A potential role for a genetic variation of AKAP5 in human aggression and anger control

Sylvia Richter1,2,3, Xenia Gorny2, Josep Marco-Pallares4, Ulrike M. Krämer5, Judith Machts6, Adriana Barman2, Hans-Gert Bernstein1, Rebecca Schüle6, Ludger Schöls8,9, Antoni Rodriguez-Fornells4,10, Carsten Reissner11, Torsten Wüstenberg12, Hans-Jochen Heinz2,3,6, Eckart D. Gundelfinger2, Emrah Düzel3,6,13,14, Thomas F. Münte5, Constanze I. Seidenbecher2 and Björn H. Schott2,6,12*

1 Department of Clinical Psychology, University of Salzburg, Salzburg, Austria
2 Leibniz Institute for Neurobiology, Magdeburg, Germany
3 Helmholtz Center for Neurodegenerative Diseases, Magdeburg, Germany
4 Department of Physiology II, University of Barcelona and IDIBELL, Barcelona, Spain
5 Department of Neurology, University of Lübeck, Lübeck, Germany
6 Department of Neurology, University of Magdeburg, Magdeburg, Germany
7 Department of Psychiatry, University of Magdeburg, Magdeburg, Germany
8 Department of Neurology, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
9 German Center of Neurodegenerative Diseases, Tübingen, Germany
10 Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain
11 Department of Anatomy, University of Münster Medical School, Münster, Germany
12 Department of Psychiatry, Campus Mitte, Charité University Hospital, Berlin, Germany
13 Institute of Cognitive Neuroscience, University College London, London, UK
14 Institute of Cognitive Neurology and Dementia Research, University of Magdeburg, Magdeburg, Germany

The A-kinase-anchoring protein 5 (AKAP5), a post-synaptic multi-adaptor molecule that binds G-protein-coupled receptors and intracellular signaling molecules has been implicated in emotional processing in rodents, but its role in human emotion and behavior is up to now still not quite clear. Here, we report an association of individual differences in aggressive behavior and anger expression with a functional genetic polymorphism (Pro100Leu) in the human AKAP5 gene. Among a cohort of 527 young, healthy individuals, carriers of the less common Leu allele (15.6% allele frequency) scored significantly lower in the physical aggression domain of the Buss and Perry Aggression Questionnaire and higher in the anger control dimension of the state-trait anger expression inventory. In a functional magnetic resonance imaging experiment we could further demonstrate that AKAP5 Pro100Leu modulates the interaction of negative emotional processing and executive functions. In order to investigate implicit processes of anger control, we used the well-known flanker task to evoke processes of action monitoring and error processing and added task-irrelevant neutral or angry faces in the background of the flanker stimuli. In line with our predictions, Leu carriers showed increased activation of the anterior cingulate cortex (ACC) during emotional interference, which in turn predicted shorter reaction times and might be related to stronger control of emotional interference. Conversely, Pro homozygotes exhibited increased orbitofrontal cortex (OFC) activation during emotional interference, with no behavioral advantage. Immunohistochemistry revealed AKAP5 expression in post mortem human ACC and OFC. Our results suggest that AKAP5 Pro100Leu contributes to individual differences in human aggression and anger control. Further research is warranted to explore the detailed role of AKAP5 and its gene product in human emotion processing.

Keywords: AKAP5, genetic, aggression, anger, fMRI

INTRODUCTION

Human aggression shows considerable interindividual variability. Significant contributions to aggression originate in the emotion of anger, which itself shows high variability within the population (Berkowitz and Harmon-Jones, 2004). Several studies suggest that aggressive behavior is related to interactions of environmental factors like aversive childhood experience or substance-related disorders with genetic variations in monoaminergic neuromodulatory systems, specifically dopaminergic, noradrenergic, and serotonergic neurotransmission, might influence aggressive behavior (Caspri et al., 2002; Panksepp, 2006; Kang et al., 2008; Kulikova et al., 2008; Heinz et al., 2011). Functional neuroimaging studies have demonstrated that genetic variants linked to aggression and anger are associated with altered neuronal activation patterns during emotional processing (Meyer-Lindenberg et al., 2006; Buckholtz and Meyer-Lindenberg, 2008). Up to now, genetic studies on anger and aggression have focused on variants directly related to these transmitter systems, like receptors or metabolizing...

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.