Phacomatoses (s. Neurocutaneous Disorders, Neuroectodermal Dysplasias)

Last updated: April 17, 2019

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

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 >>	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 >>	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 >>	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 >>	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) >>		Multiple angiomas (skin and mucous membranes); bleeding from any site: nose, GI, pulmonary, GU
*Proteus** *syndrome* see p. Mus9 >>		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

Disorder	Gene	Main Features
Ataxia-telangiectasia see p. Mov50 >>	ATM gene (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) >>	CHS gene (1q)	Phagocyte disorder (recurring infection): partial oculocutaneous albinism, photophobia, neuropathy
Refsum disease (phytanic acid storage disease) see p. 750 >>	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) >>		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

Disorder	Gene	Main Features
Incontinentia pigmenti (Bloch-Sulzberger disease) see p. 2997 >>	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 >>	X-linked recessive –	Endothelial accumulation of globosides - angiokeratosis; vascular accidents; dorsal root ganglia neuronopathy; ocular, cardiac, GI, renal disease

	GLA* gene (Xq)	
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

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

BIBLIOGRAPHY for ch. "Phakomatoses" → follow this LINK >>