NUCLEAR & CYTOPLASMIC ANTIBODIES (CLASSIC PARANEOPLASTIC ANTIBODIES)

Antibody	Antigen	Cancer association	Clinical presentation
ANNA-1 (Hu)	Hu (ELAVL) Drosophila embryonic lethal abnormal visual like protein	Small cell lung cancer (80%) Neuroendocrine tumors	Limbic encephalitis Brainstem encephalitis Peripheral neuropathy (mainly sensory & autonomic)
ANNA-2 (Ri)	Ri (NOVA)	Small cell lung cancer Breast adenocarcinoma (50%) Ovarian, uterine cancer	Limbic encephalitis Brainstem encephalitis **Paraneoplastic Opsoclonus-Myoclonus Ataxia syndrome (POMA)** Cerebellar ataxia Myelopathy Peripheral neuropathy
ANNA-3	Unknown	Small cell lung cancer Digestive system carcinomas	Limbic encephalitis Brainstem encephalitis Myelopathy Peripheral neuropathy
Ma1 – Ma2	PNMA-1 PNMA-2	Ma2: Testicular cancer Ma1: Testicular, breast & colon	**Hypothalamic disorders** **Limbic encephalitis** Brainstem encephalitis
PCA-1 (Yo)	CDR2	Mullerian/breast adenocarcinoma	**Paraneoplastic cerebellar degeneration** Brainstem encephalitis Myelopathy Peripheral neuropathy
PCA-2	MAP1B	Small cell lung cancer	**Paraneoplastic cerebellar degeneration** Limbic encephalitis Brainstem encephalitis Peripheral neuropathy **LEMS**
CRMP-5 (CV2)	Collapsin response-mediator protein	Small cell lung cancer Thymoma	**Subacute dementia, Depression** **Cerebellar ataxia, Chorea** Myelopathy Radiculopathy, Neuropathy **LEMS**
Amphiphysin	Amphiphysin (Protein present on cytoplasmic surface of synaptic vesicles)	Small cell lung cancer Breast adenocarcinoma	**Subacute dementia** **Aphasia** Limbic encephalitis **Stiff person syndrome** Myelopathy Neuropathy
GAD65	GAD65 (Glutamic acid decarboxylase)	Rarely Thymoma, Renal cell carcinoma, Breast or colon adenocarcinoma	**Cerebellar ataxia** **Seizures** Limbic encephalitis Brainstem encephalitis **Parkinsonism** **Ophthalmoplegia** Myelopathy

			Stiff person syndrome **Stiff Person Syndrome Plus (PERM; progressive encephalopathy, rigidity & myoclonus)**
GFAP	GFAP	Teratoma	Meningoencephalitis
Recoverin	Recoverin	Small cell lung cancer Neuroendocrine carcinomas	Retinopathy
AGNA(anti-glial nuclear)	SOX-1	Small cell lung cancer	Limbic encephalitis **LEMS** Peripheral neuropathy
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ANNA: anti-neuronal nuclear antibody – AGNA: anti-glial nuclear antibodies - ELAVL: Drosophila Embryonic lethal abnormal visual like protein – LEMS: Lambert Eaton Myasthenic syndrome

Steps to memorize clinical manifestations of classical Paraneoplastic antibodies:

- **There are 12 cytoplasmic/nuclear antibodies, 11 are classic and only one (GAD65) is not classic.** Classic means associated with cancer and poor response to immunotherapy.
- **Antibody-based memorization:**
  Out of the 12, 2 are associated with single Paraneoplastic syndrome (GFAP – Recoverin), while 10 may present with multiple syndromes.
  The other 10, all can cause limbic encephalitis, myelopathy and neuropathy plus the following:
  - ANNA2: Opsoclonus-myoclonus
  - Ma: hypothalamic dysfunction
  - PCA1: cerebellar ataxia
  - PCA2: ataxia and LEMS
  - CRMP: ataxia, LEMS and Subacute dementia
  - Amphiphysin: Stiff person syndrome, aphasia & Subacute dementia
  - GAD65: Stiff person syndrome, parkinsonism, seizures, ataxia, Ophthalmoplegia
  - AGNA: LEMS
- **Syndrome-based memorization:**
  - Paraneoplastic Limbic encephalitis (LE): Almost all classic antibodies can cause it, big ones are ANNA1, ANNA2, Ma2, CRMP5.
  - Paraneoplastic cerebellar degeneration (PCD): PCA1, PCA2, ANNA2, Ma, CRMP5, AGNA, DNER (surface Ab).
  - Paraneoplastic Opsoclonus myoclonus syndrome (POMS/POMA): ANNA1 in children (with neuroblastoma), ANNA2 in adults (with breast cancer).
  - Paraneoplastic Encephalomyelitis: ANNA1, CRMP5, Ma2, Amphiphysin
  - Paraneoplastic Subacute sensory neuropathy (SSN): ANNA1, CRMP5
  - Paraneoplastic Stiff person syndrome: Amphiphysin