Multi-ancestry genetic study in 5,876 patients identifies an association between excitotoxic genes and early outcomes after acute ischemic stroke

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ABSTRACT

During the first hours after stroke onset neurological deficits can be highly unstable: some patients rapidly improve, while others deteriorate. This early neurological instability has a major impact on long-term outcome. Here, we aimed to determine the genetic architecture of early neurological instability measured by the difference between NIH stroke scale (NIHSS) within six hours of stroke onset and NIHSS at 24h (Δ NIHSS). A total of 5,876 individuals from seven countries (Spain, Finland, Poland, United States, Costa Rica, Mexico and Korea) were studied

using a multi-ancestry meta-analyses. We found that 8.7% of Δ NIHSS variance was explained by common genetic variations, and also that early neurological instability has a different genetic architecture than that of stroke risk. Seven loci (2p25.1, 2q31.2, 2q33.3, 4q34.3, 5q33.2, 6q26 and 7p21.1) were genome-wide significant and explained 2.1% of the variability suggesting that additional variants influence early change in neurological deficits. We used functional genomics and bioinformatic annotation to identify the genes driving the association from each loci. eQTL mapping and SMR indicate that *ADAM23* (log Bayes Factor (LBF)=6.34) was driving the association for 2q33.3. Gene based analyses suggested that *GRIA1* (LBF=5.26), which is predominantly expressed in brain, is the gene driving the association for the 5q33.2 locus. These analyses also nominated *PARK2* (LBF=5.30) and *ABCB5* (LBF=5.70) for the 6q26 and 7p21.1 loci. Human brain single nuclei RNA-seq indicates that the gene expression of *ADAM23* and *GRIA1* is enriched in neurons. *ADAM23*, a pre-synaptic protein, and *GRIA1*, a protein subunit of the AMPA receptor, are part of a synaptic protein complex that modulates neuronal excitability. These data provides the first evidence in humans that excitotoxicity may contribute to early neurological instability after acute ischemic stroke.

Evidence before this study No previous genome-wide association studies have investigated the genetic architecture of early outcomes after ischemic stroke.

Added Value of this study This is the first study that investigated genetic influences on early outcomes after ischemic stroke using a genome-wide approach, revealing seven genome-wide significant loci. A unique aspect of this genetic study is the inclusion of all of the major ethnicities by recruiting from participants throughout the world. Most genetic studies to date have been limited to populations of European ancestry.

Implications of all available evidence The findings provide the first evidence that genes implicating excitotoxicity contribute to human acute ischemic stroke, and demonstrates proof of principle that GWAS of acute ischemic stroke patients can reveal mechanisms involved in ischemic brain injury.

Competing Interest Statement

CC receives research support from: Biogen, Eisai, Alector and Parabon, and is a member of the advisory board of ADx Healthcare and Vivid Genomics. JML receives research support from Biogen, and is a consultant for Regenera. EAT and LCB are employed by Biogen. JFA has received speaker or consultant honoraria from Bayer, Boehringer Ingelheim, Pfizer-BMS, Daiichi Sankyo, Amgen and Medtronic. TT receives or has received research support from Bayer, Boehringer Ingelheim and Bristol Myers Squibb; he is a member of advisory boards for Bayer, Boehringer Ingelheim, Bristol Myers Squibb and Portola Pharmaceuticals; and he is granted international patents: new therapeutic uses (method to prevent brain edema and reperfusion injury), and thrombolytic compositions (method to prevent post-thrombolytic hemorrhage formation). The

fundamental of the study had no role in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication

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Author Declarations

I confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained.

Yes

The details of the IRB/oversight body that provided approval or exemption for the research described are given below:

The study was approved by the Institutional Review Boards at every participating site. Written informed consent was obtained from all participants or their family members. All research was performed according to the approved protocols and consents

All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Yes

I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).

Yes

I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.

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