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UNIVERSITY OF TORONTO

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Toronto, Ontario, Canada

CERTIFICATE OF PARTICIPATION IN HGV2008

This letter certifies that Mohammad Mahdi Ghahramani Seno participated in the Tenth Annual Human Genome Variation Meeting.

Dr. Seno submitted the abstract, "Mutation Screening of the 3'-UTR of SHANK3 in Autism Spectrum Disorder", which was presented as a poster at the meeting.

Sincerely,

Dr. Stephen Scherer, PhD, FRSC
Senior Scientist, Genetics and Genomic Biology
Director, The Centre for Applied Genomics
Associate Chief, Research Institute, Hospital for Sick Children and
Professor, University of Toronto

Phone: 416-813-7654 x1574
Fax: 416-813-8319

On Behalf of the Organizing Committee:
Goncalo Abecasis (University of Michigan)
Anthony Brookes (University of Leicester)
Stephen Chanock (National Cancer Institute)
Thomas Hudson (Ontario Institute for Cancer Research, Toronto)
Pui-Yan Kwok (University of California, San Francisco)
Leena Peltonen (Wellcome Trust Sanger Institute)
Stephen Scherer (The Hospital for Sick Children, Toronto)

Mohammad Ghahramani Seno

Mutation Screening of the 3'-UTR of SHANK3 in Autism Spectrum Disorder

Mohammad Ghahramani Seno, Hospital For Sick Children (mgseno@sickkids.ca)

Mohammad M. Ghahramani Seno, Maryam Mashreghi-Mohammadi, Meng Sun, Jennifer Skaug, Stephen W. Scherer.

Single nucleotide mutations and CNVs at the SHANK3 locus have already been associated with Autism Spectrum Disorder (ASD). However, the 3'-untranslated region (3'-UTR) of this gene has not been evaluated in ASD for possible mutations. 3'-UTRs are targeted by microRNAs (miRNA) and any changes in these regions can potentially result in modifying/destroying miRNAs target sites or may even create new targets for miRNAs. Accordingly, we sequenced the 3'-UTR (approx. 2kb) of SHANK3 in around 90 affected individuals to check for possible single nucleotide changes (SNC) in this region. We also sequenced a small region from the last intron of SHANK3.This region has been identified as part of an EST (CR625313) which is expressed in the foetal brain. This may be indicative of a novel isoform, and mutations in that region could potentially have an adverse effect on the normal development of foetal brain. 3'-UTR sequencing of SHANK3 identified two individuals each carrying one unreported SNC. The genotype of one of these individuals at position Chr. 22: 49518335 (USCS, March 2006) was C/T. The UCSC reference genome is T at this region. The proband has an affected sibling with the same genotype at this position, while their unaffected sibling, their mother and maternal grand parents carry a T/T genotype. The father's DNA was not available for testing. The second individual had a C/T genotype at position chr. 22: 49517084 (UCSC reference genome: C). The unaffected sibling of this individual is of C/C genotype at this position. Parents were not available for genotyping. A third individual was identified to have a homozygous (T/T) SNC at the genomic position chr. 22: 49514900 (UCSC reference genome: C) at the EST region expressed in the foetal brain. Both parents and the unaffected sibling of this case have a C/T genotype at this position. Currently, we are investigating whether these SNCs have any functional effect on the expression level of the SHANK3 protein. Moreover, we are investigating whether CR625313 might be indicative of the presence of a previously unidentified isoform of SHANK3 expressed in foetal brain.