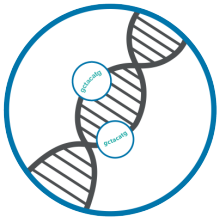
variantyx

Genomic Unity® Testing

Spotlight on genetic testing for ataxia

Obtaining a molecular diagnosis for ataxia patients can be challenging. It often involves a delicate balance between the type of variants and breadth of genes covered by a test versus its cost, which frequently leads to iterative testing. Genomic Unity® testing provides a single method approach for detection of multiple variant types from a single patient sample. The result is a cost-effective, comprehensive analysis of your patient's DNA summarized in a single, unified clinical report.

Traditional genetic testing path



The decision of which single gene or panel test is the best choice for a patient presenting with ataxia has traditionally been guided by the overlap of two lines of inquiry. A detailed family history and assessment of clinical features is typically compared against the specific disorders associated with the gene(s) targeted by the test. Testing often targets one or a few genes that most closely match, reflexing to a progressively broader set of genes when a negative result is returned.

For example, consider a patient presenting with an autosomal dominant family history and clinical symptoms of neuropathy. Traditional genetic testing approaches would suggest to first test for ATXN1, ATXN2 and ATNX3 repeat expansions, followed by sequencing additional autosomal dominant ataxia-associated genes including AFG3L2, SPTBN2 and others. With another negative result, it would be suggested to reflex to testing for additional repeat expansions including ATN1 and PPP2R2B.

This approach has been driven in part by the nature of the variants which cause ataxia and their different methods of detection. SNVs and indels in ataxia genes are typically assessed using Sanger and/or NGS techniques. Del/dups are assessed using qPCR and MLPA. While assessment of tandem repeat expansions requires specialized PCR and/or Southern blot gene-by-gene analysis.

These specialized tests, performed by a small number of labs, are often expensive. Especially when bundled into a larger "comprehensive" panel. In comparison, the Genomic Unity® single method approach makes truly comprehensive testing more accessible and cost effective while simultaneously providing a higher diagnostic yield.

Comprehensive whole genome testing

Genomic Unity® testing pairs PCR-free whole genome sequencing (WGS) with in-silico analyses to comprehensively evaluate ataxia-associated genes for all relevant variant types. Including SNVs and indels, small and large structural variants (including translocations) and the ataxia-related tandem repeat expansions listed here:

Disorder	Gene	Repeat
Dentatorubral-pallidoluysian atrophy (DRPLA)	ATN1	CAG
Friedreich's ataxia	FXN	GAA
Spinocerebellar ataxia 1	ATXN1	CAG
Spinocerebellar ataxia 2	ATXN2	CAG
Spinocerebellar ataxia 3	ATXN3	CAG
Spinocerebellar ataxia 6	CACNA1A	CAG
Spinocerebellar ataxia 7	ATXN7	CAG
Spinocerebellar ataxia 8	ATXN8OS	CTG
Spinocerebellar ataxia 10	ATXN10	ATTCT
Spinocerebellar ataxia 12	PPP2R2B	CAG

Genomic Unity ® Movement Disorders Analysis provides a broad yet targeted approach, with an option to automatically reflex up to a full Genomic Unity® Exome Plus Analysis if the initial results are negative.

The following ataxia-associated genes are screened as part of Genomic Unity® Movement Disorders Analysis:

Spinocerebellar ataxias

Disorder	Inheritance	Gene	Variantyx	Athena
Spinocerebellar ataxia 1	AD	ATXN1*	X	X
Spinocerebellar ataxia 2	AD	ATXN2*	X	X
Spinocerebellar ataxia 3	AD	ATXN3*	X	X
Spinocerebellar ataxia 5	AD	SPTBN2	X	X
Spinocerebellar ataxia 6	AD	CACNA1A*	X	X
Spinocerebellar ataxia 7	AD	ATXN7*	X	X
Spinocerebellar ataxia 8	AD	ATXN98OS*	X	X
Spinocerebellar ataxia, AR 8	AR	SYNE1	X	X
Spinocerebellar ataxia 10	AD	ATXN10*	X	X
Spinocerebellar ataxia, AR 10	AR	ANO10	X	X
Spinocerebellar ataxia 11	AD	TTBK2	X	X
Spinocerebellar ataxia, AR 11	AR	SYT14	X	X
Spinocerebellar ataxia 12	AD	PPP2R2B*	X	X
Spinocerebellar ataxia 13	AD	KCNC3	X	X
Spinocerebellar ataxia, AR 13	AR	GRM1	X	X
Spinocerebellar ataxia 14	AD	PRKCG	X	X
Spinocerebellar ataxia, AR 16	AR	STUB1	X	
Spinocerebellar ataxia 19	AD	KCND3	X	X
Spinocerebellar ataxia, AR 20	AR	SNX14	X	
Spinocerebellar ataxia 21	AD	TMEM240	X	
Spinocerebellar ataxia 23	AD	PDYN	X	X
Spinocerebellar ataxia 26	AD	EEF2	X	X
Spinocerebellar ataxia 27	AD	FGF14	X	X
Spinocerebellar ataxia 28	AD	AFG3L2	X	X
Spinocerebellar ataxia 29	AD	ITPR1	X	X
Spinocerebellar ataxia 34	AD	ELOVL4	X	
Spinocerebellar ataxia 35	AD	TGM6	X	X
Spinocerebellar ataxia 38	AD	ELOVL5	X	
Spinocerebellar ataxia 42	AD	CACNA1G	X	
Spinocerebellar ataxia with neuropathy 43	AD	MME	X	
Spinocerebellar ataxia 48	AD	STUB1	X	
Spinocerebellar ataxia, AR with axonal neuropathy	AR	TDP1	X	X
Spinocerebellar ataxia, infantile-onset	AD	TWNK	X	
Spinocerebellar ataxia, X-linked 1	X-linked	ATP2B3	X	

Spastic ataxias

Disorder	Inheritance	Gene	Variantyx	Athena
Spastic ataxia 1	AD	VAMP1	X	X
Spastic ataxia 4	AR	MTPAP	X	X
Spastic ataxia 5	AR	AFG3L2	X	X
Spastic ataxia, Charlevoix-Saguenay type	AR	SACS	X	X

Episodic ataxias

Disorder	Inheritance	Gene	Variantyx	Athena
Episodic ataxia 1	AD	KCNA1	X	X
Episodic ataxia 2	AD	CACNA1A	X	X
Episodic ataxia 5	AD	CACNB4	X	X
Episodic ataxia 6	AD	SLC1A3	X	X

Other ataxias

Disorder	Inheritance	Gene	Variantyx	Athena
Ataxia-Telangiectasia	AR	ATM	X	X
Ataxia-Telangiectasia like syndrome	AR	MRE11A	X	X
Dentatorubral-pallidoluysian atrophy (DRPLA)	AR	ATN1*	X	X
Friedreich's ataxia	AR	FXN*	X	X
Ataxia with oculomotor apraxia, type I	AR	APTX	X	X
Ataxia with oculomotor apraxia, type II	AR	SETX	X	X
Ataxia, posterior column, with retinitis pigmentosa	AR	FLVCR1	X	X
Ataxia with vitamin E deficiency	AR	TTPA	X	X
Coenzyme Q10 deficiency, primary, 4	AR	COQ8A	X	X
Marinesco-Sjogren syndrome	AR	SIL1	X	X
Mitochondrial recessive ataxia syndrome	AR	POLG	X	X
Sideroblastic anaemia and ataxia	X-linked	ABCB7	X	

A * indicates that tandem repeat expansion analysis is performed.

All comparisons are made against Athena's Ataxia, Comprehensive Evaluation panel.

For a complete list of genes screened as part of Genomic Unity® Movement Disorders Analysis, including dystonia-related and other genes, please see www.variantyx.com/movement-analysis/.

Additional ataxia-associated genes

Inheritance	Gene	Variantyx	Athena
AR	CAPN1	X	
AR	CWF19L1	X	
AR	GRID2	X	
AR	PEX10	X	
AR	POLR3A	X	
AR	RNF216	X	
AR	SCN2A	X	
AR	SPG7	X	

Notes about Genomic Unity® testing

Similar to Athena's tests, Genomic Unity® testing does not currently detect tandem repeat expansions in the following genes:

- TBP - CAG expansion causes spinocerebellar ataxia 17 which is estimated to account for 0.3% of autosomal dominant spinocerebellar ataxias
- BEAN1 - TGGAA expansion causes spinocerebellar ataxia 31 which is most prevalent in Japan and extremely rare in other asian and Western countries
- NOP56 - GGCCTG expansion causes spinocerebellar ataxia 36 which is estimated to account for 0.7% of autosomal dominant spinocerebellar ataxias
- DAB1 - ATTTC expansion causes spinocerebellar ataxia 37 which has so far only been found in Spain and Portugal