Letter to the Editor

Mutations in the PDYN gene (SCA23) are not a frequent cause of dominant ataxia in Central Europe

To the Editor:

Autosomal-dominant spinocerebellar ataxia (SCA) is a clinically and genetically heterogeneous neurodegenerative disorder characterized by progressive ataxia of gait, limbs and speech as well as eye movement disturbances because of cerebellar degeneration. Further complicating neurological deficits, including pyramidal or extrapyramidal signs, spasticity, ophthalmoplegia and dementia, vary between subforms (1). Genetically, an increasing number of SCA genes have been reported in the last years [e.g. SCA11 (2) or SCA28 (3)] counting up to currently 19 different SCA genes and 12 additional genetic loci. To guide cost- and time-efficient genetic screening, more information about the exact frequency of newly identified SCA subtypes is highly warranted.

Very recently, Bakalkin et al. reported four missense mutations in the PDYN gene (GenBank accession number: NM024411.3) as underlying genetic cause of SCA23 (4). PDYN, as the precursor protein for the opioid neuropeptides α-neoendorphin and dynorphins A and B (Dyn A and B), represents yet another functional aspect into the already complex pathophysiology of SCAs. Although the success rate of screening for classical SCA mutations in their cohort was low (~20%), the authors identified two unique PDYN mutations among those index patients showing dominant ataxia inheritance (n = 88; 8% of 1100 ataxia patients), thus yielding a frequency estimate of 2.3% (2/88) in their cohort. This suggests that in a screening cohort with strict autosomal dominant inheritance, which is more enriched for SCA mutations and where more previously defined SCA subtypes have already been excluded, SCA23 might even be significantly more frequent. SCA23 would then outnumber most of the ‘rare’ non-trinucleotide SCAs like SCA11 (5) or SCA28 (6), which would have immediate impact on cost- and time-efficient screening strategies in this genetically heterogeneous condition.

We set out to test the hypothesis of PDYN mutations to be a comparatively common cause of SCA. To this end, a consecutive series of 314 German families with dominant transmission of ataxia was recruited from the ataxia clinics in Bochum and Tübingen, which had been ascertained over several years and clinically evaluated by one and the same neurologist (L. S.). All patients had undergone extensive genetic diagnostics not only of common SCA repeat expansions, but also of rare SCA subtypes, leaving a cohort of 104 families negative for repeat expansions causing SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17 and for mutations causing SCA11, SCA14, SCA15 and SCA27. Mean age of onset of these index patients was 42.8 years (range 3–71). Clinically, 56% (58/104) of the index patients presented with pure cerebellar ataxia and 44% (46/104) with additional non-cerebellar signs such as gaze palsy, epilepsy, spasticity, dystonia, parkinsonism or peripheral neuropathy. No patient showed retinal degeneration.

By direct sequencing (ABI 3100, Applied Biosystems, Foster City, CA) we did not identify a single patient to carry a potentially causative mutation in PDYN coding exons 3 and 4. Twenty-five percent (26/104) of the patients harboured at least one of the three single nucleotide polymorphisms in exon 4 (rs77155664, rs45469293, and rs6045819), which are known to be evenly distributed between ataxia cases and controls (4), and no other polymorphisms were found (for polymerase chain reaction conditions and primer sequences see Table S1, Supporting information).

These findings clearly indicate a very low frequency of SCA23 caused by PDYN mutations in Germany – although the presence of macrodeletions not detectable by direct sequencing cannot be excluded. In contrast to the cohort from Bakalkin and colleagues, we identified established mutations in common SCA genes in 67% (210/314 patients) of our families, thus yielding similar mutation rates.
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as in other European populations (1). This indicates the quality of our initial screening cohort, but at the same time emphasizes the notion that SCA23 is very infrequent even in SCA cohorts enriched for ‘new SCAs’ by the previous exclusion of established SCA subtypes. We thus suggest that SCA23 should not be given a high priority when considering genetic screening for SCA mutations. Future studies are, however, needed to scrutinize the frequency of SCA23 in non-European populations.

Supporting Information
The following Supporting information is available for this article: Table S1. Polymerase chain reaction conditions and primer sequences of PDYN sequencing.

Additional Supporting information may be found in the online version of this article.

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References

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