The FGF14 gene is a milestone in ataxia genetics

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The recent discovery of spinocerebellar ataxia 27b (SCA27b) due to deep intronic GAA repeat expansions in the FGF14 gene should be regarded a milestone in neurology and neurogenetics.\(1,2\) Firstly, these expansions explain 30 percent of previously genetically undiagnosed, autosomal dominant ataxia in families.\(1\) The relative frequency seems to match that of Spinocerebellar ataxia type 3 (SCA3), so far the most common dominant ataxia worldwide. Secondly, as the GAA expansions appear to be meiotically unstable—with further expansion upon maternal but contraction with paternal transmission—SCA27b families may show imperfect dominant inheritance, and SCA27b may present sporadically. Indeed, many patients with sporadic, late-onset ataxia who had been diagnosed with idiopathic, degenerative ataxia appear to carry expansions in FGF14. Where the field has long assumed missing heritability within these idiopathic, late-onset ataxias, it is only now, through more advanced genomic technologies and bioinformatics, that we are able to detect these genetic variants. Still, the high frequency of these FGF14 expansions was rather unexpected.

Other groups have rapidly screened their cohorts for FGF14 expansions and a consistent clinical and genetic picture is already starting to emerge.\(4,5\) GAA expansion of 300 repeats or more (GAA\(\geq300\)) are considered pathogenic and fully penetrant, while GAA\(\geq250,299\) are reduced penetrance alleles. Expansions in FGF14 have been identified across the globe in 10–60% of mostly late-onset ataxia patients from cohorts with mixed sporadic and familial ataxia. Disease manifests mostly between 55 and 65 years, but with a wide range; importantly, many cohorts have a selection bias due to the applied age-at-onset cut-offs. The repeat size shows no or only weak correlations with onset age. In up to 60% of the patients, there is an initial phase with episodic symptoms prior to the evolution of gait and balance difficulties. Cerebellar oculomotor disturbances are the rule rather than exception, and in particular the presence of downbeat nystagmus (DBN) may be a tell-tale sign of SCA27b. Non-cerebellar features, such as afferent sensory deficits, vestibulopathy, peripheral neuropathy, dysautonomia, spasticity, and parkinsonian features, do occur but seem to never dominate the phenotype and to vary across the investigated cohorts. Disease progression is very slow, with many patients still ambulant after 15 years of disease.\(6\) Brain MRI often—but not invariably—shows cerebellar atrophy that is most pronounced in the verman region. Real-world data and a small number of n-of-1 trials suggest that 4-aminopyridine symptomatically impacts on the attacks and ataxia severity, but randomized trials are needed to confirm this.\(7\) The effect of this drug supports the first hypotheses of SCA27b being a Purkinje cell channelopathy.\(1,4\)

In the January 2024 issue of eBioMedicine, Méreaux and colleagues describe one of the largest and most comprehensive FGF14 screening studies so far.\(7\) Their effort provides further clinicogenetic insights into SCA27b and reveals some important diagnostic caveats. The investigated cohort not only included 875 ataxia patients (the majority of whom had had prior comprehensive genetic testing) and 475 controls, but also more than 500 affected and unaffected relatives. They identified GAA\(\geq300\) expansions in 10.1% of ataxia patients (15.7% for familial and 6.5% for sporadic cases). They were able to summarize and substantiate the phenotype with a key triad of an onset after age 45 years, episodic features, and DBN. As observed by other groups,\(8\) dysarthria was remarkably absent in many patients, particularly in those with shorter disease durations. Interestingly, disease onset was under 30 years in 5.6% of cases. Extracted clinical and imaging data are largely in line with what has been observed so far. Based on several observations, the authors point to diagnostic caution when GAA\(\geq250,299\) expansions are found. First, the frequency of these expansions was similar for the ataxia and control cohorts (1.7%), although it has to be noted that the control carriers were all under 65 years and might thus still develop symptoms. Second, 28.6% of these GAA\(\geq250,299\) ataxia cases had a pathogenic variant in another ataxia gene. Third, segregation studies indicated a discordance rate of 50%. However, some of the ataxia patients with GAA\(\geq250,299\) expansions had the key triad, indeed corroborating that these may represent reduced penetrance alleles. This observation is not new to repeat disorders in ataxia, where the majority of genes (i.e. ATXN2, ATXN3, ATXN7, TBP and CACNA1A) have uncertain and/or reduced penetrance alleles. Thus, when detecting GAA\(\geq250,299\) alleles, segregation studies and more elaborate genetic testing seems indicated. Further studies are needed to more firmly establish the

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diagnostic thresholds of the GAA repeat expansions, particularly as other data suggest that even smaller GAA200-249 repeats can lead to mild forms of SCA27b, e.g. with isolated or predominant DBN.10

Because Méreaux and colleagues had access to large numbers of relatives, they were able to study the inter-generational dynamics of the expansions to explain the bias of maternal over paternal transmission of the disease. Indeed, on maternal transmission, approximately 50% of children were affected—as expected for an autosomal dominant disease—but on paternal transmission this was only 30%. They found that all maternal alleles above 100 GAA repeats were unstable and expanded with a median of 18 repeats per generation, while on paternal transmission such repeats contracted with a median of 15. This has implications for genetic counseling of patients with a pathogenic or reduced penetrance allele and their family members. Additionally, it may have consequences for genetic reporting of alleles ranging from 100 to 250. Further studies are needed to establish what range should be considered premutation alleles with sex-dependent risk to offspring.

We will need to gain more insight into the underlying mechanisms as this will pave the way for future therapeutics in this common form of genetic ataxia. Surely, with the numbers of patients being identified, a proper clinical trial of 4-aminopyridine will be one of the next feasible, collaborative efforts within the ataxia community. The FGF14 repeat expansion discovery marks the fact that we are now able to genetically explain a significant portion of ataxias previously labeled as idiopathic, which is thus likely a finite concept.

Contributors

Bart van de Warrenburg drafted the first version of this commentary, which was reviewed and edited by Erik-Jan Kamsteeg. Both have read and approved the final version of the text.

Declaration of interests

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