FGF14

FGF14 (Fibroblast Growth Factor 14) is an atypical member of the fibroblast growth factor family. Unlike classical FGFs, it is not secreted and does not act as a ligand for FGF receptors. Instead, it functions intracellularly, primarily within the central nervous system.

Key Features

Gene location: Chromosome 13q33.1 (human)

Expression: Highly expressed in the brain, including the cerebellum, hippocampus, and cerebral cortex

Main function: Modulates voltage-gated sodium channels (Nav), particularly at the axon initial segment. This affects neuronal excitability, action potential initiation, and signal propagation.

Protein interactions: Binds to Nav α-subunits (e.g., Nav1.6), regulating their trafficking, localization, and kinetics.

Clinical Relevance

Mutations in FGF14 are linked to:

Spinocerebellar ataxia type 27 (SCA27):

Autosomal dominant neurodegenerative disorder

Onset often in childhood or adolescence

Characterized by ataxia, tremor, dysarthria, and sometimes cognitive impairment

Epilepsy and neuropsychiatric disorders: Due to its role in ion channel modulation, FGF14 dysfunction has also been implicated in epilepsy, bipolar disorder, and schizophrenia in some studies.

Animal Models

Fgf14 knockout mice show:

Gait ataxia

Motor hyperactivity

Impaired hippocampal-dependent learning These phenotypes resemble aspects of human SCA27 and support FGF14's critical role in neuronal function.

An intronic repeat expansion (GAA•TTC)exp in the FGF14 gene (FGF14 (GAA•TTC)exp) has recently been found to cause dominantly inherited ataxia SCA27B. The core phenotype consists of late-onset and slowly progressing ataxia with down-beat nystagmus and episodic features. Disease penetrance depends on the number of repeat units and ≥300 is widely used pathogenic threshold for complete penetrance. The Finnish population is genetically unique and SCA27B has not previously been reported in Finland.

Methods: We investigated FGF14 (GAA•TTC)exp in a cohort of 96 Finnish patients with suspected hereditary ataxia or ataxia of unknown etiology, of whom 62 patients had no previous genetic diagnosis. We also assessed FGF14 (GAA•TTC)exp in 561 controls in order to estimate its population prevalence in North Ostrobothnia.

Results: We found five patients with FGF14 (GAA•TTC)≥250 giving a frequency of 5.2 % in the ataxia cohort. One patient had a rare biallelic genotype. Four patients had the classical SCA27B phenotype with no atypical features. Two of the patients had a previous genetic diagnosis and digenic contribution could not be excluded. Moreover, we found one patient with suspected FGF14 disease and with (GAA•TTC)248, but the segregation analysis remained inconclusive. The (GAA•TTC)≥250 frequency was 2.7 % in the general population. Population prevalence was 1.7 per 100 000 in North Ostrobothnia. The frequency of alleles harboring 200-249 repeats was 2.2 % in patients and 1.5 % in controls.

Conclusion: Our results suggest that screening of FGF14 expansion should be carried out in Finnish patients with suspected hereditary ataxia or ataxia of unknown etiology [1)].

1)
Kytövuori L, Pellerin D, Kärppä M, Sipilä JOT, Dicaire MJ, Iruzubieta P, Brais B, Majamaa K. FGF14 (GAA•TTC) repeat expansion-related ataxia SCA27B is common in Northern Finland. Parkinsonism Relat Disord. 2025 Jul 3;137:107943. doi: 10.1016/j.parkreldis.2025.107943. Epub ahead of print. PMID: 40623333.