

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/20412> holds various files of this Leiden University dissertation.

Author: Niks, E.H.

Title: Myasthenia gravis with antibodies to muscle-specific kinase : clinical characteristics, epidemiology, and immunological aspects

Issue Date: 2013-01-17

X

Appendices

List of abbreviations

AAEM	American Association of Electrodiagnostic Medicine
Ab +/-	antibody positive / negative
ACh	acetylcholine
AChE	acetylcholinesterase
AChEI	acetylcholinesterase inhibitor
AChR	acetylcholine receptor
AChR MG	myasthenia gravis with autoantibodies to AChR
ATP	adenosine triphosphate
AU	arbitrary units
CI	confidence interval
CK	creatine kinase
CMAP	compound muscle action potential
ColQ	collagen Q
CV	coefficient of variation
DHPR	dihydropyridine receptor
DSS	disease severity score
EGFP	enhanced green fluorescent protein
EMG	electromyography
EPP	endplate potential
FACS	fluorescence-activated cell sorting
GMG	generalised myasthenia gravis
HEK	human embryonic kidney
HLA	human leukocyte antigen
Ig	immunoglobulin
IV	intravenous
IVIG	intravenous human immunoglobulin
kDa	kilo Dalton
LEMS	Lambert-Eaton myasthenic syndrome
LRP4	low-density lipoprotein receptor-related protein
MASC	myotube associated specificity component
MEPP	miniature endplate potential
MFI	mean fluorescence intensity
MG	myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MIP	maximal inspiratory pressure
MRI	magnetic resonance imaging

MuSK	muscle-specific kinase
MuSK MG	myasthenia gravis with autoantibodies to MuSK
NHS	normal human serum
NMJ	neuromuscular junction
OD	optical density
OMG	ocular myasthenia gravis
OR	odds ratio
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PE	plasma exchange
PEI	polyethylenimine
PV	pemphigus vulgaris
RIA	radioimmunoassay
RNA	ribonucleic acid
RNS	repetitive nerve stimulation
RT	room temperature
SFEMG	single-fiber electromyography
SNMG	seronegative MG – MG without autoantibodies to AChR or MuSK
Tid1	tumorous imaginal disc protein
TX	thymectomy
VGCC	voltage-gated calcium channel

List of publications

P.K. Gregersen, R. Kosoy, A.T. Lee, J. Lamb, J. Sussman, D. McKee, K.R. Simpfendorfer, R. Pirskanen-Matell, F. Pieh, Q. Pan-Hammarstrom, J.J.G.M. Verschuuren, M.J. Titulaer, **E.H. Niks**, A. Marx, P. Ströbel, B. Tackenberg, M. Püetz, A. Maniaol, A. Elsaï, C. Tallaksen, H.F. Harbo, B.A. Lie, S. Raychaudhuri, P.I.W. de Bakker, A. Melms, H.J. Garchon, N. Willcox, L. Hammarstrom, M.F. Seldin. Risk for Myasthenia Gravis maps to 151Pro→Ala change in TNIP1 and to HLA-B*08. *Ann Neurol* 2012. Epub 2012 Oct 10.

E.H. Niks, M.H. De Baets, J.J.G.M. Verschuuren. IgG4-related disease. *N Engl J Med*. 2012; 366(17):1644-5.

R. Klooster, J.J. Plomp, M.G. Huijbers, **E.H. Niks**, K.R. Straasheijm, F.J. Detmers, P.W. Hermans, K. Sleijpen, A. Verrips, M. Losen, P. Martinez-Martinez, M.H. De Baets, S.M. van der Maarel, J.J.G.M. Verschuuren. Muscle-specific kinase myasthenia gravis IgG4 autoantibodies cause severe neuromuscular junction dysfunction in mice. *Brain* 2012; 135:1081-1101. Epub 2012 Mar 6.

I.A. Ketelslegers, C.E. Catsman-Berrevoets, R.F. Neuteboom, M. Boon, K.G. van Dijk, M.J. Eikelenboom, R.H. Gooskens, **E.H. Niks**, W.C. Overweg-Plandsoen, E.A. Peeters, C.M. Peeters-Scholte, B.T. Poll-The, J.F. de Rijk-van Andel, J.P. Samijn, I.N. Snoeck, H. Stroink, R.J. Vermeulen, A. Verrips, J.S. Vles, M.A. Willemsen, R. Rodrigues Pereira, R.Q. Hintzen. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. *J Neurol*. 2012; 259(9):1929-35. Epub 2012 Feb 17.

K. Vrolix, **E.H. Niks**, R. Le Panse, M.M. van Ostaijen-Ten Dam, A.H. Muris, C.M. Jol-van der Zijde, M.J. van Tol, M. Losen, P.C. Molenaar, E.J. van Zoelen, S. Berrih-Aknin, M.H. De Baets, J.J. Verschuuren, P. Martínez-Martínez. Reduced thymic expression of ErbB receptors without auto-antibodies against synaptic ErbB in myasthenia gravis. *J Neuroimmunol* 2011; 232(1-2):158-165. Epub 2010 Dec 18.

M.H. Selman, **E.H. Niks**, M.J. Titulaer, J.J.G.M. Verschuuren, M. Wuhler, A.M. Deelder. IgG Fc N-Glycosylation Changes in Lambert-Eaton Myasthenic Syndrome and Myasthenia Gravis. *J Proteome Res*. 2011; 10(1):143-152. Epub 2010 Jul 30.

E.H. Niks, J.B.M. Kuks, J.H.J. Wokke, H. Veldman, E. Bakker, J.J.G.M. Verschuuren, J.J. Plomp. Pre- and postsynaptic neuromuscular junction abnormalities in MuSK myasthenia. *Muscle Nerve* 2010; 42(2): 283-288.

A.M.G. Sas, **E.H. Niks**, M.H. Lequin, C.E. Catsman-Berrevoets, M.C.Y. de Wit. Herpes simplex virus type-1 encephalitis and occipital ischemic stroke. *Pediatr Neurol*. 2009; 41(4): 294-296.

W.P. ter Beek, Martínez-Martínez, M. Losen, M.H. de Baets, A.R. Wintzen, J.J.G.M. Verschuuren, **E.H. Niks**, S.G. van Duinen, A. Vincent, P.C. Molenaar. The Effect of Plasma From Muscle-Specific Tyrosine Kinase Myasthenia Patients on Regenerating Endplates. *Am J Pathol* 2009; 175(4): 1536-1544. Epub 2009 Sep 10.

F.M. Cox, J.J.G.M. Verschuuren, B.M. Verbist, **E.H. Niks**, A.R. Wintzen, U.A. Badrising. Detecting dysphagia in inclusion body myositis. *J Neurol* 2009; 256(12): 2009-2013. Epub 2009 Jul 15.

E.H. Niks, Y. van Leeuwen, M.I. Leite, F.W. Dekker, A.R. Wintzen, P.W. Wirtz, A. Vincent, M.J.D. van Tol, C.M. Jol-van der Zijde, J.J.G.M. Verschuuren. Clinical fluctuations in MuSK myasthenia gravis are related to antigen-specific IgG4 instead of IgG1. *J Neuroimmunol* 2008; 195(1-2): 151-156. Epub 2008 Apr 1.

E.H. Niks, A. Verrips, B.A. Semmekrot, M.J.J. Prick, A. Vincent, M.J.D. van Tol, C.M. Jol-van der Zijde, J.J.G.M. Verschuuren. A transient neonatal myasthenic syndrome with anti-MuSK antibodies. *Neurology* 2008; 70(14): 1215-1216.

M.I. Leite, M. Jones, P. Strobel, A. Marx, R. Gold, **E.H. Niks**, J.J.G.M. Verschuuren, S. Berrih-Aknin, F. Scaravilli, A. Canelhas, B.P. Morgan, A. Vincent, N. Willcox. Myasthenia Gravis Thymus: Complement Vulnerability of Epithelial and Myoid Cells, Complement Attack on Them, and Correlations with Autoantibody Status. *Am J Pathol* 2007; 171(3): 893-905.

E.H. Niks, J.B.M. Kuks, J.J.G.M. Verschuuren. Epidemiology of myasthenia gravis with anti-muscle specific kinase antibodies in The Netherlands. *J Neurol Neurosurg Psychiatry* 2007; 78(4): 417-418. Epub 2006 Oct 20.

E.H. Niks, J.B.M. Kuks, B.O. Roep, G.W. Haasnoot, W. Verduijn, B.E.P.B. Ballieux, M.H. De Baets, A. Vincent, J.J.G.M. Verschuuren. Strong association of MuSK antibody-positive myasthenia gravis and HLA-DR14-DQ5. *Neurology* 2006; 66(11): 1772-1774.

M.I. Leite, P. Strobel, M. Jones, K. Micklem, R. Moritz, R. Gold, **E.H. Niks**, S. Berrih-Aknin, F. Scaravilli, A. Canelhas, A. Marx, J. Newsom-Davis, N. Willcox, A. Vincent. Fewer thymic changes in MuSK antibody-positive than in MuSK antibody-negative MG. *Ann Neurol* 2005; 57(3): 444-8.

E.H. Niks, J.B.M. Kuks, M.H. De Baets, J.J.G.M. Verschuuren. Myasthenia gravis door antilichamen tegen het Muscle Specific Kinase. *Tijdschrift voor Neurologie en Neurochirurgie* 2004; 105(6): 253-258.

E.H. Niks, U.A. Badrising, J.J.G.M. Verschuuren, J.G. van Dijk. Decremental response of the nasalis and hypothenar muscles in myasthenia gravis. *Muscle Nerve* 2003; 28(2): 236-238.

E.H. Niks, J.J.G.M. Verschuuren. Een patiënt met een wisselende, asymmetrische ptosis. *Nederlands Tijdschrift voor Neurologie* 2002; 3: 212-214.

Curriculum Vitae

Erik Harmen Niks was born on May 7, 1972 in Veenendaal, the Netherlands. He attended secondary school at the Christelijk Lyceum Veenendaal, and graduated with an average final mark of 9.5 in 1990. In 1991 he started his medical training at the University of Utrecht, and graduated cum laude for the propaedeutic diploma the next year. After obtaining his physician's degree in 1999 at the University Medical Center in Utrecht, he became a resident in pediatrics at the Leiden University Medical Center (LUMC, Prof. Dr. J.M. Wit). In 2000, he started as a resident in neurology at the LUMC (Prof. Dr. R.A.C. Roos). Part of his training was at the Haga Hospital in The Hague (Dr. S.F.T.M. de Bruijn). He started his PhD study in 2002 (Prof. Dr. A.R. Wintzen and Prof. Dr. J.J.G.M. Verschuuren). In 2008, he was trained in pediatric neurology at the Erasmus Medical Center in Rotterdam (Prof. Dr. W.F. Arts). Later that year, he joined the neurology staff at the LUMC. He registered as pediatric neurologist in 2009. He received a Prinses Beatrix Fonds fellowship to specialise in myology. This fellowship, completed in 2012, included the work as honorary clinical fellow at the Dubowitz Neuromuscular Centre in London (Prof. F. Muntoni). He is currently involved in the care of children with neuromuscular disorders, and in the translational research of Duchenne muscular dystrophy at the LUMC.

During secondary school he received piano lessons from Ton Hartsuiker, head of the Utrecht Conservatory of Music. In 1988 he made his solo debut in Mozart's eleventh piano concerto. In that same year, he commenced the preparatory class at the Utrecht School of the Arts. He received prizes in various youth music contests, including the Prinses Christina competition and the Steinway competition. In 1990 he started his master study piano with the Dutch pianist Herman Uhlhorn. From 1993 until his graduation as soloist in 1996, he studied with the Norwegian pianist Håkon Austbø. Until 1999 he performed frequently with the Rosa Ensemble, an ensemble specialising in contemporary music and theatre productions. In 2006 and 2007 he played the Grieg piano concerto, accompanied by the I Medici orchestra, consisting of medical professionals. Currently, he performs with his wife, the viola player Karen de Wit. They live in Leiden and have two children, Geert and Elin.

Dankwoord

Dit onderzoek was onmogelijk geweest zonder de hulp van patiënten en collegae uit heel Nederland. Ik ben de patiënten dankbaar voor de wijze waarop zij belangeloos hebben meegewerkt door hun verhaal te delen, herhaald onderzoek te ondergaan en bloed af te staan. De collegae wil ik bedanken voor de enthousiaste samenwerking en de hulp bij het verzamelen van de vele gegevens.

References

1. Osserman K. Myasthenia gravis. New York: Grune & Stratton; 1958.
2. Erb W. Zur Casuistik der bulbären Lähmungen. 3 Ueber einen neuen, wahrscheinlich bulbären Symptomencomplex. Archiv für Psychiatrie und Nervenkrankheiten 1879;9:336-350.
3. Goldflam S. Ueber einen scheinbar heilbaren bulbär paralytischen Symptomencomplex mit Beteiligung der Extremitäten. Deutsches Zeitschrift für Nervenheilkunde 1893;4:213-352.
4. Walker MB. Treatment of myasthenia gravis with physostigmine. Lancet 1934;223(5779):1200-1201.
5. Dale HH, Feldberg W. Chemical transmission at motor nerve endings in voluntary muscle. J Physiol (Lond) 1934;81:39P.
6. Coërs C, Desmedt JE. Mise en évidence d'une malformation caractéristique de la jonction neuromusculaire dans la myasthénie. Acta Neurol Psychiatr Belg 1959;59(5):539-561.
7. Simpson JA. Myasthenia gravis: a new hypothesis. Scot Med J 1960;5(10):419-436.
8. Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. Science 1973;180(88):871-872.
9. Lindstrom JM, Seybold ME, Lennon VA, Whittingham S, Duane DD. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates, and diagnostic value. Neurology 1976;26(11):1054-1059.
10. Besinger UA, Toyka KV, Homberg M, Heininger K, Hohlfeld R, Fateh-Moghadam A. Myasthenia gravis: long-term correlation of binding and bungarotoxin blocking antibodies against acetylcholine receptors with changes in disease severity. Neurology 1983;33(10):1316-1321.
11. Drachman DB, Angus CW, Adams RN, Michelson JD, Hoffman GJ. Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. N Engl J Med 1978;298(20):1116-1122.
12. Lennon VA, Seybold ME, Lindstrom JM, Cochrane C, Ulevitch R. Role of complement in the pathogenesis of experimental autoimmune myasthenia gravis. J Exp Med 1978;147(4):973-983.
13. Engel AG, Lambert EH, Howard FM. Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. Mayo Clin Proc 1977;52(5):267-280.
14. Sahashi K, Engel AG, Lambert EH, Howard FM, Jr. Ultrastructural localization of the terminal and lytic ninth complement component (C9) at the motor end-plate in myasthenia gravis. J Neuropathol Exp Neurol 1980;39(2):160-172.

15. Rodgaard A, Nielsen FC, Djurup R, Somnier F, Gammeltoft S. Acetylcholine receptor antibody in myasthenia gravis: predominance of IgG subclasses 1 and 3. *Clin Exp Immunol* 1987;67(1):82-88.
16. Hunt PJ, Marshall SE, Weetman AP et al. Histocompatibility leucocyte antigens and closely linked immunomodulatory genes in autoimmune thyroid disease. *Clin Endocrinol (Oxf)* 2001;55(4):491-499.
17. Alper CA, Fleischnick E, Awdeh Z, Katz AJ, Yunis EJ. Extended major histocompatibility complex haplotypes in patients with gluten-sensitive enteropathy. *J Clin Invest* 1987;79(1):251-256.
18. Wirtz PW, Willcox N, van der Slik AR et al. HLA and smoking in prediction and prognosis of small cell lung cancer in autoimmune Lambert-Eaton myasthenic syndrome. *J Neuroimmunol* 2005;159(1-2):230-237.
19. Price P, Witt C, Allcock R et al. The genetic basis for the association of the 8.1 ancestral haplotype (A1, B8, DR3) with multiple immunopathological diseases. *Immunol Rev* 1999;167:257-274.
20. Giraud M, Beaurain G, Yamamoto AM et al. Linkage of HLA to myasthenia gravis and genetic heterogeneity depending on anti-titin antibodies. *Neurology* 2001;57(9):1555-1560.
21. Janer M, Cowland A, Picard J et al. A susceptibility region for myasthenia gravis extending into the HLA-class I sector telomeric to HLA-C. *Hum Immunol* 1999;60(9):909-917.
22. Kuks JBM, Lems SPM, Oosterhuis HJGH. HLA type is not indicative for the effect of thymectomy in myasthenia gravis. *J Neuroimmunol* 1992;36(2-3):217-224.
23. Compston DA, Vincent A, Newsom-Davis J, Batchelor JR. Clinical, pathological, HLA antigen and immunological evidence for disease heterogeneity in myasthenia gravis. *Brain* 1980;103(3):579-601.
24. Feltkamp TE, van den Berg-Loonen PM, Nijenhuis LE et al. Myasthenia gravis, autoantibodies, and HL-A antigens. *Br Med J* 1974;1(899):131-133.
25. Oosterhuis HJ, Feltkamp TE, van Rossum AL, van den Berg-Loonen PM, Nijenhuis LE. HL-A antigens, autoantibody production, and associated diseases in thymoma patients, with and without myasthenia gravis. *Ann N Y Acad Sci* 1976;274:468-474.
26. Antozzi C, Gemma M, Regi B et al. A short plasma exchange protocol is effective in severe myasthenia gravis. *J Neurol* 1991;238(2):103-107.
27. Evoli A, Bartoccioni E, Batocchi AP, Scuderi F, Tonali P. Anti-AChR-negative myasthenia gravis: clinical and immunological features. *Clin Invest Med* 1989;12(2):104-109.

28. Garlepp MJ, Dawkins RL, Christiansen FT et al. Autoimmunity in ocular and generalised myasthenia gravis. *J Neuroimmunol* 1981;1(3):325-332.
29. Lefvert AK, Bergstrom K, Matell G, Osterman PO, Pirskanen R. Determination of acetylcholine receptor antibody in myasthenia gravis: clinical usefulness and pathogenetic implications. *J Neurol Neurosurg Psychiatry* 1978;41(5):394-403.
30. Lennon VA, Howard FM. Serologic diagnosis of myasthenia gravis. In: Nakamura R, editor. *Clinical laboratory molecular analyses*. Orlando, FL: Grune & Stratton; 1985:29-44.
31. Limburg PC, The TH, Hummel-Tappel E, Oosterhuis HJ. Anti-acetylcholine receptor antibodies in myasthenia gravis. Part 1. Relation to clinical parameters in 250 patients. *J Neurol Sci* 1983;58(3):357-370.
32. Morel E, Raimond F, Goulon-Goeau C et al. Le dosage des anticorps anti-recepteurs de l'acetylcholine dans la myasthenie: etude de 329 serums. *Nouv Presse Med* 1982;11(24):1849-1854.
33. Newsom-Davis J, Willcox N, Schluep M et al. Immunological heterogeneity and cellular mechanisms in myasthenia gravis. *Ann N Y Acad Sci* 1987;505:12-26.
34. Soliven BC, Lange DJ, Penn AS et al. Seronegative myasthenia gravis. *Neurology* 1988;38(4):514-517.
35. Tindall RS. Humoral immunity in myasthenia gravis: biochemical characterization of acquired antireceptor antibodies and clinical correlations. *Ann Neurol* 1981;10(5):437-447.
36. Sanders DB, Andrews PI, Howard JF, Massey JM. Seronegative myasthenia gravis. *Neurology* 1997;48(Suppl 5):S40-S45.
37. Oosterhuis HJ, Limburg PC, Hummel-Tappel E, The TH. Anti-acetylcholine receptor antibodies in myasthenia gravis. Part 2. Clinical and serological follow-up of individual patients. *J Neurol Sci* 1983;58(3):371-385.
38. Birmanns B, Brenner T, Abramsky O, Steiner I. Seronegative myasthenia gravis: clinical features, response to therapy and synthesis of acetylcholine receptor antibodies in vitro. *J Neurol Sci* 1991;102(2):184-189.
39. Andrews PI, Massey JM, Sanders DB. Acetylcholine receptor antibodies in juvenile myasthenia gravis. *Neurology* 1993;43(5):977-982.
40. Oger J, Kaufman R, Berry K. Acetylcholine receptor antibodies in myasthenia gravis: use of a qualitative assay for diagnostic purposes. *Can J Neurol Sci* 1987;14(3):297-302.
41. Marengo TS, Harrison R, Lunt GG, Behan PO. Rat or human acetylcholine-receptor antigen for investigation of myasthenia gravis? *Lancet* 1979;1(8113):442.

42. Vincent A, Newsom-Davis J. Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays. *J Neurol Neurosurg Psychiatry* 1985;48(12):1246-1252.
43. Beeson D, Jacobson L, Newsom-Davis J, Vincent A. A transfected human muscle cell line expressing the adult subtype of the human muscle acetylcholine receptor for diagnostic assays in myasthenia gravis. *Neurology* 1996;47(6):1552-1555.
44. Leite MI, Jacob S, Viegas S et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. *Brain* 2008;131(Pt 7):1940-1952.
45. Burke G, Cossins J, Maxwell S et al. Rapsyn mutations in hereditary myasthenia: Distinct early- and late-onset phenotypes. *Neurology* 2003;61(6):826-828.
46. Muller JS, Herczegfalvi A, Vilchez JJ et al. Phenotypical spectrum of DOK7 mutations in congenital myasthenic syndromes. *Brain* 2007;130(Pt 6):1497-1506.
47. Grob D, Simpson D, Mitsumoto H et al. Treatment of myasthenia gravis by immunoadsorption of plasma. *Neurology* 1995;45(2):338-344.
48. Miller RG, Milner-Brown HS, Dau PC. Antibody-negative acquired myasthenia gravis: successful therapy with plasma exchange. *Muscle Nerve* 1981;4(3):255.
49. Melber D. Maternal-fetal transmission of myasthenia gravis with acetylcholine-receptor antibody. *N Engl J Med* 1988;318(15):996.
50. Mier AK, Havard CW. Diaphragmatic myasthenia in mother and child. *Postgrad Med J* 1985;61(718):725-727.
51. Burges J, Vincent A, Molenaar PC, Newsom-Davis J, Peers C, Wray D. Passive transfer of seronegative myasthenia gravis to mice. *Muscle Nerve* 1994;17(12):1393-1400.
52. Mossman S, Vincent A, Newsom-Davis J. Myasthenia gravis without acetylcholine-receptor antibody: a distinct disease entity. *Lancet* 1986;1(8473):116-119.
53. Blaas F, Beeson D, Plested P, Lang B, Vincent A. IgG from "seronegative" myasthenia gravis patients binds to a muscle cell line, TE671, but not to human acetylcholine receptor. *Ann Neurol* 2000;47(4):504-510.
54. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001;7(3):365-368.
55. Scuderi F, Marino M, Colonna L et al. Anti-p110 autoantibodies identify a subtype of "seronegative" myasthenia gravis with prominent oculobulbar involvement. *Lab Invest* 2002;82(9):1139-1146.
56. Evoli A, Tonali PA, Padua L et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain* 2003;126(10):2304-2311.
57. Evoli A, Batocchi AP, Lo MM et al. Clinical heterogeneity of seronegative myasthenia gravis. *Neuromuscular Disorders* 1996;6(3):155-161.

58. Reist NE, Werle MJ, McMahan UJ. Agrin released by motor neurons induces the aggregation of acetylcholine receptors at neuromuscular junctions. *Neuron* 1992;8(5):865-868.
59. Jennings CG, Dyer SM, Burden SJ. Muscle-specific trk-related receptor with a krigle domain defines a distinct class of receptor tyrosine kinases. *Proc Natl Acad Sci USA* 1993;90(7):2895-2899.
60. Hopf C, Hoch W. Dimerization of the muscle-specific kinase induces tyrosine phosphorylation of acetylcholine receptors and their aggregation on the surface of myotubes. *J Biol Chem* 1998;273(11):6467-6473.
61. Valenzuela DM, Stitt TN, DiStefano PS et al. Receptor tyrosine kinase specific for the skeletal muscle lineage: expression in embryonic muscle, at the neuromuscular junction, and after injury. *Neuron* 1995;15(3):573-584.
62. Till J, Becerra M, Watty A et al. Crystal structure of the MuSK tyrosine kinase: insights into receptor autoregulation. *Structure* 2002;10(9):1187-1196.
63. Johnson LN, Noble ME, Owen DJ. Active and inactive protein kinases: structural basis for regulation. *Cell* 1996;85(2):149-158.
64. Zhu D, Yang Z, Luo Z, Luo S, Xiong WC, Mei L. Muscle-specific receptor tyrosine kinase endocytosis in acetylcholine receptor clustering in response to agrin. *J Neurosci* 2008;28(7):1688-1696.
65. DeChiara TM, Bowen DC, Valenzuela DM et al. The receptor tyrosine kinase MuSK is required for neuromuscular junction formation in vivo. *Cell* 1996;85(4):501-512.
66. Kong XC, Barzaghi P, Ruegg MA. Inhibition of synapse assembly in mammalian muscle in vivo by RNA interference. *EMBO Rep* 2004;5(2):183-188.
67. Gautam M, Noakes PG, Moscoso L et al. Defective neuromuscular synaptogenesis in agrin-deficient mutant mice. *Cell* 1996;85(4):525-535.
68. Mittaud P, Camilleri AA, Willmann R, Erb-Vogtli S, Burden SJ, Fuhrer C. A single pulse of agrin triggers a pathway that acts to cluster acetylcholine receptors. *Mol Cell Biol* 2004;24(18):7841-7854.
69. Stiegler AL, Burden SJ, Hubbard SR. Crystal structure of the agrin-responsive immunoglobulin-like domains 1 and 2 of the receptor tyrosine kinase MuSK. *J Mol Biol* 2006;364(3):424-433.
70. Glass DJ, Bowen DC, Stitt TN et al. Agrin acts via a MuSK receptor complex. *Cell* 1996;85(4):513-523.
71. Glass DJ, Apel ED, Shah S et al. Kinase domain of the muscle-specific receptor tyrosine kinase (MuSK) is sufficient for phosphorylation but not clustering of acetylcholine receptors: required role for the MuSK ectodomain? *Proc Natl Acad Sci USA* 1997;94(16):8848-8853.

72. Weatherbee SD, Anderson KV, Niswander LA. LDL-receptor-related protein 4 is crucial for formation of the neuromuscular junction. *Development* 2006;133(24):4993-5000.
73. Kim N, Stiegler AL, Cameron TO et al. Lrp4 is a receptor for Agrin and forms a complex with MuSK. *Cell* 2008;135(2):334-342.
74. Zhang B, Luo S, Wang Q, Suzuki T, Xiong WC, Mei L. LRP4 serves as a coreceptor of agrin. *Neuron* 2008;60(2):285-297.
75. Gautam M, Noakes PG, Mudd J et al. Failure of postsynaptic specialization to develop at neuromuscular junctions of rapsyn-deficient mice. *Nature* 1995;377(6546):232-236.
76. Borges LS, Yechikhov S, Lee YI et al. Identification of a motif in the acetylcholine receptor beta subunit whose phosphorylation regulates rapsyn association and postsynaptic receptor localization. *J Neurosci* 2008;28(45):11468-11476.
77. Okada K, Inoue A, Okada M et al. The muscle protein Dok-7 is essential for neuromuscular synaptogenesis. *Science* 2006;312(5781):1802-1805.
78. Bergamin E, Hallock PT, Burden SJ, Hubbard SR. The cytoplasmic adaptor protein Dok7 activates the receptor tyrosine kinase MuSK via dimerization. *Mol Cell* 2010;39(1):100-109.
79. Linnoila J, Wang Y, Yao Y, Wang ZZ. A mammalian homolog of *Drosophila* tumorous imaginal discs, Tid1, mediates agrin signaling at the neuromuscular junction. *Neuron* 2008;60(4):625-641.
80. Cartaud A, Strochlic L, Guerra M et al. MuSK is required for anchoring acetylcholinesterase at the neuromuscular junction. *J Cell Biol* 2004;165(4):505-515.
81. Lu Z, Je HS, Young P, Gross J, Lu B, Feng G. Regulation of synaptic growth and maturation by a synapse-associated E3 ubiquitin ligase at the neuromuscular junction. *J Cell Biol* 2007;177(6):1077-1089.
82. Hezel M, de Groat WC, Galbiati F. Caveolin-3 promotes nicotinic acetylcholine receptor clustering and regulates neuromuscular junction activity. *Mol Biol Cell* 2009;21(2):302-310.
83. Ghazanfari N, Fernandez KJ, Murata Y et al. Muscle specific kinase: organiser of synaptic membrane domains. *Int J Biochem Cell Biol* 2011;43(3):295-298.
84. Lin W, Burgess RW, Dominguez B, Pfaff SL, Sanes JR, Lee KF. Distinct roles of nerve and muscle in postsynaptic differentiation of the neuromuscular synapse. *Nature* 2001;410(6832):1057-1064.
85. Yang X, Arber S, William C et al. Patterning of muscle acetylcholine receptor gene expression in the absence of motor innervation. *Neuron* 2001;30(2):399-410.

86. Kim N, Burden SJ. MuSK controls where motor axons grow and form synapses. *Nat Neurosci* 2008;11(1):19-27.
87. Chen F, Liu Y, Sugiura Y, Allen PD, Gregg RG, Lin W. Neuromuscular synaptic patterning requires the function of skeletal muscle dihydropyridine receptors. *Nat Neurosci* 2011;14(5):570-577.
88. Beeson D, Higuchi O, Palace J et al. Dok-7 mutations underlie a neuromuscular junction synaptopathy. *Science* 2006;313(5795):1975-1978.
89. Chevessier F, Faraut B, Ravel-Chapuis A et al. MUSK, a new target for mutations causing congenital myasthenic syndrome. *Hum Mol Genet* 2004;13(24):3229-3240.
90. Ohno K, Engel AG, Shen XM et al. Rapsyn mutations in humans cause endplate acetylcholine-receptor deficiency and myasthenic syndrome. *Am J Hum Genet* 2002;70(4):875-885.
91. Huzé C, Bauché S, Richard P et al. Identification of an agrin mutation that causes congenital myasthenia and affects synapse function. *Am J Hum Genet* 2009;85(2):155-167.
92. Sanders DB, El Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. *Neurology* 2003;60(12):1978-1980.
93. McConville J, Farrugia ME, Beeson D et al. Detection and characterization of MuSK antibodies in seronegative myasthenia gravis. *Ann Neurol* 2004;55(4):580-584.
94. Romi F, Aarli JA, Gilhus NE. Seronegative myasthenia gravis: disease severity and prognosis. *Eur J Neurol* 2005;12(6):413-418.
95. Yeh JH, Chen WH, Chiu HC, Vincent A. Low frequency of MuSK antibody in generalized seronegative myasthenia gravis among Chinese. *Neurology* 2004;62(11):2131-2132.
96. Wirtz PW, Nijhuis MG, Sotodeh M et al. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. *J Neurol* 2003;250(6):698-701.
97. Phillips LH, Torner JC. Epidemiologic evidence for a changing natural history of myasthenia gravis. *Neurology* 1996;47(5):1233-1238.
98. Tron F, Gilbert D, Mouquet H et al. Genetic factors in pemphigus. *J Autoimmun* 2005;24(4):319-328.
99. Niks EH, Kuks JBM, Roep BO et al. Strong association of MuSK antibody-positive myasthenia gravis and HLA-DR14-DQ5. *Neurology* 2006;66(11):1772-1774.
100. Higuchi O, Hamuro J, Motomura M, Yamanashi Y. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. *Ann Neurol* 2011;69(2):418-422.

101. Pevzner A, Schoser B, Peters K et al. Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis. *J Neurol* 2011;259(3):427-435.
102. Zhang B, Tzartos JS, Belimezi M et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. *Arch Neurol* 2011;69(4):445-451.
103. Vincent A, Bowen J, Newsom-Davis J, McConville J. Seronegative generalised myasthenia gravis: clinical features, antibodies, and their targets. *Lancet Neurol* 2003;2(2):99-106.
104. Lavrnjc D, Losen M, Vujic A et al. The features of myasthenia gravis with autoantibodies to MuSK. *J Neurol Neurosurg Psychiatry* 2005;76(8):1099-1102.
105. Padua L, Tonali P, Aprile I, Caliendo P, Bartocconi E, Evoli A. Seronegative myasthenia gravis: comparison of neurophysiological picture in MuSK+ and MuSK- patients. *Eur J Neurol* 2006;13(3):273-276.
106. Deymeer F, Gungor-Tuncer O, Yilmaz V et al. Clinical comparison of anti-MuSK- vs anti-AChR-positive and seronegative myasthenia gravis. *Neurology* 2007;68(8):609-611.
107. Ohta K, Shigemoto K, Fujinami A, Maruyama N, Konishi T, Ohta M. Clinical and experimental features of MuSK antibody positive MG in Japan. *Eur J Neurol* 2007;14(9):1029-1034.
108. Huang YC, Yeh JH, Chiu HC, Chen WH. Clinical Characteristics of MuSK Antibody-positive Myasthenia Gravis in Taiwan. *J Formos Med Assoc* 2008;107(7):572-575.
109. Pasnoor M, Wolfe GI, Nations S et al. Clinical findings in MuSK-antibody positive myasthenia gravis: A U.S. experience. *Muscle Nerve* 2010;41(3):370-374.
110. Gupitill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. *Muscle Nerve* 2011;44(1):36-40.
111. Zhou L, McConville J, Chaudhry V et al. Clinical comparison of muscle-specific tyrosine kinase (MuSK) antibody-positive and -negative myasthenic patients. *Muscle Nerve* 2004;30(1):55-60.
112. Stickler DE, Massey JM, Sanders DB. MuSK-antibody positive myasthenia gravis: Clinical and electrodiagnostic patterns. *Clin Neurophysiol* 2005;116(9):2065-2068.
113. Jaretzki A, Barohn RJ, Ernstoff RM et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;55(1):16-23.
114. Nemoto Y, Kuwabara S, Misawa S et al. Patterns and severity of neuromuscular transmission failure in seronegative myasthenia gravis. *J Neurol Neurosurg Psychiatry* 2005;76(5):714-718.

115. Niks EH, Kuks JB, Verschuuren JJ. Epidemiology of myasthenia gravis with anti-muscle specific kinase antibodies in The Netherlands. *J Neurol Neurosurg Psychiatry* 2007;78(4):417-418.
116. Farrugia ME, Robson MD, Clover L et al. MRI and clinical studies of facial and bulbar muscle involvement in MuSK antibody-associated myasthenia gravis. *Brain* 2006;129(Pt 6):1481-1492.
117. Muller JS, Baumeister SK, Rasic VM et al. Impaired receptor clustering in congenital myasthenic syndrome with novel RAPSN mutations. *Neurology* 2006;67(7):1159-1164.
118. Alseth EH, Maniaol AH, Elsaï A et al. Investigation for RAPSN and DOK-7 mutations in a cohort of seronegative myasthenia gravis patients. *Muscle Nerve* 2011;43(4):574-577.
119. Verduyn W, Doxiadis II, Anholts J et al. Biotinylated DRB sequence-specific oligonucleotides. Comparison to serologic HLA-DR typing of organ donors in eurotransplant. *Hum Immunol* 1993;37(1):59-67.
120. Schipper RE, Schreuder GM, D'Amaro J, Oudshoorn M. HLA gene and haplotype frequencies in Dutch blood donors. *Tissue Antigens* 1996;48(5):562-574.
121. Ahmed AR, Wagner R, Khatri K et al. Major histocompatibility complex haplotypes and class II genes in non-Jewish patients with pemphigus vulgaris. *Proc Natl Acad Sci USA* 1991;88(11):5056-5060.
122. Delgado JC, Hameed A, Yunis JJ et al. Pemphigus vulgaris autoantibody response is linked to HLA-DQB1*0503 in Pakistani patients. *Hum Immunol* 1997;57(2):110-119.
123. Bhol K, Natarajan K, Nagarwalla N, Mohimen A, Aoki V, Ahmed AR. Correlation of peptide specificity and IgG subclass with pathogenic and nonpathogenic autoantibodies in pemphigus vulgaris: A model for autoimmunity. *Proc Natl Acad Sci USA* 1995;92(11):5239-5243.
124. Jha S, Xu K, Maruta T et al. Myasthenia gravis induced in mice by immunization with the recombinant extracellular domain of rat muscle-specific kinase (MuSK). *J Neuroimmunol* 2006;175(1-2):107-117.
125. Shiraishi H, Motomura M, Yoshimura T et al. Acetylcholine receptors loss and postsynaptic damage in MuSK antibody-positive myasthenia gravis. *Ann Neurol* 2005;57(2):289-293.
126. Selcen D, Fukuda T, Shen XM, Engel AG. Are MuSK antibodies the primary cause of myasthenic symptoms? *Neurology* 2004;62(11):1945-1950.
127. Brooke MH. *A Clinician's View of Neuromuscular Diseases*. 2 ed. Baltimore: Williams & Wilkins; 1986.

128. Bartoccioni E, Scuderi F, Minicuci GM, Marino M, Ciaraffa F, Evoli A. Anti-MuSK antibodies: Correlation with myasthenia gravis severity. *Neurology* 2006;67(3):505-507.
129. Aalberse RC, van der Gaag R, van Leeuwen J. Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. *J Immunol* 1983;130(2):722-726.
130. Matsumoto T, Shima M, Fukuda K et al. Immunological characterization of factor VIII autoantibodies in patients with acquired hemophilia A in the presence or absence of underlying disease. *Thromb Res* 2001;104(6):381-388.
131. Hillman M, Törn C, Thorgeirsson H, Landin-Olsson M. IgG4-subclass of glutamic acid decarboxylase antibody is more frequent in latent autoimmune diabetes in adults than in type 1 diabetes. *Diabetologia* 2004;47(11):1984-1989.
132. Hamano H, Kawa S, Horiuchi A et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344(10):732-738.
133. Futei Y, Amagai M, Ishii K, Kuroda-Kinoshita K, Ohya K, Nishikawa T. Predominant IgG4 subclass in autoantibodies of pemphigus vulgaris and foliaceus. *J Dermatol Sci* 2001;26(1):55-61.
134. Chan KH, LaChance DH, Harper CM, Lennon VA. Frequency of seronegativity in adult-acquired generalized myasthenia gravis. *Muscle Nerve* 2007;36(5):651-658.
135. Muppidi S, Wolfe GI. Muscle-specific receptor tyrosine kinase antibody-positive and seronegative myasthenia gravis. *Front Neurol Neurosci* 2009;26:109-119.
136. Drachman DB. Myasthenia gravis. *N Engl J Med* 1994;330(25):1797-1810.
137. Jo SA, Zhu X, Marchionni MA, Burden SJ. Neuregulins are concentrated at nerve-muscle synapses and activate ACh-receptor gene expression. *Nature* 1995;373(6510):158-161.
138. Rimer M. Neuregulins: Primary or secondary signals for the control of synapse-specific gene expression. *J Neurocytol* 2003;32(5-8):665-675.
139. Zhu X, Lai C, Thomas S, Burden SJ. Neuregulin receptors, erbB3 and erbB4, are localized at neuromuscular synapses. *EMBO J* 1995;14(23):5842-5848.
140. Buonanno A, Fischbach GD. Neuregulin and ErbB receptor signaling pathways in the nervous system. *Curr Opin Neurobiol* 2001;11(3):287-296.
141. Sanes JR, Lichtman JW. Development of the vertebrate neuromuscular junction. *Annu Rev Neurosci* 1999;22:389-442.
142. Lemke G. Neuregulins in development. *Mol Cell Neurosci* 1996;7(4):247-262.
143. Trinidad JC, Fischbach GD, Cohen JB. The Agrin/MuSK signaling pathway is spatially segregated from the neuregulin/ErbB receptor signaling pathway at the neuromuscular junction. *J Neurosci* 2000;20(23):8762-8770.

144. Sandrock A, Dryer S, Rosen K et al. Maintenance of acetylcholine receptor number by neuregulins at the neuromuscular junction in vivo. *Science* 1997;276:599-603.
145. Kummer TT, Misgeld T, Sanes JR. Assembly of the postsynaptic membrane at the neuromuscular junction: paradigm lost. *Curr Opin Neurobiol* 2006;16(1):74-82.
146. Mencarelli C, Hammels C, Van Den Broeck J et al. The expression of the Goodpasture antigen-binding protein (ceramide transporter) in adult rat brain. *J Chem Neuroanat* 2009;38(2):97-105.
147. Ross JS, Slodkowska EA, Symmans WF, Puzsai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;14(4):320-368.
148. Cobleigh MA, Vogel CL, Tripathy D et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;17(9):2639-2648.
149. Baselga J, Tripathy D, Mendelsohn J et al. Phase II study of weekly intravenous trastuzumab (Herceptin) in patients with HER2/neu-overexpressing metastatic breast cancer. *Semin Oncol* 1999;26(4 Suppl 12):78-83.
150. Le PR, Cizeron-Clairac G, Bismuth J, Berrih-Aknin S. Microarrays reveal distinct gene signatures in the thymus of seropositive and seronegative myasthenia gravis patients and the role of CC chemokine ligand 21 in thymic hyperplasia. *J Immunol* 2006;177(11):7868-7879.
151. Cizeron-Clairac G, Le PR, Frenkian-Cuvelier M et al. Thymus and Myasthenia Gravis: what can we learn from DNA microarrays? *J Neuroimmunol* 2008;201-202:57-63.
152. Lefvert AK, Osterman PO. Newborn infants to myasthenic mothers: a clinical study and an investigation of acetylcholine receptor antibodies in 17 children. *Neurology* 1983;33(2):133-138.
153. Ahlsten G, Lefvert AK, Osterman PO, Stålberg E, Säfwenberg J. Follow-up study of muscle function in children of mothers with myasthenia gravis during pregnancy. *J Child Neurol* 1992;7(3):264-269.
154. Morel E, Eymard B, Vernet-der Garabedian B, Pannier C, Dulac O, Bach JF. Neonatal myasthenia gravis: a new clinical and immunologic appraisal on 30 cases. *Neurology* 1988;38(1):138-142.
155. Tzartos SJ, Efthimiadis A, Morel E, Eymard B, Bach JF. Neonatal myasthenia gravis: antigenic specificities of antibodies in sera from mothers and their infants. *Clin Exp Immunol* 1990;80(3):376-380.
156. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996;36(5):248-255.

157. Vincent A, Leite MI, Farrugia ME et al. Myasthenia gravis seronegative for acetylcholine receptor antibodies. *Ann N Y Acad Sci* 2008;1132:84-92.
158. Farrugia ME, Bonifati DM, Clover L, Cossins J, Beeson D, Vincent A. Effect of sera from AChR-antibody negative myasthenia gravis patients on AChR and MuSK in cell cultures. *J Neuroimmunol* 2007;185(1-2):136-144.
159. Song Y, Balice-Gordon R. New dogs in the dogma: Lrp4 and Tid1 in neuromuscular synapse formation. *Neuron* 2008;60(4):526-528.
160. Storchli L, Cartaud A, Cartaud J. The synaptic muscle-specific kinase (MuSK) complex: new partners, new functions. *Bioessays* 2005;27(11):1129-1135.
161. Niks EH, van Leeuwen Y, Leite MI et al. Clinical fluctuations in MuSK myasthenia gravis are related to antigen-specific IgG4 instead of IgG1. *J Neuroimmunol* 2008;195(1-2):151-156.
162. Plomp JJ, Van Kempen GT, De Baets MB, Graus YM, Kuks JB, Molenaar PC. Acetylcholine release in myasthenia gravis: regulation at single end-plate level. *Ann Neurol* 1995;37(5):627-636.
163. Pestronk A, Drachman DB. A new stain for quantitative measurement of sprouting at neuromuscular junctions. *Muscle Nerve* 1978;1(1):70-74.
164. Elmqvist D, Hofmann WW, Kugelberg J, Quastel DM. An electrophysiological investigation of neuromuscular transmission in myasthenia gravis. *J Physiol* 1964;174:417-434.
165. Cull-Candy SG, Miledi R, Trautmann A, Uchitel OD. On the release of transmitter at normal, myasthenia gravis and myasthenic syndrome affected human end-plates. *J Physiol* 1980;299:621-638.
166. Shigemoto K, Kubo S, Maruyama N et al. Induction of myasthenia by immunization against muscle-specific kinase. *J Clin Invest* 2006;116(4):1016-1024.
167. Slater CR, Lyons PR, Walls TJ, Fawcett PR, Young C. Structure and function of neuromuscular junctions in the vastus lateralis of man. A motor point biopsy study of two groups of patients. *Brain* 1992;115:451-478.
168. Ip FC, Glass DG, Gies DR et al. Cloning and characterization of muscle-specific kinase in chicken. *Mol Cell Neurosci* 2000;16(5):661-673.
169. Maselli RA, Wollman RL, Leung C et al. Neuromuscular transmission in amyotrophic lateral sclerosis. *Muscle Nerve* 1993;16(11):1193-1203.
170. Tsujihata M, Hazama R, Yoshimura T, Satoh A, Mori M, Nagataki S. The motor end-plate fine structure and ultrastructural localization of acetylcholine receptors in amyotrophic lateral sclerosis. *Muscle Nerve* 1984;7(3):243-249.
171. Cole RN, Reddel SW, Gervásio OL, Phillips WD. Anti-MuSK patient antibodies disrupt the mouse neuromuscular junction. *Ann Neurol* 2008;63(6):782-789.

172. Chang T, Gunaratne P, Gamage R, Riffsy MTM, Vincent A. MuSK-antibody-positive myasthenia gravis in a South Asian population. *J Neurol Sci* 2009;284(1-2):33-35.
173. Oh SJ, Morgan MB, Lu L et al. Racial differences in myasthenia gravis in Alabama. *Muscle Nerve* 2009;39(3):328-332.
174. Behin A, Mayer M, Kassis-Makhoul B et al. Severe neonatal myasthenia due to maternal anti-MuSK antibodies. *Neuromuscular Disorders* 2008;18(6):443-446.
175. Murray EL, Kedar S, Vedanarayanan VV. Transmission of maternal muscle-specific tyrosine kinase (MuSK) to offspring: report of two cases. *J Clin Neuromuscul Dis* 2010;12(2):76-79.
176. O'Carroll P, Bertorini TE, Jacob G, Mitchell CW, Graff J. Transient neonatal myasthenia gravis in a baby born to a mother with new-onset anti-MuSK-mediated myasthenia gravis. *J Clin Neuromuscul Dis* 2009;11(2):69-71.
177. Mori S, Yamada S, Kubo S et al. Divalent and monovalent autoantibodies cause dysfunction of MuSK by distinct mechanisms in a rabbit model of myasthenia gravis. *J Neuroimmunol* 2012.
178. Klooster R, Plomp JJ, Huijbers MG et al. Muscle-specific kinase myasthenia gravis IgG4 autoantibodies cause severe neuromuscular junction dysfunction in mice. *Brain* 2012;135(4):1081-1101.
179. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science* 2006;313(5787):670-673.
180. Van de Geijn FE, Wuhler M, Selman MH et al. Immunoglobulin G galactosylation and sialylation are associated with pregnancy-induced improvement of rheumatoid arthritis and the postpartum flare: results from a large prospective cohort study. *Arthritis Res Ther* 2009;11(6):R193.
181. Selman MH, Niks EH, Titulaer MJ, Verschuuren JJ, Wuhler M, Deelder AM. IgG f_c N-glycosylation changes in Lambert-Eaton myasthenic syndrome and myasthenia gravis. *J Proteome Res* 2011;10(1):143-152.
182. Diaz-Manera J, Martinez-Hernandez E, Querol L et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology* 2012;78(3):189-193.
183. Perosa F, Prete M, Racanelli V, Dammacco F. CD20-depleting therapy in autoimmune diseases: from basic research to the clinic. *J Intern Med* 2010;267(3):260-277.
184. Liewluck T, Selcen D, Engel AG. Beneficial effects of albuterol in congenital endplate acetylcholinesterase deficiency and Dok-7 myasthenia. *Muscle Nerve* 2011;44(5):789-794.

185. Lashley D, Palace J, Jayawant S, Robb S, Beeson D. Ephedrine treatment in congenital myasthenic syndrome due to mutations in DOK7. *Neurology* 2010;74(19):1517-1523.
186. Ryall JG, Church JE, Lynch GS. Novel role for β -adrenergic signalling in skeletal muscle growth, development and regeneration. *Clin Exp Pharmacol Physiol* 2010;37(3):397-401.
187. Maselli RA, Ng JJ, Anderson JA et al. Mutations in LAMB2 causing a severe form of synaptic congenital myasthenic syndrome. *J Med Genet* 2009;46(3):203-208.
188. Provenzano C, Marino M, Scuderi F, Evoli A, Bartoccioni E. Anti-acetylcholinesterase antibodies associate with ocular myasthenia gravis. *J Neuroimmunol* 2010;218(1-2):102-106.
189. Romi F, Suzuki S, Suzuki N, Petzold A, Plant GT, Gilhus NE. Anti-voltage-gated potassium channel Kv1.4 antibodies in myasthenia gravis. *J Neurol* 2011;259(7):1312-1316.
190. Kaminski HJ, Richmonds CR, Kusner LL, Mitsumoto H. Differential susceptibility of the ocular motor system to disease. *Ann N Y Acad Sci* 2002;956:42-54.
191. Punga AR, Maj M, Lin S, Meinen S, Ruegg MA. MuSK levels differ between adult skeletal muscles and influence postsynaptic plasticity. *Eur J Neurosci* 2011;33(5):890-898.