Mountain medicine CORRADO ANGELINI ,MIJA MEZNARIC , MARIKA FALLA

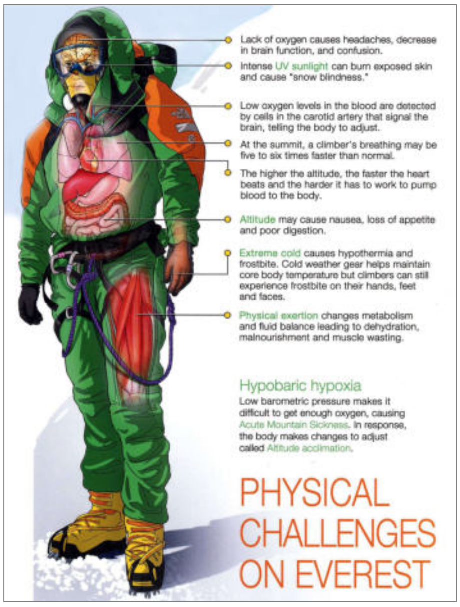
11th European Hypoxia Symposium

Training Centre German Federal Police, Kührointalm / Berchtesgaden (Germany), 27th September 2025

Corrado Angelini

NEUROMUSCULAR SYSTEM AND CNS IN HYPOXIA

INTERACTION BRAIN, HEART, POLMONE, MUSCLES IN ALTA QUOTA



Data collected in Everest base camp might help treat patients

MITOCONDRIA in mountain environment

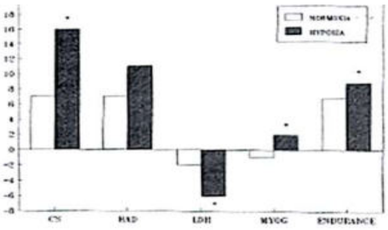


Fig. 2 Summary of the main changes with normoxic and hypoxic training. Basal line is the value before the training program, bars are difference after the training (* = $p < 0.05$).

Muscle enzyme activities (μmol/g per min at 37 °C).

Enzyme	Ox[1]	Sherpa[2]	Quechua[2]	Marathon Runner[2]	Humming-bird[3]
CS	10.0	17.9 (2.7)	16.4 (6.0)	44.1	343
HOAD	4.0	29.1 (4.2)	29.6 (2.4)	67.9	97
PK	675	401 (72)	619 (66)	654	672
LDH	2100	376 (60)	453 (41)	458	230

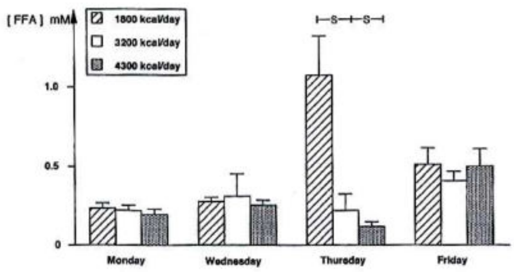
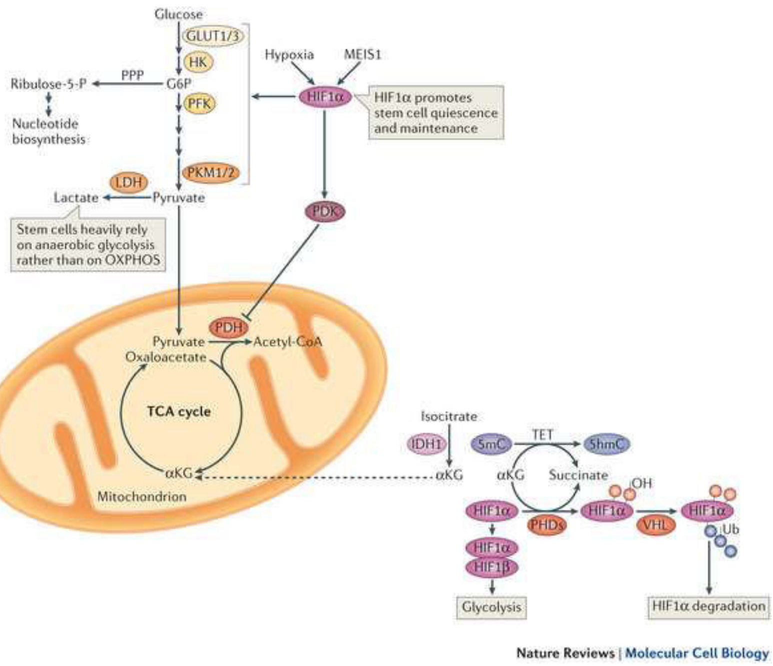


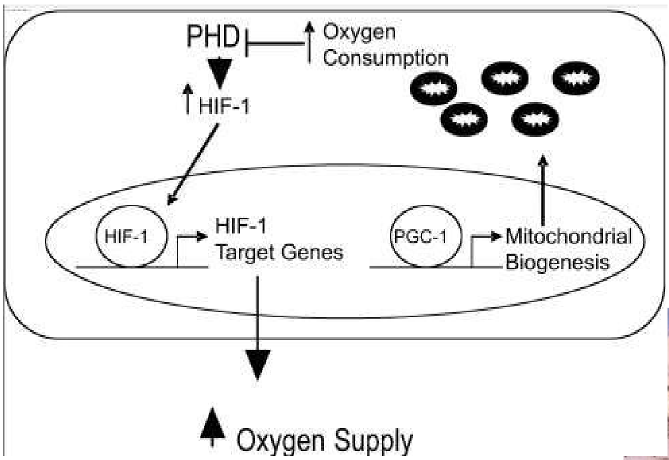
Fig. 1 Free fatty acids plasma concentration at rest during a commando raid in a mountain environment with three levels of caloric diet.
s: significant difference between groups of various caloric diet.



PGC-1α ESPRESSED by GENE HIF-1α increases OXYGEN MITOCONDRIAL USE

Reduced oxygen levels leads to a shift in cellular metabolism. hypoxia, the mitochondria undergo several adaptations to optimize energy .

A key adaptation is an increase in the number and size mitochondrial biogenesis, is regulated by various signaling pathways, such as the hypoxia-inducible factor (HIF)

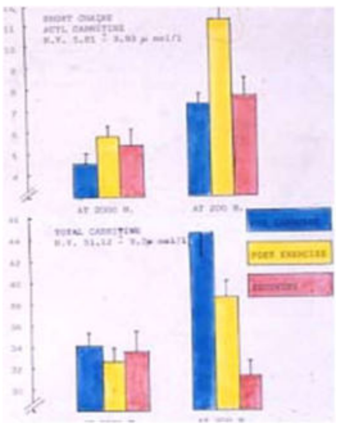


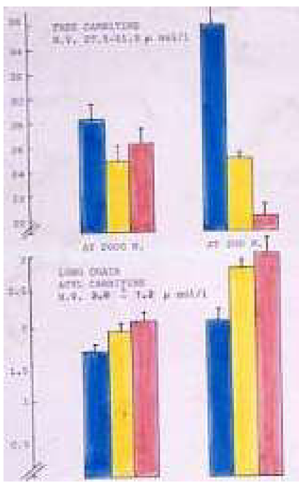
O'Hagan et al. PNAS 2009

ATHLETIC TRAINING IN HYPOXIA

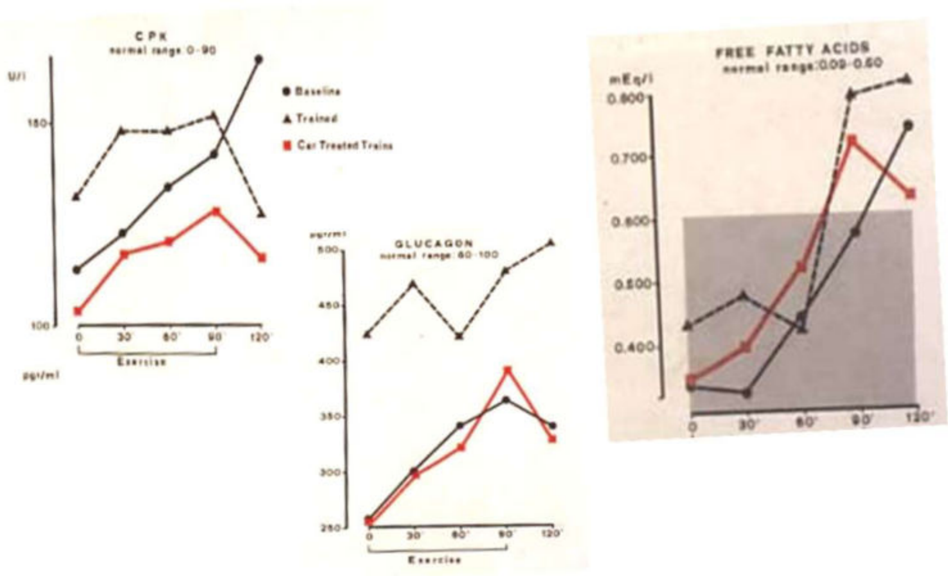
Muscoli e polmoni d'acciaio allenandosi alle medie quote

Gli sciatori del «Gardena» seguiti per 4 mesi durante un intenso ciclo di allenamenti a 2000 metri di altezza - Risultato: prestazioni maggiori con minore fatica - CAI, ospedale, università di Padova e 4° C. A. hanno collaborato allo studio

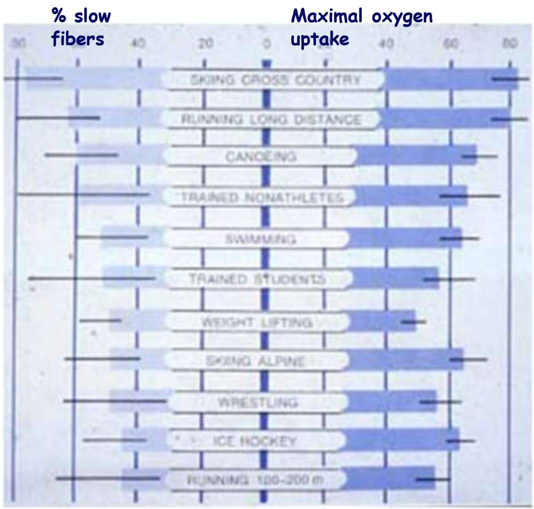




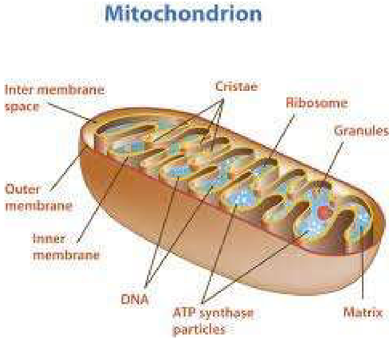
SUBSTRATES AT 2000 m.

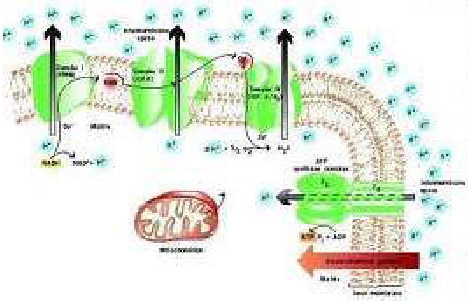


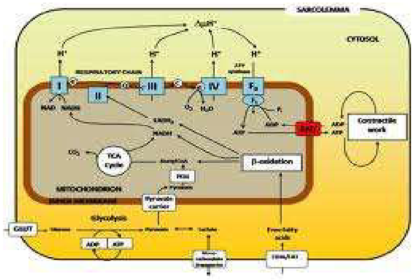
SLOW FIBRES (TYPE 1) Maxymal oxygen uptake in sport activities



MITOCHONDRIAL BIOMARKERS







Lactic acid,
Pyruvate
Alanine
Carnitine, acyl-carnitines
Ketones,Organic acids
Reactive Oxygen Species (ROS)

MITOCHONDRIA AND ROS

OBJECTIVES

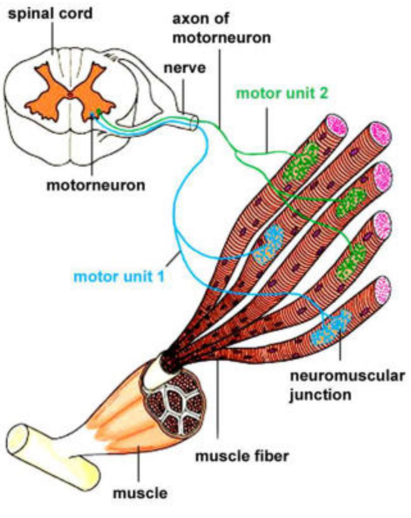
Additionally, in hypoxic conditions, the mitochondria may switch to alternative metabolic pathways to generate ATP. For example, anaerobic glycolysis becomes more prominent, producing ATP but with a lower efficiency compared to oxidative phosphorylation. Mitochondrial damage is often present and leads to the "lactate paradox", fatigue, and sarcopenia. Moreover, mitochondria play a crucial role in the production of reactive oxygen species (ROS), which are byproducts of oxygen metabolism. In hypoxic conditions, the imbalance between ROS production and clearance can occur, resulting in oxidative stress. This oxidative stress can damage the mitochondria and other cellular components, leading to various physiopathological consequences and changes in neurotransmitters, which might change the mood, toward depression or euphoria. The mitochondrial adaptations aim to maintain cellular energy production and homeostasis under low oxygen, as in the MELAS (3) condition.

OBJECTIVE

What are neuromuscular diseases?

- Can neuromuscolar patients go to mountain?
- At which altitude?
- What precautions ?

NEUROMUSCULAR DISEASES



Include numerous clinical disorders for dysfunction of motor unit

- Motoneuron
- Nerve
- Axon
- Neuromuscular junction
- Muscle

NEUROMUSCULAR JUNCTION DISEASES

HEREDITARY
- Myasthenia congenita

ACQUIRED
- Miasthenia gravis
- - Lambert Eaton Syndrome

LOWER MOTONEURON NERVE-AXON

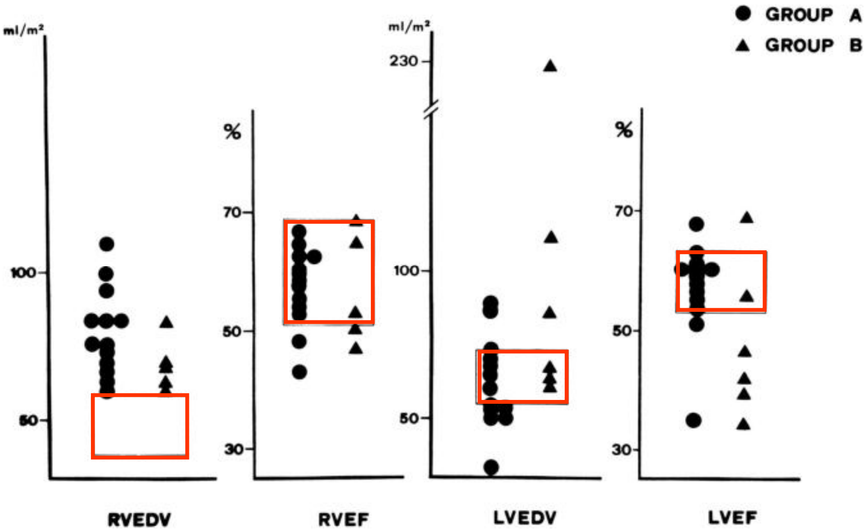
HEREDITARY
- Progressive Spinal Amyotrophy
- Peripheral Neuropathy (e.g. Charcot-Marie-Tooth)

ACQUIRED
- Amyotrophic Lateral Sclerosis (ALS)
- Progressive muscular atrophy
- Peripheral Neuropathy

MUSCULAR SYNDROMES

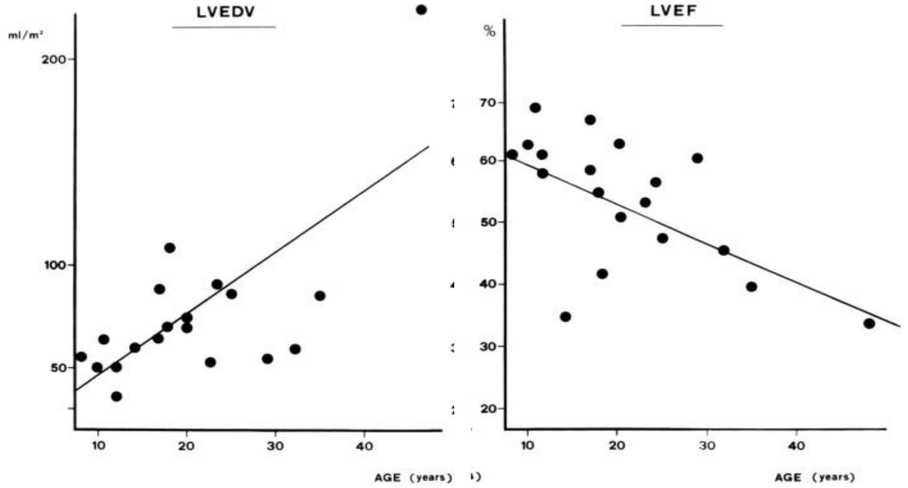
- **Cramps**, causes: neurogenic, energetic failurer or myofiber necrosis
- **Fatigability**, metabolic exhaustion lactic acidosis
- **CK elevation**, caused by muscular necrosis
- **Mioglobinuria** due to dehydration ,metabolic disorders ,channellopathy, disionia

ECHOCARDIOGRAPHy BECKER SUBCLINIC



RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction
LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction

CORRELATION LVEDV / LVEF WITH THE PATIENT BECKER'S AGE

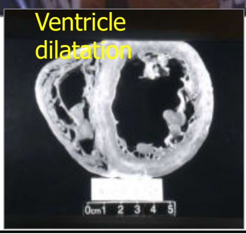


LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction

BENEFIT OF REHABILITATION

32 year old BMD case after cardiac traplant , in rehabilitation ardiologica at Codivilla Hospital in Cortina (1200 m).

neuro-motor rehabilitation: 20-40 minutes cyclette X 3 days week

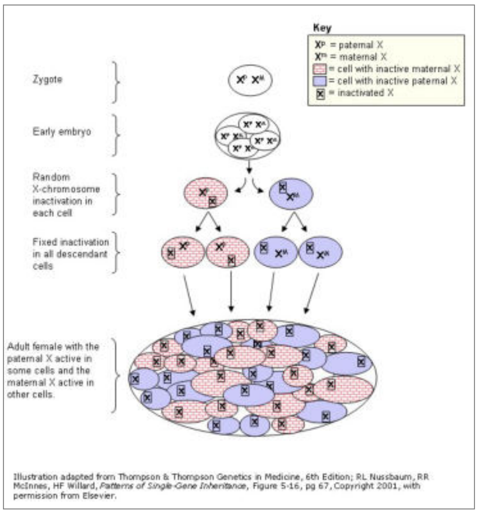


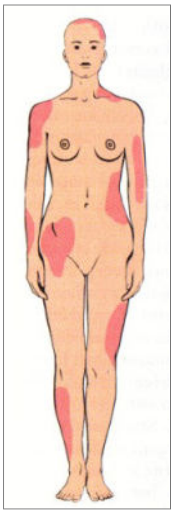
FEMALE DUCHENNE CARRIER

Inactivation cromosome X (Lyonization)

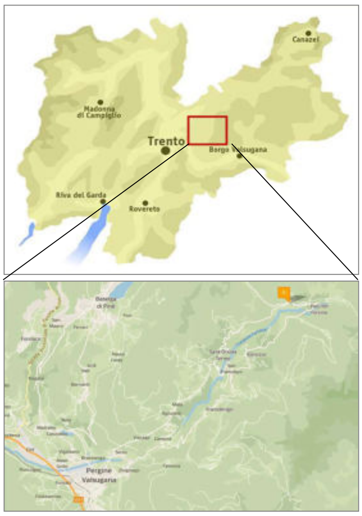
X Y

X X



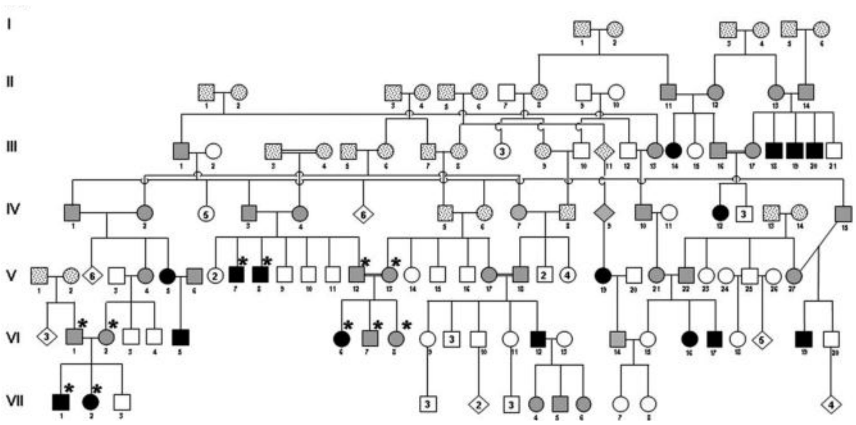


(LGMD2A): GENETIC ISOLATE IN ALPS (Valle dei Mocheni)



La valle ysuperiore del fiume Fersina è una enclave of german speaking people since medioeval time ***"Mòcheni"***. I "Mòcheni" a isolato linguistic and genetic, geografic, caused consanguinity.

MUTATION INTRONIC CAUSES LGMD2A: IN ALPINE GENETIC POPULATION (Valle dei Mocheni)



Mutatine PRIVATe IN FAMILY (c.1193+6T>A) FOUNDER EFFECT

GLICOGENOSIS TYPE 2 with respiratory diaphragmatic insufficiesy

(no altitude over 2000 m)




GLYCOGENOSIS TYPE 5, McArdle's disease

CLINICAL SIGNS

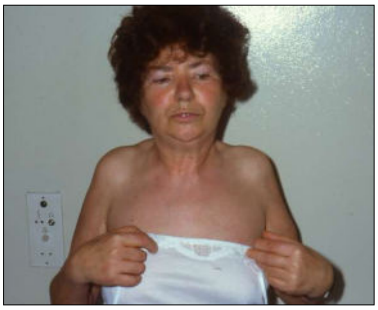
- Exercise intolerance
- myopathy
- myoglobinuria
- cramps or contractures
- defective lactic acid in ischemic exercise
- "second wind" fatty acid utilization

GENE

Muscle glycogen phosporylase (*PYGM*)

MOTONEURON DISEASE

bulbar ALS



ALS (FVC < 50%)

Myasthenia Gravis and Endurance Exercise

Scheer BV, Valero-Burgos E, Costa R: Myasthenia gravis and endurance exercise. Am J Phys Med Rehabil 2012;91:725–727.

This is the first report of a runner with myasthenia gravis who completed an ultra endurance event. Myasthenia gravis, a neuromuscular disease that usually results in skeletal muscle weakness, which worsens with exercise and strenuous aerobic exercise, is generally contraindicated. Our runner completed a 220-km, 5-day ultramarathon and presented with various symptoms including muscular skeletal weakness, cramps, generalized fatigue, unintelligible speech, involuntary eye and mouth movements, problems swallowing, food lodging in his throat, and problems breathing. Risk factors identified for exacerbations are running in extreme temperatures, prolonged runs (especially a distance of 30 km or more), running uphill, lack of sleep, and stress. The medical team was in the novel situation to look after a runner with myasthenia gravis and needed to be aware of the patient's condition, symptoms, and risk factors to safely care for him.

ACTIVITY GUIDELINES

- Avoid activity and running in extreme temperatures
- Try to avoid prolonged endurance type of exercise
- Modify activities that include running or exercising uphill or on stairs
- Make sure to exercise after adequate sleep and try to avoid stress
- Exercise at peak energy times of the day

Hypoxic neuropathy: Does hypoxia play a role in diabetic neuropathy?

The 1988 Robert Wartenberg Lecture

Peter James Dyck, MD

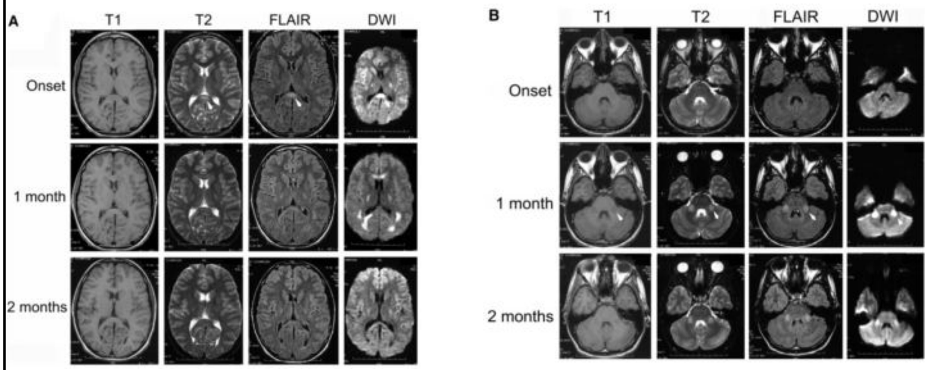
Article abstract—In this report I review: (1) the blood supply and endoneurial microenvironment of nerve; (2) the class, type, and spatial distribution of nerve fiber degeneration as a function of number, site, and class of vessels occluded; (3) the putative mechanisms of nerve hypoxia; and (4) the role of hypoxia in diabetic polyneuropathy.

NEUROLOGY 1989;39:111-118

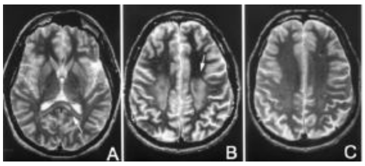
Figure 3. Light photomicrograph of methylene blue-stained semi-thin transverse section of sural nerve fixed in glutaraldehyde and osmium tetroxide from patient with diabetic polyneuropathy illustrates striking focal loss of myelinated fibers (MF), suggesting ischemic injury. Lower picture is higher magnification of frame shown in upper picture; density of MF in fascicle shown on right is moderately decreased from normal, whereas essentially no MF are seen in fascicle on left. Left fascicle also shows thickened perineurium, protein-rich endoneurial fluid, and excessive cellularity—other suggestive hallmarks of ischemic injury. (From Dyck PJ et al, "Fiber loss is primary and multifocal in sural nerves," Ann Neurol

Transient Central Nervous System White Matter Abnormality in X-Linked Charcot-Marie-Tooth disease

Ann Neurol 2002;52:429–434



CMTX (Cx32)

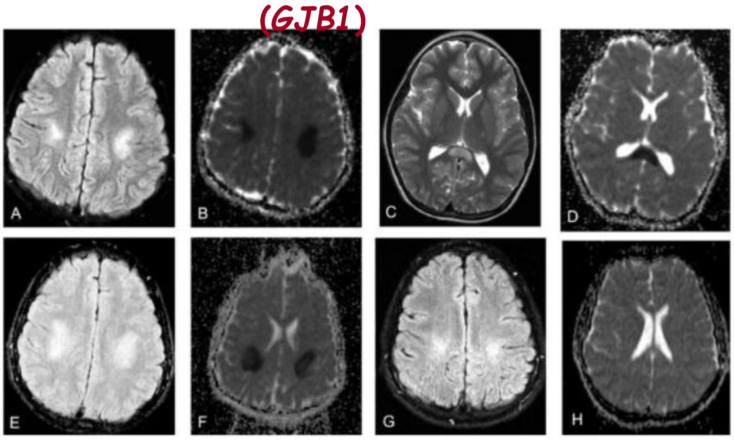


The CNS phenotype of X-linked Charcot-Marie-Tooth disease

More than a peripheral problem

Neurology 2003;61:1475

CMTX (GJB1)



Cold Agglutinin Disease and Cryoglobulinemia

Morie A. Gertz

Cold agglutinin disease is a form of direct, extravascular, antiglobulin-positive hemolysis. In vivo, immunoglobulin (Ig) M fixes complement molecules to the red cell membrane. Successive passages through the mononuclear phagocyte system result in loss of red cell membrane. The resultant spherocytes lose resiliency and are ultimately lost from the circulation extravascularly. The high concentration of complement molecules on the red cell surfaces makes this syndrome resistant to the standard therapies for immune-mediated hemolysis. Rituximab has been reported to reduce the severity of hemolysis. Type II cryoglobulins are composed of a monoclonal IgM and a polyclonal IgG. These complexes have rheumatoid factor activity and can produce immune-complex vasculitis. The target organs are the skin, nerves, kidney, liver, and joints. More than 80% of patients have evidence of hepatitis C infection. Interferon and interferon plus ribavirin have been shown to produce serologic responses. When vasculitis is active, corticosteroids are often required to permit healing of ulcers in the skin or to treat the membranoproliferative glomerulonephritis that is seen, thereby preventing loss of renal function. Rituximab therapy has been found to be effective in mixed cryoglobulinemia, with decreases in cryoglobulin values and improvement in complement values.

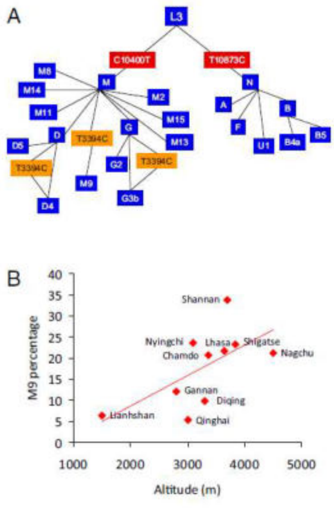
Clinical Lymphoma, Vol. 5, No. 4, 290-293, 2005

PNAS

Mitochondrial DNA variant associated with Leber hereditary optic neuropathy and high-altitude Tibetans

Fuyun Ji[a], Mark S. Sharpley[b,c], Olga Derbeneva[b,c], Leonardo Scherer Alves[b,c], Pin Qian[d], Yaoli Wang[a], Dimitra Chalkia[b,c], Maria Lvova[b,c], Jiancheng Xu[a], Wei Yao[a], Mariella Simon[c], Julia Platt[c], Shiqin Xu[c], Alessia Angelin[b,c], Antonio Davila[b,c], Taosheng Huang[c], Ping H. Wang[e], Lee-Ming Chuang[f], Lorna G. Moore[g], Guisheng Qian[a], and Douglas C. Wallace[b,c,1]

[a]Institute of Human Respiratory Disease, [d]Institute of Field Internal Medicine, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China; [b]Center for Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA 19104; [c]Center for Molecular and Mitochondrial Medicine and Genetics, and [e]Department of Medicine, Center for Diabetes Research and Treatment, University of California, Irvine, CA 92697; [f]Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan; and [g]Graduate School of Arts and Sciences, Wake Forest University, Winston-Salem, NC 27157



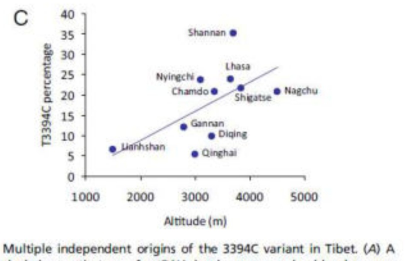
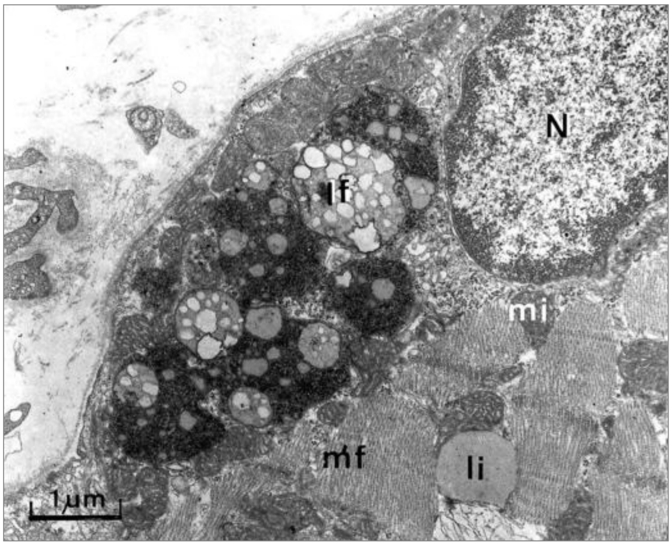


Fig. 3. Multiple independent origins of the 3394C variant in Tibet. (*A*) A simplified phylogenetic tree of mtDNA haplogroups and subhaplogroups observed among native Tibetans in sample 1. Steps in which the T3394C variant must have occurred are shown, revealing three independent mutational events. Note that all 3394C variants are associated with macrohaplogroup M, which is also true for the C4a4 mtDNAs of the Deccan plateau, Karnataka State. (*B*) A positive linear relationship between the frequency of the haplogroup M9 and altitude in Tibetan villages (R^2 = 0.4018). (*C*) A positive linear relationship between the frequency of the 3394C variant and altitude in Tibetan villages (R^2 = 0.3748). The names of the villages sampled are presented next to each symbol and the M9 and 3394C frequencies are provided in Table S12.

CRONIC HYPOXIC MYOPATHY IN EXTREME ALTITUDE



Lf:

RUN AT HIGH ALTITUDE

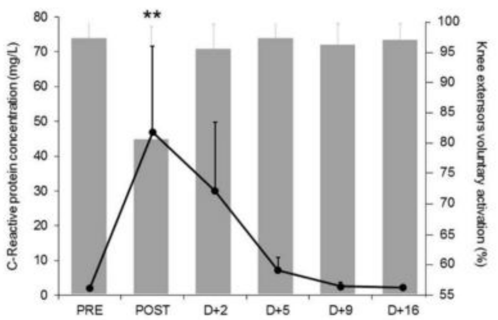


Fig. 3 Means and standard deviations of C-reactive protein concentration (*black circles*) and knee extensors maximal voluntary activation (*gray bars*) before (PRE), after (POST), and 2, 5, 9, and 16 days after (D + 2, D + 5, D + 9, and D + 16, respectively) a 166-km ultra-trail race with ±9500 m of positive and negative elevation. *Double asterisks* indicates a significant difference with PRE values ($P < 0.01$) Adapted from Millet et al. (2011a, b)

Increased C-reactive protein after exercise (Giandolini et al. Eur.J.Appl.Physiol. 2016)

hyponatremia in ultra-marathon runners (Cuthill et al. Emerg.Med.J. 2009)

MUSCULAR SYNDROMES: CONTROINDICATIONS FOR TREKKING

-Muscular Dystrophies,

- DMD Carriers,

-Myotonic Dystrophy

-GSD II

-ALS disease with respiratory insufficiency

PERIFERAL NEUROPATHIES

Trekking not advised:

- **Charcot-Marie-Tooth disease**: pes cavus. So stroke-like episodes at 700 m. (Sagnelli et al. JPNS 2014)

diabetic neuropathy: hischemic vessel hypoxia is controindicated

CONCLUSION

Can neuromuscular patients climb mountains?
No problems at middle altitude.

- Which altitude? 1500 m.LGMD patients live at this altitude.
- Which precautions? Monitor cardiac , respiratory,metabolic ,blood pressure status and biomarkers.

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5. Angelini C, Tasca E, Nascimbeni AC, Fanin M. Muscle fatigue, nNOS and muscle fiber atrophy in limb girdle muscular dystrophy. Acta Myol. 2014 Dec;33(3):119-26. PMID: 25873780; PMCID: PMC4369848.