
MYASTHENIA GRAVIS.
TECAN.

MYASTHENIA GRAVIS DIAGNOSTICS.

Supporting Myasthenia Gravis Care: ARAb RRA & MuSK-Ab ELISA solutions for serological testing.

Myasthenia gravis (MG) is a chronic autoimmune disorder characterized by weakness and rapid fatigue of the voluntary muscles. It occurs when the immune system mistakenly attacks the communication between nerves and muscles, specifically targeting the acetylcholine receptors at the neuromuscular junction. This disruption leads to symptoms such as drooping eyelids, difficulty swallowing, and impaired speech, which can vary in severity among individuals. While the exact cause of myasthenia gravis remains unknown, it is often associated with abnormalities in the thymus gland. Treatment typically involves medications that improve neuromuscular transmission and therapies that modulate the immune system to alleviate symptoms.

Myasthenia gravis is considered a rare autoimmune disorder, with prevalence rates varying across different regions and populations. Globally, the prevalence is estimated to be approximately 10 to 20 cases per 100,000 people, although this can differ based on factors such as age, ethnicity, and geographic location. The incidence rate, which refers to the number of new cases diagnosed annually, is generally reported to be around 0.3 to 2.8 per 100,000 people per year. Advances in diagnostic techniques and increased awareness have contributed to a rise in reported cases, suggesting that the condition may be more common than previously thought.

About 80 percent of patients with MG express autoantibodies against AChRs (ARAbs). The other 20 percent of cases are known as seronegative MG. There are clear clinical symptoms in patients with seronegative MG, but no detectable ARAbs. Approximately half of these ARAb-seronegative patients will express autoantibodies against another MG-related protein, muscle-specific tyrosine kinase (MuSK). MuSK is part of an agrin receptor complex and mediates the agrin-induced clustering of acetylcholine receptors, playing a key role in cross-linking the AChR to the musculature. Patients expressing anti-MuSK autoantibodies tend to have a more severe form of MG, with worse symptoms.

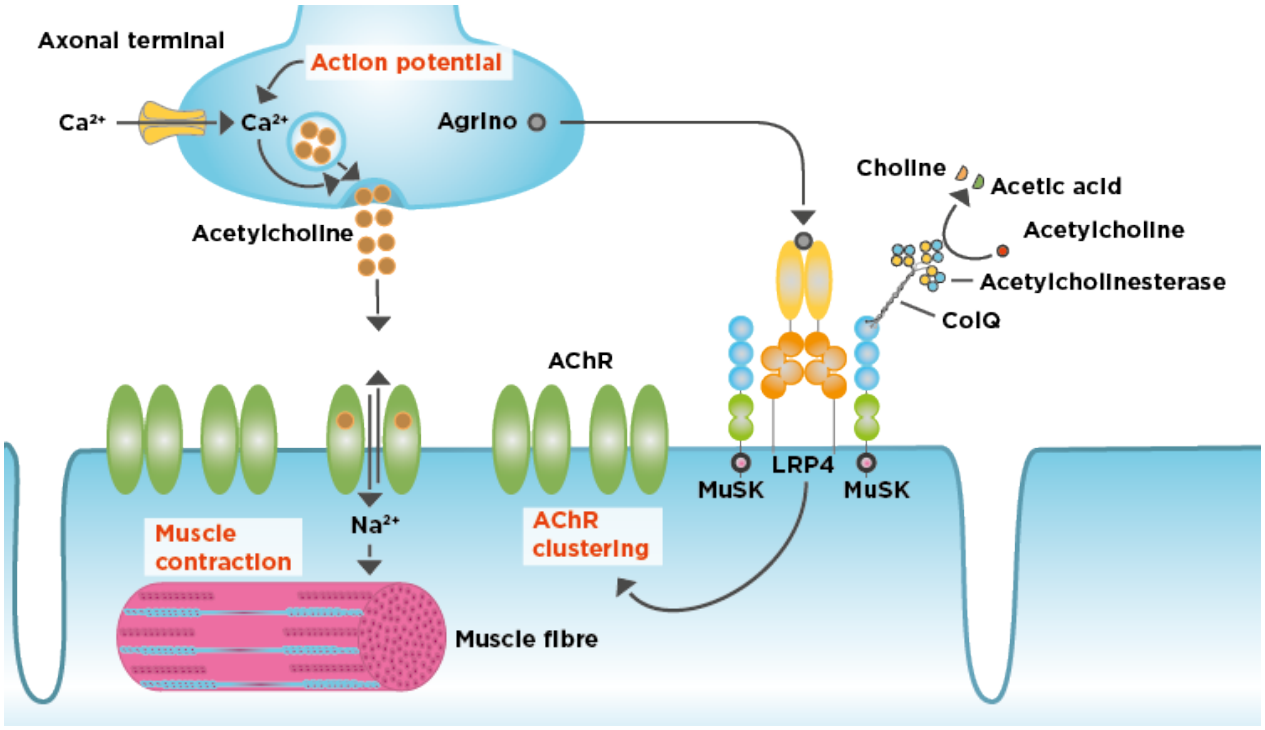
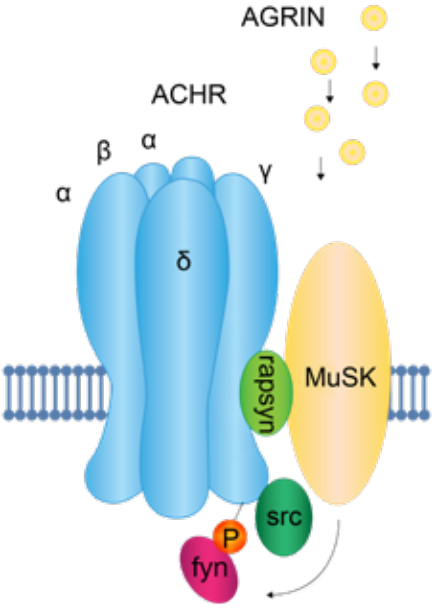


Figure 1: Neuromuscular junction in MG.[1]

ARAb and anti-MuSK autoantibodies are the gold standard serological biomarkers for diagnosing MG.[7] Tecan offers serological assays for both these biomarkers, to support clinicians and laboratories in the reliable and accurate diagnostic of the disease.

The In Vitro Diagnostic Regulation (IVDR) is crucial for myasthenia gravis diagnostics as it ensures high standards of safety, performance, and reliability for diagnostic tests, ultimately enhancing patient care and clinical outcomes. Tecans Acetylcholine Receptor Autoantibodies (ARAb) RRA as well as MuSK-Ab ELISA are already IVDR certified, demonstrating its compliance with these stringent regulatory requirements and reinforcing its credibility and effectiveness in accurately diagnosing myasthenia gravis.



ACETYLCHOLINE RECEPTOR AUTOANTIBODIES (ARAB) RRA – IVDR CERTIFIED.

In most cases of MG, autoantibodies target the acetylcholine receptors (AChR) – transmembrane proteins present on muscle cells – that carry electrical signals between nerve endings and stimulate the muscles to contract. MG patients produce anti-AChR autoantibodies (ARAbs) that prevent acetylcholine from binding to the receptor, blocking normal muscle contractions.

The acetylcholine receptor (AChR) is a key protein at nerve-muscle connections, enabling muscle contraction by responding to the neurotransmitter acetylcholine. The most common type, the nicotinic acetylcholine receptor (nAChR), is made of five subunits arranged around a central pore. In adult muscle, these subunits are two alpha (α1), one beta (β1), one delta (δ), and one epsilon (ε).

Acetylcholine binds to two specific sites on the receptor's extracellular surface, located between the alpha subunits and their neighbors. This binding opens the channel, allowing ions to enter the cell and trigger muscle movement.

The receptor also has important sites for antibody binding, especially the main immunogenic region (MIR) on the alpha subunit. In autoimmune diseases like myasthenia gravis, antibodies target this region, leading to muscle weakness (Tzartos & Lindstrom, 1980; Vincent, 2002). Other drugs and toxins can also bind to the receptor, either activating or blocking its function.

In summary, the acetylcholine receptor's structure includes multiple binding sites for neurotransmitters, antibodies, and drugs, making it essential for healthy muscle activity.

Tecan's ARAb radioreceptor assay (RRA) for the determination of anti-AChR autoantibodies has been available for many years. The unsurpassed diagnostic specificity and sensitivity of the RRA is the gold standard for serological diagnostics for MG.

Proven excellent performance – a method comparison study.

A direct method comparison between the ARAb RRA and a commercially available anti-AChR ELISA was performed, analyzing 106 samples: 89 clinically confirmed negative samples (with no anti-AChR autoantibodies), including 28 with clinically confirmed autoantibodies against AMA, ANA, ANCA or RF. In addition, 17 clinically confirmed positive samples were included in the study.

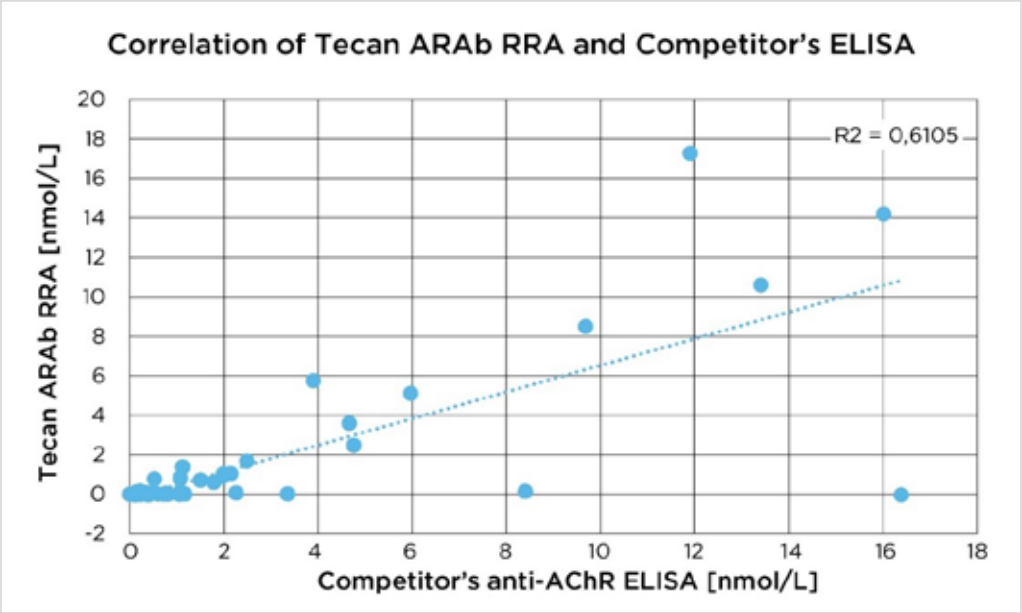


Figure 2: Comparison study of the Tecan ARAb RRA and a competitor anti-AChR ELISA. Correlation between the assays was poor, and false positive results were noted for the competitor ELISA.

Table 1: Summary of results of direct method comparison between the Tecan ARAb RRA and a competitor anti-AChR ELISA.

N=106		Competitor anti-AChR ELISA			
		negative	borderline	positive	∑
Tecan ARAb RRA	negative	70	6	13	**89**
	positive			17	**17**
Sum	∑	**70**	**6**	**30**	106

Of the 89 clinically confirmed negative samples, 13 false positives were obtained with the anti-AChR ELISA (15 %), and 6 samples had borderline measurements. The anti-AChR ELISA also showed 25 % cross-reactivity (7 false positives) for the 28 samples with other autoantibodies.

As expected from these findings, the correlation coefficient between the two assays is poor (R2 = 0.61, Figure 2).

This study demonstrates the clinical diagnostic performance of the ARAb RRA compared to the competitor anti-AChR ELISA. This is not only due to the anti-AChR ELISA's high cross-reactivity (25 %) to non-ARAb antibodies, but also its lack of specificity for autoantibodies against AChR (15 % false positive results).

The advantages of using Tecan's ARAb RRA at a glance:

- Gold standard method for the first line serological marker, autoantibodies against AChR
- Excellent performance due to the use of human receptor materials and thus outstanding specificity
- Well-accepted use on the market for years

MUSK-AB ELISA – IVDR CERTIFIED.

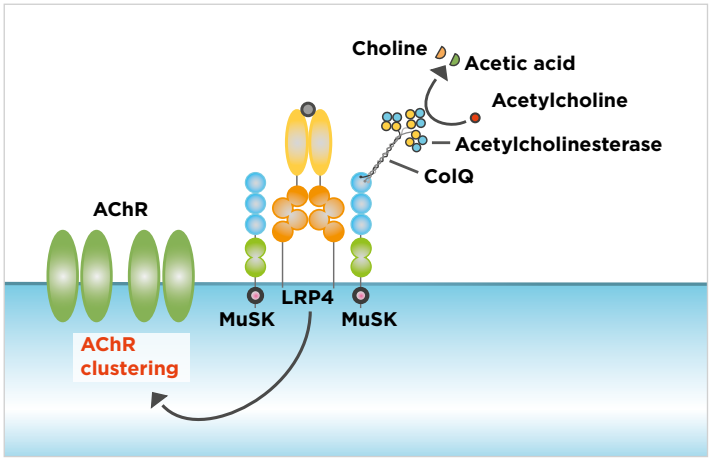
MuSK antibodies are particularly important in diagnosing a subset of myasthenia gravis known as MuSK-positive myasthenia gravis, which often presents with distinct clinical features compared to AChR-positive cases. Patients with MuSK antibodies may experience more pronounced bulbar symptoms, such as difficulty swallowing and speaking, and may have less involvement of ocular muscles. The presence of MuSK antibodies can influence treatment strategies, as these patients may respond differently to certain therapies, necessitating tailored approaches to manage their symptoms effectively.

Muscle-Specific Kinase (MuSK) is a crucial protein involved in the formation and maintenance of the neuromuscular junction, where nerve cells communicate with muscle fibers.

MuSK is a receptor tyrosine kinase located on the muscle cell surface. It is activated by a complex of the protein agrin and its co-receptor LRP4, which are released from motor neurons. Upon activation, MuSK initiates a signaling cascade that leads to the clustering of acetylcholine receptors (AChRs) at the neuromuscular junction, ensuring efficient signal transmission and muscle contraction.

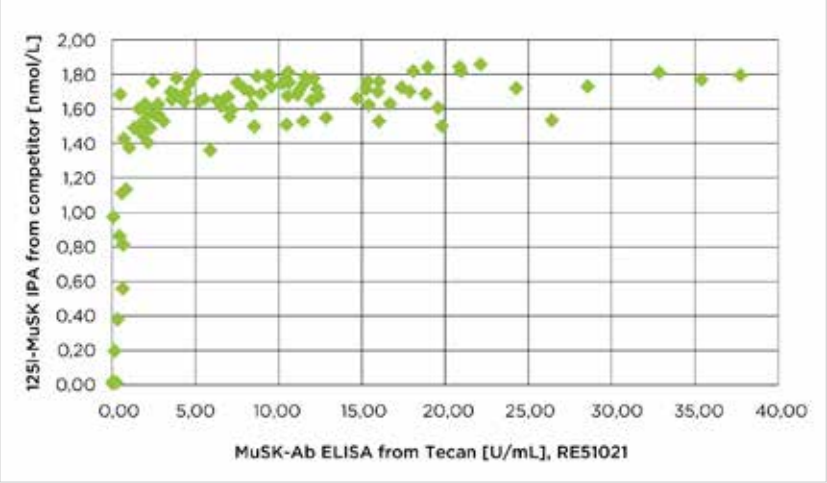
MuSK is essential for organizing the neuromuscular junction and maintaining muscle strength.

Several studies have shown the presence of anti-MuSK antibodies in the sera of about 50 % of putative seronegative MG patients. These patients are mostly female, have prominent cranial and bulbar involvement and tend to experience earlier onset of the disease (third or fourth decade) compared to ARAb-positive MG patients. The measurement of anti-MuSK antibodies will substantially aid diagnosis and clinical management of MG, particularly for suspected MG in ARAb seronegative patients, and those with atypical clinical presentation (eg. oropharyngeal myasthenia).



- Tecan's only commercially available ELISA for measuring anti-MuSK autoantibodies is offering: Excellent clinical sensitivity (95.8 %) and specificity (100 %)
- Qualitative (cut-off) and quantitative (standard curve) evaluation of results
- High performance – low cross reactivity, good linearity and high precision

Figure 3: Comparison study between Tecan's MuSK-Ab ELISA and a 125I-MuSK RIA, showing the large measurement range of the quantitative ELISA.



Comparison to commercially available radioimmunoassay (RIA).

Tecan's MuSK-Ab ELISA (RE51021) was compared to a competitor immunoprecipitation RIA (IPA/RIA, 125I-MuSK IPA). 128 serum samples (93 positive, 35 negative by RIA) were measured by both RIA and ELISA. The data is shown in Figure 3. The MuSK-Ab ELISA showed good correlation to the competitor assay, identifying 90 positive and 38 negative samples, which equates to a specificity of 100 % and a sensitivity of 96.7 % compared to RIA. Due to the large measurement range of the MuSK-Ab ELISA and the good correlation, positive data and results can be well differentiated. RIA is not able to differentiate positive titers, as it is a qualitative test.

This study demonstrates the outstanding measurement range of the MuSK-Ab ELISA, as well as its capability to differentiate results effectively. These features are particularly valuable for patient follow-up and the classification of results and are well-accepted in clinical practice.

Furthermore, the straightforward design of the assay ensures ease of use, enabling users to obtain reliable results efficiently and with minimal complexity.

TECANS MYASTHENIA GRAVIS DIAGNOSTIC – YOUR BENEFITS.

Tecan is one of the market leaders for Myasthenia Gravis diagnostics, offering a holistic solution that combines expertise and IVDR-certified reagents. For MuSK-Ab ELISA also automated solutions are served. Our ARAb RRA is recognized as the gold standard for its high specificity using native human muscle material, while the MuSK-Ab ELISA is the first commercially available quantitative assay for differential diagnosis and disease monitoring. Tecans portfolio covers the most important parameters for comprehensive and early diagnosis, ensuring high data integrity and future-proof solutions. By choosing Tecan, your lab benefits from reliable, efficient diagnostics and your patients receive timely, accurate care.

Benefits of using Tecan tools for MG diagnostics

- ARAb detection using RRA is seen as the gold standard for the supportive diagnosis of MG
- Free-of-charge quality assessment scheme for ARAb RRA
- Tecan was first to market with a quantitative MuSK-Ab ELISA
- Both assays are already IVDR certified and available

Our values and promise

- Highest quality – ARAb RRA and MuSk-Ab ELISA are seen as standard serological tools to aid MG diagnostics
- Trusted partner – Both assays are IVDR certified, making them your safe and future-proof laboratory solution

Tecan provides reliable and accurate solutions for laboratories and patients, helping to ensure diagnostic care for Myasthenia Gravis.

Product availability and regulatory status may vary across regions outside the EU, depending on local country-specific registration. Consult with your Tecan associate for further information.

	Acetylcholine Receptor-Ab (ARAb) RRA; REF. 30221148	MuSK-Ab ELISA; REF RE51021
Description	The Acetylcholine autoantibody radio receptor assay is intended for the semi-quantitative determination of autoantibodies against the acetylcholine receptor in adult human serum and EDTA plasma.	The MuSK-Ab ELISA is intended for the qualitative and semi-quantitative measurement of autoantibodies against muscle-specific receptor tyrosine kinase (MuSK) from adult patient's serum samples.
Regulatory status	EU: CE IVDR	EU: CE IVDR
Kit size	100 det	96 det
Method	RRA	ELISA
Measuring range	0 - 8 nmol/L, cut-off 0.25 nmol/L	0 - 12 U/mL
Sample type	20 µL serum, plasma	10 µL serum
Availability	On stock *	On stock

*The product release schedule for radioactive material can be found on our website.

https://ibl-international.com/product-release-schedule

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