PM3 For recessive disorders, detected in *trans* with a pathogenic variant

- Ataxia Telangiectasia (A-T) is a rare, severe, early-onset disease with some exceptions denoted 'variant' or 'atypical' A-T in which cases phenotypes are more mild with slower progression. Phenotypes associated with A-T are very specific and do not generally require differential diagnosis. Therefore, publications that claim a 'clinical diagnosis of A-T' are taken at face value and granted a 'confident diagnosis. Specific phenotype criteria may qualify for 'confident or 'consistent' diagnosis of A-T based on the below criteria. No additional weight modifications are made for 'atypical' cases if they meet 'confident or 'consistent' criteria as although the disease progression is different, the clinical features are the same.
- General Considerations
  - Variant may not exceed general population frequency >0.01%.
  - Consider other gene panel test results as potential explanation for phenotype.
  - Multiple unrelated cases are additive.
- CONFIDENT PHENOTYPE (must include Laboratory result)
  - Presence of ≥2 Laboratory results 1-4 (see notes) -OR-
  - Presence of Clinical feature 1a or 1b **AND** presence of Laboratory result 1 or 2 -OR-
  - Presence of Clinical feature 2 or 3 **AND** Laboratory result 1 or 2
- CONSISTENT PHENOTYPE (does not require laboratory result)
  - Presence of two or more Clinical features of ataxia (1a-1e) -OR-
  - Presence of one Clinical feature 1a or 1b **AND** either Clinical feature 2 or 3

Clinical features (Neurological and MRI findings):

1. Progressive cerebellar ataxia, manifesting as:
   a. Progressive truncal/limb ataxia
   b. Cerebellar degeneration (atrophy of the frontal and posterior vermis and both hemispheres by MRI).
   c. Oculomotor apraxia (inability to follow an object across visual fields) or abnormal ocular saccades (rapid refixation from one object to another).
   d. Choreoathetosis or dystonia (involuntary movements; twisting and repetitive movements, abnormal postures).
   e. Peripheral axonal neuropathy OR Anterior horn cell neuronopathy
2. Oculocutaneous telangiectasia of the conjunctivae, ears, or face.
3. Immunodeficiency (often frequent infections) and/or leukemia/lymphoma.

Laboratory Results:

1. ATM protein levels ≤ 15% of controls in patient fibroblast or lymphoblastoid cell lines. If ATM protein levels are slightly greater than 15%, the ATM kinase activity must be shown to be "negative or low or residual" (see notes).
2. Elevated serum alpha-fetoprotein (AFP) levels >65ug/L in a patient ≥ 2 years old.
3. Increased sensitivity to ionizing radiation in patient fibroblast or lymphoblastoid cell lines.
4. Presence of a 7;14 chromosomal translocation in patient peripheral blood cells (≥ 5% of cells).

Related publication(s):

Notes:

1. ATM protein levels ≤15% of control levels show >95% sensitivity and >98% specificity for diagnosing ataxia-telangiectasia (A-T). Protein levels >15% may arise due to a missense variant, a leaky splicing variant, a variant resulting in a kinase-dead protein (where protein levels may not be affected), or a diagnosis other than A-T.
2. When assigning case report criteria based solely on laboratory results (i.e., presence of TWO or more of laboratory results 1-4), there is a greater likelihood that the most specific laboratory results #1 and #2 will be available, and that there will be some clinical indication that the individual(s) has A-T.
3. When assessing homozygous or *in trans* variants (with a likely pathogenic or pathogenic ATM variant) for possible downgrade in an unaffected individual, the individual should be 18 years or older with no evidence of A-T.

BP2 Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.

- When assessing homozygous or in trans variants (with a likely pathogenic or pathogenic ATM variant) for possible downgrade in an unaffected individual, the individual should be 18 years or older with no evidence of A-T.

Ataxia Telangiectasia PM3|BP2 table:

Classification/ Zygosity of other variant[1]	Points per unrelated A-T Proband (PM3)			
	Confirmed in *trans*[2]	Phase unknown	Second variant unidentified or VUS	Homozygous (max 2 individuals)
Phenotype *confident*	4.0	2.0	1.0	2.0
Phenotype *consistent*	2.0	1.0	0.5	1.0

	Points per Unaffected (non-A-T) Adult (>18yo) Proband (BP2)		
	Confirmed in *trans*[3]	Phase Unknown	Homozygous (max -2.0)[4]
Pathogenic or Likely pathogenic variant in a patient	-4.0	-2.0	Laboratory Setting -2.0 Database Setting -1.0

Supporting	Moderate	Strong	Very Strong
PM3_			
1.0	2.0	4.0	8.0
BP2_			
-1.0	-2.0	≤-4.0	N/A

[1]Variant under assessment (VUA) must be sufficiently rare (not meeting a benign population evidence code). Consider other gene panel test results as potential explanation for phenotype.
[2]Co-occurrent P or LP variant should be assigned classification using VCEP specifications. Stipulation for in *trans* can be met by genotyping of at least one parent or assumed if VUA is seen with at least 2 different P/LP variants. If there are multiple phase unknown co-occurrences with different P/LP variants, at least one should be weighed as phase unknown to allow for the probability of one co-occurrence in *cis* and the remaining can be weighed as in trans.
[3]VUA should not be bioinformatically predicted (or experimentally proven) to have a clinically important effect on protein or mRNA splicing. Co-occurrent P or LP variant should be assigned classification using VCEP specifications. See footnote 2 for stipulation for in trans.
[4]Apply only for phenotyped individuals from clinical or research cohorts. NOT to be applied for data used to assign frequency-based codes; we have observed that variants observed as ≥2 homozygotes in gnomAD data (assumed unaffected adults of unspecified age) are already captured by the BA1 or BS1 frequency codes. **Do not use observations *in cis***