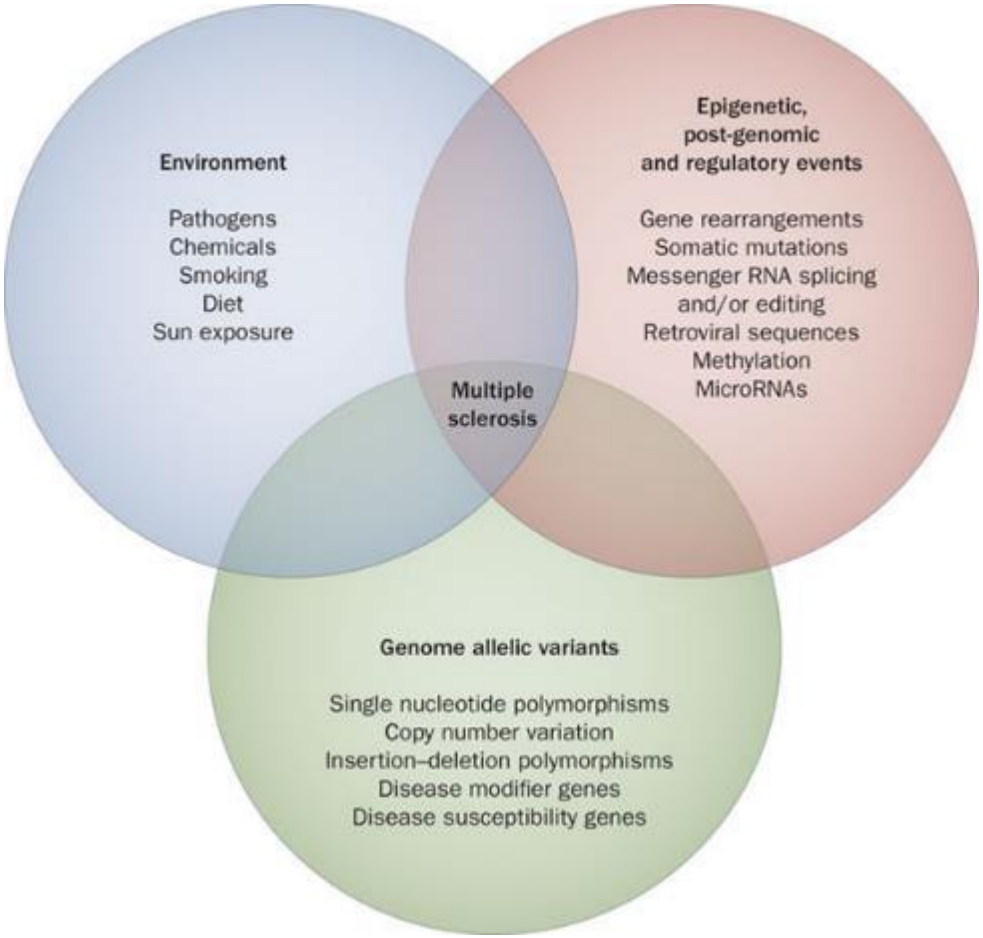
Genetics in Multiple Sclerosis

Amiel Dror | Neurology clerkship| 4 year program| Tel Aviv University

MS as a complex disease



Oksenberg, J. R. & Baranzini, S. E. (2010) Multiple sclerosis genetics - is the glass half full, or half empty? *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2010.91

Why Genetics?

- Identify risk factors
- Better understand disease
- Uncover new targets for specific therapies
- Understand differences between patients
- Find better match between patient & treatment

Role of the Genes in MS

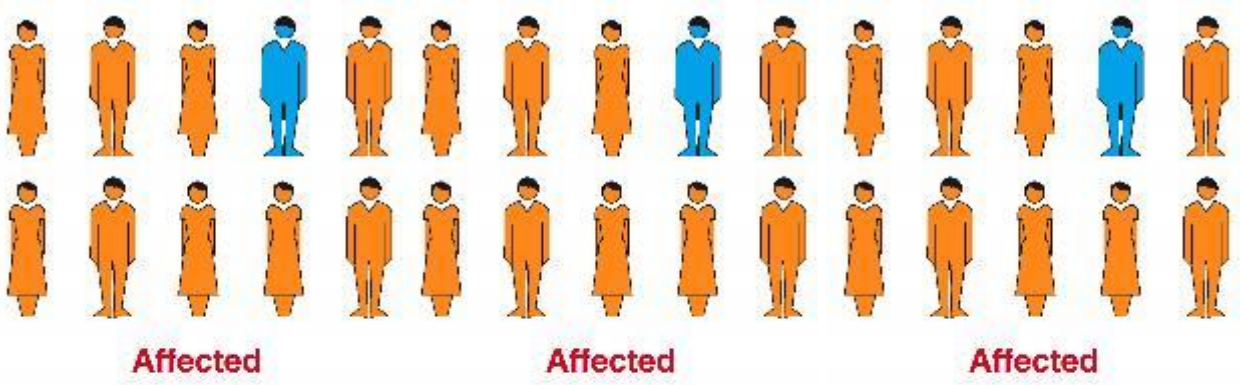
Monozygotic twin concordance rate of 30% compared to dizygotic twin concordance rate of ~5%

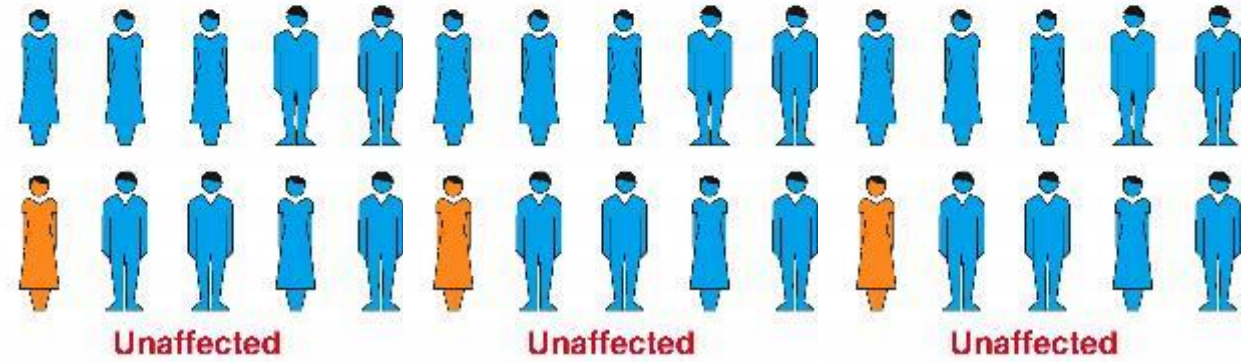
Multiple sclerosis seems to be genuinely polygenic

Genome-wide Association (GWA) Studies

Finding Genetic Risk Factors

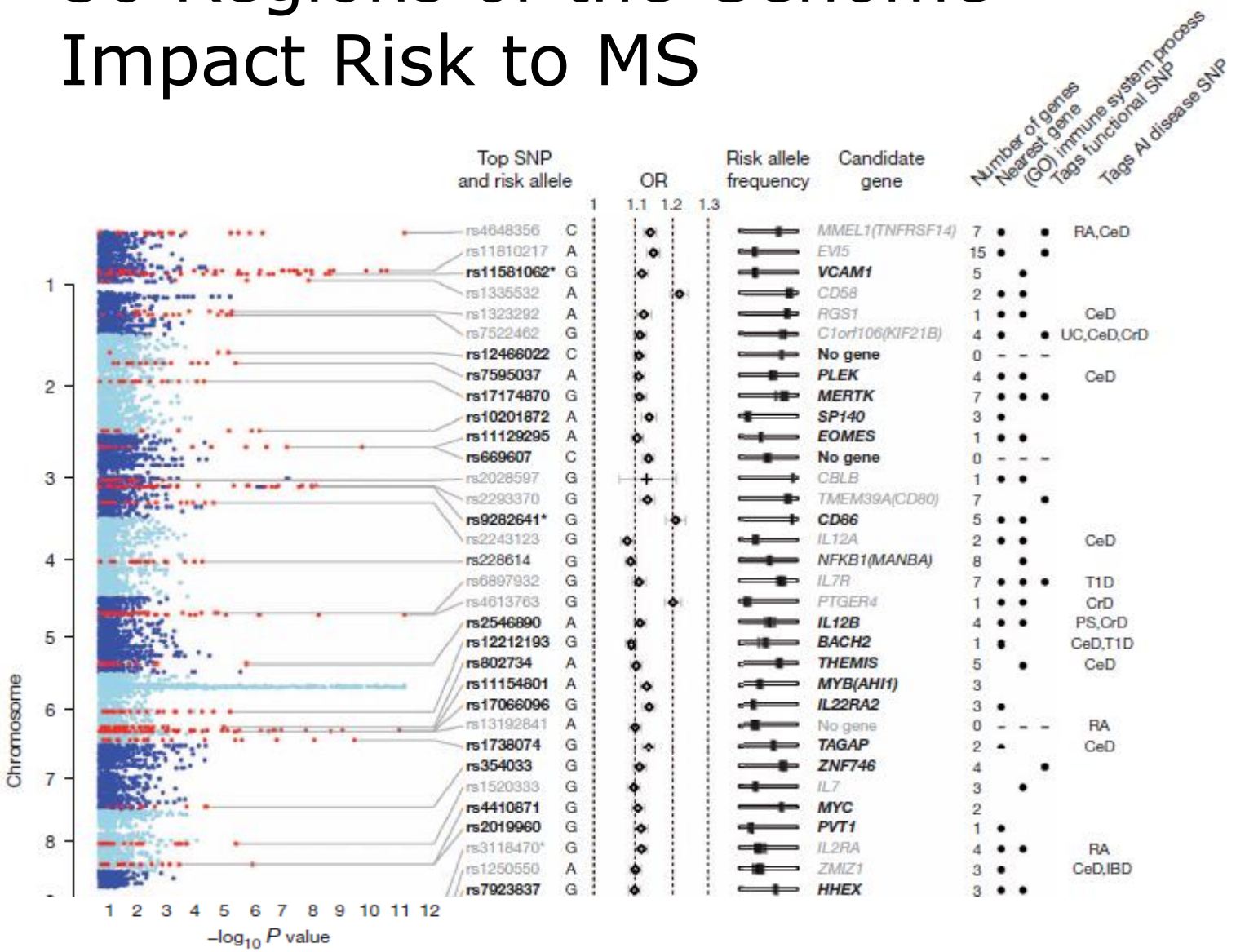
Patients





Controls (Healthy volunteers)

50 Regions of the Genome Impact Risk to MS



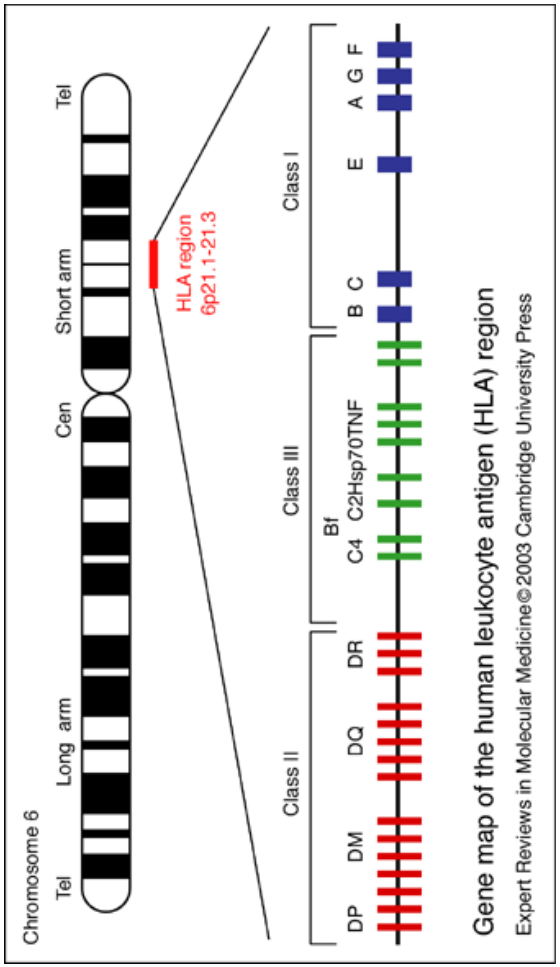
Chromosome 6 and MS

The major histocompatibility complex (MHC).

This group of genes encodes cell-surface antigen-presenting proteins.

Plays pivotal role in the immune system

A subset of genes in MHC region implicated in MS



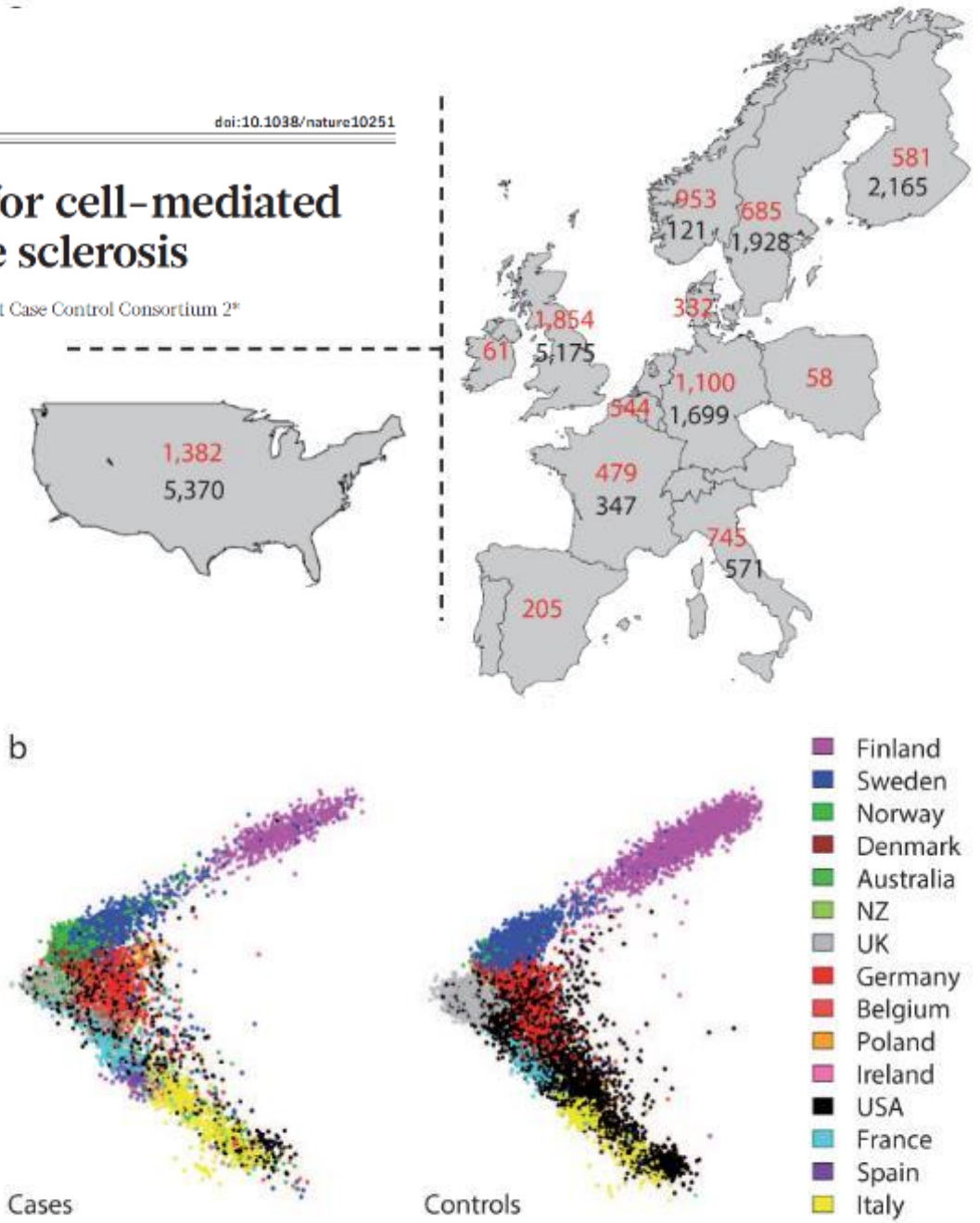
LETTER

doi:10.1038/nature10251

Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis

The International Multiple Sclerosis Genetics Consortium* & the Wellcome Trust Case Control Consortium 2*

Immunologically relevant genes are significantly overrepresented among multiple sclerosis affected individuals.



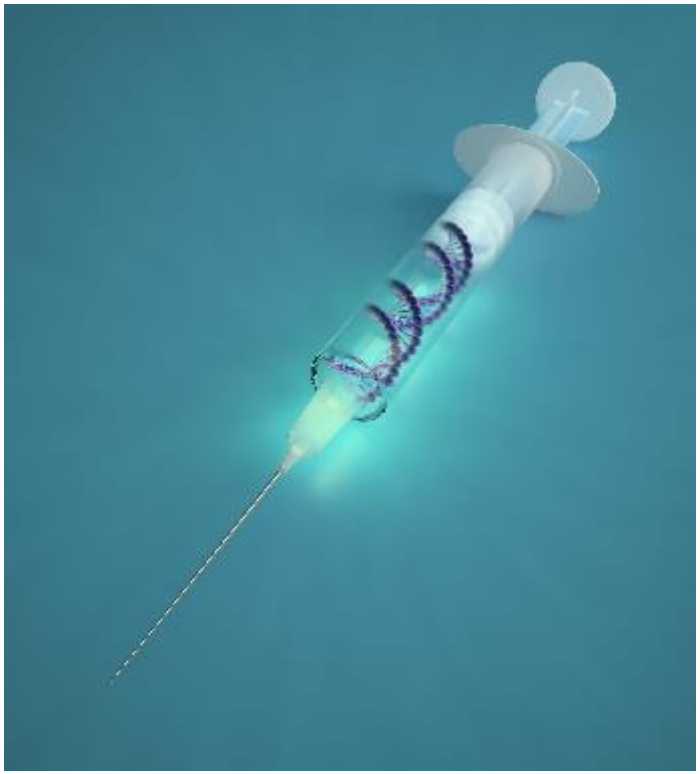
LETTER

doi:10.1038/nature11307

TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis

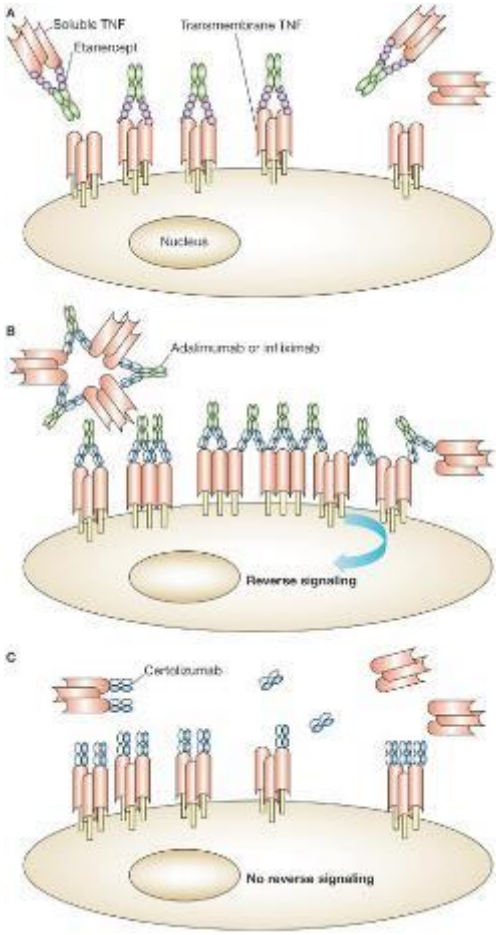
Adam P. Gregory[1]*, Calliope A. Dendrou[2]*, Kathrine E. Attfield[2], Aiden Haghikia[2,3], Dionysia K. Xifara[4], Falk Butter[5], Gereon Poschmann[6], Gurman Kaur[1], Lydia Lambert[2], Oliver A. Leach[2], Simone Prömel[2], Divya Punwani[1], James H. Felce[1], Simon J. Davis[1], Ralf Gold[3], Finn C. Nielsen[7], Richard M. Siegel[8], Matthias Mann[5], John I. Bell[9], Gil McVean[4] & Lars Fugger[1,2,10]

Genetic heterogeneity in MS and the response to immunotherapy



TNF receptor 1 genetic in MS

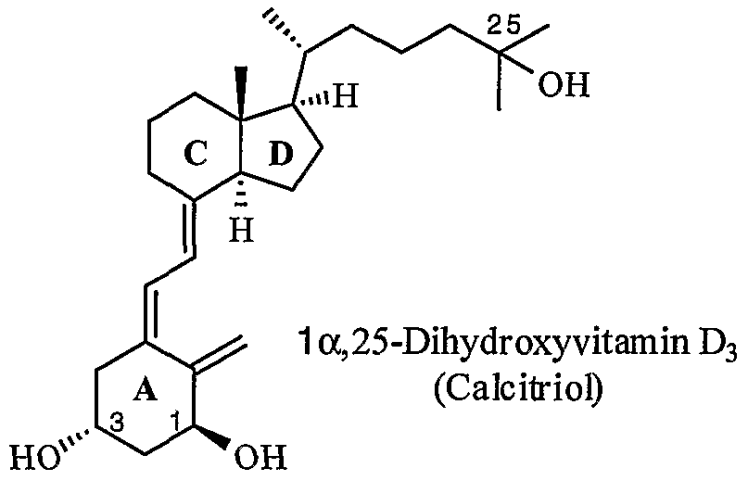
- TNFRSF1A - encodes tumour necrosis factor receptor 1 (TNFR1)
- SNP in TNFRSF1A associated with MS
- MS risk allele directs expression of a novel, soluble form of TNFR1 that can block TNF.



Rare Variants in the CYP27B1 Gene Are Associated with Multiple Sclerosis

- MS patients have lower level of precursors of vitamin D in serum

- CYP27B1 encodes the vitamin Dactivating 1-alpha hydroxylase enzyme



1α,25-Dihydroxyvitamin D_3
(Calcitriol)

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Thanks!