Evolutionary Applications www.evolutionaryapplications.org

Evolutionary Applications ISSN 1752-4571

ORIGINAL ARTICLE

Evolutionary genomics of human intellectual disability

Bernard Crespi,[1] Kyle Summers[2] and Steve Dorus[3]

1 Department of Biosciences, Simon Fraser University, Burnaby, BC, Canada
2 Department of Biology, East Carolina University, Greenville, NC, USA
3 Department of Biology and Biochemistry, University of Bath, Bath, UK

Keywords
genetic, genomic, intellectual disability, positive selection.

Correspondence
Dr Bernard Crespi, Department of Biological Sciences, 8888 University Drive, Simon Fraser University, Burnaby, BC V5A 1S6, Canada.
Tel.: 778 782-3533; fax: 778 782-3496;
e-mail: crespi@sfu.ca

Received: 20 July 2009
Accepted: 28 July 2009
First published online: 7 September 2009

doi:10.1111/j.1752-4571.2009.00098.x

Abstract

Previous studies have postulated that X-linked and autosomal genes underlying human intellectual disability may have also mediated the evolution of human cognition. We have conducted the first comprehensive assessment of the extent and patterns of positive Darwinian selection on intellectual disability genes in humans. We report three main findings. First, as noted in some previous reports, intellectual disability genes with primary functions in the central nervous system exhibit a significant concentration to the X chromosome. Second, there was no evidence for a higher incidence of recent positive selection on X-linked than autosomal intellectual disability genes, nor was there a higher incidence of selection on such genes overall, compared to sets of control genes. However, the X-linked intellectual disability genes inferred to be subject to recent positive selection were concentrated in the Rho GTP-ase pathway, a key signaling pathway in neural development and function. Third, among all intellectual disability genes, there was evidence for a higher incidence of recent positive selection on genes involved in DNA repair, but not for genes involved in other functions. These results provide evidence that alterations to genes in the Rho GTP-ase and DNA-repair pathways may play especially-important roles in the evolution of human cognition and vulnerability to genetically-based intellectual disability.

Introduction

Human intellectual disability, formally defined as full-scale IQ of 70 and below (Kleefstra and Hamel 2005; Chelly et al. 2006; Raymond 2006), is caused in many cases by rare, highly-penetrant loss-of-function mutations affecting a set of identified genes (Chiurazzi et al. 2004; Inlow and Restifo 2004). Lehrke (1972, 1974) first suggested that such 'mental retardation genes', especially X-linked ones, might exhibit variants affecting 'intelligence' (defined by clinicians in terms of IQ) in nonclinical populations. This prediction was based on early studies showing an excess of males over females with intellectual disability, a wider distribution of IQ in males, and segregation patterns of intellectual disability within families, and it has since been reiterated by other authors as more evidence on the genetic bases of cognitive abilities and intellectual disability has become available (Turner and Partington 1991; Turner 1996; Lubs 1999; Neri and Opitz 2000; Spinath et al. 2004; Ropers and Hamel 2005; Arden and Plomin 2006; Plomin et al. 2006). Darwin's own pedigree has indeed been used as an example of potential X-linked inheritance of high cognitive ability (Turner 1996), given that such abilities have been traced down female lines from Josiah Wedgwood to Charles Darwin, and from Erasmus Darwin to Francis Galton.

Zechner et al. (2001) extended Lehrke's hypothesis in proposing that X-linked intellectual disability genes 'have had a major impact on the rapid development of cognitive abilities during human evolution', an idea inspired by the apparent differential presence of genes with cognitive functions on the X chromosome and by the exposure of X-linked genes in males directly to selection (Graves et al. 2002; Vicoso and Charlesworth 2006). The X chromosome

also bears a strong enrichment of brain-expressed genes compared to autosomes (Vallender and Lahn 2004; Nguyen and Disteche 2006), and exhibits a stronger overall signal of positive selection than autosomes (Nielsen et al. 2005; Wang et al. 2006; Zhang et al. 2006a), but the degree to which such findings apply to X-linked genes affecting intellectual disability or cognitive functions remains unknown.

Despite a concentration of intellectual disability genes on the X chromosome that is apparently not due to ascertainment bias (Zechner et al. 2001; Gécz 2004; Inlow and Restifo 2004; Ropers and Hamel 2005; Willems 2007; Delbridge et al. 2008), the hypothesis that genes underlying human intelligence differentially reside on the X chromosome, and the degree to which 'intellectual disability' genes in general have been involved in the evolution of human cognition, have yet to be systematically investigated (Hook 1996; Willems 2007). Indeed, the only previous evidence bearing more or less directly on these hypotheses includes a study by Boda et al. (2002) showing that four X-linked mental retardation genes are involved in activity-dependent neuronal plasticity, and data linking alleles of the autosomal SSADH gene (coding for succinate semialdehyde dehydrogenase) to both mental retardation (via deactivating mutations) and high versus normal IQ (via variants of a functional polymorphism, with the high-IQ allele derived in humans) (Akaboshi et al. 2003; Gibson et al. 2003; Plomin et al. 2004; Blasi et al. 2006; Leone et al. 2006; see also De Rango et al. 2008). The only previous study on the molecular-evolutionary genetics of intellectual disability (Kitano et al. 2003) investigated patterns of gene diversity for 10 X-linked loci in chimps and humans, and inferred high levels of functional constraint on most of the genes, but possible evidence of positive selection on one gene, FMR2, along the human lineage. Analyses of molecular-evolutionary patterns for intellectual-disability genes should yield insights into the genetic architecture of human intelligence (Deary et al. 2009), with important implications for the forms of genetic perturbation that can disrupt this complex human phenotype (Inlow and Restifo 2004; Ropers and Hamel 2005; Gécz et al. 2009).

In this study, we present the results of tests for positive Darwinian selection along the human lineage on a comprehensive set of intellectual disability genes, compiled by Inlow and Restifo (2004), Appendix 1. Using tests for selective sweeps from the human HapMap data (Voight et al. 2006) and maximum likelihood tests for adaptive protein evolution (Yang 2007; Nickel et al. 2008), we evaluate the hypothesis that X-linked intellectual disability genes, or intellectual disability genes in general, have been differentially subject to positive selection in recent human evolution. We also investigate patterns of selection in relation to gene function, to determine if functional subsets of intellectual disability genes have differentially undergone adaptive evolution.

Methods

Intellectual disability genes

We based our analysis on the list of 282 intellectual disability genes compiled by Inlow and Restifo (2004), which also includes information on the biological functions of the genes involved. Mitochondrial genes were not analyzed, and sufficient data for analysis were unavailable for seven autosomal genes, leaving a total of 264 genes, 44 of which were X-linked.

Tests for positive selection

We used two approaches to infer positive selection during human evolution, the iHS test for recent selective sweeps developed by Voight et al. (2006), and maximum likelihood tests of adaptive protein evolution as deployed in PAML (Yang 2007; Nickel et al. 2008). For the iHS tests, we used data from the human haplotype map (phase I), the data source for which genome-wide iHS values are currently available for both the autosomes and X chromosome (Voight et al. 2006). Results from available phase II data analyses were closely similar, as described below. For the three genotyped populations, evidence of positive selection is indicated by the tendency of recently-selected alleles to sweep a set of tightly-linked sites to relatively high frequency. Our criterion for positive selection in these data was a probability value of 0.05 or lower for one or more of the three populations. Gene-specific probability values of the iHS statistics, calculated and presented in Haplotter (Voight et al. 2006; http://hg-wen.uchicago.edu/selection/haplotter.htm), are empirically derived, separately for the X chromosome and the autosomes, given their different effective population sizes and inheritance systems. For the maximum-likelihood tests of adaptive protein evolution, we used branch-site models in PAML (Yang 2007) as calculated and deployed in PAML browser (Nickel et al. 2008; http://mendel.gene.cwru.edu/adamslab/pbrowser.py), focusing on the hypothesis of adaptive protein evolution along the human lineage. These tests were based on aligned sequence from a subset of the taxa chimpanzee, orangutan, rhesus macaque, mouse, rat, rabbit, dog, cow, armadillo, elephant, tenrec, opossum, chicken, frog, zebrafish, tetraodon and fugu, with the great majority of the genes including data at least from human, chimpanzee, orangutan, macaque, rat, mouse, dog and cow.

We tested for a differential incidence of positive selection on intellectual disability genes in two ways. First, we

compared the overall proportions of genes inferred as subject to positive selection between: (a) intellectual disability genes and (b) control genes derived from a random sample of genes in the Panther gene-ontology (GO) category 'neuronal activities' (Mi et al. 2005). This GO category of genes should be most similar, in terms of function, to genes known to mediate intellectual disability. We also note that the category 'developmental processes' yielded very similar results as regards the proportion of control genes inferred as positively selected. Second, we also used another, larger set of control genes, derived from the gene-expression database http://symatlas.gnf.org/SymAtlas/ (Su et al. 2004) based on the criterion that the genes exhibited at least 1.25× higher expression in the human brain than in other tissues. With this set of controls, which includes a large diversity of genes differentially underlying brain functions, we were able to robustly compare the proportions of genes inferred as selected (using both iHS and PAML-based tests) between intellectual disability genes and control genes, separately for genes on the X chromosome and genes on autosomes. All tests were two-tailed.

Results

Overall, 33 genes exhibited a significant signature of positive selection in one or more of the HapMap populations and 231 genes yielded nonsignificant results (Table 1). The proportion of intellectual disability genes inferred as subject to positive selection using iHS did not differ between X-linked genes (4, 9.8% of 41) and autosomal genes (29, 13% of 223; Fisher's Exact test, $P = 0.79$), and similar results were obtained using human-lineage specific maximum-likelihood tests (2, 6.1% of 33 X-linked genes inferred as selected at $P < 0.05$ (*DMD* and *L1CAM*), compared to 5, 2.6% of 189 autosomal genes (*LAMA2*, *MYO5A*, *SLC12A1*, *TSHR* and *TTF1*), Fisher's exact test, $P = 0.29$). Overall, the proportion of intellectual disability genes inferred as subject to positive selection using iHS (33, 12.5% of 264) did not differ significantly from the proportion of neuronal-activities control genes inferred as selected (28, 8.8% of 330; Fisher's Exact test, $P = 0.13$). Similar results were obtained using human-lineage specific maximum-likelihood tests: 7 (3.2%) of 222 intellectual disability genes were inferred as positively selected, compared to 9 (2.8%) of 316 neuronal-activities control genes (Fisher's exact test, $P = 0.68$).

Using the set of differentially brain-expressed genes as controls, the proportion of X-linked intellectual disability genes inferred as selected using iHS (9.8%, as noted above) did not differ from the proportion of control X-linked genes inferred as selected (9, 6.6% of 136; Fisher's exact test, $P = 0.85$). Similarly, the proportion of X-linked intellectual disability genes inferred as selected using human-lineage specific maximum-likelihood tests (6.1%) did not differ from proportion of control X-linked genes inferred as selected (4, 4% of 101; Fisher's exact test, $P = 0.84$). The proportion of autosomal intellectual disability genes inferred as selected using iHS (13%) did not differ from the proportion of autosomal control genes inferred as selected (22, 10.3% of 214; Fisher's exact test, $P = 0.23$). The proportion of autosomal intellectual disability genes inferred as selected using human-lineage specific maximum-likelihood tests (5, 2.6% of 189) likewise did not differ from the proportion of autosomal control genes inferred as selected (2, 1.2% of 166; Fisher's exact test, $P = 0.28$).

Taken together, these results indicate that there is no evidence for enhanced signals of selection on X-linked intellectual disability genes, or on intellectual disability genes overall, compared to control genes.

Of the genes in the full data set, 127 are reported by Inlow and Restifo (2004) to exhibit primary functions in the central nervous system, and these exhibit a significant concentration on the X chromosome: 69.7% of X-linked intellectual disability genes show primary CNS function, compared to 49.2% of autosomal ones (Table 2). A significant concentration of X-linkage is also apparent for signaling pathway genes (Table 2), but this pattern may be caused by joint functions of these genes in the CNS and in signaling pathways: 6 (75%) of 8 X-linked signaling pathway genes also exhibited CNS functions, as did 14 (87.5%) of autosomal ones. Intellectual disability genes involved in lysosomal functions, DNA repair,

Table 1. Mental retardation genes from the compilation of Inlow and Restifo (2004), Appendix 1 that show evidence of recent positive selection in one or more HapMap populations (Voight et al. 2006).

X-linked
FACL4 (1 Yri), FGD1 (1 Ceu), FMR1 (2 Ceu), OPHN1 (3 Ceu)
Autosomal
AMT (64 Asn, 4 Yri, 0.0526), ALG12 (7 Ceu, 2 Asn, 0.0502), ASL (13 Asn, 14 Yri), CBS (2 Ceu), CLN1 (5 Asn, 2 Yri, 0.064) CREBBP (1 Yri), DBT (5 Ceu), DUOX2 (6 Ceu), ERCC8 (3 Ceu), FANCA (3 Yri), FANCC (1 Yri & 1 Asn), FOXE1 (4 Yri), GCS1 (20 Ceu), GNPAT (4 Ceu), GPH (7 Ceu, 6 Yri, 0.080), GSS (5 Ceu, 6 Asn), GUSB (13 Yri, 13 Asn), HEXA (7 Ceu), MYO5A (4 Ceu), NBS1 (2 Ceu & 2 Yri), NDUFS4 (1 Ceu, 1 Yri), NDUFV1 (24 Asn), PEX1 (7 Yri, 3 Ceu 0.094), POMT1 (2 Yri), PPOX (14 Yri), SARA2 (5 Yri), SLC12A1 (2 Ceu), SLC12A6 (5 Ceu), TTF1 (2 Ceu)

Shown after each gene is the number of contiguous genes in the inferred selective sweep, and the population showing evidence of selection at $P < 0.05$. Population and *P*-value data are also presented for these genes from any additional population showing evidence of selection at marginally nonsignificant *P*-values of $0.05 < P < 0.10$. Ceu = European, Yri = African, Asn = Asian.

Table 2. Data on chromosomal position (X linked vs autosomal) and proportions of genes inferred as subject to recent positive selection, as evidenced by selective sweeps in humans, for mental retardation genes with different biological functions as listed in Inlow and Restifo (2004), Appendix 1.

Biological function	X-linked	Autosomal	*P* (exact)	Selected, this function	Selected, other functions	*P* (exact)
CNS	23/34	104/214	0.043	18/123	15/130	0.58
Lysosomal	2/44	27/225	0.19	3/29	29/240	1.0
DNA repair	0/44	9/227	0.36	4/9	29/255	0.016
Metabolic	10/44	85/227	0.083	9/94	24/170	0.34
Transcription regulation	3/43	18/226	0.76	3/21	30/241	0.74
Signaling pathway	13/43	20/226	0.0004	2/30	31/232	0.39
Protein modification	0/44	17/224	0.084	3/17	30/244	0.46

Fisher's exact test was used to compare proportions. Biological functions listed as uncertain (with a ''?'') in Inlow and Restifo (2004), Appendix 1 are not included in the compilations, and seven genes have data on chromosomal location and biological function, but no data on the presence or absence of positive selection.

metabolism, transcription regulation, and protein modification showed no evidence of an increased frequency of X-linkage.

Intellectual disability genes with primary CNS functions did not show evidence of enhanced signals of recent positive selection in the human lineage, nor did genes with functions in lysosomal activities, metabolism, transcription regulation, or protein modification. By contrast, nearly half (44%) of the genes (ERCC8, FANCA, FANCC, and NBS1, all autosomal) with biological functions in DNA repair showed signals of recent positive selection, which was significantly higher than the proportion for genes with other functions (11.4%, Table 2). The FANCA and ERCC8 genes remained significant in analyses of phase II data (at *P* values of 0.023 and 0.033 respectively), and the FANCC and NBS1 showed borderline empirical *P* values of 0.057 and 0.056 respectively. Both of these latter genes, however, also showed evidence of selection on specific SNPs in phase II data (Voight et al. 2006). Definite or putative primary CNS function is also reported for all nine of the DNA repair genes in the data set, which suggest that joint functions in DNA repair and the CNS may represent the actual functional category of intellectual disability genes showing an enhanced signal of positive selection. Such joint functions are well documented for key genes in the BRCA/FANC pathway; for example, the Fanconi anemia complex genes, as well as BRCA1 and BRCA2, play key roles in neural stem cell development and function (Frappart et al. 2007; Sii-Felice et al. 2008; Pulvers and Huttner 2009). Overall, four (33%) of 12 of the known BRCA/FANC genes exhibit evidence of positive selection at $P < 0.05$ from the phase II HapMap data (BRCA1, FANCA, FANCE, and FANCN), as do two of the three key genes directly upstream of this pathway (ATM and CHEK2), and RAD51, which interacts directly with a domain of BRCA1 subject to adaptive amino acid evolution (Fleming et al. 2003).

The four X-linked genes inferred here as subject to positive selection also appear to represent a specific functional subset of intellectual disability genes, in that three of these genes, FGD1, FMR1, and OPHN1, are involved in the Rho GTPase signal transduction pathway (Negishi and Katoh 2005; Renieri et al. 2005). Data on positive selection are available in our dataset for seven X-linked genes involved in the Rho GTP-ase pathway; three (42.8%) of these genes have thus been inferred as selected, compared to one selected X-linked gene (2.9%) among the 34 X-linked genes not in this pathway (Fisher's exact test, $P = 0.012$). A more general pattern of recent positive selection involving genes involved in the Rho GTPase pathway is suggested by the finding that five of the 16 known ARHGEF genes (which critically regulate this pathway) show evidence of selection at $P < 0.05$ in one or more population of the phase II HapMap data (Voight et al. 2006), and four of the 11 ARHGEF genes that are not significant at the 0.05 level show nonsignificant trends ($0.05 < P < 0.10$).

Discussion

We have conducted the first comprehensive tests for positive selection on genes known to underlie human intellectual disability, to evaluate the hypothesis that some of these genes may also have been involved in the adaptive evolution of human cognition. A primary result of these tests is that there is no evidence for an enhanced signal of recent positive selection on intellectual disability genes considered as a whole, or for the subset of X-linked ones, despite the increased tendency of ascertained X-linked intellectual disability genes to exhibit functions in the central nervous system. These findings support the hypothesis that intellectual disability genes do not generally represent adaptively-evolving 'intelligence genes', but instead represent genes with important effects on cognitive

development that are subject primarily to rare, maladaptive loss-of-function mutations that are presumably selected against (Kitano et al. 2003; Tarpey et al. 2009). Our results are also generally consistent with previous studies demonstrating notable selective constraints on protein-coding brain-expressed genes in humans (Nielsen et al. 2005; Shi et al. 2006; Wang et al. 2007).

Despite the apparent lack of enhanced signals of positive selection across all intellectual disability genes, two specific categories of intellectual disability genes, (i) X-linked genes in the Rho GTPase pathway (FGD1, FMR1, and OPHN1), and (ii) autosomal genes involved in DNA repair (FANCA, FANCC, NBS1, and XRCC8), show significantly increased frequencies of recent positive selection, from the HapMap analyses, compared to other categories. These findings suggest that specific subsets of intellectual disability genes have been subject to positive selection in humans, such that they may provide important insights into the molecular-evolutionary and developmental bases of human cognition.

X-linked Rho GTPase genes

Rho GTPases function as molecular switches that mediate the activation of signal transduction pathways underlying cytoskeletal organization, cellular migration, and cell shape remodeling during differentiation, with especially-notable roles in neurodevelopment via their functions in dendritic spine elongation and cell cycle dynamics (Boettner and Van Aelst 2002; van Galen and Ramakers 2005; Govek et al. 2005; Negishi and Katoh 2005; Linseman and Loucks 2008). Genes in the Rho GTPase pathway represent the largest common functional category of X-linked intellectual disability genes, and given this pattern, Ramakers (2002) suggested that such genes may be involved in the development and evolution of normal human cognition, such that some mutations might enhance cognitive functions. In accordance with this hypothesis, pharmaceutical activation of Rho GTPases in mice can lead to enhanced learning and memory, through alterations in the actin cytoskeleton and synaptic plasticity (Diana et al. 2007).

We have reported evidence of recent positive selection on three X-linked genes, FGD1, FMR1, and OPHN1, each of which codes for a protein product that acts as an effector of Rho GTPase activity (Table 3). Some evidence consistent with positive selection has been reported for FMR1, in the contexts of an expanded length of trinucleotide repeats in primates compared to other mammals (Eichler et al. 1995), the presence of 74 fixed differences between humans and great apes (Mathews et al. 2001), and high levels of linkage disequilibrium in some human populations (Eichler et al. 1995; Kunst et al. 1996; Mathews et al. 2001). Chen et al. (2003) also reported that the efficiency of translation is highest with 30 trinucleotide repeats in the upstream region, which is also the modal number across human populations, a pattern consistent with stabilizing selection on repeat number. Evidence consistent with positive selection has also been reported for the OPHN1 gene by Wang et al. (2006), who described evidence of a selective sweep in this gene in humans; and by Tarpey et al. (2009), who used the McDonald-Kreitman test. Kitano et al. (2003) inferred that this gene underwent one nonsynonymous and one synonymous substitutions in the human lineage, compared to an absence of nonsynonymous changes in chimpanzees and orangutans.

FGD1, FMR1, and OPHN1 exhibit several notable similarities in their phenotypic effects when subject to loss-of-function mutations, and in their neurodevelopmental functions. Thus, for all three genes intellectual disability includes effects on brain size (macrocephaly), facial features (Renieri et al. 2005) and genital development as well as cognitive capacities, and their developmental effects involve alterations to dendritic spine morphology and, for FMR1 and OPHN1, glutamatergic signaling (Table 3). These developmental and phenotypic similarities are intriguing and suggest that the causes of positive selection on these genes may involve alterations of common neurogenetic pathways. This hypothesis could be evaluated by testing for cognitive or neurological effects of the selected versus nonselected haplotypes in humans, and by testing for positive selection using a larger subset of genes, including genes not previously associated with intellectual disability, that interact functionally with the gene products of FGD1, FRM1, and OPHN1. More generally, studies of positive selection focusing on genes in the Rho GTP-ase signaling pathway may provide additional insights into whether alterations to genes in this pathway have played an important role in the evolution of human brain size and cognition. Adaptive evolutionary changes to Rho GTPase genes might be expected to occur differentially for genes on the X chromosome, given the exposure of such genes directly to selection in males (Vicoso and Charlesworth 2006), which may contribute to the pattern of positive selection that we have described here.

Autosomal DNA repair genes

DNA repair was the only specific functional category of intellectual disability genes in the compilation of Inlow and Restifo (2004) to exhibit an enhanced signal of positive selection. Wang and Moyzis (2007) reported evidence of (balancing) selection on two of the genes inferred as selected in our study, FANCC and ERCC8, and Wang et al. (2006) described evidence of positive selection on

Table 3. Key characteristics of intellectual disability genes that have been inferred as subject to recent positive selection in the human lineage.

Gene	Phenotypic effects	Developmental-genetic functions
Genes in Rho-GTPase pathway		
FGD1	Mutations cause Aarskog-Scott syndrome (FacioGenital Dysplasia), which involves macrocephaly and genital anomalies (Schwartz et al. 2000; Orrico et al. 2004; Bottani et al. 2007)	FGD1 gene product acts as upstream effector of Rho GTP-ases, and is involved in neurite outgrowth and dendritic spine development (van Galen and Ramakers 2005)
FMR1	Mutations cause Fragile X syndrome, which involves macrocephaly, macroorchidism (large testis), reduced cerebellar vermis, and a high incidence of autism (Terracciano et al. 2005; Belmonte and Bourgeron 2006)	FMR1 gene product, FMRP, interacts with CYFIP1,2, which mediate Rho GTPase activation (Billuart and Chelly 2003); mental retardation involves altered glutamatergic signaling, and immature dendritic spines (van Galen and Ramakers 2005)
OPHN1	Mutations involve cerebellar hypoplasia, hypogonadism, and macrocephaly in a notable proportion of cases (Chiurazzi et al. 2004; Chabrol et al. 2005; Kleefstra and Hamel 2005; Zanni et al. 2005)	OPHN1 gene product regulates RhoA activity, affects glutamatergic signaling; mouse mutants show immature dendritic spines (Govek et al. 2005; Chabrol et al. 2005; Zanni et al. 2005; Khelfaoui et al. 2007)
Genes in DNA repair pathways		
FANCA & FANCC	Mutations cause Fanconi Anemia, an autosomal recessive condition that involves microcephaly, growth retardation, bone marrow failure, skeletal malformations and increased cancer risk (Gennery et al. 2004; Wang 2007)	FANC genes maintain genomic stability and are required for neural stem cell maintenance in brain development; aging of stem cell pools may underlie Fanconi Anemia phenotypes (Sii-Felice et al. 2008)
NBS1	Mutations cause Nijmegen Breakage syndrome, an autosomal recessive condition characterized by microcephaly, immunodeficiency, increased cancer risk, and growth retardation (Gennery et al. 2004; Demuth and Digweed 2007; O'Driscoll et al. 2007)	NBS1 gene product maintains genomic stability via repair of double-stranded DNA breaks, and helps to maintain telomeres (Matsuura et al. 2004; Zhang et al. 2006b); interacts closely with ATM gene product in DNA damage response pathway (Difilippantonio and Nussenzweig 2007)
ERCC8	Mutations are one cause of Cockayne syndrome, an autosomal recessive condition involving microcephaly, growth retardation, hypogonadism, and symptoms of premature aging (Rapin et al. 2006; Niedernhofer 2008)	ERCC8 gene product functions in repair of damage in actively-transcribed genes (Lainé and Egly 2006) and repair of oxidative DNA damage (D'Errico et al. 2007)

these same two genes; both Nielsen et al. (2005) and Wang et al. (2006) also reported a general over-representation of cell cycle genes in their surveys of positive selection along the human lineage. As noted above, DNA repair genes underlying intellectual disability also exhibit functions in the development of the central nervous system, which are evidenced by pleiotropic effects of loss of function mutations on both neurodevelopment and predisposition to cancer (Balajee 2006). The DNA repair genes inferred here as subject to selection are involved in the coordination of responses to DNA damage during cell division (e. g., McKinnon and Caldecott 2007; Wang 2007), with impaired repair and subsequent cell death during growth of the brain being responsible at least in part for effects on the expression of the intellectual disability phenotype (e. g., Frappart et al. 2007; Lee et al. 2007).

Details of the phenotypic effects and functional roles of the four positively-selected intellectual disability genes involved in DNA repair are described in Table 3. Of particular interest is the presence of microcephaly in intellectual disability due to loss-of-function mutations in all four of these genes, linkages of all four genes to aspects of aging, and the phenotypic and etiologic overlap of Fanconi Anemia (due to mutations in FANCA and FANCC) and Nijmegen Breakage Syndrome (due to mutations in NBS1) (Gennery et al. 2004), with both syndromes involving impaired responses to DNA damage. These three genes represent components of DNA-damage response and repair pathways (D'Andrea and Grompe 2003; Narod and Foulkes 2004; McKinnon and Caldecott 2007; Wang 2007; García and Benítez 2008) that also include the microcephaly-associated, positively-selected genes MCPH1 (Evans et al. 2005), and ATM (Gilad et al. 1998; Frappart et al. 2005; Voight et al. 2006), as well as the genes BLM, BRCA1, RAD51, CHEK1 and CHEK2, all of which show evidence of selection in recent human evolution (Huttley et al. 2000; Bustamante et al. 2005; Wakefield et al. 2005; Voight et al. 2006). Cochran et al. (2006) also describe evidence that some Ashkenazi-concentrated mutations, differentially found for genes in DNA repair pathways including the FANC pathway genes FANCC,

BRCA1 and BRCA2, may have mediated the evolution of enhanced cognition in this genetic isolate.

Additional microcephaly-associated genes that have been subject to apparent positive selection in the human lineage, such as AHI1 (Ferland et al. 2004; Tang 2006), ASPM (Zhang 2003; Mekel-Bobrov et al. 2005), CASK (Voight et al. 2006; Najm et al. 2008) CENPJ (Woods et al. 2005), CDK5RAP2 (Woods et al. 2005), Cernunnos-XLF (Pavlicek and Jurka 2006; Zha et al. 2007), NDE1 (Feng and Walsh 2004; Voight et al. 2006), NIPBL (Borck et al. 2006; Wang et al. 2006) PCNT (Voight et al.; Rauch et al. 2008), and SHH (Hehr et al. 2004; Dorus et al. 2006), are also involved in cell cycle progression, but appear to mediate brain size through other DNA repair pathways, through effects on centrosome function, or via other neurodevelopmental processes (Woods et al. 2005; Cox et al. 2006; Fish et al. 2006; Pavlicek and Jurka 2006; Griffith et al. 2008). The mechanisms whereby such microcephaly genes cause altered brain development require further study, but they appear to involve the survival and maintenance of neural progenitor cells, rates of apoptosis in neural development, efficiency and timing of symmetric and asymmetric neural cell divisions, depletion of neural stem cell pools, and tradeoffs between cell proliferation and repair (Korhonen et al. 2003; Bond and Woods 2006; Cox et al. 2006; Tang 2006; Lee et al. 2007; Griffith et al. 2008; Sii-Felice et al. 2008; Stiff et al. 2008). The clearest potential links of such processes to cognition are positive correlations between brain size and intelligence within humans (Witelson et al. 2006; Narr et al. 2007) as well as across nonhuman primate species (Deaner et al. 2007), and data showing that IQ is positively-associated with rapidity of growth in thickness of the cerebral cortex during human childhood (Shaw et al. 2006).

Intellectual disability associated with the autosomal DNA repair genes analyzed here is due to recessive mutations in both sexes, in contrast to X-linked mutations which are manifested and subject to selection predominantly in males. O'Driscoll et al. (2007) and O'Driscoll (2008) describe evidence that haploinsufficiency of such DNA repair genes is sufficient to cause notable phenotypic effects, which suggests that adaptive mutations may be expressed as dominant or codominant mutations subject to strong selection. A possible example is MCPH1, which exhibits a common, derived single nucleotide polymorphism associated with larger cranial volume in males of an Asian population, although no signal of recent positive selection was detected in the vicinity of this marker (Wang et al. 2008). More generally, haplotypes of ERCC8, FANCA, FANCC and NBS1 subject to apparent positive selection should represent good candidates for genetic variants with effects on brain size and cognitive capacity in nonclinical human populations.

Conclusions

Interpretation of signals of positive selection, such as the ones described here, is subject to several important caveats (Hughes 2007). First, the time scale of inferences from HapMap data is on the order of several tens of thousands of years (Voight et al. 2006), while the fossil record provides evidence of human anatomical modernity by about 100 000–80 000 years ago (Bouzouggar et al. 2007), with large brain size itself evolving considerably earlier (Rightmire 2004). These lines of evidence imply that signals of selection inferred in this study would be related to aspects of brain function not evident from the archeological record, which is broadly consistent with an acceleration of positive selection in humans over the past 10 000 or so years (Hawks et al. 2007). Second, high-density SNP genotyping across multiple populations are required for robust inference and localization of selective effects, and inferences regarding the causes of selection require functional-genomic or ecological-genomic data (Hughes 2007), such as localization of signals to particular functional domains. Third, given strong pleiotropic effects of genes across multiple phenotypes, such as cancer predisposition and brain development (Gennery et al. 2004; McKinnon and Caldecott 2007), or brain and gonadal functions (Guo et al. 2003, 2005; Meizel 2004), it is challenging to ascribe selective effects of particular genetic variants to specific phenotypes. Despite these limitations, our study provides useful new insights into the evolutionary-genetic bases of intellectual disability, in showing that signals of recent positive selection on intellectual disability genes are enhanced for two functional categories of gene. These findings suggest that allelic variants of some types of intellectual disability genes may have mediated the evolution of human brain size and cognition, and they provide a clear focus for future studies along these lines.

In addition to providing insights into the evolution of human intellectual capacities, our results may also be useful in ascertaining the genetic bases of idiopathic cases of intellectual disability, in that: (i) candidates for genes subject to loss-of-function or other mutations may, in some cases, be better-recognized though tests for recent adaptive evolution, given that such tests are strongly indicative of functional differences between specific haplotypes or alleles, and (ii) genes involved in the DNA repair and Rho-GTPase pathways may represent especially strong candidates for involvement in intellectual disability, according to the analyses conducted here. More generally, integration of evolutionary tools and perspectives into studies dissecting the genetic bases of human intellectual

capacities (Deary et al. 2009) should accelerate progress into understanding both the evolution of human intelligence and the causes of variation in intellectual abilities within extant populations.

Acknowledgements

We thank members of the SFU Evolutionary Genomics group for advice and comments. This work was funded by grants from NSERC and the Canada Council for the Arts to B. C., an ECU College Research Award to K. S., and an NIH Ruth L. Kirschstein National Research Service Award to S. D.

Literature cited

Akaboshi, S., B. M. Hogema, A. Novelletto, P. Malaspina, G. S. Salomons, G. D. Maropoulos, C. Jakobs *et al.* 2003. Mutational spectrum of the succinate semialdehyde dehydrogenase (ALDH5A1) gene and functional analysis of 27 novel disease-causing mutations in patients with SSADH deficiency. Human Mutation **22**:442–450.

Arden, R., and R. Plomin. 2006. Sex differences in variance of intelligence across childhood. Personality and Individual Differences **41**:39–48.

Balajee, A. S. (ed.) 2006. DNA Repair and Human Disease. Springer Science, New York, NY.

Belmonte, M. K., and T. Bourgeron. 2006. Fragile X syndrome and autism at the intersection of genetic and neural networks. Nature Neuroscience **9**:1221–1225.

Billuart, P., and J. Chelly. 2003. From fragile X mental retardation protein to Rac1 GTPase: new insights from Fly CYFIP. Neuron **38**:843–845.

Blasi, P., F. Palmerio, A. Aiello, M. Rocchi, P. Malaspina, and A. Novelletto. 2006. SSADH variation in primates: intra- and interspecific data on a gene with a potential role in human cognitive functions. Journal of Molecular Evolution **63**:54–68.

Boda, B., C. Mas, and D. Muller. 2002. Activity-dependent regulation of genes implicated in X-linked non-specific mental retardation. Neuroscience **114**:13–17.

Boettner, B., and L. Van Aelst. 2002. The role of Rho GTPases in disease development. Gene **286**:155–174.

Bond, J., and C. G. Woods. 2006. Cytoskeletal genes regulating brain size. Current Opinion in Cell Biology **18**:95–101.

Borck, G., M. Zarhrate, C. Cluzeau, E. Bal, J. Bonnefont, A. Munnich, V. Cormier-Daire *et al.* 2006. Father-to-daughter transmission of Cornelia de Lange syndrome caused by a mutation in the 5′ untranslated region of the NIPBL gene. Human Mutation **27**:731–735.

Bottani, A., A. Orrico, L. Galli, O. Karam, C. A. Haenggeli, S. Ferey, and B. Conrad. 2007. Unilateral focal polymicrogyria in a patient with classical Aarskog-Scott syndrome due to a novel missense mutation in an evolutionary conserved RhoGEF domain of the faciogenital dysplasia gene FGD1. American Journal of Medical Genetics. Part A **143**:2334–2338.

Bouzouggar, A., N. Barton, M. Vanhaeren, F. d'Errico, S. Collcutt, T. Higham, E. Hodge, *et al.* 2007. 82,000-year-old shell beads from North Africa and implications for the origins of modern human behavior. Proceedings of the National Academy of Sciences of the United States of America **104**:9964–9969.

Bustamante, C. D., A. Fledel-Alon, S. Williamson, R. Nielsen, M. T. Hubisz, S. Glanowski, D. M. Tanenbaum *et al.* 2005. Natural selection on protein-coding genes in the human genome. Nature **437**:1153–1157.

Chabrol, B., N. Girard, K. N'Guyen, A. Gérard, M. Carlier, L. Villard, and N. Philip. 2005. Delineation of the clinical phenotype associated with OPHN1 mutations based on the clinical and neuropsychological evaluation of three families. American Journal of Medical Genetics. Part A **138**:314–317.

Chelly, J., M. Khelfaoui, F. Francis, B. Chérif, and T. Bienvenu. 2006. Genetics and pathophysiology of mental retardation. European Journal of Human Genetics **14**:701–713.

Chen, L., F. Tassone, P. Sahota, and P. J. Hagerman. 2003. The (CGG)n repeat element within the 5′ untranslated region of the FMR1 message provides both positive and negative cis effects on in vivo translation of a downstream reporter. Human Molecular Genetics **12**:3067–3074.

Chiurazzi, P., E. Tabolacci, and G. Neri. 2004. X-linked mental retardation (XLMR): from clinical conditions to cloned genes. Critical Reviews in Clinical Laboratory Sciences **41**:117–158.

Cochran, G., J. Hardy, and H. Harpending. 2006. Natural history of Ashkenazi intelligence. Journal of Biosocial Science **38**:659–693.

Cox, J., A. P. Jackson, J. Bond, and C. G. Woods. 2006. What primary microcephaly can tell us about brain growth. Trends in Molecular Medicine **12**:358–366.

D'Andrea, A. D., and M. Grompe. 2003. The Fanconi Anaemia/BRCA pathway. Nature Reviews. Cancer **3**:23–34.

D'Errico, M., E. Parlanti, M. Teson, P. Degan, T. Lemma, A. Calcagnile, I. Iavarone *et al.* 2007. The role of CSA in the response to oxidative DNA damage in human cells. Oncogene **26**:4336–4343.

De Rango, F., O. Leone, S. Dato, A. Novelletto, A. C. Bruni, M. Berardelli, V. Mari *et al.* 2008. Cognitive functioning and survival in the elderly: the SSADH C538T polymorphism. Annals of Human Genetics **72**:630–635.

Deaner, R. O., K. Isler, J. Burkart, and C. van Schaik. 2007. Overall brain size, and not encephalization quotient, best predicts cognitive ability across non-human primates. Brain, Behavior and Evolution **70**:115–124.

Deary, I. J., W. Johnson, and L. M. Houlihan. 2009. Genetic foundations of human intelligence. Human Genetics **126**:215–232.

Delbridge, M. L., D. A. McMillan, R. J. Doherty, J. E. Deakin, and J. A. M. Graves. 2008. Origin and evolution of candi-

date mental retardation genes on the human X chromosome (MRX). BMC Genomics **9**:65.

Demuth, I., and M. Digweed. 2007. The clinical manifestation of a defective response to DNA double-strand breaks as exemplified by Nijmegen breakage syndrome. Oncogene **26**:7792–7798.

Diana, G., G. Valentini, S. Travaglione, L. Falzano, M. Pieri, C. Zona, S. Meschini *et al.* 2007. Enhancement of learning and memory after activation of cerebral Rho GTPases. Proceedings of the National Academy of Sciences of the United States of America **104**:636–641.

Difilippantonio, S., and A. Nussenzweig. 2007. The NBS1-ATM connection revisited. Cell Cycle **6**:2366–2370.

Dorus, S., J. R. Anderson, E. J. Vallender, S. L. Gilbert, L. Zhang, L. G. Chemnick, O. A. Ryder *et al.* 2006. Sonic Hedgehog, a key development gene, experienced intensified molecular evolution in primates. Human Molecular Genetics **15**:2031–2037.

Eichler, E. E., C. B. Kunst, K. A. Lugenbeel, O. A. Ryder, D. Davison, S. T. Warren, and D. L. Nelson. 1995. Evolution of the cryptic FMR1 CGG repeat. Nature Genetics **11**:301–308.

Evans, P. D., S. L. Gilbert, N. Mekel-Bobrov, E. J. Vallender, J. R. Anderson, L. M. Vaez-Azizi, S. A. Tishkoff *et al.* 2005. Microcephalin, a gene regulating brain size, continues to evolve adaptively in humans. Science **309**:1717–1720.

Feng, Y., and C. A. Walsh. 2004. Mitotic spindle regulation by Nde1 controls cerebral cortical size. Neuron **44**:279–293.

Ferland, R. J., W. Eyaid, R. V. Collura, L. D. Tully, R. S. Hill, D. Al-Nouri, A. Al-Rumayyan *et al.* 2004. Abnormal cerebellar development and axonal decussation due to mutations in AHI1 in joubert syndrome. Nature Genetics **36**:1008–1013.

Fish, J. L., Y. Kosodo, W. Enard, S. Pääbo, and W. B. Huttner. 2006. ASPM specifically maintains symmetric proliferative divisions of neuroepithelial cells. Proceedings of the National Academy of Sciences of the United States of America **103**:10438–10443.

Fleming, M. A., J. D. Potter, C. J. Ramirez, G. K. Ostrander, and E. A. Ostrander. 2003. Understanding missense mutations in the BRCA1 gene: an evolutionary approach. Proceedings of the National Academy of Sciences of the United States of America **100**:1151–1156.

Frappart, P., W. Tong, I. Demuth, I. Radovanovic, Z. Herceg, A. Aguzzi, M. Digweed *et al.* 2005. An essential function for NBS1 in the prevention of ataxia and cerebellar defects. Nature Medicine **11**:538–544.

Frappart, P., Y. Lee, J. Lamont, and P. J. McKinnon. 2007. BRCA2 is required for neurogenesis and suppression of medulloblastoma. EMBO Journal **26**:2732–2742.

van Galen, E. J. M., and G. J. A. Ramakers. 2005. Rho proteins, mental retardation and the neurobiological basis of intelligence. Progress in Brain Research **147**:295–317.

García, M. J., and J. Benítez. 2008. The Fanconi Anaemia/BRCA pathway and cancer susceptibility. Searching for new therapeutic targets. Clinical & Translational Oncology **10**:78–84.

Gécz, J. 2004. The molecular basis of intellectual disability: novel genes with naturally occurring mutations causing altered gene expression in the brain. Frontiers in Bioscience **9**:1–7.

Gécz, J., C. Shoubridge, and M. Corbett. 2009. The genetic landscape of intellectual disability arising from chromosome X. Trends in Genetics **25**:308–316.

Gennery, A. R., M. A. Slatter, A. Bhattacharya, D. Barge, S. Haigh, M. O'Driscoll, R. Coleman *et al.* 2004. The clinical and biological overlap between Nijmegen Breakage Syndrome and Fanconi Anemia. Clinical Immunology **113**:214–219.

Gibson, K. M., M. Gupta, P. L. Pearl, M. Tuchman, L. G. Vezina, O. C. Snead, L. M. E. Smit *et al.* 2003. Significant behavioral disturbances in succinic semialdehyde dehydrogenase (SSADH) deficiency (gamma-hydroxybutyric aciduria). Biological Psychiatry **54**:763–768.

Gilad, S., L. Chessa, R. Khosravi, P. Russell, Y. Galanty, M. Piane, R. A. Gatti *et al.* 1998. Genotype-phenotype relationships in ataxia-telangiectasia and variants. American Journal of Human Genetics **62**:551–561.

Govek, E., S. E. Newey, and L. Van Aelst. 2005. The role of the Rho GTPases in neuronal development. Genes and Development **19**:1–49.

Graves, J. A. M., J. Gécz, and H. Hameister. 2002. Evolution of the human X – a smart and sexy chromosome that controls speciation and development. Cytogenetic and Genome Research **99**:141–145.

Griffith, E., S. Walker, C. Martin, P. Vagnarelli, T. Stiff, B. Vernay, N. Al Sanna *et al.* 2008. Mutations in pericentrin cause Seckel syndrome with defective ATR-dependent DNA damage signaling. Nature Genetics **40**:232–236.

Guo, J., P. Zhu, C. Wu, L. Yu, S. Zhao, and X. Gu. 2003. In silico analysis indicates a similar gene expression pattern between human brain and testis. Cytogenetic and Genome Research **103**:58–62.

Guo, J. H., Q. Huang, D. J. Studholme, C. Q. Wu, and Z. Zhao. 2005. Transcriptomic analyses support the similarity of gene expression between brain and testis in human as well as mouse. Cytogenetic and Genome Research **111**:107–109.

Hawks, J., E. T. Wang, G. M. Cochran, H. C. Harpending, and R. K. Moyzis. 2007. Recent acceleration of human adaptive evolution. Proceedings of the National Academy of Sciences of the United States of America **104**:20753–20758.

Hehr, U., C. Gross, U. Diebold, D. Wahl, U. Beudt, P. Heidemann, A. Hehr *et al.* 2004. Wide phenotypic variability in families with holoprosencephaly and a Sonic Hedgehog mutation. European Journal of Pediatrics **163**:347–352.

Hook, E. B. 1996. Intelligence and the X chromosome. Lancet **348**:826.

Hughes, A. L. 2007. Looking for Darwin in all the wrong places: the misguided quest for positive selection at the nucleotide sequence level. Heredity **99**:364–373.

Huttley, G. A., S. Easteal, M. C. Southey, A. Tesoriero, G. G. Giles, M. R. McCredie, J. L. Hopper *et al.* 2000. Adaptive evolution of the tumour suppressor BRCA1 in humans and chimpanzees. Australian breast cancer family study. Nature Genetics **25**:410–413.

Inlow, J. K., and L. L. Restifo. 2004. Molecular and comparative genetics of mental retardation. Genetics **166**:835–881.

Khelfaoui, M., C. Denis, E. van Galen, F. de Bock, A. Schmitt, C. Houbron, E. Morice *et al.* 2007. Loss of X-linked mental retardation gene oligophrenin1 in mice impairs spatial memory and leads to ventricular enlargement and dendritic spine immaturity. Journal of Neuroscience **27**:9439–9450.

Kitano, T., C. Schwarz, B. Nickel, and S. Pääbo. 2003. Gene diversity patterns at 10 X-chromosomal loci in humans and chimpanzees. Molecular Biology and Evolution **20**:1281–1289.

Kleefstra, T., and B. C. J. Hamel. 2005. X-linked mental retardation: further lumping, splitting and emerging phenotypes. Clinical Genetics **67**:451–467.

Korhonen, L., K. Brännvall, Y. Skoglösa, and D. Lindholm. 2003. Tumor suppressor gene BRCA1 is expressed by embryonic and adult neural stem cells and involved in cell proliferation. Journal of Neuroscience Research **71**:769–776.

Kunst, C. B., C. Zerylnick, L. Karickhoff, E. Eichler, J. Bullard, M. Chalifoux, J. J. Holden *et al.* 1996. FMR1 in global populations. American Journal of Human Genetics **58**:513–522.

Lainé, J., and J. Egly. 2006. When transcription and repair meet: a complex system. Trends in Genetics **22**:430–436.

Lee, W., W. Chang, C. Huang, and K. Wu. 2007. NBS1, the Nijmegen Breakage Syndrome gene product, regulates neuronal proliferation and differentiation. Journal of Neurochemistry **102**:141–152.

Lehrke, R. 1972. Theory of X-linkage of major intellectual traits. American Journal of Mental Deficiency **76**:611–619.

Lehrke, R. 1974. X-linked mental retardation and verbal disability. Birth Defects Original Article Series **10**:1–100.

Leone, O., P. Blasi, F. Palmerio, A. I. Kozlov, P. Malaspina, and A. Novelletto. 2006. A human derived SSADH coding variant is replacing the ancestral allele shared with primates. Annals of Human Biology **33**:593–603.

Linseman, D. A., and F. A. Loucks. 2008. Diverse roles of rho family GTPases in neuronal development, survival, and death. Frontiers in Bioscience **13**:657–676.

Lubs, H. A. 1999. The other side of the coin: a hypothesis concerning the importance of genes for high intelligence and evolution of the X chromosome. American Journal of Medical Genetics **85**:206–208.

Mathews, D. J., C. Kashuk, G. Brightwell, E. E. Eichler, and A. Chakravarti. 2001. Sequence variation within the Fragile X locus. Genome Research **11**:1382–1391.

Matsuura, S., J. Kobayashi, H. Tauchi, and K. Komatsu. 2004. Nijmegen breakage syndrome and DNA double strand break repair by NBS1 complex. Advances in Biophysics **38**:65–80.

McKinnon, P. J., and K. W. Caldecott. 2007. DNA strand break repair and human genetic disease. Annual Review of Genomics and Human Genetics **8**:37–55.

Meizel, S. 2004. The sperm, a neuron with a tail: 'neuronal' receptors in mammalian sperm. Biological Reviews of the Cambridge Philosophical Society **79**:713–732.

Mekel-Bobrov, N., S. L. Gilbert, P. D. Evans, E. J. Vallender, J. R. Anderson, R. R. Hudson, S. A. Tishkoff *et al.* 2005. Ongoing adaptive evolution of ASPM, a brain size determinant in *Homo sapiens*. Science **309**:1720–1722.

Mi, H., B. Lazareva-Ulitsky, R. Loo, A. Kejariwal, J. Vandergriff, S. Rabkin, N. Guo *et al.* 2005. The PANTHER database of protein families, subfamilies, functions and pathways. Nucleic Acids Research **33**:D284–D288.

Najm, J., D. Horn, I. Wimplinger, J. A. Golden, V. V. Chizhikov, J. Sudi, S. L. Christian *et al.* 2008. Mutations of CASK cause an X-linked brain malformation phenotype with microcephaly and hypoplasia of the brainstem and cerebellum. Nature Genetics **40**:1065–1067.

Narod, S. A., and W. D. Foulkes. 2004. BRCA1 and BRCA2: 1994 and beyond. Nature Reviews. Cancer **4**:665–676.

Narr, K. L., R. P. Woods, P. M. Thompson, P. Szeszko, D. Robinson, T. Dimtcheva, M. Gurbani *et al.* 2007. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cerebral Cortex **17**:2163–2171.

Negishi, M., and H. Katoh. 2005. Rho family GTPases and dendrite plasticity. Neuroscientist **11**:187–191.

Neri, G., and J. M. Opitz. 2000. Sixty years of X-linked mental retardation: a historical footnote. American Journal of Medical Genetics **97**:228–233.

Nguyen, D. K., and C. M. Disteche. 2006. High expression of the mammalian X chromosome in brain. Brain Research **1126**:46–49.

Nickel, G. C., D. Tefft, and M. D. Adams. 2008. Human PAML browser: a database of positive selection on human genes using phylogenetic methods. Nucleic Acids Research **36**:D800–D808.

Niedernhofer, L. J. 2008. Tissue-specific accelerated aging in nucleotide excision repair deficiency. Mechanisms of Ageing and Development **129**:408–415.

Nielsen, R., C. Bustamante, A. G. Clark, S. Glanowski, T. B. Sackton, M. J. Hubisz, A. Fledel-Alon *et al.* 2005. A scan for positively selected genes in the genomes of humans and chimpanzees. PLoS Biology **3**:e170.

O'Driscoll, M. 2008. Haploinsufficiency of DNA damage response genes and their potential influence in human genomic disorders. Current Genomics **9**:137–146.

O'Driscoll, M., W. B. Dobyns, J. M. van Hagen, and P. A. Jeggo. 2007. Cellular and clinical impact of haploinsufficiency for genes involved in ATR signaling. American Journal of Human Genetics **81**:77–86.

Orrico, A., L. Galli, M. L. Cavaliere, L. Garavelli, J. P. Fryns, E. Crushell, M. M. Rinaldi *et al.* 2004. Phenotypic and molecular characterisation of the Aarskog-Scott syndrome: a survey of

the clinical variability in light of FGD1 mutation analysis in 46 patients. European Journal of Human Genetics **12**:16–23.

Pavlicek, A., and J. Jurka. 2006. Positive selection on the non-homologous end-joining factor Cernunnos-XLF in the human lineage. Biology Direct **1**:15.

Plomin, R., D. M. Turic, L. Hill, D. E. Turic, M. Stephens, J. Williams, M. J. Owen *et al.* 2004. A functional polymorphism in the succinate-semialdehyde dehydrogenase (aldehyde dehydrogenase 5 family, member A1) gene is associated with cognitive ability. Molecular Psychiatry **9**:582–586.

Plomin, R., J. K. J. Kennedy, and I. W. Craig. 2006. The quest for quantitative trait loci associated with intelligence. Intelligence **34**:513–526.

Pulvers, J. N., and W. B. Huttner. 2009. Brca1 is required for embryonic development of the mouse cerebral cortex to normal size by preventing apoptosis of early neural progenitors. Development **136**:1859–1868.

Ramakers, G. J. A. 2002. Rho proteins, mental retardation and the cellular basis of cognition. Trends in Neurosciences **25**:191–199.

Rapin, I., K. Weidenheim, Y. Lindenbaum, P. Rosenbaum, S. N. Merchant, S. Krishna, and D. W. Dickson. 2006. Cockayne syndrome in adults: review with clinical and pathologic study of a new case. Journal of Child Neurology **21**:991–1006.

Rauch, A., C. T. Thiel, D. Schindler, U. Wick, Y. Crow, J. Ekici, A. J. van Essen *et al.* 2008. Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. Science **319**:816–819.

Raymond, F. L. 2006. X linked mental retardation: a clinical guide. Journal of Medical Genetics **43**:193–200.

Renieri, A., C. Pescucci, I. Longo, F. Ariani, F. Mari, and I. Meloni. 2005. Non-syndromic X-linked mental retardation: from a molecular to a clinical point of view. Journal of Cellular Physiology **204**:8–20.

Rightmire, G. P.. 2004. Brain size and encephalization in early to Mid-Pleistocene Homo. American Journal of Physical Anthropology **124**:109–123.

Ropers, H., and B. C. J. Hamel. 2005. X-linked mental retardation. Nature Reviews. Genetics **6**:46–57.

Schwartz, C. E., G. Gillessen-Kaesbach, M. May, M. Cappa, J. Gorski, K. Steindl, and G. Neri. 2000. Two novel mutations confirm FGD1 is responsible for the Aarskog syndrome. European Journal of Human Genetics **8**:869–874.

Shaw, P., D. Greenstein, J. Lerch, L. Clasen, R. Lenroot, N. Gogtay, A. Evans *et al.* 2006. Intellectual ability and cortical development in children and adolescents. Nature **440**:676–679.

Shi, P., M. A. Bakewell, and J. Zhang. 2006. Did brain-specific genes evolve faster in humans than in chimpanzees? Trends in Genetics **22**:608–613.

Sii-Felice, K., V. Barroca, O. Etienne, L. Riou, F. Hoffschir, P. Fouchet, F. D. Boussin *et al.* 2008. Role of Fanconi DNA repair pathway in neural stem cell homeostasis. Cell Cycle **7**:1911–1915.

Spinath, F. M., N. Harlaar, A. Ronald, and R. Plomin. 2004. Substantial genetic influence on mild mental impairment in early childhood. American Journal of Mental Retardation **109**:34–43.

Stiff, T., K. Cerosaletti, P. Concannon, M. O'Driscoll, and P. A. Jeggo. 2008. Replication independent ATR signaling leads to G2/M arrest requiring Nbs1, 53BP1 and MDC1. Human Molecular Genetics **17**:3247–3253.

Su, A. I., T. Wiltshire, S. Batalov, H. Lapp, K. A. Ching, D. Block, J. Zhang *et al.* 2004. A gene atlas of the mouse and human protein-encoding transcriptomes. Proceedings of the National Academy of Sciences of the United States of America **101**:6062–6067.

Tang, B. L. 2006. Molecular genetic determinants of human brain size. Biochemical and Biophysical Research Communications **345**:911–916.

Tarpey, P. S., R. Smith, E. Pleasance, A. Whibley, S. Edkins, C. Hardy, S. O'Meara *et al.* 2009. A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation. Nature Genetics **41**:535–543.

Terracciano, A., P. Chiurazzi, and G. Neri. 2005. Fragile X syndrome. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics **137**:32–37.

Turner, G. 1996. Intelligence and the X chromosome. Lancet **347**:1814–1815.

Turner, G., and M. W. Partington. 1991. Genes for intelligence on the X chromosome. Journal of Medical Genetics **28**:429.

Vallender, E. J., and B. T. Lahn. 2004. Positive selection on the human genome. Human Molecular Genetics **13** Spec No 2:R245–R254.

Vicoso, B., and B. Charlesworth. 2006. Evolution on the X chromosome: unusual patterns and processes. Nature Reviews. Genetics **7**:645–653.

Voight, B. F., S. Wen, and J. K. Pritchard. 2006. A map of recent positive selection in the human genome. PLoS Biology **4**:e72.

Wakefield, M. J., P. Maxwell, and G. A. Huttley. 2005. Vestige: maximum likelihood phylogenetic footprinting. BMC Bioinformatics **6**:130.

Wang, W. 2007. Emergence of a DNA-damage response network consisting of Fanconi Anaemia and BRCA proteins. Nature Reviews. Genetics **8**:735–748.

Wang, E. T., and R. K. Moyzis. 2007. Genetic evidence for ongoing balanced selection at human DNA repair genes ERCC8, FANCC, and RAD51C. Mutation Research **616**: 165–174.

Wang, E. T., G. Kodama, P. Baldi, and R. K. Moyzis. 2006. Global landscape of recent inferred Darwinian selection for homo sapiens. Proceedings of the National Academy of Sciences of the United States of America **103**:135–140.

Wang, H., H. Chien, N. Osada, K. Hashimoto, S. Sugano, T. Gojobori, C. Chou *et al.* 2007. Rate of evolution in

brain-expressed genes in humans and other primates. PLoS Biology **5**:e13.

Wang, J., Y. Li, and B. Su. 2008. A common SNP of MCPH1 is associated with cranial volume variation in Chinese population. Human Molecular Genetics **17**:1329–1335.

Willems, P. J. 2007. Cognition genes on autosomes: the paradox. Clinical Genetics **72**:9–12.

Witelson, S. F., H. Beresh, and D. L. Kigar. 2006. Intelligence and brain size in 100 postmortem brains: sex, lateralization and age factors. Brain **129**:386–398.

Woods, C. G., J. Bond, and W. Enard. 2005. Autosomal recessive primary microcephaly (MCPH): a review of clinical, molecular, and evolutionary findings. American Journal of Human Genetics **76**:717–728.

Yang, Z. 2007. PAML 4: phylogenetic analysis by maximum likelihood. Molecular Biology and Evolution **224**:1586–1591.

Zanni, G., Y. Saillour, M. Nagara, P. Billuart, L. Castelnau, C. Moraine, L. Faivre *et al.* 2005. Oligophrenin 1 mutations frequently cause X-linked mental retardation with cerebellar hypoplasia. Neurology **65**:1364–1369.

Zechner, U., M. Wilda, H. Kehrer-Sawatzki, W. Vogel, R. Fundele, and H. Hameister. 2001. A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution? Trends in Genetics **17**:697–701.

Zha, S., F. W. Alt, H. Cheng, J. W. Brush, and G. Li. 2007. Defective DNA repair and increased genomic instability in cernunnos-XLF-deficient murine ES cells. Proceedings of the National Academy of Sciences of the United States of America **104**:4518–4523.

Zhang, J. 2003. Evolution of the human ASPM gene, a major determinant of brain size. Genetics **165**:2063–2070.

Zhang, C., D. K. Bailey, T. Awad, G. Liu, G. Xing, M. Cao, V. Valmeekam *et al.* 2006a. A whole genome long-range haplotype (WGLRH) test for detecting imprints of positive selection in human populations. Bioinformatics **22**:2122–2128.

Zhang, Y., J. Zhou, and C. U. Lim. 2006b. The role of NBS1 in DNA double strand break repair, telomere stability, and cell cycle checkpoint control. Cell Research **16**:45–54.

