

Mapping of chromosomal breakpoints associated with corpus callosum agenesis and epilepsy: a bypass for isolation of candidate disease genes

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Purpose

Agenesis of corpus callosum is a congenital anomaly, which is a part of more than 50 different human congenital syndromes; however non-syndromic forms are the most common. In the majority of the non-syndromic forms the underlying gene defects are unknown. Here we report an 11 year old girl with a *de novo* balanced translocation t(2;11)(p25.1;p15.1), mental retardation, epilepsy and partial agenesis of corpus callosum.

Methods

Cytogenetic analysis was conducted on G-banded metaphases of cultured peripheral lymphocytes. Translocation breakpoints were mapped by fluorescence in situ hybridisation (FISH) using bacterial artificial chromosomes (BACs) from the regions of interest.

Results

By cytogenetic analysis, a balanced translocation t(2;11)(p25.1;p15.1) *de novo* was identified. The breakpoint on chromosome 2p25 is mapped within a 200 kb region and the 11p15 breakpoint disrupts an evolutionary conserved gene empty region (gene desert) located downstream of the transcription factor SOX6. We propose that the translocation removes distant *cis*-acting regulatory elements causing aberrant expression of SOX6 during development.

Conclusions

The present study describes a balanced translocation in a patient with epilepsy and partial corpus callosum agenesis, where one of the breakpoints is in a gene desert, that might be of interest. This study may add new genes and regulatory mechanisms to the current list of candidate loci involved in epilepsy and corpus callosum agenesis.

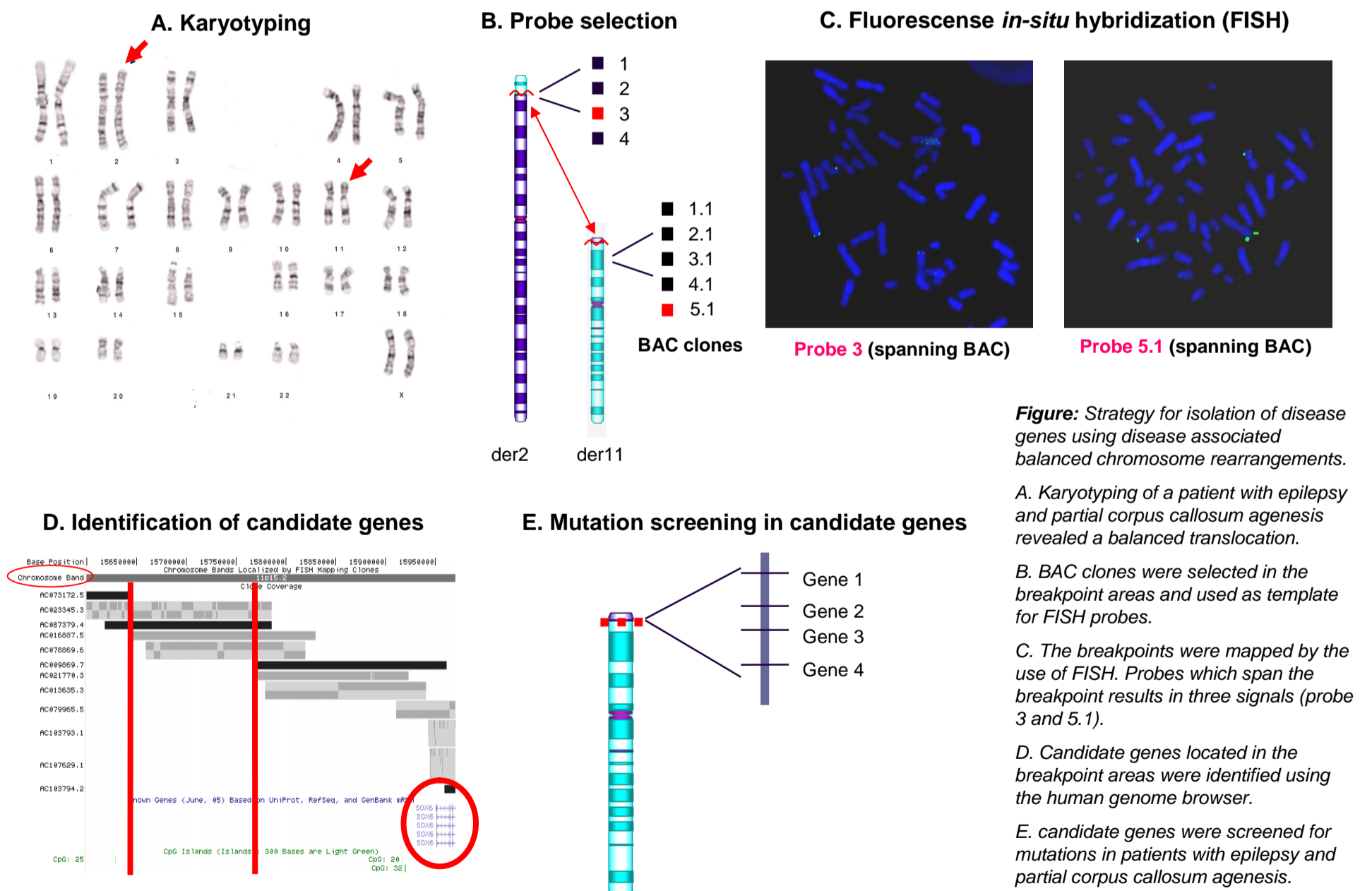


Figure: Strategy for isolation of disease genes using disease associated balanced chromosome rearrangements.

A. Karyotyping of a patient with epilepsy and partial corpus callosum agenesis revealed a balanced translocation.

B. BAC clones were selected in the breakpoint areas and used as template for FISH probes.

C. The breakpoints were mapped by the use of FISH. Probes which span the breakpoint results in three signals (probe 3 and 5.1).

D. Candidate genes located in the breakpoint areas were identified using the human genome browser.

E. candidate genes were screened for mutations in patients with epilepsy and partial corpus callosum agenesis.