

Can genetics explain the higher risk of worsening knee pain in offspring of people with total knee replacement for severe primary knee osteoarthritis?

We read with great interest a recent paper by Pan *et al.*¹ The authors found that offspring of those with severe knee osteoarthritis (OA) had an increased risk of worsening knee pain over 8 years when compared with controls who had no family history of OA.¹ Based on these results, the authors suggested that genetic factors may be involved in the pathogenesis of knee pain.¹

We commend the authors for performing a longitudinal study on the offspring of people with a total knee replacement (TKR) for severe OA. However, we would like to comment on several issues besides those raised by Zeng *et al.*² First, since the study duration was long and patient characteristics were only assessed at the beginning of the study, it is unclear if any change in group composition has occurred during the study period. For example, some patients' weight may have changed significantly in 8 years. Similarly, some members of the control group may have parents developing OA that required TKR during this period. We would also like to note that the parents' age was not controlled in this study. The controls' parents may not have had enough time to develop OA at the beginning of the study if their age was significantly younger than that of the offspring's parents.

Second, we believe that a longitudinal human study is a poor way to support genetic factor as a potential explanation for the worsening knee pain in the offspring when compared with the controls. Many other factors besides structural and genetic can be implicated the difference in pain tolerance between two groups. For example, offspring are more likely to have history of smoking than controls ($p=0.008$). Previous large epidemiologic studies have shown that former and current heavy smokers have higher odds for experiencing moderate and intense pain in more locations than people who never smoked.³ This relation held true even after adjustment for analgesic medicament use and behaviour-related risk factors.³ In addition, during phase 1, the percentage of offspring with knee pain was significantly higher than that of controls (<0.001). This indicates that offspring were more likely to have knee pain at baseline than

controls. Increase in pain perception can be exponential, which explains why the knee pain scale was not different at phase 2, but was different at phase 3. Finally, the assessment of knee pain is very subjective. All the subscales used were probably correlated with each other.

In conclusion, a longitudinal human study without adequate assessment of patient characteristics at baseline and at the end of the study is a poor way to decipher genetic contribution towards difference in pain perception.

Ting Zou,¹ Li Yang,¹ Ashley M Lee,² Xia Tan,¹ Elizabeth Wong,² Harrison X Bai²

¹Department of Neurology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, P.R. China

²Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence to Dr Li Yang, Department of Neurology, The Second Xiangya Hospital, Central South University, No. 139 Middle Renmin Road, Changsha, Hunan 410011, P.R. China; yangli762@gmail.com

Contributors TZ, LY and HXB conceived of the study. TZ, AML, LY, XT and EW drafted the letter. All authors discussed the data and contributed to and approved the final version.

Funding LY was supported by the Sheng-Hua Yuying project of Central South University.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.



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To cite Zou T, Yang L, Lee AM, *et al.* *Ann Rheum Dis* 2016;**75**:e45.

Received 17 February 2016

Accepted 20 February 2016

Published Online First 8 March 2016

Ann Rheum Dis 2016;**75**:e45. doi:10.1136/annrheumdis-2016-209380

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