Causes du tremblement essentiel

- Toxiques ?
- Génétiques?
  - Cas familiaux dans 50-70% des cas; transmission autosomique dominante; âge de début et formes cliniques variables dans une même famille; maladie multifactorielle

Données récentes en génétique moléculaire

- Récepteur dopaminergique:

  - mutation du gène du récepteur dopaminergique D3 proche du locus ETM1 du chr. 3q13 sur familles françaises et nord-américaines, données non confirmées en Asie, et sur populations allemandes et danoises

Genetics of essential tremor

Meta-analysis and review

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ABSTRACT

Objective: To provide a comprehensive meta-analysis and review of the clinical and molecular genetics of essential tremor (ET).

Methods: Studies were reviewed from the literature. Linkage studies were analyzed applying criteria used for monogenic disorders. For association studies, allele counts were extracted and allelic association calculated whenever possible. A meta-analysis was performed for genetic markers investigated in more than 3 studies.

Results: Linkage studies have shown conclusive results in a single family only for the locus ETM2 (essential tremor monogenetic locus 2, logarithm of odds score [lod] > 3.3). None of the 3 ETM loci has been confirmed independently with a lod score >2.0 in a single family. A mutation in the *FUS* gene (fused in sarcoma) was found in one ET family by exome sequencing. Two genome-wide association studies demonstrated association between variants in the *LINGO1* gene (leucine-rich repeat and Ig domain containing 1) and the *SLC1A2* gene (solute carrier family 1 member 2) and ET, respectively. Our meta-analysis confirmed the association of rs9652490 in *LINGO1* with ET. Candidate gene mutation analysis and association studies have not identified reproducible associations.

Conclusion: Problems of genetic studies of ET are caused by the lack of stringent diagnostic criteria, small sample sizes, lack of biomarkers, a high phenocopy rate, evidence for nonmendelian inheritance, and high locus heterogeneity in presumably monogenic ET. These issues could be resolved by better worldwide cooperation and the use of novel genetic techniques. **Neurology® 2014;82:1000–1007**

Données anatomiques récentes sur le TE

- Depuis plus d'un siècle, plusieurs études anatomiques ont été réalisées, mais avec des résultats contradictoires, le plus souvent normaux
- Elan Louis, New York:

doi:10.1093/brain/awm266 *Brain* (2007), **130**, 3297–3307

Neuropathological changes in essential tremor: 33 cases compared with 21 controls

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- Tronc cérébral: corps de Lewy

- Cervelet: réduction du nombre de cellules de Purkinje, hétérotopies et présence de dilatations dendritiques ou « torpedoes » dans le cervelet

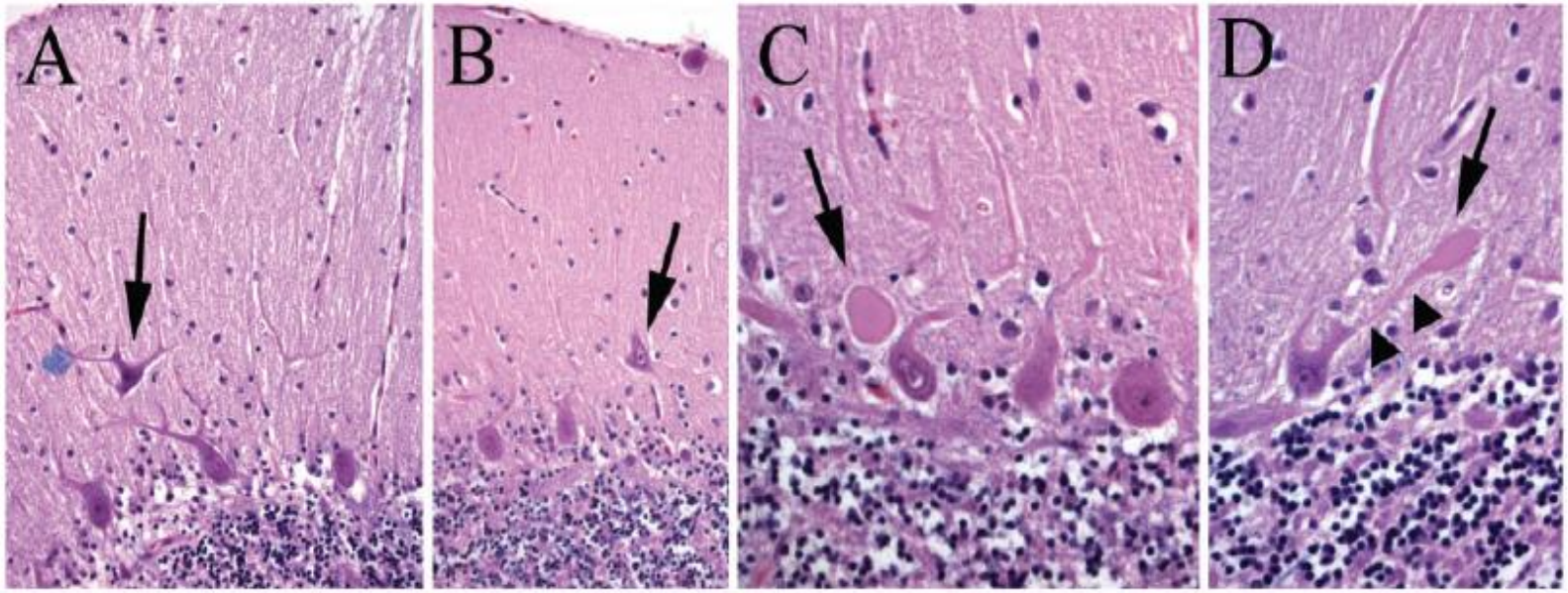
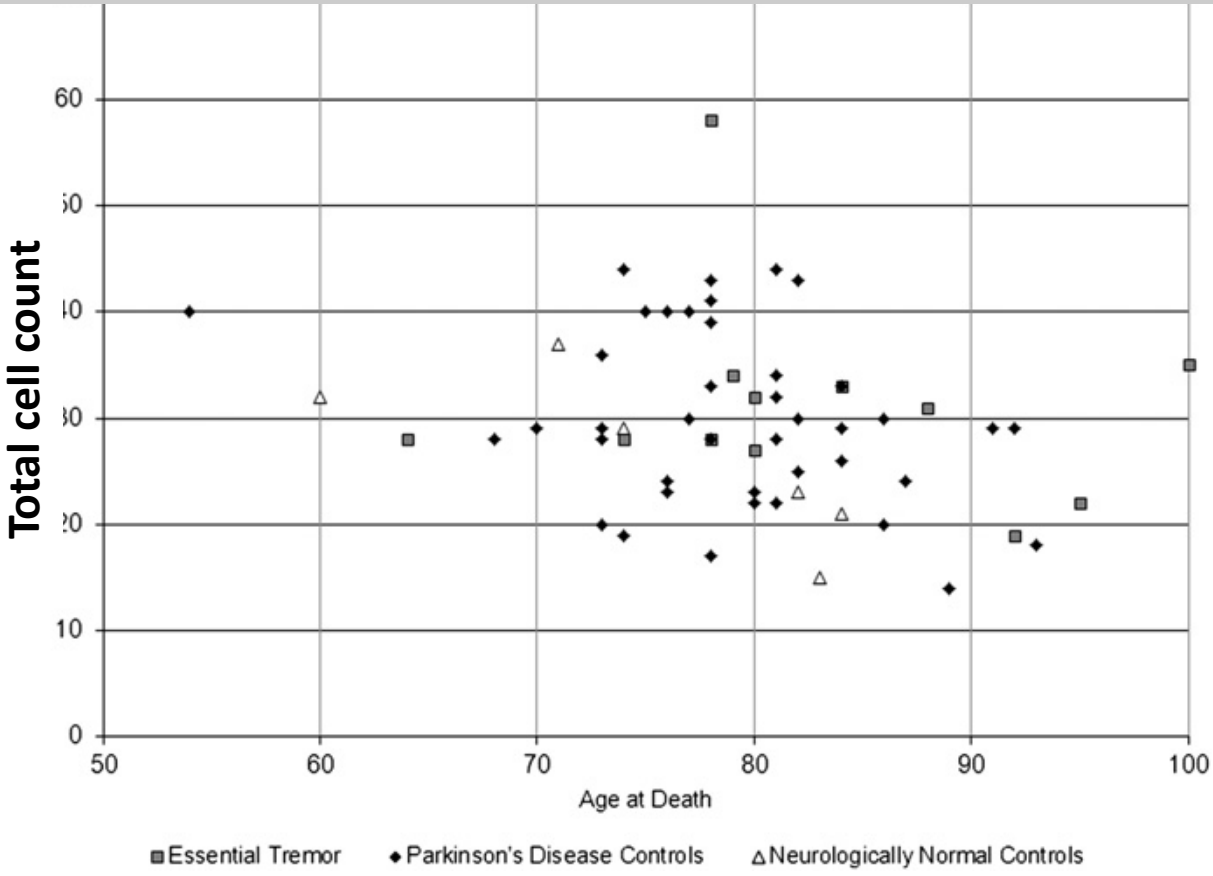


Fig. 3 Purkinje cell heterotopias and dendrite swellings in cerebellum from an ET case. LH&E-stained cerebellar cortical sections. In **A** and **B**, the cell body of an occasional Purkinje cell is displaced upward into the molecular layer (arrows) (200× magnification). In **C** and **D**, there are glassy, eosinophilic swellings in the molecular layer adjacent to Purkinje cell bodies (arrows). Connection to a Purkinje cell dendrite (arrowheads in **D**) clearly identifies this as a dendrite swelling (400× magnification).

Essential tremor is not dependant upon cerebellar Purkinje cell loss

Rajput et al., Parkinsonism and Related Disorders 2012:1-3



Pas de diminution du nombre de cellules de Purkinje

(12 ET vs 6 témoins et 41 parkinsoniens), jusqu'à 34 ans d'évolution du TE

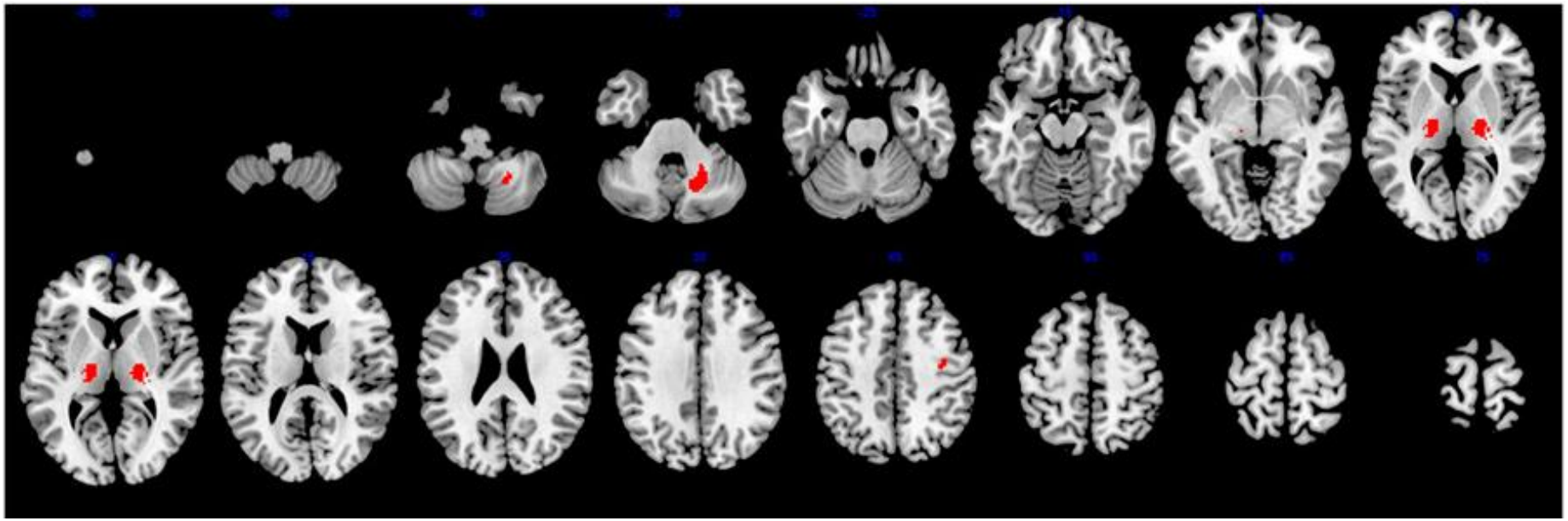
Etude de « Non lewy body variant »

GABAergic dysfunction in essential tremor: an 11C-flumazenil PET study.

J Nucl Med. 2010 Jul;51(7):1030-5.

Boecker et al.

Hypothèse GABA-ergique dysfonctionnelle



Augmentation de la liaison du 11C-flumazenil (agoniste des récepteurs GABA-A dans le TE: Noyau dentelé / thalamus ventrolatéral, cortex prémoteur

doi:10.1093/brain/awr301 Brain 2012: 135; 105–116 | 105

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Defective dentate nucleus GABA receptors in essential tremor

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The development of new treatments for essential tremor, the most frequent movement disorder, is limited by a poor understanding of its pathophysiology and the relative paucity of clinicopathological studies. Here, we report a post-mortem decrease in $GABA_A$ (35% reduction) and $GABA_B$ (22–31% reduction) receptors in the dentate nucleus of the cerebellum from individuals with essential tremor, compared with controls or individuals with Parkinson's disease, as assessed by receptor-binding autoradiography. Concentrations of $GABA_B$ receptors in the dentate nucleus were inversely correlated with the duration of essential tremor symptoms ($r^2 = 0.44$, $P < 0.05$), suggesting that the loss of $GABA_B$ receptors follows the progression of the disease. *In situ* hybridization experiments also revealed a diminution of $GABA_{B(1a+b)}$ receptor messenger RNA in essential tremor (↓27%). In contrast, no significant changes of $GABA_A$ and $GABA_B$ receptors (protein and messenger RNA), GluN2B receptors, cytochrome oxidase-1 or GABA concentrations were detected in molecular or granular layers of the cerebellar cortex. It is proposed that a decrease in GABA receptors in the dentate nucleus results in disinhibition of cerebellar pacemaker output activity, propagating along the cerebello-thalamo-cortical pathways to generate tremors. Correction of such defective cerebellar GABAergic drive could have a therapeutic effect in essential tremor.

Defective dentate nucleus GABA receptors in essential tremor

Paris-Robidas S et al., **Brain 2012**:135;105-116