Elsevier statement on Research4Life

Research4Life—Hinari, Agora, and Oare—is a cornerstone in Elsevier’s goal of achieving universal access to scientific, technical, and medical research information. We were among the founders of the initiative, and we are the largest contributor of journals to the programme. We have continually added more journals and now more books to the programme.

Achieving our goal of universal access to high-quality information in a sustainable way will require a number of different models for getting information to those who need it, both commercial and philanthropic. Free and low-cost access in countries that cannot afford to purchase journals and books will continue to be a central element of that effort. In some countries this will be provided through philanthropic programmes. In other countries it will be through highly discounted commercial agreements for access, because these can offer greater flexibility in terms of content and services provided. The right options will vary from country to country and between institutions within a country, depending on their particular circumstances. Full access has the additional advantage of offering more content than is available to Research4Life; greater flexibility in choosing content, and more service and more support for institutions that are rapidly developing their research capacity; some countries and institutions may prefer to have these options as they develop their research programmes.

During the past 2 years, Elsevier has been working closely and collaboratively with the University Grants Commission of Bangladesh, all the key universities, and the World Bank to establish a proposed consortium agreement, recognising that Bangladesh might well be a country that could move from access under Research4Life to access under a discounted commercial agreement. The culmination of this effort is a commitment to move to a free access trial of Elsevier’s SciVerse ScienceDirect in 2011, with the aim to become a consortium agreement in 2012 at the latest. Unfortunately, there were technical delays in Bangladesh and access under Research4Life was terminated before the free access trial began. This was not well communicated to all Research4Life users and we are correcting our mistake. Access in Bangladesh under Research4Life is now restored so we can accomplish the transition without disrupting access.

Research4Life is not our only access programme in Bangladesh. Some institutions in Bangladesh have ongoing access through our agreement with the Royal Tropical Institute in Amsterdam. However, the temporary disruption of access in Bangladesh highlighted the potential that, in the course of our planned transition, some deserving institutions in the country may not be covered under the planned consortium agreement. We are therefore reviewing our transition plan in an effort to avoid creating new access gaps in our transition to a more sustainable model.

As with Bangladesh, in the future other countries will be able to transition from Research4Life to commercial agreements that are responsive to the needs of the country, affordable, and offer more value for the research community. However, we will not implement any new exclusions until we can be sure that they can be accomplished without significant disruption to research.

In 2010 alone, there were 3.1 million downloads from SciVerse ScienceDirect from Research4Life by researchers in Bangladesh, a 20% increase over the previous year. As a reflection of our commitment to its continued success, we are now overseeing Elsevier’s contribution to Research4Life as part of our Universal Access group and strategy.

Our strong support for Research4Life continues, as will its success as the primary channel in countries that could not otherwise afford access to the world’s scientific literature.

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Structural variations in attention-deficit hyperactivity disorder

Nigel Williams and colleagues (Oct 23, p 1401) report a higher frequency of large structural variants in children with attention-deficit hyperactivity disorder (ADHD) than in individuals without this diagnosis. We feel that their conclusion of an excess rate of large copy number variants (CNVs) in individuals with ADHD is not supported by the evidence presented.

The paper reports 5.6-fold enrichment of large CNVs in children with ADHD and an intelligence quotient (IQ) of less than 70, and a 2.1-fold enrichment in children with ADHD and an IQ of greater than 70. However, the mean IQ of the latter group (89) is still presumably lower than that of controls (unreported). A more informative approach would have been to match cases and controls closely for IQ. Without this correction, the ADHD enrichment is likely to be a confounding variable of the established causal relation between large CNVs and intellectual disability. Our previous study that corrected for IQ did not find an increase in CNV frequency in ADHD.1

Furthermore, the CNV size threshold of 500 kb seems arbitrary. We suggest as a more valid approach either a gene-based analysis or one that considers all CNVs with a threshold based on content of single nucleotide polymorphisms (SNPs) and that meets an acceptable detection quality standard (typically 10–20 SNPs for Illumina
arrays). In fact, results from Williams and colleagues’ supplementary table 3 (webappendix p 26) indicate that, when a threshold of 200 kb is used, ADHD CNV enrichment is no longer seen.

Williams and colleagues’ study merely contributes to a substantial body of existing work that has established ADHD as a highly heritable disorder with unique variants that are shared by other neuropsychiatric disorders.

We declare that we have no conflicts of interest.

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2 Elia J, Gai X, Xie HM, et al. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry 2010; 15: 537–46.

Authors’ reply

Josephine Elia and colleagues suggest that the enrichment of large, rare copy number variants (CNVs) in attention-deficit hyperactivity disorder (ADHD) that we reported is likely to be a confounding variable of the known causal relation between large CNVs and intellectual disability.

We of course recognise that ADHD (as with other neurodevelopmental disorders) is associated with a lower intelligence quotient (IQ) and with intellectual disability, and for this reason all our main analyses are based on those with an IQ greater than 70. In these children we saw no association between possession of large, rare CNVs and IQ test scores (p=0.13). Unfortunately, we cannot do the corresponding analyses in the control sample because the IQ data are not available; however, since they were collected as part of a UK birth cohort they include individuals spanning a wide IQ spectrum which presumably includes those with a lower IQ.

Furthermore, since evidence suggests that ADHD and IQ have shared genetic influences, the suggestion by Elia and colleagues that we should have closely matched IQ in the cases and controls is in our view unwarranted, with some arguing that for disorders such as ADHD this can result in overmatching and lead to anomalous and counter-intuitive findings. Elia and colleagues’ suggestion is surprising since in their previous paper there is no evidence to support their claim that the CNV data reported were corrected for IQ.

The CNV size threshold we applied was not “arbitrary”: there are good reasons to focus on large rare CNVs and these led to our a-priori decision to restrict our analysis to CNVs larger than 500 kb. As we stated in our paper, CNVs in this size range are called with greater accuracy and show better concordance across different platforms. Moreover, large, rare CNVs currently show the most robust evidence for association with neurodevelopmental disorders such as schizophrenia. In fact, 51 of the 58 syndromes associated with sub-microscopic chromosomal imbalances described in the DECIPHER database are attributable to CNVs larger than 500 kb. This association could be due to one very obvious biological distinction between small and large CNVs—that larger CNVs are much more likely to affect multiple genes.

Although not our primary analysis, analysis of all rare CNVs larger than 200 kb shows a significant increase in the average CNV size per person (p=1.1×10^−10), which again indicates that the children with ADHD have more large CNVs. Elia and colleagues suggest instead a gene-based approach, but do not provide any evidence that this confers superior validity. Such an approach requires several arbitrary assumptions, not least in the definition of gene boundaries and that all exons and gene isoforms are functionally equal.

We agree that our results build on a large body of genetics research on ADHD, and that is cited in the paper. We do not agree that our specific findings of (a) an increased burden of large, rare CNVs in ADHD, (b) overlap of ADHD CNVs and specific loci implicated in autism and schizophrenia, and (c) significant excess of a specific CNV in ADHD have been previously shown.

Finally, we agree that our findings must be tested in other samples, and this is highlighted in our Discussion. We are aware that such work is being undertaken and look forward to the results being published.

We declare that we have no conflicts of interest.

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3 Elia J, Gai X, Xie HM, et al. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry 2010; 15: 537–46.

Nigel Williams and colleagues’ make an important contribution to the question of whether attention-deficit hyperactivity disorder (ADHD) has a genetic component. Despite this, we have concerns about the press release
issued by The Lancet, and its effect on the wider reporting of the study.

The press release (which we have access to, but to our knowledge is not widely available in the public domain) was issued with the following title: “Study is the first to find direct evidence that ADHD is a genetic disorder”. One of the authors of Williams and colleagues’ paper is quoted as saying that “Now we can say with confidence that ADHD is a genetic disease and that the brains of children with this condition develop differently to those of other children”. We question whether these statements accurately summarise the evidence presented in the Article, which itself concludes with the more moderate: “findings provide genetic evidence of an increased rate of large [copy number variants] in individuals with ADHD and suggest that ADHD is not purely a social construct”.

Therefore, in our opinion, this press release carries the potential to misinform journalists and, by extension, the general public. We raise concerns about the potential oversimplification and the confusing effect this has for journalists attempting to further interpret and report what is a complex scientific paper.

We declare that we have no conflicts of interest.

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SNPs and coronary heart disease

The paper by Samuli Ripatti and colleagues (Oct 23, p 1393)1 on a multilocus genetic risk score for predicting coronary heart disease (CHD) concludes that the clinical use of this panel of 13 single nucleotide polymorphisms remains to be defined. One conclusion is clear: the score is not useful in predicting CHD and hence in screening for this disorder. Ripatti and colleagues conclude that it is possible to identify the 20% of individuals who are at about a 70% increased risk of a first CHD event by comparing the risk in the top 20% with that in the lowest 20%. The risk difference is small (relative risk 1.7) and what is relevant to risk prediction is even smaller. It is the increase in risk compared with people who have not been tested, which is only 40%, not 70%. The relative risk of 1.7 in their paper translates into a detection rate (sensitivity) of 14% for a 10% false-positive rate, indicating no practical discriminatory value. This translation can be calculated using a published risk-screening converter.2

If there is to be any clinical value of the proposed genetic risk score for CHD it will not be in screening or disease prediction.

We declare that we have no conflicts of interest.

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Samuli Ripatti and colleagues examined 13 recently discovered genetic risk factors for coronary heart disease (CHD) to estimate the magnitude of risk they confer above and beyond traditionally established risk factors. Ripatti and colleagues conclude that a genetic risk score comprising these 13 single nucleotide polymorphisms (SNPs) was associated with a significant increase in the risk of prevalent and incident CHD in a subsample of individuals of European ancestry.

Although this is an important question and the study is methodologically sound and represents the largest effort to date on this topic, it was very disappointing to see that, after millions, and perhaps billions, of dollars invested in genomic research over the past few years, there is so little to show for it. Although the score was associated with incident disease, it failed to improve risk discrimination. The fact that non-invasive, easily available, and often inexpensive traditional risk factors for CHD such as age, gender, or blood pressure outperform by a large margin a genetic risk score reaffirms the importance of comprehensive physical examination and medical history as the cornerstones of the diagnostic process for CHD.3

I declare that I have no conflicts of interest.

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Authors’ reply

The main aim of our study was to validate recently discovered genetic risk factors for coronary heart disease (CHD) and to estimate the magnitude of risk conferred by these genetic risk factors in population-based prospective cohort studies. We showed that the joint effect of 13 known genetic loci—when measured as relative risk between the top and bottom 20% of individuals—was 1.7 (95% CI 1.4–2.0), even after adjusting for known Framingham risk factors1 and family history of CHD. The effect is comparable to that of systolic blood pressure (hazard ratio 1.7, 95% CI 1.2–2.3) but slightly smaller than for LDL cholesterol (2.1, 1.6–2.8).

The figure further compares the distributions of the genetic risk score...