ALPHA-1 ANTITRYPSIN GENETIC TESTING in British Columbia

Alpha 1 antitrypsin deficiency may be tested for by a number of algorithms. In BC, the disorder may be investigated by following the protocol advocated by Snyder et al[1] with some modifications. The protocol is summarized below and included in more detail on page 2:

a) Initial test: Serum A1AT level – stop here if A1AT level is > 1.15 g/L.
b) Presumptive diagnostic test(s): – stop here if diagnosis is clear.
   - PCR analysis (to detect "S" and "Z" alleles)
   - Isoelectric focusing (phenotype identification, if indicated)
c) Definitive diagnostic test:
   a) Gene sequencing – to be performed when presumptive diagnostic test(s) yield ambiguous results.

To Test Your Patient:

1. Send your patient to the lab with:
   a. a completed copy of the attached requisition with your patient
   b. If available, a copy of the hospital/lab serum level report (quantitative alpha-1 antitrypsin (AAT) level)

LABORATORIES WILL SHIP BOTH EDTA WHOLE BLOOD AND SERUM SAMPLES TO:

Dr. Andre Mattman
Dept of Pathology & Laboratory Medicine
St Paul's Hospital
1081 Burrard St., Vancouver, British Columbia, V6Z 1Y6

Alpha-1-Antitrypsin genetic testing in BC

Ship Samples c/o
Dr. Andre Mattman
Dept of Pathology & Laboratory Medicine
St Paul's Hospital
1081 Burrard St.,
Vancouver, British Columbia, V6Z 1Y6

PATIENT NAME:	AGE:	BIRTHDATE:
MRN:	REFERRING PHYSICIAN	
ADDRESS OF REFERRING LABORATORY:	CONTACT TEL. NUMBER:	DATE & TIME OF COLLECTION :

CLINICAL HISTORY INCLUDES REFERRAL REQUEST AND HOSPITAL TELEPHONE NUMBERS

Reason for Testing	Lung Disease	Liver Disease
1. Adult with clinical symptoms of A1AT deficiency* (investigation warranted for patients with a serum A1AT quantitative level < 1.15 g/L)		
2. Neonate with cholestatic jaundice (send DNA extract, or whole blood, or NBS filter paper card)		
3. Asymptomatic patient – genetic testing for genetic counseling purposes only*		

IF previous investigations for A1AT deficiency have been done, list them below:	**Date and Location of Test (include lab report if available)**	**Patient results**	**Normal Value for lab**
Serum A1AT quantitative level			**g/L**
Previous Genotyping or Phenotyping Result			N/A

Send to Hospital Laboratory*
1)Serum: minimum volume 2 mL – must be sent frozen if transport delayed.
2)EDTA whole blood: minimum volume 2 mL – ship < 4°C (frozen acceptable).

ALPHA-1 ANTITRYPSIN (A1AT) GENETIC TESTING in British Columbia

		Patient Type		
Test Type	**Test Method**	**Symptomatic Patient**	**1st Degree Relative of Proband**	**Preconceptual Counseling**
Initial Investigation	**Serum A1AT Level**	A1AT level determines need to proceed to Diagnostic test	Proceed to Diagnostic test regardless of the serum A1AT level	
Preliminary Diagnostic:	**PCR based DNA testing for S and Z mutations**	Stop here if the preliminary diagnostic test result agrees with the serum A1AT level (see Table of Expected Values by Presumptive Genotype)		
	Protease inhibitor Isoelectric focusing (if indicated)			
Definitive Diagnostic	**Gene Sequencing of coding region of the *SERPINA1* gene**	Utilize to investigate cases in which the preliminary diagnostic test does not explain a relatively low serum A1AT level.		

Table of Expected Values by Presumptive Genotype[1]

Genotype	mean	-1.28 SD (10th percentile)	+2 SD (97.5th percentile)
MM	1.47	0.91	2.35
MS	1.2	0.73	1.94
SS	0.88	0.65	1.24
MZ	0.85	0.59	1.25
SZ	0.6	NA	0.82
ZZ	0.28	N/A	0.72

References:

1. Snyder MR, Katzmann JA, Butz ML, et al. Diagnosis of alpha-1-antitrypsin deficiency: An algorithm of quantification, genotyping, and phenotyping. *Clin Chem*. 2006;52(12):2236-2242.
2. Prins J, van der Meijden BB, Kraaijenhagen RJ, Wielders JP. Inherited chronic obstructive pulmonary disease: New selective-sequencing workup for alpha1-antitrypsin deficiency identifies 2 previously unidentified null alleles. *Clin Chem*. 2008;54(1):101-107.