

Thank you for covering this topic, it is nice that you think the Risch et al paper is newsworthy.

Thank you also for contacting us. We are currently travelling, and thus are unable to take part in an interview. However, we provide the following comments, which we hope are useful for you.

Our overall summary is: What is needed is not less research into gene-environment interaction, as Risch et al recommend, but more research of better quality, and a more thorough and thoughtful evaluation of it.

There are 4 points we think your readers ought to understand.

1. This article ignores the complete body of scientific evidence. In the past 6 years, extensive research in experimental neuroscience using both animals and humans has validated the original report by showing that 5-HTTLPR short allele-carriers are excessively vulnerable to stress. Experimental studies that expose human participants to stressors in the laboratory show that individuals having the 5-HTTLPR short genotype have greater stress responses on measures of cognitive reactivity (e.g. Beevers et al. 2007; Fox et al. 2009), hormonal reactivity (e.g. Chen et al., 2009; Gotlib et al. 2008), physiological reactivity (e.g. Lonsdorf et al. 2009) and reactivity in the brain's emotion-circuitry (e.g. Hariri et al. 2005; Canli et al. 2006). This vulnerability of 5-HTTLPR S carriers has also been confirmed in animal research (e.g., Carola et al. 2008; Barr et al. 2004; Kalin et al. 2008; Watson et al. 2009). Further validation comes from studies which have shown that 5-HTTLPR Short allele carriers are vulnerable not only to depression, but also to other mental-health problems caused by stress, including PTSD and anxiety (e.g. Gunthert et al., 2007; Kilpatrick et al. 2007).
2. This article misrepresents the body of observational studies. The article not only opted not to analyse, but also failed to mention, the existence of well-designed studies that compared individuals exposed to stress. For example, studies of children who are victims of abuse (e.g., Cicchetti et al. 2007; Kaufman et al. 2004) and patients suffering hip fractures, strokes and coronary heart disease (Kohen et al. 2008; Lenze et al., 2007; Otte et al. 2007) have shown that people exposed to these stressors are more vulnerable to mental health problems if they carry the short allele of the 5-HTTLPR. Several other positive replications from studies with very strong research designs were omitted from the meta-analysis as well (Kendler et al. 2005; Drachmann-Bukh et al. 2009; Lazary et al. 2008).

3. Within the smaller subset of studies that is covered in the meta-analysis, there is wide variation in the findings; some reported positive replication, others did not. Whenever an inconsistent pattern of results like this is observed across studies, the next step in science is to try to understand why some studies report a positive finding and others do not. In the article, an attempt was made to test whether this variation across studies was significant enough to warrant investigation; the article says it was not statistically significant. However, we have learned that the test fell just short of statistical significance. This means that it is essential for researchers to now look for commonalities among the studies that do, versus do not, replicate the original finding.
4. One obvious characteristic that varies widely across studies in the meta-analysis is quality. Not all scientific studies are created equal. For example, meta-analysis gives more mathematical weight to studies with the largest samples. But in this case the studies having the largest number of participants were not the best quality studies. The big studies had to collect their data through telephone calls or self-complete postal questionnaires, which are known to be weak methods of measuring life events and assessing mental health problems such as depression. Approximately 14,000 individuals were analyzed, but over 8,000 of them reported their stress and depression over the phone or through the mail. Not surprisingly, these big studies with weak measures did not find positive results, and this tilted the meta-analysis toward a null finding.

What is needed is not less research into gene-environment interaction, as Risch et al. recommend, but more research of better quality, and more thorough and thoughtful evaluation of it.

Science aside, we are musing about why these respected scientists are concerned that, as they write “substantial resources have been devoted to” research on genetic sensitivity to environmental causes of disease. In fact, the funding devoted to gene-environment studies has been miniscule in comparison to the funding devoted to genome-wide association studies. It has not escaped our notice that the loudest objections to gene-environment research generally come from research teams who have collected only DNA, but neglected to collect any data on environmental causes of disease.

Other scientists who may be able to speak about this area of research:

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