Phacomatoses (s. Neurocutaneous Disorders, Neuroectodermal Dysplasias)

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**Phacomatoses** - heterogeneous genetic neurocutaneous disorders characterized by ectoderm-based ***dysplasia***, ***hamartomas*** and ***neoplasia***.

* **CNS, optic system,** and **skin** are primarily involved – *both originate from ectoderm* (other organ systems can also be affected) – most correct term ***neuroectodermal dysplasias***.

*Van der Hoeve believed that ocular findings of neurofibromatosis and tuberous sclerosis were similar and suggested that they be classified together under inappropriate term phakomatosis* (Gr. *phakos* - lentil, mole, birthmark, mother-spot).

Autosomal Dominant Phacomatoses

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| **Disorder** | **Gene** | **Main Features** |
| *Neurofibromatosis type 1*  (von Recklinghausen’s disease) | NF1 (17q) | neurofibroma, low-grade gliomas (optic, brain stem, cerebellar) |
| *Neurofibromatosis type 2* | NF2 (22q12) | ependymoma, astrocytoma, acoustic neuroma, meningioma |
| *Tuberous sclerosis* (Bourneville’s disease) | TSC1 (9q), TSC2 (16p13) | 1. Brain - tubers, subependymal nodules, subependymal giant cell astrocytoma; 2. Skin - adenoma sebaceum in face; “ash leaf” macules; fibromas; 3. Heart rhabdomyomas; 4. Lung lymphangioleiomyomatosis; 5. Renal angiomyolipomata |
| *von Hippel-Lindau disease*  [see p. Onc24 >>](http://www.neurosurgeryresident.net/Onc.%20Oncology\Onc24.%20Vascular%20Tumors.pdf) | tumor-suppressor gene  (3p25-26) | 1. Retinal angiomatosis 2. Cerebellar hemangioblastomas 3. Various visceral tumors - kidneys [*renal cel carcinoma*, cysts, angiomas], adrenal glands [*pheochromocytoma*], pancreas [cysts], epididymis [papillary cystadenomas, cysts], liver [angiomas, cysts], endolymphatic sac tumors |
| *Incontinentia pigmenti achromians* (hypomelanosis of Ito) [see p. 2997 >>](http://www.neurosurgeryresident.net/USMLE%202\Skin%20(2931-3030)\2997.%20Pigmentation%20Disorders.pdf) | different forms of *genetic mosaicism* | asymmetrical (unilateral or bilateral) areas of hypopigmented macules in whorls, streaks, patches ("marble-cake"), ± epidermal nevi, alopecia, anomalies of eyes, neuro, skeleton |
| *Waardenburg's syndrome*  *(type I)*  [see p. 98 >>](http://www.neurosurgeryresident.net/USMLE%202\Histology%20(1-150)\98.jpg) | PAX3 gene (2q) | Frontal patch of white hair, heterochromia iridis, lateral displacement of inner canthus, cochlear deafness, synophrys |
| *Waardenburg's syndrome*  *(type II)* [see p. 98 >>](http://www.neurosurgeryresident.net/USMLE%202\Histology%20(1-150)\98.jpg) | MITF gene (3p) | Similar to type I *without lateral displacement of inner canthus*; deafness is more common |
| *Rendu-Osler-Weber disease* (hereditary hemorrhagic telangiectasia)  [see p. 1606 (1-4) >>](HTTP://WWW.NEUROSURGERYRESIDENT.NET/USMLE%202/Hematology%20(1501-1649)/1606_(5).%20Vascular%20bleeding%20disorders.pdf) |  | Multiple angiomas (skin and mucous membranes); bleeding from any site: nose, GI, pulmonary, GU |
| *Proteus*\**syndrome*  [see p. Mus9 >>](http://www.neurosurgeryresident.net/Mus.%20Muscular,%20Neuromuscular%20disorders\Mus9.%20Congenital%20Myopathies,%20Congenital%20Muscle%20Anomalies.pdf) |  | Macrocephaly, mental deficiency, seizures, hemihypertrophy (asymmetrical arms or legs), large flat feet (“moccasin feet”), thickened skin, hyperpigmented areas, hemangiomata and lipomata (subcutaneous and abdominal), bony defects, macrodactyly, hypocalcemia |

\*Proteus - Greek god who appeared in different forms

Autosomal Recessive Phacomatoses

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| **Disorder** | **Gene** | **Main Features** |
| *Ataxia-telangiectasia*  [see p. Mov50 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders,%20Ataxias\Mov50.%20Ataxias.pdf) | ATMgene (11q22.3-q23.1) | 1. Progressive cerebellar degeneration 2. Telangiectasias (bulbar conjunctivae, malar eminences, ear lobes, upper neck, antecubital and popliteal spaces) 3. Combined (T & B cell) immunodeficiency |
| *Chédiak-Higashi syndrome*  [see p. 1671 (8-9) >>](HTTP://WWW.NEUROSURGERYRESIDENT.NET/USMLE%202/Immunology%20(1650-1700)/1671_(8).jpg) | CHS gene (1q) | Phagocyte disorder (recurring infection): partial oculocutaneous albinism, photophobia, neuropathy |
| *Refsum disease* (phytanic acid storage disease)  [see p. 750 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\750.%20Fatty%20Acid%20Oxidation%20Disorders.pdf) | PEX1 gene (7q) | Disorder of α-oxidation of phytanic acid - retinal pigmentary degeneration, ichthyosis, demyelinating polyneuropathy, ataxia, sensorineural deafness, anosmia, cardiomyopathy |
| *Xeroderma pigmentosum*  [see p. 3001 (9-10) >>](http://www.neurosurgeryresident.net/USMLE%202\Skin%20(2931-3030)\3001.%20Skin%20Cancer.pdf#XERODERMA_PIGMENTOSUM) |  | DNA repair defects → premature aging and cancer of tissues exposed to sunlight; severe neurologic and ocular changes. |
| **Rothmund-Thomson syndrome** |  | 1. Erythemas (in early life) → telangiectasias → atrophy, hypo- / hyperpigmentation, ectodermal dysplasia. 2. Sparse or absent body hair. 3. Juvenile cataracts, short stature, hypogonadism, saddle nose, skeletal abnormalities. 4. Normal intelligence. |
| **Sjögren-Larsson syndrome** | FALDH\* gene (17p) | Congenital ichthyosis, oligophrenia, corticospinal tract dysfunction |

\*fatty aldehyde dehydrogenase gene

*Ataxia-telangiectasia* is the only **AR** disorder among “common” neurocutaneous disorders!

X-linked Phacomatoses

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| **Disorder** | **Gene** | **Main Features** |
| *Incontinentia pigmenti* (Bloch-Sulzberger disease)  [see p. 2997 >>](http://www.neurosurgeryresident.net/USMLE%202\Skin%20(2931-3030)\2997.%20Pigmentation%20Disorders.pdf) | X-linked dominant (***lethal in males***!) | Skin lesions in 4 stages (in 3rd stage – hyperpigmentation in bizarre configurations); ± anomalies of CNS, heart, eyes, skeleton, teeth, nails, hair |
| *Fabry disease* (diffuse angiokeratoma)  [see p. 761 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\761.jpg) | X-linked recessive – GLA\* gene (Xq) | Endothelial accumulation of globosides - angiokeratosis; vascular accidents; dorsal root ganglia neuronopathy; ocular, cardiac, GI, renal disease |
| **Rud syndrome** | X-linked recessive or sporadic | 1. Ichthyosis (ichthyosiform erythroderma). 2. Hypogonadism. 3. Less frequent - microcephaly, dwarfism, sensorineural deafness, polyneuropathy, hypoplastic teeth and nails, acanthosis nigricans. |

\*α-galactosidase gene

Sporadic Phacomatoses

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| **Disorder** | **Gene** | **Main Features** |
| *Sturge-Weber syndrome* (encephalotrigeminal angiomatosis) | unknown | Angiomas in leptomeninges, skin of face, eye |

Bibliography for ch. “Phakomatoses” → follow this [link >>](http://www.neurosurgeryresident.net/Pha.%20Phacomatoses,%20Neurocutaneous%20disorders\Pha.%20Bibliography.pdf)

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