced by natural selection. For instance, when peacocks develop tails that are too large, they cannot escape predators. Therefore, regarding human evolution we propose the following model: one of the most important factors contributing to the uniqueness of human evolution is that at some point human females decided to select males according to their advanced cognitive abilities. The same cognitive abilities are selected for in the struggle for survival. In humans, the development of the mating characteristic is augmented by natural selection. This is an ongoing

Table 2. Number and relative frequency of X chromosomal and autosomal OMIM entries obtained when queried with commonly observed defect phenotypes^a

Defect phenotype	Number (and frequency) of defect phenotypes ^b		Percentage X chromosomal loci/percentage autosomal loci ^c
	X chromosome (%)	Autosomes (%)	
Polydactyly	5 (1.21)	35 (0.55)	2.20
Cleft palate	10 (2.34)	56 (0.88)	2.76
Facial dysplasia	7 (1.70)	45 (0.71)	2.39
Skeletal dysplasia	11 (2.67)	76 (1.19)	2.24
Growth retardation	13 (3.16)	94 (1.48)	2.14
Mental retardation	103 (25.0)	222 (3.49)	7.16
Mental retardation and (hypogonadism/ cryptorchidism/ macroorchidism)	17 (4.13)	27 (0.42)	9.83

^aThe data are based on the Online Mendelian Inheritance in Man (OMIM) database statistics from 28 January 2001.

^bThe number and frequency (in parenthesis) of X chromosomal and autosomal OMIM entries obtained when queried with several commonly observed defect phenotypes. The frequency was calculated relative to the total number of X chromosomal ($n = 412$) and autosomal ($n = 6367$) OMIM entries.

^cThe ratio between the relative frequency of X chromosomal defects and the relative frequency of autosomal defects. The search was limited to entries with an asterisk as a prefix (i.e. mode of inheritance is proven).

process with exponential acceleration, which will propel the development of general cognitive abilities in humans into areas we cannot imagine now.

According to this model, general intelligence is a secondary sexual ornament and works as a fitness

indicator. This is in complete accordance with Miller's hypothesis in *The Mating Mind*¹⁷. The human mind has been shaped during evolution by female mate choice. The high frequency of genes responsible for cognitive functions on the X chromosome constitutes a formal proof of Miller's hypothesis.

The brain and testis association

Many mental disability syndromes are associated with decreased fertility. In ten of the X-chromosomal syndromes listed in Table 1, reduced fertility or infertility is an additional symptom. We again performed X-chromosome- and autosome-specific queries of the OMIM database for entries containing both 'mental retardation' and symptoms influencing testis function ('hypogonadism' or 'cryptorchidism' or 'macroorchidism'). Interestingly, we found that entries matching these search criteria are about fourfold more-frequently associated with the X chromosome than with autosomes (Table 2). This observation is of particular interest in the context of the 'brain and testis' association, which describes the expression of certain genes both in brain and testis¹⁸. Indeed, in humans, the highest evolutionary stress is on brain and testis function. Mate choice and fertility competition have led to the same degree of complex genetic networking in the testis as is evident in the brain. We suggest that the X-chromosomal genes involved in the development of cognitive abilities also contribute to increased fertility. It is the male's dilemma that these genes are concentrated on their

Table 3. Summary of cloned genes associated with non-syndromal mental retardation in human

Gene symbol	Gene	Position	Expression	Function	Orthologous EST sequence ^a	Refs ^b
FMR2	Fragile X mental retardation 2	Xq27.3	Neocortex, Purkinje cells, hippocampus, testis, thymus, placenta	Nuclear protein, putative transcription activator	<i>Drosophila melanogaster</i>	23
GDI1	GDP dissociation inhibitor 1	Xq28	Differentiated neuronal cells of the central and peripheral nervous system	Helps to maintain a soluble pool of Rab-GDP, participates in vesicle fusion	<i>Saccharomyces cerevisiae</i>	24
OPHN1	Oligophrenin 1	Xq12	Fetal brain, lung, kidney, placenta	Rho-GTPase activating protein	<i>Onchocerca volvulus</i>	25
PAK3	p21 (CDKN1A)-activated kinase 3	Xq22	Brain, spinal cord, lung, testis	Downstream effector of Rho-GTPases	<i>Saccharomyces cerevisiae</i>	26
RPS6KA3	Ribosomal protein S6 kinase, 90KD, polypeptide 3	Xp22.2	Brain, kidney, pituitary and thyroid gland	MAPK-activated signalling pathway	<i>Danio rerio</i>	27
IL1RAPL1	Interleukin 1 receptor accessory protein-like 1	Xq21	Not known	IL1 signalling during inflammation	<i>Danio rerio</i>	28
TM4SF2	Transmembrane 4 superfamily member 2	Xp11.4	Cerebral cortex, hippocampus, adult heart, brain, liver, kidney, pancreas	Organization of actin-cytoskeleton via β -integrins	<i>Torpedo marmorata</i>	29
ARHGEF6	Rho guanine nucleotide exchange factor 6	Xq26	Ubiquitous	Rho-GTPase activating	<i>Danio rerio</i>	30
RPS6KA6	Ribosomal protein S6 kinase, 90KD, polypeptide 6	Xp21.3-p22.1	Brain, kidney, placenta, pancreas	MAPK-activated signalling pathway	<i>Danio rerio</i>	31

^aThe most distantly related organism from human for which orthologous expressed sequence tag (EST) sequences were identified.

^bFor recent reviews see Refs 32–34.

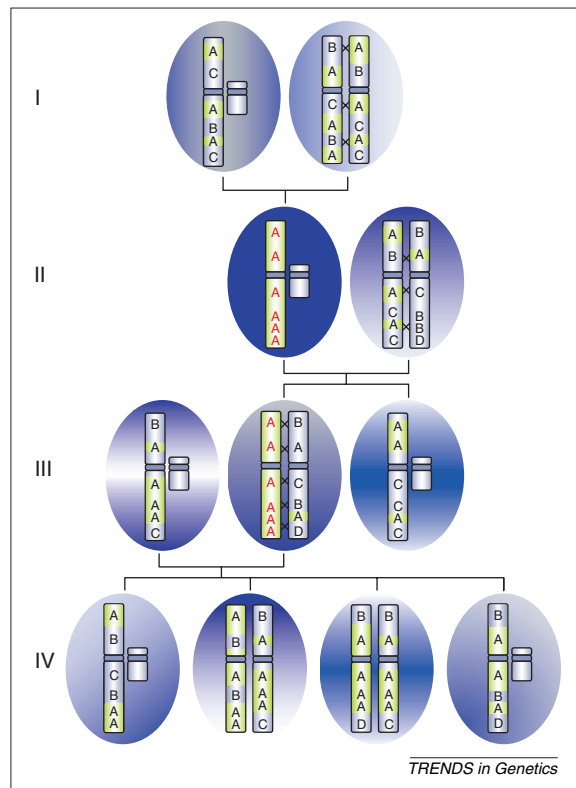


Fig. 1. Inheritance of an X-chromosomal superhaplotype that confers high cognitive abilities. In the model only six genes with several alleles (A, B, C, D) spread over the whole X chromosome are shown. In the mother of the first generation the superhaplotype (red), which is characterized by the presence of A alleles of all six genes on the same X chromosome, is formed by meiotic recombination. This superhaplotype is expressed in the son of the second generation. The son of the second generation transmits the superhaplotype to the daughter of the third generation, where it occurs together with a second normal haplotype X chromosome. In the daughter of the third generation, obligatory meiotic recombination in the short and long arm leads to a breakdown of the superhaplotype. Consequently, the superhaplotype is no longer present in any individual of the fourth generation. Therefore, the formation of a superhaplotype is a random, unique event within a family, but the respective alleles are present within the population.

haploid X chromosome, which makes them exceptionally prone to dysfunction in both the brain and the testis.

The X chromosome in the evolution of vertebrate diversification and human cognitive abilities

Finally, there is a really surprising observation. The X chromosome has been in use as a sex chromosome for nearly 300 million years¹¹, and its gene content has been conserved^{9,10}. However, evolution and speciation genetics revealed that the X chromosome was engaged in a dominant manner in the development of all characteristics that have been sexually selected for in the past 300 million years¹⁹. Therefore, the

most-conserved gene array was engaged in a dominant manner in the morphological and functional diversification of the vertebrates. This is another interpretation of the hypothesis mentioned before: that it is not new genes but recruitment of old genes for new functions that drives vertebrate evolution²⁰.

As outlined above, the X chromosome is enriched for genes responsible for the development of general intelligence in humans. Intelligence test scores have repeatedly shown that males present with a higher variance²¹. They are the highest proportion of low-scoring individuals but also of high-scoring individuals. For being consequent and attributing brain malfunction to the X chromosome, one would attribute also the better functioning of the brain to the X chromosome. The better functioning of a certain X-chromosomal haplotype in an individual is different from selection of specific genes during evolution. In which way the better functioning may be explained?

For cognitive abilities, we consider a quantitative trait loci (QTL) model with additive effects from multiple polymorphic gene loci^{8,22}. Selection has favoured the development of certain X-chromosomal genes that confer high cognitive abilities. These genes can be recombined in a female to give a superhaplotype that confers highest cognitive abilities (Fig. 1). The carrier of this superhaplotype transmits the superhaplotype to his daughters only, who, by obligatory meiotic recombination, break up the superhaplotype. A simple calculation of a model in which the superhaplotype is made up of a certain allele combination of only two genes (with the alleles A1, B1 [gene 1], and A2, B2 [gene 2]) shows that the frequency of the male superhaplotype A1A2 is four times higher than the frequency of the female supergenotype A1A1/A2A2. Because we expect more than 100 general intelligence genes with multiple alleles on the X chromosome, the chance that a male will be carrier of a superhaplotype outnumbers the chance of a female carrier of a supergenotype by several orders of magnitude. Furthermore, the model makes clear that a superhaplotype is formed by chance in a female and is broken up by law in a female two generations later, but benefits a single male in the generation in between.

In this paper, we have outlined only one specific genetic aspect of the evolution of general intelligence in humans. General cognitive ability is a complex trait with both multiple genetic and environmental components⁸. It should be stressed here that a healthy lifestyle of the mother during pregnancy, well-balanced nutrition, and intensive and responsible care by the parents are far more important factors in a child's cognitive ability than its genetic make up.

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References

- Johnson, G.E. (1897) Contribution to the psychology and pedagogy of feeble-minded children. *J. Psycho-Asthenics* 2, 26–32
- Penrose, L.S. (1938) A clinical and genetic study of 1280 cases of mental defects (The Colchester Survey). MCR Special Report 229 (Her Majesty's Stationary Office, London)
- Lehrke, R. (1974) X-linked mental retardation and verbal disabilities. *Birth Defects* 10, 1–7
- Herbst, D.S. and Miller, J.R. (1980) Non-specific X-linked mental retardation. II. The frequency in British Columbia. *Am. J. Med. Genet.* 28, 378–382
- Opitz, J.M. and Sutherland, G.R. (1984) Conference report: International Workshop on the fragile X and X-linked mental retardation. *Am. J. Med. Genet.* 17, 5–94
- Chirazzi, P. et al. (2001) XLMR genes: update 2000. *Eur. J. Hum. Genet.* 9, 71–81
- Venter, J.C. et al. (2001) The sequence of the human genome. *Science* 291, 1304–1351
- Plomin, R. (1999) Genetic and general cognitive ability. *Nature* 402, C25–C29

- 9 The First International Workshop on Comparative Genome Organization (1996) Comparative genome organization of vertebrates. *Mamm. Genome* 7, 717–734
- 10 Lahn, B.T. and Page, D.C. (1999) Four evolutionary strata on the human X chromosome. *Science* 286, 964–967
- 11 Ohno, S. (1967) *Sex Chromosomes and Sex Limited Genes*, Springer-Verlag
- 12 Saifi, G.M. and Chandra, H.S. (1999) An apparent excess of sex- and reproduction-related genes on the human X chromosome. *Proc. R. Soc. London Ser. B* 266, 203–209
- 13 Wu, C.I. and Davis, A.W. (1993) Evolution of postmating reproductive isolation: the composite nature of Haldane's rule and its genetic bases. *Am. Nat.* 142, 187–212
- 14 Turelli, M. and Orr, H.A. (1995) The dominance theory of Haldane's rule. *Genetics* 140, 389–402
- 15 Fisher, R.A. (1930) *The Genetical Theory of Natural Selection*, Clarendon Press
- 16 Lande, R. and Arnold, S.J. (1985) Evolution of mating preference and sexual dimorphism. *J. Theor. Biol.* 117, 651–664
- 17 Miller, G. (2000) *The Mating Mind: How Sexual Choice Shaped the Evolution of Human Nature*, Heinemann/Doubleday
- 18 Baechner, D. *et al.* (1993) Enhanced expression of the murine FMR1 gene during germ cell proliferation suggests a special function in both the male and the female gonad. *Hum. Mol. Genet.* 2, 2043–2050
- 19 Coyne, J.A. (1992) Genetics and speciation. *Nature* 355, 511–515
- 20 Duboule, D. and Wilkins, A.S. (1998) The evolution of 'bricolage'. *Trends Genet.* 14, 54–59
- 21 Hedges, L.V. and Nowell, A. (1995) Sex differences in mental test scores, variability, and numbers of high-scoring individuals. *Science* 269, 41–45
- 22 Phillips, P.C. (1999) From complex traits to complex alleles. *Trends Genet.* 15, 6–8
- 23 Gécz, J. *et al.* (1996) Gene structure and subcellular localization of FMR2, a member of a new family of putative transcription activators. *Nat. Genet.* 13, 105–108
- 24 D'Adamo, P. *et al.* (1998) Mutations in GDI1 are responsible for X-linked non-specific mental retardation. *Nat. Genet.* 19, 134–139
- 25 Billuart, P. *et al.* (1998) Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. *Nature* 392, 923–926
- 26 Allen, K.M. *et al.* (1998) PAK3 mutation in nonsyndromic X-linked mental retardation. *Nat. Genet.* 20, 25–30
- 27 Trivier, E. *et al.* (1996) Mutations in the kinase Rsk-2 associated with Coffin–Lowry syndrome. *Nature* 384, 567–570
- 28 Carrié, A. (1999) A new member of the IL-1 receptor family highly expressed in hippocampus and involved in X-linked mental retardation. *Nat. Genet.* 23, 25–31
- 29 Zemni, R. *et al.* (2000) A new gene involved in X-linked mental retardation identified by analysis of an X;2 balanced translocation. *Nat. Genet.* 24, 167–171
- 30 Kutsche, K. *et al.* (2000) Mutations in ARHGEF6, encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. *Nat. Genet.* 26, 247–250
- 31 Yntema, H.G. *et al.* (1999) A novel ribosomal S6-kinase (RSK4; RPS6KA6) is commonly deleted in patients with complex X-linked mental retardation. *Genomics* 62, 332–343
- 32 Chelly, J. (1999) Breakthroughs in molecular and cellular mechanisms underlying X-linked mental retardation. *Hum. Mol. Genet.* 8, 1833–1838
- 33 Gécz, J. and Mulley, J. (2000) Genes for cognitive function: developments on the X. *Genome Res.* 10, 157–163
- 34 Toniolo, D. and D'Adamo, P. (2000) X-linked non-specific mental retardation. *Curr. Opin. Genet. Dev.* 10, 280–285

Chaperone overload is a possible contributor to 'civilization diseases'

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Molecular chaperones dampen the effect of damaging mutations that would otherwise be removed from the population by natural selection. Here, I propose that the development of modern medical practice depressed this process, leading to a rise of phenotypically silent mutations in the genome. The background of misfolded proteins increases during ageing and, by competition, prevents the chaperone-mediated buffering of silent mutations. Phenotypically exposed mutations contribute to a more-abundant manifestation of multigene-diseases. This 'chaperone overload' hypothesis emphasizes the need for efficient ways to enhance chaperone capacity in ageing subjects, and will hopefully lead to the identification and 'repair' of silent mutations.

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Recently, a surprising ~60 000 single nucleotide polymorphisms (SNPs) were found in exons of the human genome¹ (i.e. an average of two per gene). Some of these variations, together with other mutations, could cause the affected proteins to fold incorrectly. Another recent development showed that defective protein folding is the source of numerous monogenic diseases², emphasizing the importance of

the correct balance between molecular chaperones (the proteins that help to refold damaged proteins^{3–5}) and their targets. The investigations of Rutherford and Lindquist⁶ connected chaperone-overload with evolution, identifying one of the most abundant cytoplasmic chaperones, the 90-kDa heat shock protein (Hsp90) as a capacitor of morphological evolution (Box 1)⁶. Recently, the *Drosophila* chaperone Hsp70 (Ref. 7) and the *Saccharomyces cerevisiae* prion⁸ [PSI⁺] were also shown to have roles in the stress-related exposure of pre-existing genetic variations. Furthermore, chaperones can have more-direct effects on DNA recombination and repair: integrating several mechanisms, Hsp70 has been recently proposed as a facilitator of evolution⁹.

'Genome cleansing'

Under normal conditions, chaperones repair the conformational defects of some mutated proteins, thus reducing their phenotypic effects and dampening genome cleansing – the elimination of damaged genes from the gene pool of a population, which would normally occur through natural selection. After severe stress, however, chaperones become occupied by stress-damaged proteins and several mutations could begin to affect phenotypes (Box 1)⁶. If the functional consequence of the stress-exposed mutation(s) is life threatening, the organism could die as a result of the combined challenge (stress and mutation). These lethal competitions between genetically encoded folding defects and stress-induced chaperone occupancy usually occur before the organism reaches reproductive age, therefore the mutation is not inherited in later generations. Thus, stress exposes potentially dangerous mutations, allowing them to