Identification of Quantitative Trait Loci for deglycosylated Iga1 serum levels in familial IgA nephropathy

Francesco Pesce[1,3], Sharon N Cox[1], Grazia Serino[1], Giuseppe De Palma[2], Fabio Sallustio[1], Francesco P Schena[2] and Mario Falchi[3]

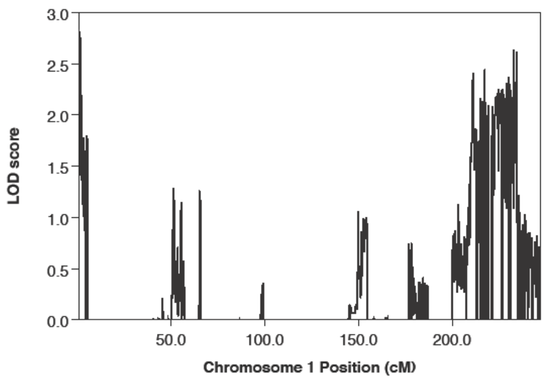
1) Nephrology, Dialysis and Transplantation Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), University of Bari, Bari, Italy
2) Centro Addestramento Ricerca Scientifica in Oncologia (C.A.R.S.O.) Consortium, University of Bari, Valenzano (Bari), Italy
3) Dept of Genomics of Common Disease, School of Public Health, Imperial College London, London, United Kingdom

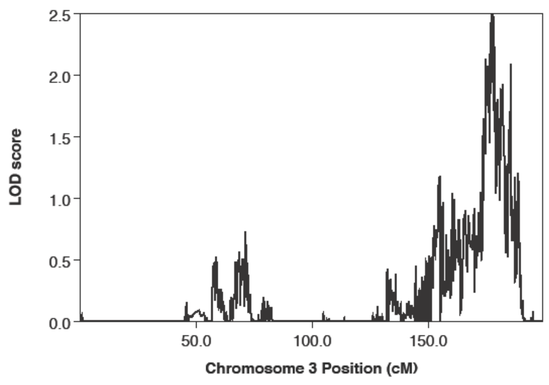
OBJECTIVES

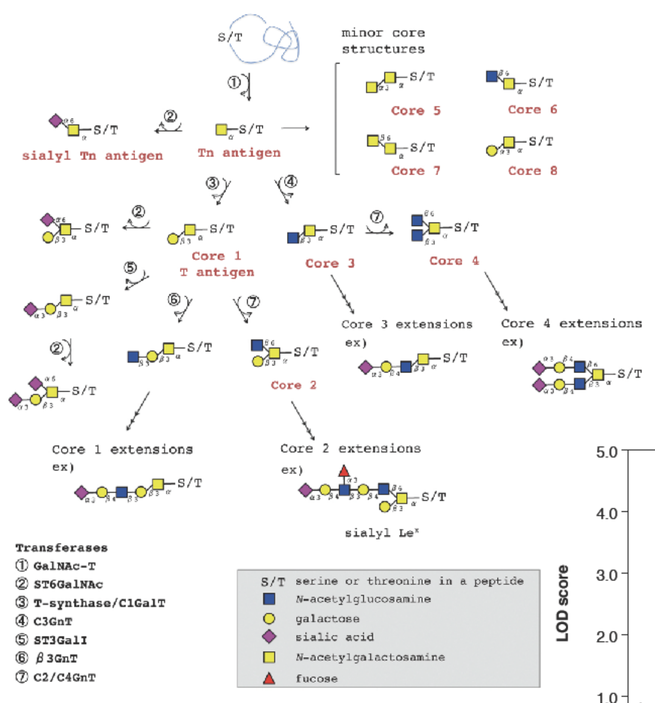
IgA nephropathy (IgAN), the most common form of primary glomerulonephritis, is a complex genetic disease.
Deglycosylated IgA1, which is inherited in familial and sporadic IgAN, has a central role in the pathogenesis of the disease and is considered an intermediate phenotype.
We aimed to identify genetic loci harboring genes that underlie deglycosylated IgA1 serum levels in familial IgAN.

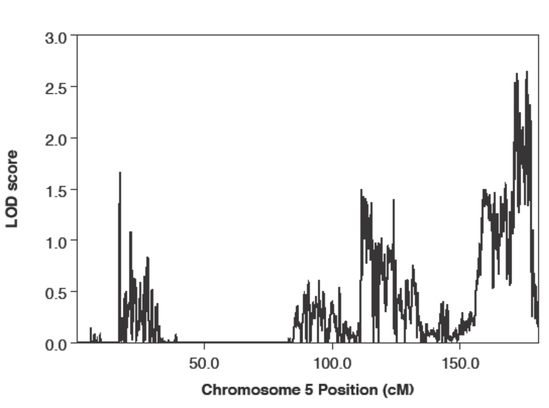
METHODS

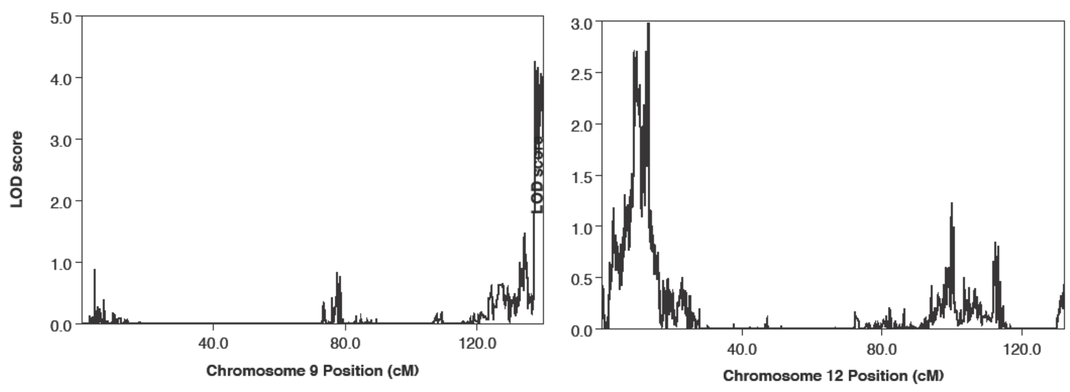
We genotyped 26 families of South Italian ancestry from the European IgAN Consortium (EIC) with the Illumina HumanCytoSNP-12 BeadChip. Individuals with more than 5% missing genotypes and more than 5% Mendelian errors were excluded. Markers that failed the Hardy-Weinberg test (P≤1E- 6) and those with MAF≤0.05 were excluded. Genotyping errors were also detected and removed using Merlin.
Total IgA levels in serum were measured in duplicate using ELISA. Gal-deficient IgA1 levels were detected by binding of the lectin, HAA (Sigma-Aldrich), which is specific for terminal GalNAc. After quality control and pedigree corrections, 164 individuals (40 affected) and 227,114 SNPs were available for analyses.
Deglycosylated IgA1 serum levels were analyzed as quantitative trait with gender, age and total IgA levels as covariates using Merlin.











RESULTS

Five quantitative trait loci (QTL) were identified:

1) Chromosome 1q41 (LOD = 1.8) which includes UDP-N-acetyl-alpha-D-galactosamine:polypeptide N acetylgalactosaminyltransferase 2 (*GALNT2*) gene
2) Chromosome 3q28 (LOD = 2.5) which includes tumor necrosis factor (ligand) superfamily, member 10 (*TNFSF10*) and UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5 (*B3GNT5*) genes
3) Chromosome 5q23 (LOD = 2.4)
4) Chromosome 9q34 (LOD = 3.8)
5) Chromosome 12p13 (LOD = 2.9)

CONCLUSIONS

These results suggest that different key genes are specifically involved in determining the levels of deglycosylated IgA1 in serum of IgAN patients. We dectected QTL encompassing previously identified candidate genes such as *TNFSF10*, *GALNT2* and *B3GNT5*. Further evaluation of their associated pathways can provide novel insight into the pathogenesis of IgAN and a valuable aid to identify potential therapeutic targets.

REFERENCES:

1) Kiryluk K et al. *Pediatr Nephrol*. 2010; 25:2257-2268
2) Gharavi AG et al. *J Am Soc Nephrol*. 2008; 19:1008-1014
3) Novak J et al. *Semin Immunopathol*. 2012; 34:365-382
4) Lai KN. *Nat Rev Nephrol*. 2012; 20; 8:275-283
5) Daha MR, van Kooten C. *Nephrol Dial Transplant*. 2013; 28:794-797
6) Nakayama Y et al. 2013; Genetic Diseases Associated with Protein Glycosylation Disorders in Mammals. Prof. Maria Puiu (Ed.), ISBN: 978-953-51-0886-3