Hereditary disorders

Hereditary (genetic) disorders are a health problem caused by one or more abnormalities in the genome. It is caused by a mutation in a single gene (monogenic) or multiple genes (polygenic) or by a chromosome abnormality (the polygenic disorders are common). The responsible mutation occurs spontaneously before embryonic development (a de novo mutation), or the abnormality is inherited from two parents. The parents may be carriers of a faulty gene (autosomal recessive inheritance) or one of the parents possesses the disorder (autosomal dominant inheritance). Some disorders are caused by a mutation on the X chromosome and have X-linked inheritance. Infrequently, disorders are inherited on the mitochondrial DNA. Representative examples of the hereditary disorders are presented below.

Ref.: Roth TL, Marson A. Genetic disease and therapy. Annu Rev Pathol Mechan Dis 2021; 16: 145-166. doi: 10.1146/annurev-pathmechdis-012419-032626

Congenital diseases

- Single gene diseases

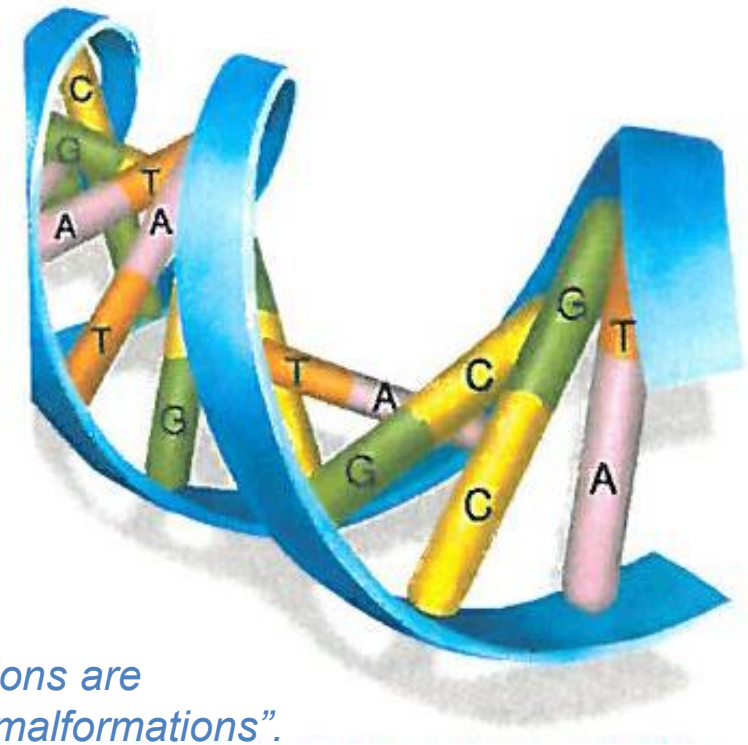
  1) autosomal dominant trait

  2) autosomal recessive trait

  3) X-linked recessive trait

  4) mitochondrial trait

- Polygenic diseases
- Chromosomal abnormalities
- Congenital malformations



Chromosomal abnormalities and congenital malformations are summarized in a separate volume entitled "congenital malformations".

The mode of inheritance

- **Mendel's laws of inheritance:**

  ① Law of dominance and uniformity, ② Law of segregation,

  ③ Law of independent assortment

  1) autosomal dominant trait

  2) autosomal recessive trait

  3) X-liked recessive trait

- **Non-Mendelian inheritance**

  1) Multigene inheritance

  2) Mitochondrial inheritance (cytoplasmic inheritance)

  = maternal inheritance

  3) Epigenetics (genomic imprinting, DNA methylation and gene silencing)

Genetic diseases and diseases of the gene (genopathy)

- Genetic diseases ＝gene abnormality in germ cells

  ～inherited diseases: transmitted from the parents to children～

- Diseases of the gene: gene abnormality in somatic cells

  ～Acquired abnormality of the gene～

  ～Not inherited from the parents to children～

  ～Represented by cancer～

・Hereditary cancer (exceptional)

Single gene disorders

- **Hereditary disorders are not necessarily familial.**
  - ～Point mutation in germ cells～
  - ～Penetrance rates are not 100%～
- **Autosomal dominant ionheritance**

  A single copy of the mutation from either parent is enough to cause the disease.

  The disease name with “familial” accompanies an autosomal dominant trait.
- **Autosomal recessive inheritance**

  Both alleles of the gene should have a pathogenic variant.

  Inheritance of the single mutated allele causes a carrier state.

  Most hereditary metabolic disorders show autosomal recessive trait
- **X-linked inheritance**

  The disease is seen only in male patients
- **Mitochondirial inheritance**

  It shows maternal inheritance (Mitochondria of the zygote are of maternal origin)

Congenital metabolic disorders

Lysosomal diseases (with defective lysosomal enzymes)

Tay–Sacks disease, Gaucher disease, Niemann–Pick disease, Fabry disease, Hurler–Hunter syndrome, metachromatic leukodystrophy, Krabbe disease

Glycogen storage diseases

von Gierke disease (type I), Pompe disease (type II), McArdle disease (type V)

Liver type: types I and VI, *muscle type*: types V and VII

Liver/muscle type: types III and IV, *systemic type*: type II

Abnormal carbohydrate metabolism

galactosemia

Abnormal amino acid metabolism

phenylketonuria, alkaptonuria, cystinuria, homocystinuria,

maple syrup urine disease

Hereditary disorders and modes of inheritance

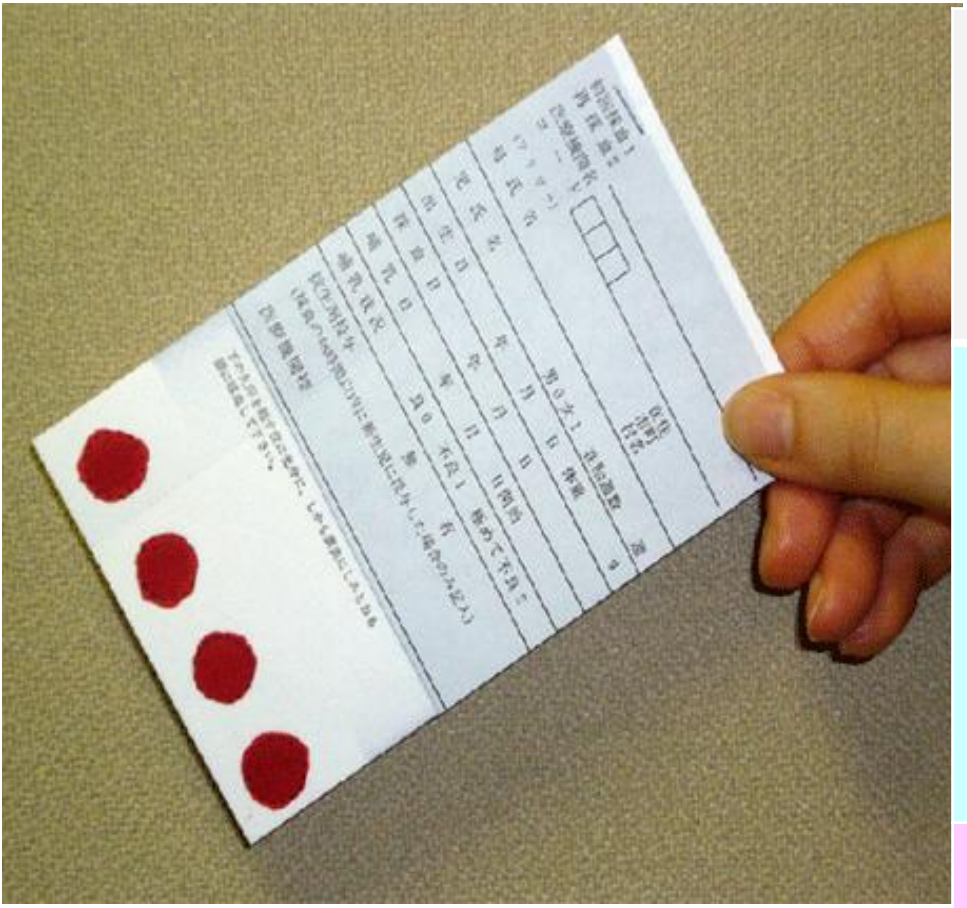
Autosomal dominant hereditary disorder	hypercholesterolemia, von Recklinghausen disease, tuberous sclerosis, von Hippel Lindau disease, Huntington disease, dentato-ruburo-pallido-luysian atrophy, familial amyloid polyneuropathy, Charcot-Marie-Tooth disease, myotonic dystrophy, marble bone disease, osteogenesis imperfecta, achondroplasia, ichthyosis vulgaris, Marfan syndrome, adult-type polycystic kidney, thalassemia, sickle cell anemia, hereditary spherocytosis, Peutz-Jeghers syndrome, familial adenomatosis coli, Gardner syndrome, Lynch syndrome, multiple endocrine neoplasia (types I and II), retinoblastoma
Autosomal recessive hereditary disorder	Gaucher disease, Niemann-Pick disease, Hurler syndrome, pyruvate kinase deficiency, von Gierke disease, Pompe disease, phenylketonuria, homocystinuria, maple syrup urine disease, galactosemia, abetalipoproteinemia, Wilson disease, xeroderma pigmentosum, Bartter syndrome, Werner syndrome, Refsum disease, Friedreich ataxia, hemochromatosis, cystic fibrosis, Louis-Bar syndrome, thrombasthenia, Bernard-Soulier syndrome, severe combined immunodeficiency, Chediak-Higashi syndrome
X-linked recessive hereditary disorder	Hemophilia (A/B), color-vision deficiency, Duchenne-type/Becker-type muscular dystrophy, X-linked ichthyosis, Hunter disease, adrenoleukodystrophy, Fabry disease, Lowe disease, G6PD deficiency, Lesch-Nyhan syndrome, androgen insensitivity syndrome, chronic granulomatous disease, Bruton-type agammaglobulinemia, Wiscott-Aldrich syndrome

Diagnosis of hereditary disorders

- **Prenatal testing**
  - Preimplantation genetic testing
  - Amniotic fluid genetic testing
  - Genetic testing using peripheral blood of pregnant women
  - Imaging by ultrasonography and CT scan
- **Mass screening of the newborn baby (newborn screening)**
- **Postnatal DNA testing** using polymerase chain reaction

“Right to know” and “Right not to know”

It should be noted that DNA testing using the peripheral blood is applicable to adult-onset hereditary disorders without treatment.



Newborn screening for a total of 20 genetic disorders (primary screening) in Japan

Amino acid disorders	Phenylketonuria Maple syrup urine disease Homocystinuria Citrullinemia type I Argininosuccinic aciduria
Organic acid disorders	Methylmalonic acidemia Propionic acidemia Isovaleric acidemia Methylcrotonyl glycinuria Hydroxymethylglutaric acidemia Multiple carboxylase deficiency Glutaryl acidemia, type I
Faty acid disorders	MCAD deficiency VLCAD deficiency Trifunctional protein/TFP deficiency CPT1 and CPT2 deficiency
Carbo-hydrate disorder	Galactosemia
Endocrine disorders	Congenital hypothyroidism Congenital adrenal hyperplasia

Adult-onset hereditary disorders

Often times, the patient has children.

The disease may show autosomal dominant inheritance.

No treatment is known.

The diagnosis can be established by genetic testing during childhood without signs and symptoms.

It is important to protect “the right not to know” of the patient.

- Huntington disease
- Spinocerebellar degeneration (dominant or recessive trait)
- Adrenoleukodystrophy (peroxisome disease, X-linked recessive)
- Myotonic dystrophy
- Familial amyloid neuropathy (treated with liver transplantation)
- Adult-type pol;ycystic kidney (treated with renal transplantation)

Genetic diseases in Africa may protect the patient from malaria

Sickle cell anemia (Hemoglobin S disease)

- Sickled red cells show resistance to malaria infection.
- 7% of American people of African lineage manifest the disease.
- 30% of certain areas in Africa manifest the disease.

The diseases with malaria resistance

1) Sickle cell anemia (autosomal dominant trait)
2) Thalassemia (autosomal dominant/recessive trait)
3) Glucose 6-phosphate dehydrogenase (G6PD) deficiency (X-linked recessive trait)
4) Pyruvate kinase (PK) deficiency (autosomal recessive trait)
5) Loss of Duffy blood group antigen Fy(a-b-): resistance to vivax malaria

Presentation of autosomal dominant hereditary disorders

Familial amyloid neuropathy

Huntington disease

Phacomatosis

- von Recklinghausen disease (neurofibromatosis)
- Kasabach–Merritt syndrome

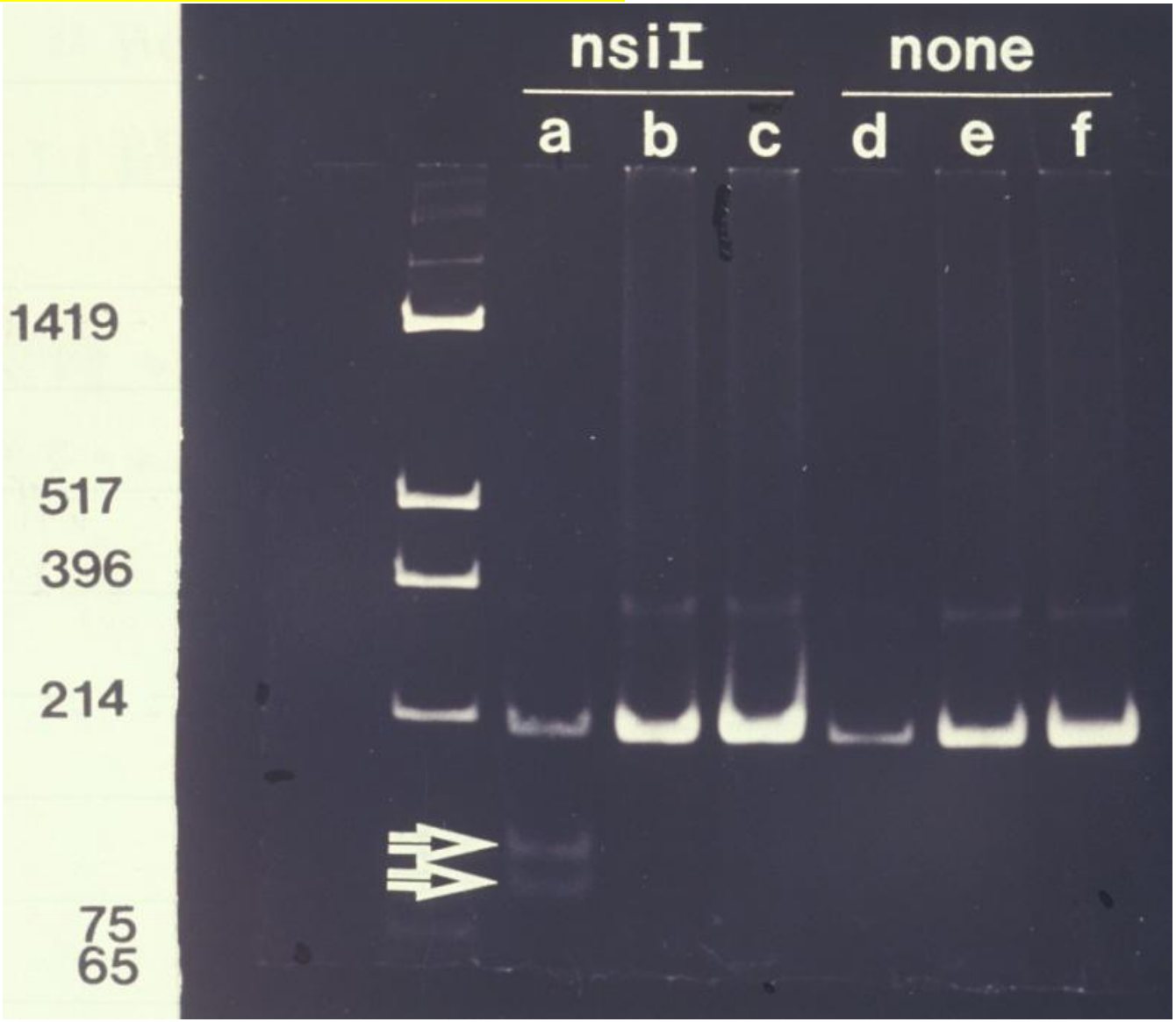
Adult-type polycystic kidney

Marble bone disease

Osteogenesis imperfecta

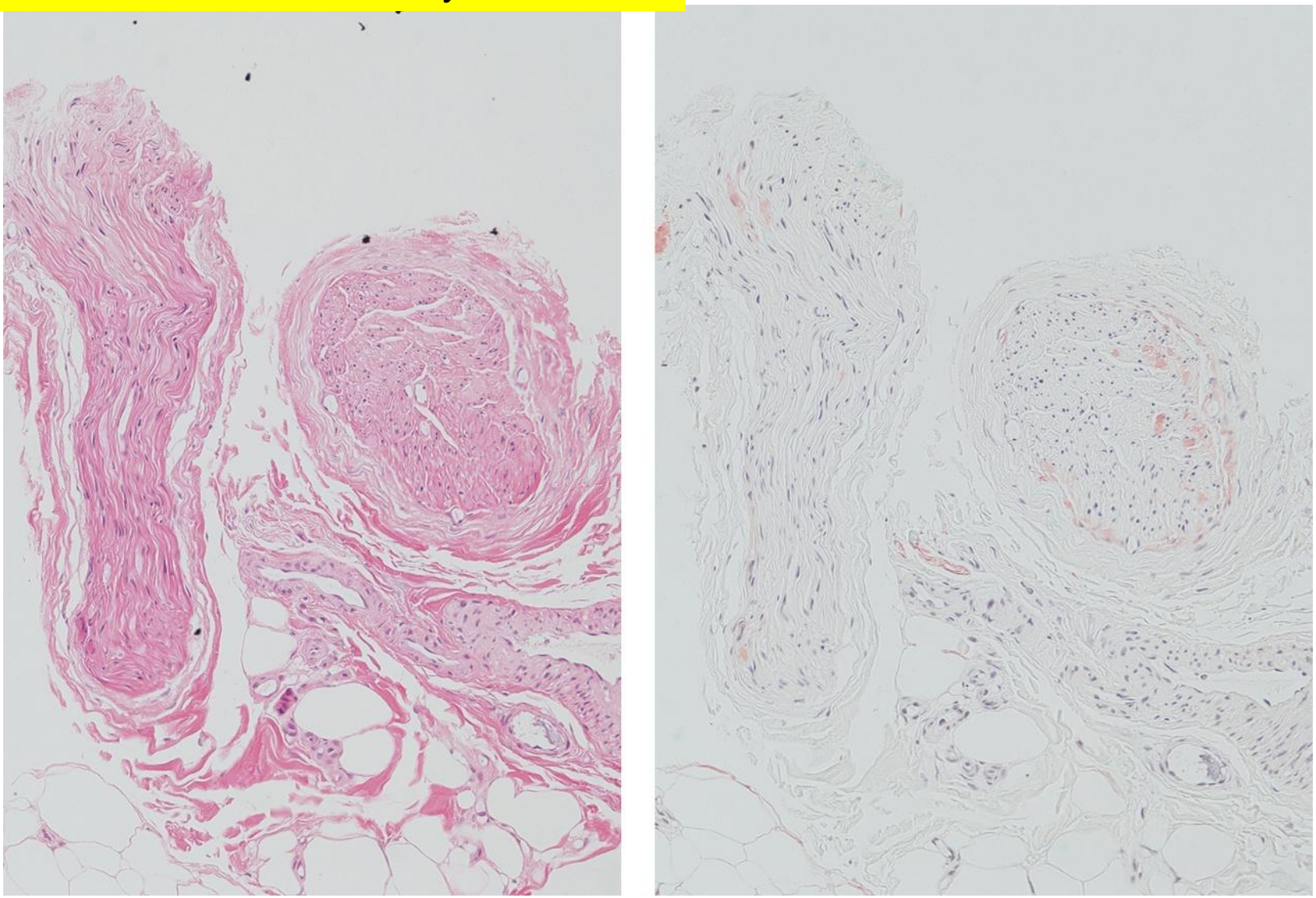
Achondroplasia

Autosomal dominant hereditary disorder-1



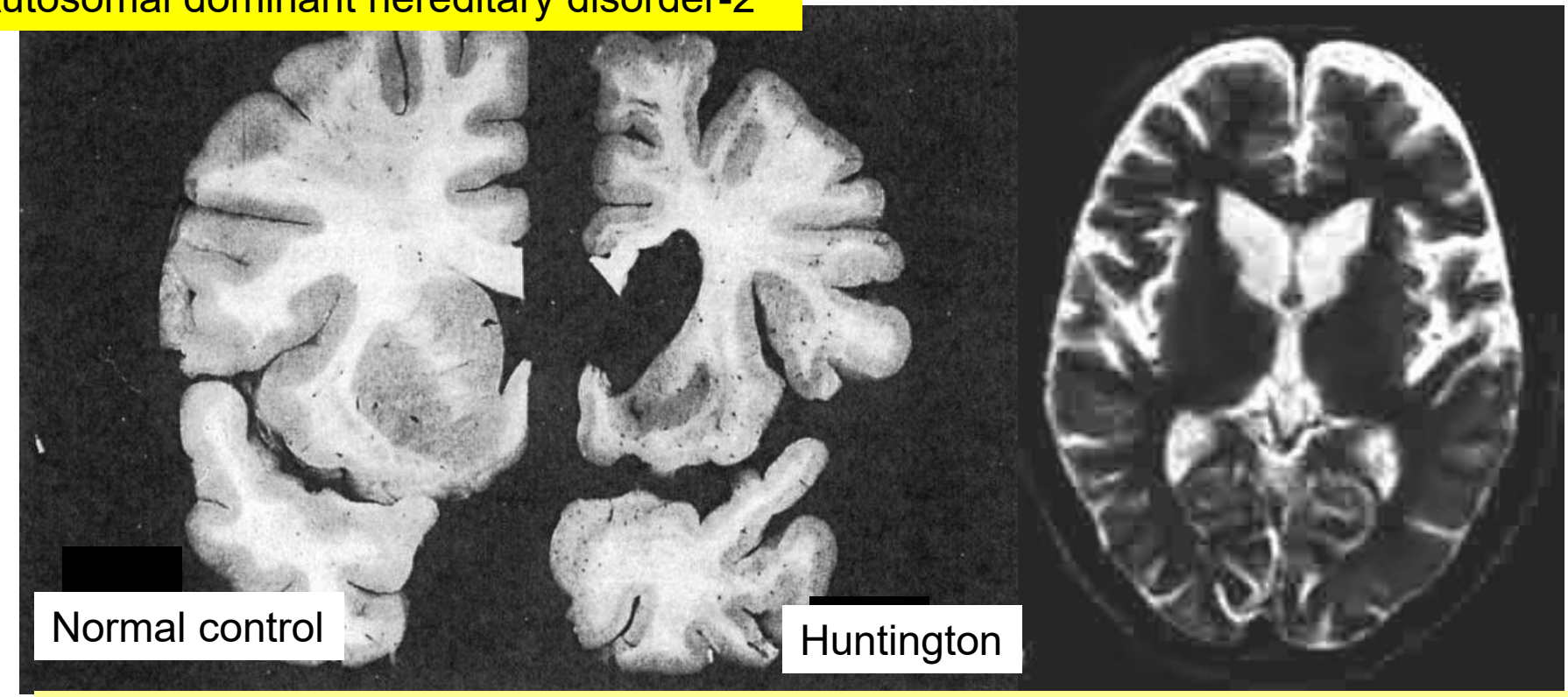
PCR analysis of familial amyloid polyneuropathy: Restriction enzyme nsiI cleaves peripheral blood DNA (lane a: arrows)

Autosomal dominant hereditary disorder-1



Familial amyloid polyneuropathy: amyloid deposition on the biopsied sural nerve (left: H&E, right: Dylon staining)

Autosomal dominant hereditary disorder-2



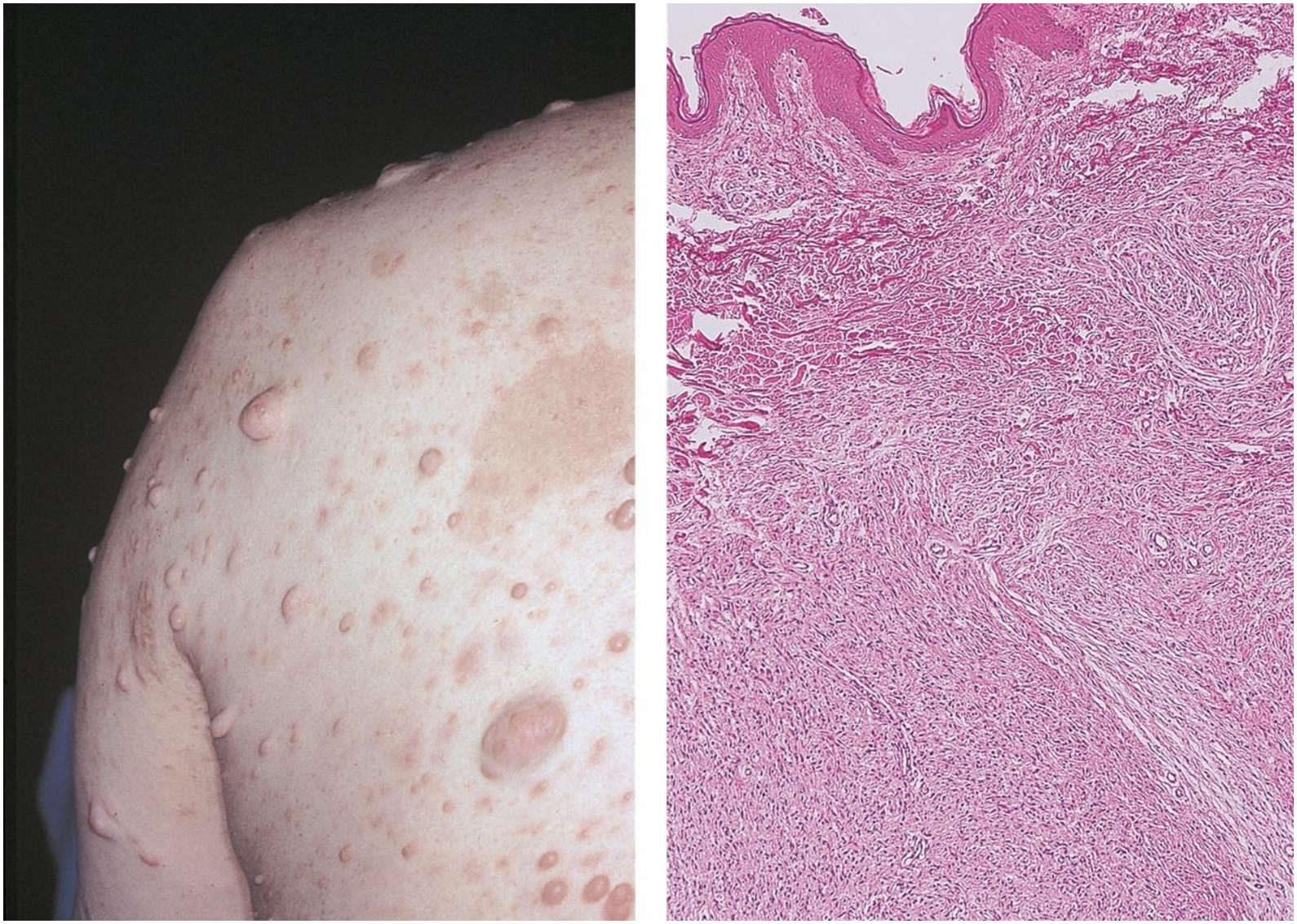
Huntington disease (frontal cut surfaces of the brain, left: normal control, right: marked atrophy of the caudate nucleus/MRI image: atrophy of the caudate nucleus and dilatation of the lateral ventricle)

Adult-onset hereditary neurological disorders

① Huntington disease, ② spinocerebellar degeneration,

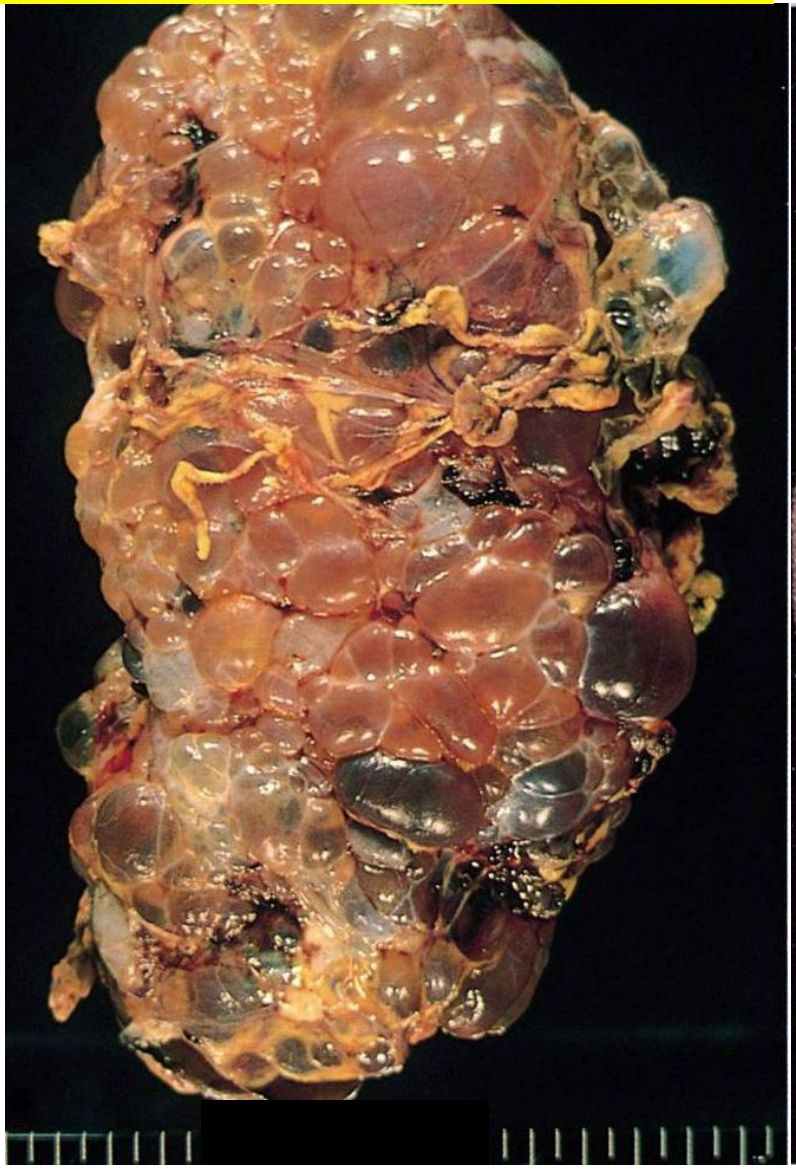
③ adrenoleukodystrophy, ④ familial amyloid polyneuropathy

Autosomal dominant hereditary disorder-3

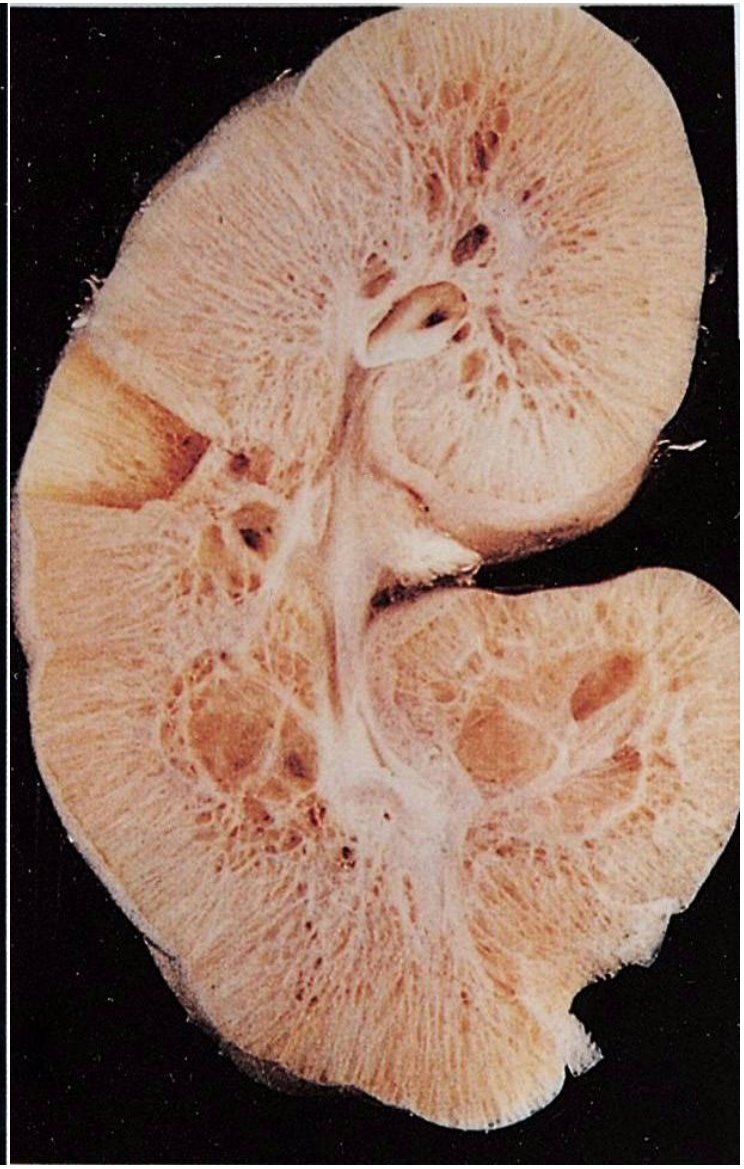


Neurofibromatosis (von Recklinghausen disease): left: gross appearance of multiple neurofibromas and Cafe au lait spots, right: skin biopsy, H&E)

Autosomal dominant hereditary disorder-4

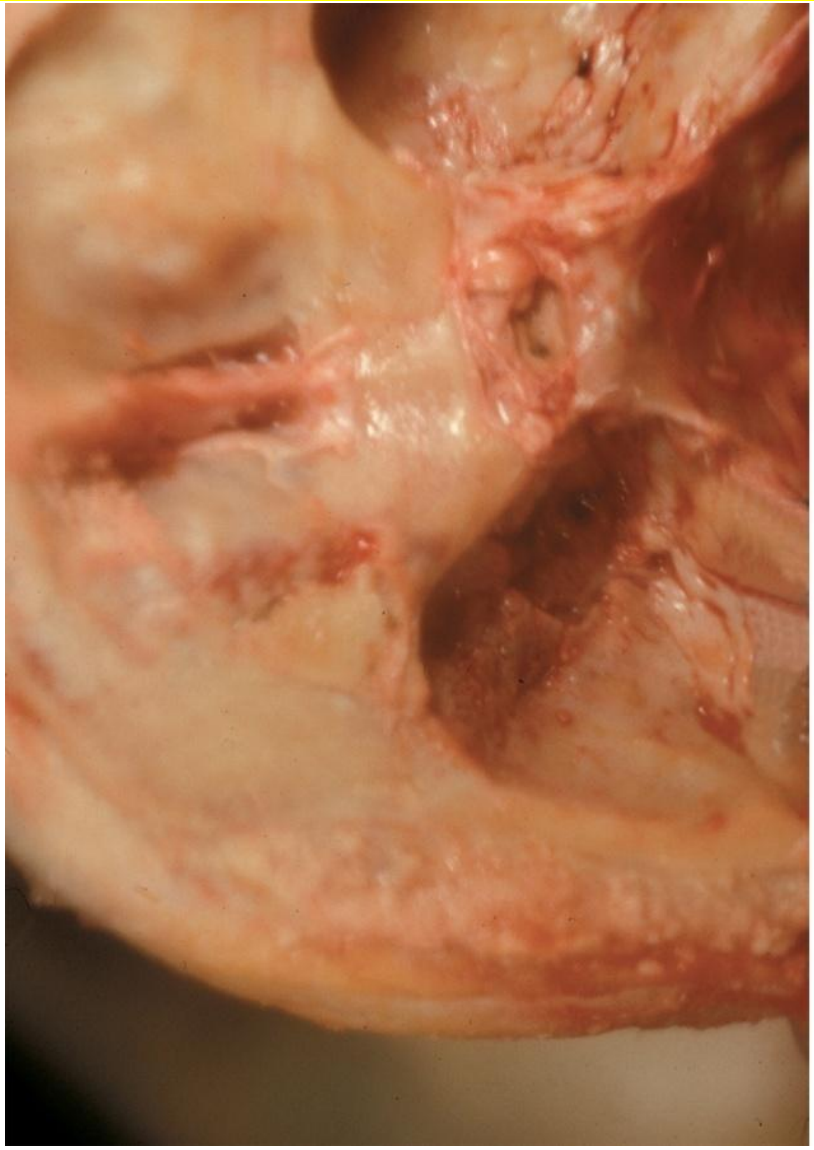


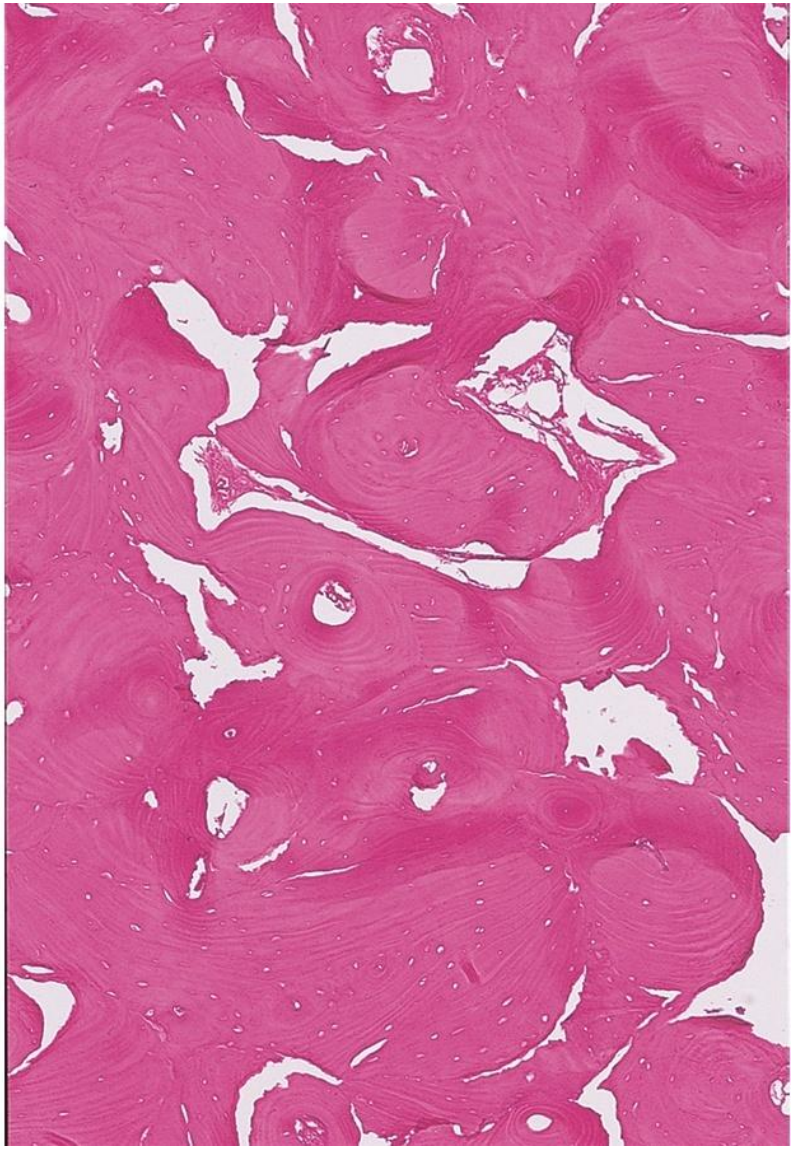
Adult-type polycystic kidney (large-sized, weighing 1 kg)



Infantile-type polycystic kidney (spongy appearance, no enlargement seen)

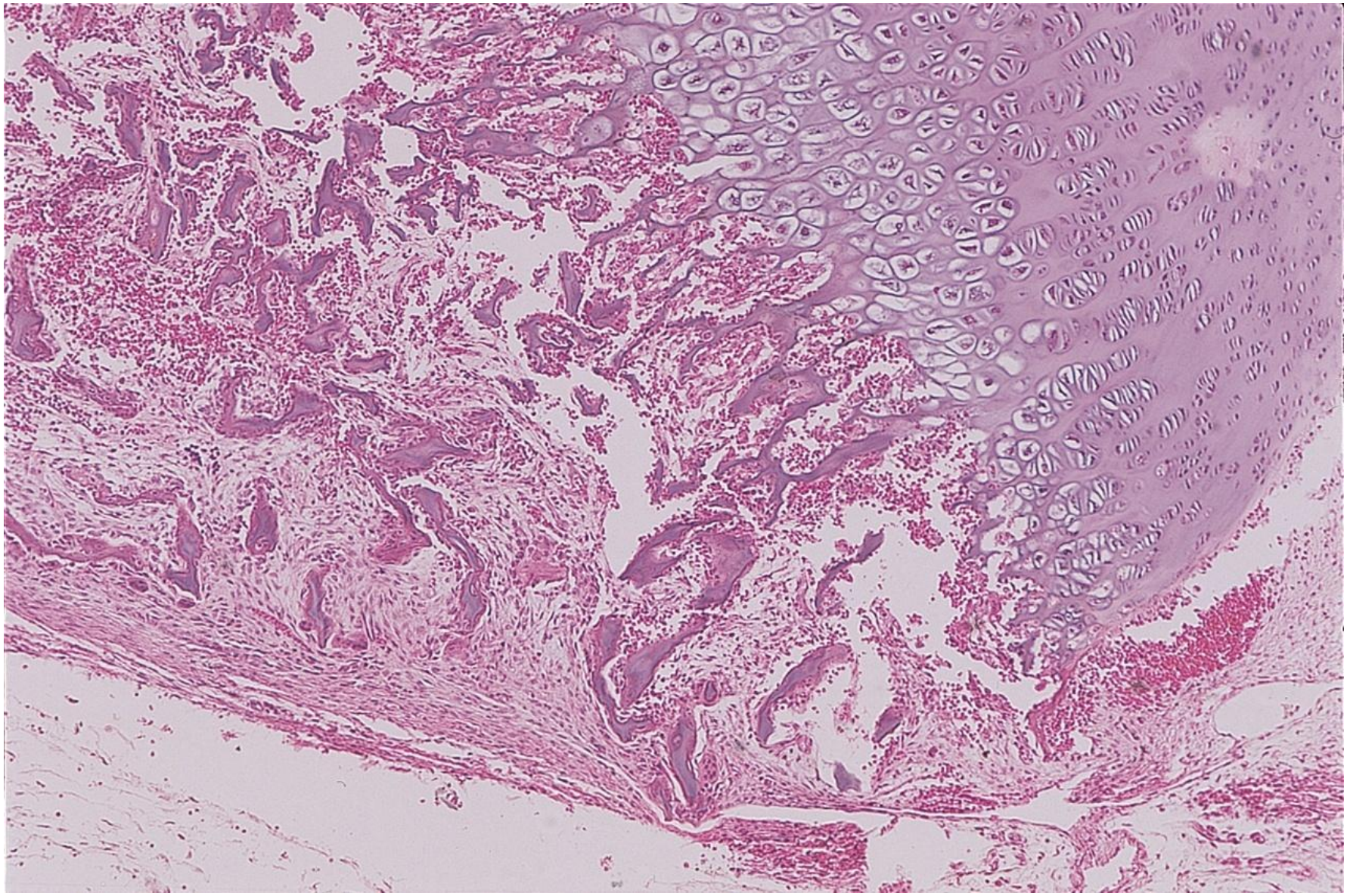
Autosomal dominant hereditary disorder-5





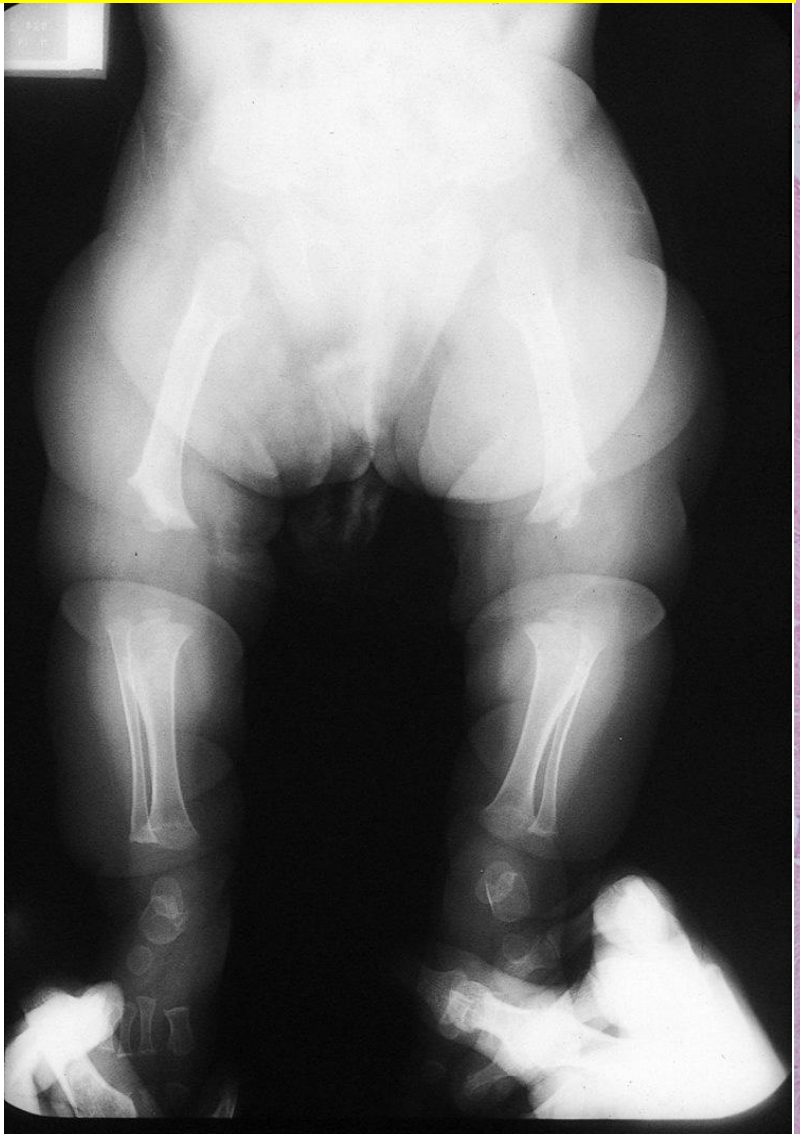
Marble bone disease (left: gross appearance of the basal part of the skull, right: thickening of bone trabeculae, H&E)

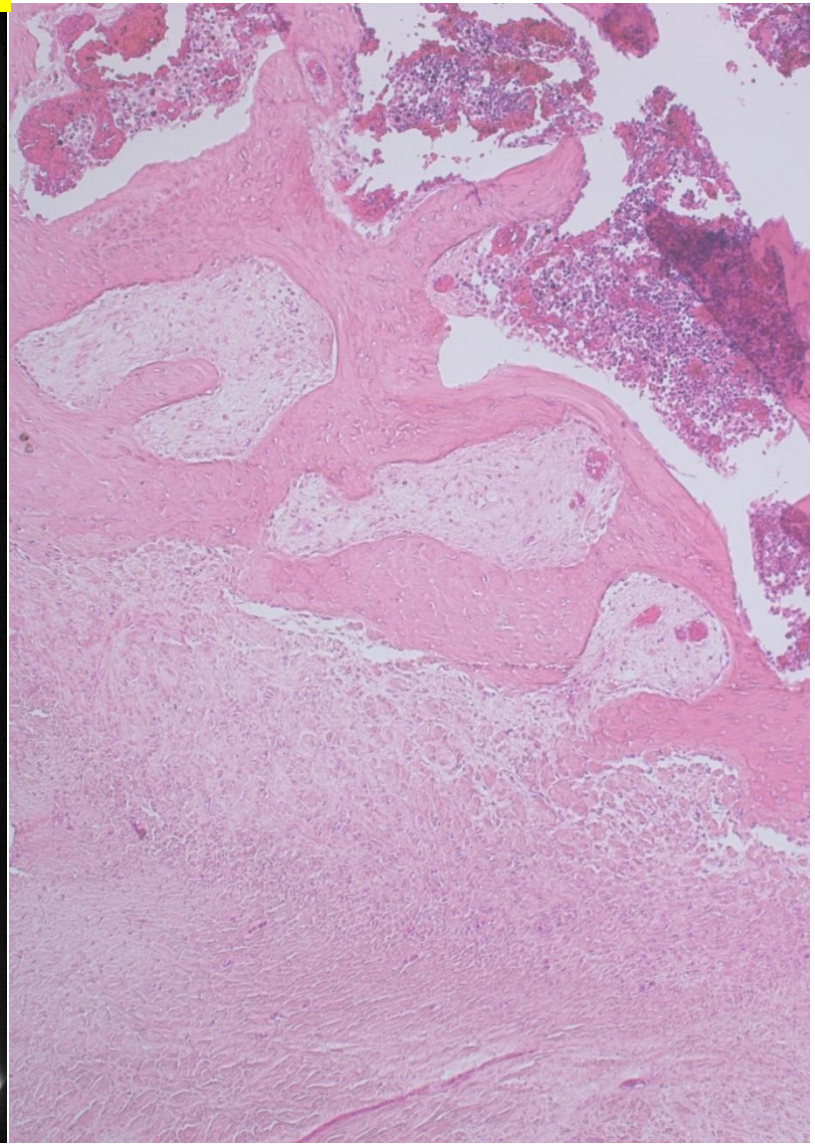
Autosomal dominant hereditary disorder-6



Osteogenesis imperfecta: poorly formed cortical bone at the epiphysis (H&E)

Autosomal dominant hereditary disorder-7





Achondroplasia (chondrodysplasia). Left: X-ray appearance demonstrating a short stature with short legs, right: microscopic appearance of the epiphysis of the long bone in the newborn showing the paucity of cartilage

Presentation of diseases with autosomal recessive inheritance

Glycogen storage disease

- von Gierke disease (type I)

Amino acid metabolic disorders

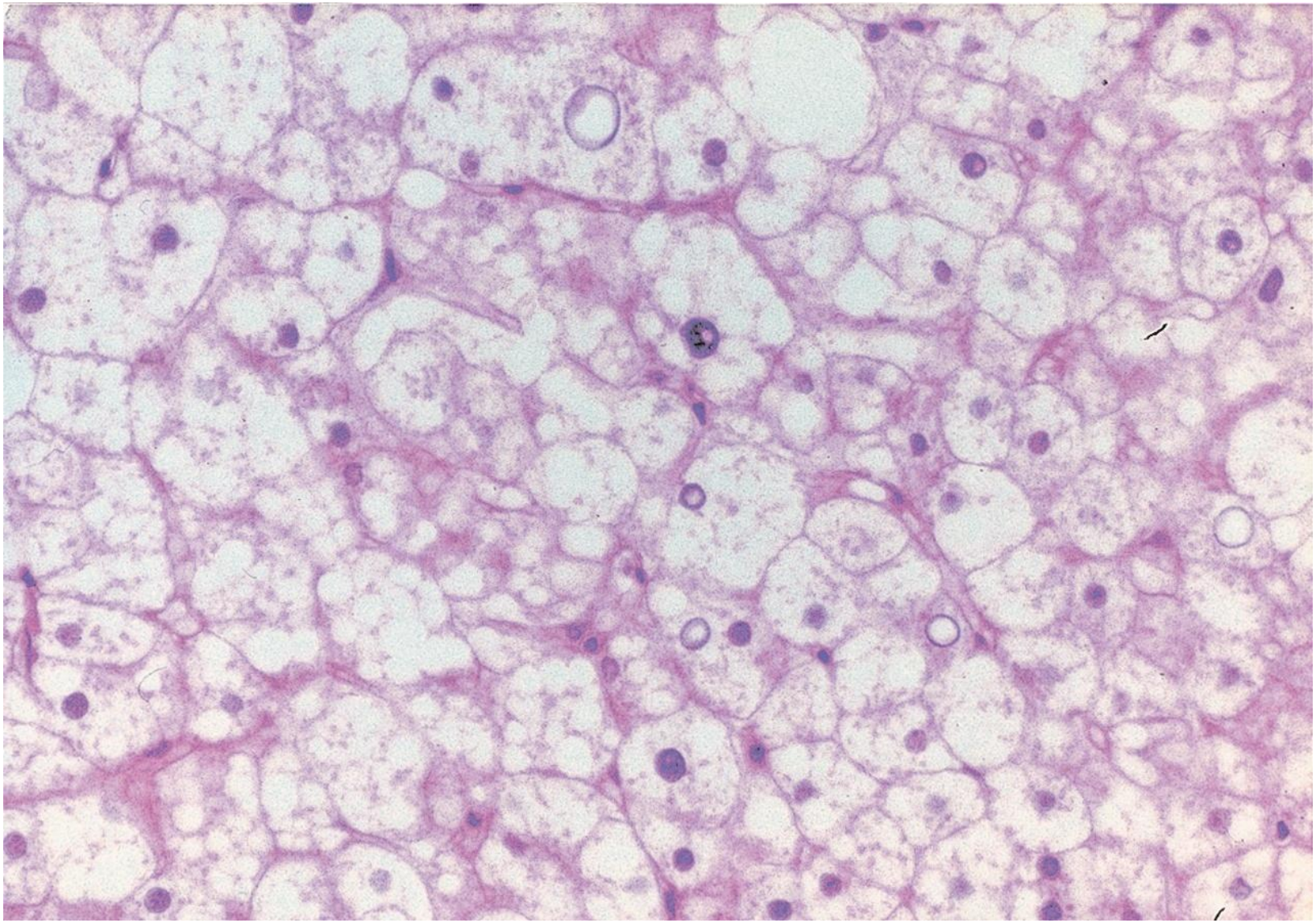
- cystinuria
- tyrosinemia

Ichthyosis (autosomal recessive type)

Abetalipoproteinemia

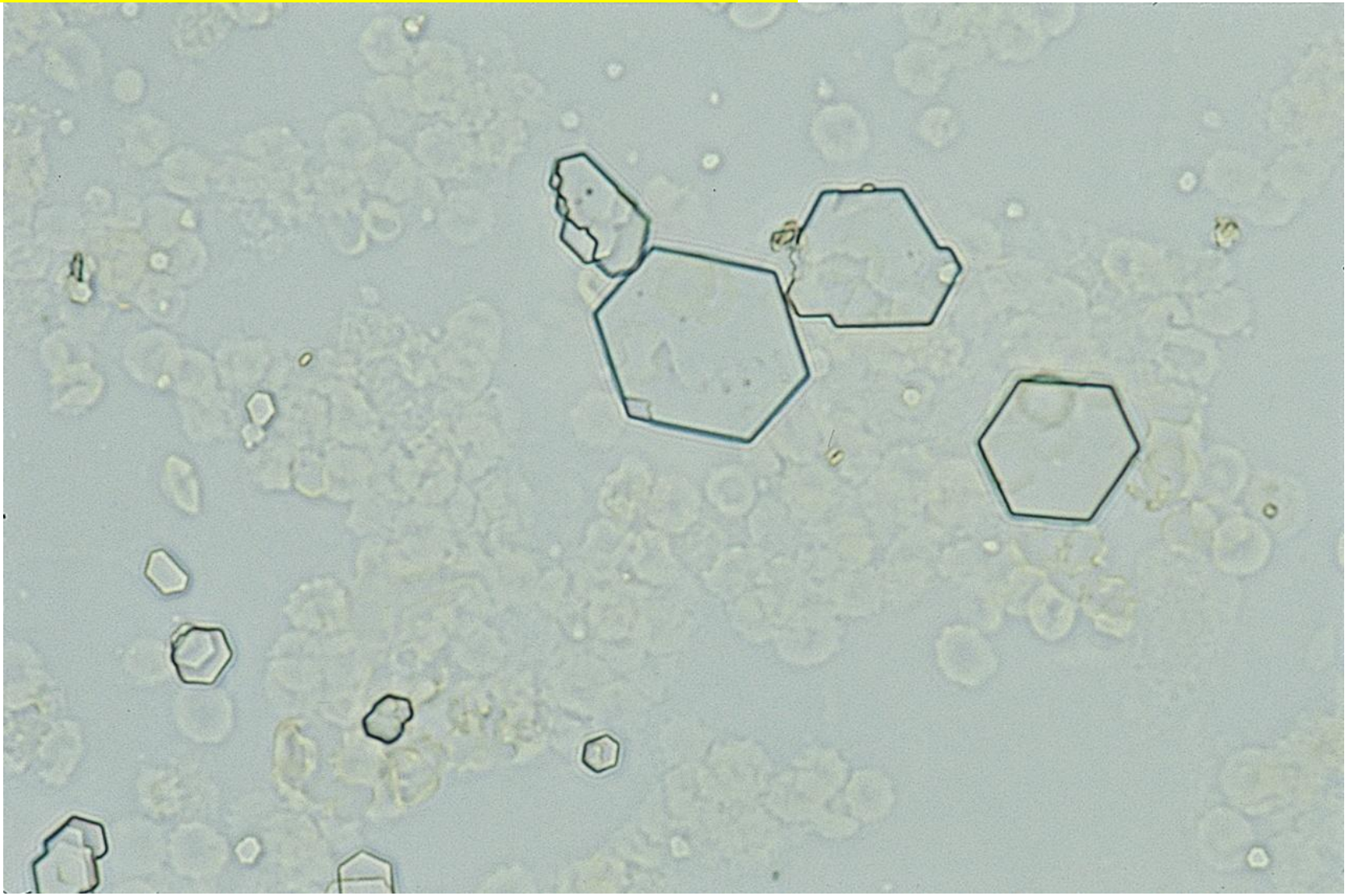
Chediac–Higashi syndrome

Autosomal recessive hereditary disorder-1



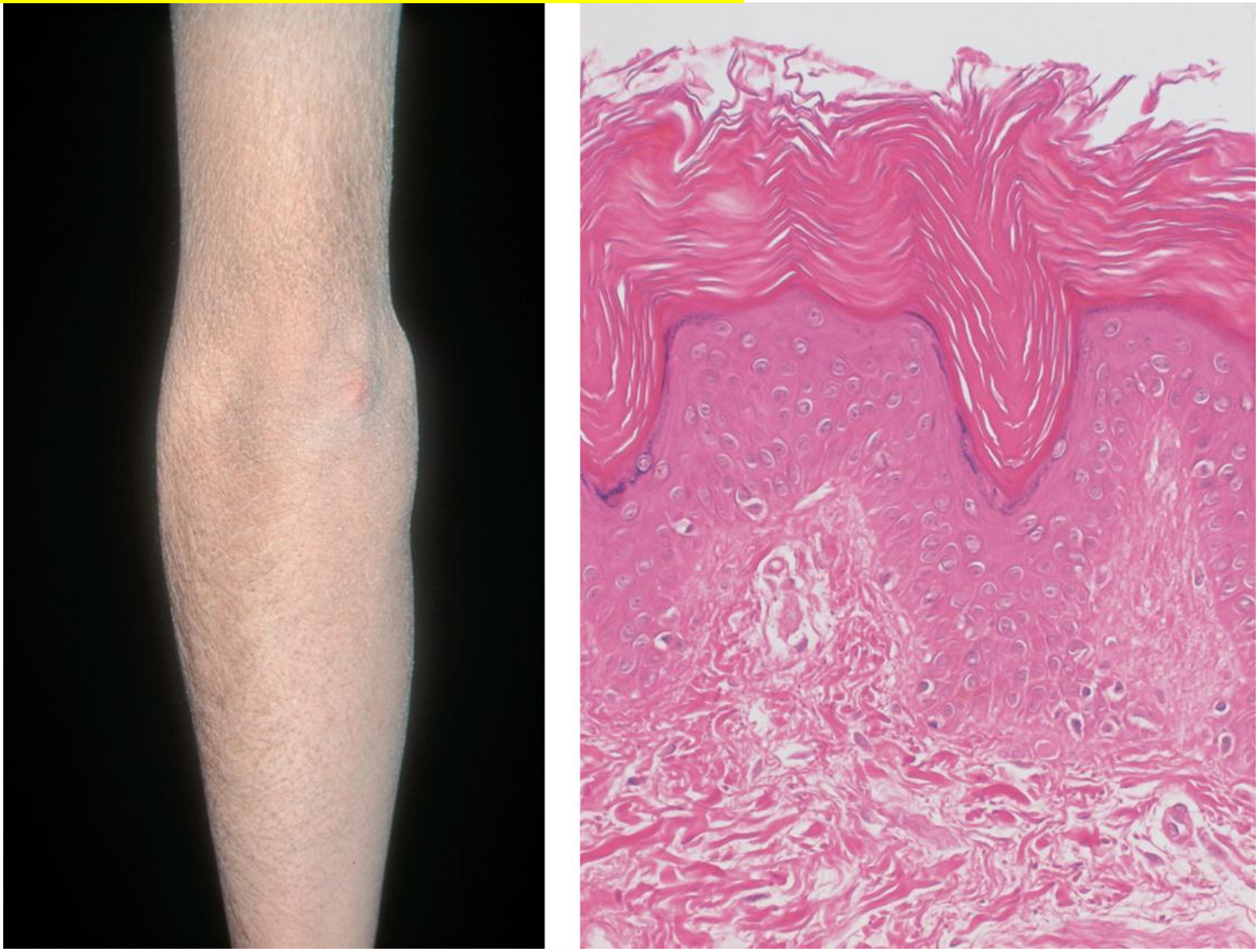
von Gierke disease. Marked glycogen deposition is seen in the hepatocytes (liver biopsy, H&E)

Autosomal recessive hereditary disorder-2



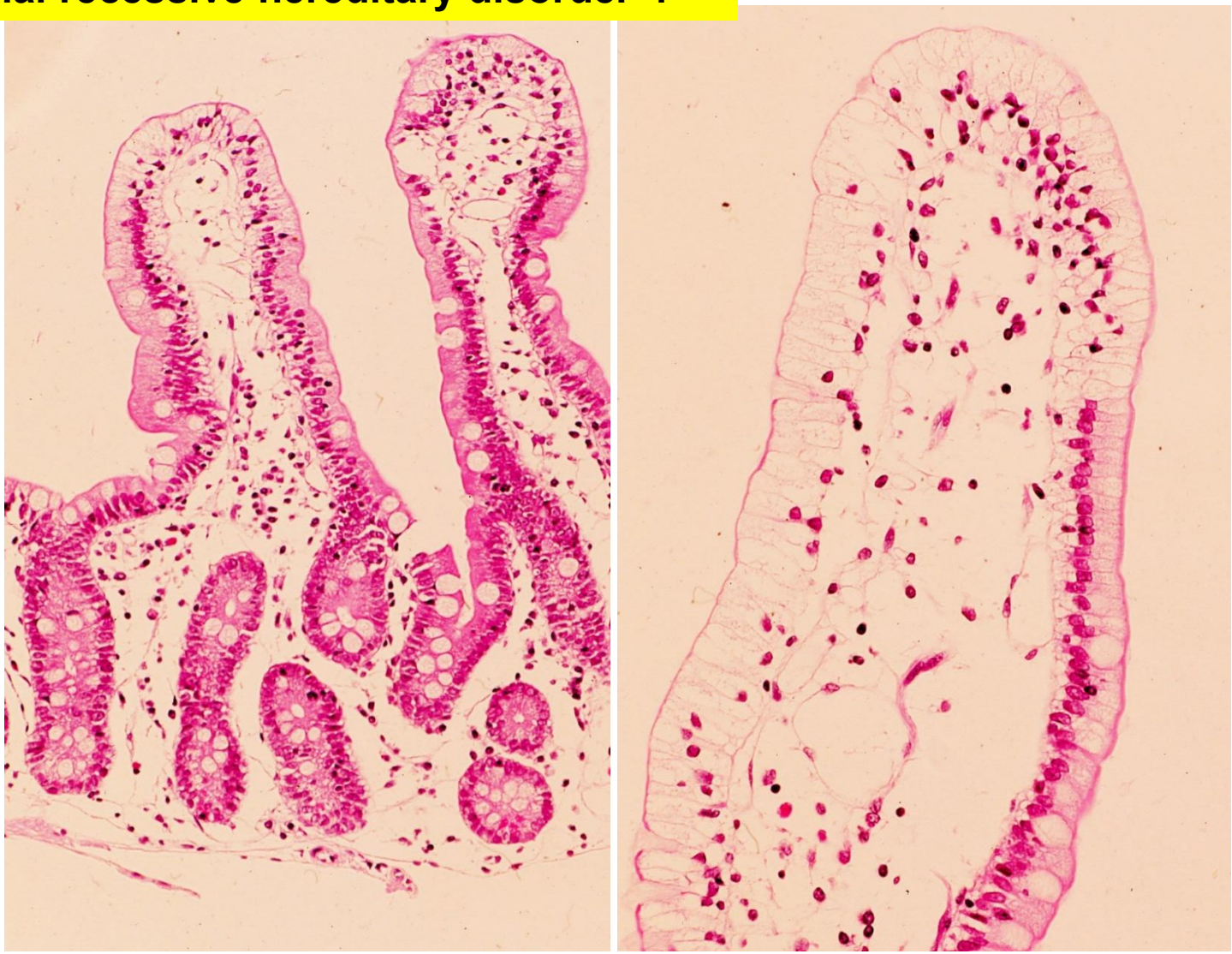
Cystinuria with urinary lithiasis in an intellectually normal male adult patient. Unstained urine sediment with transparent hexagonal cystine crystals is shown. Note hematuric background.

Autosomal recessive hereditary disorder-3



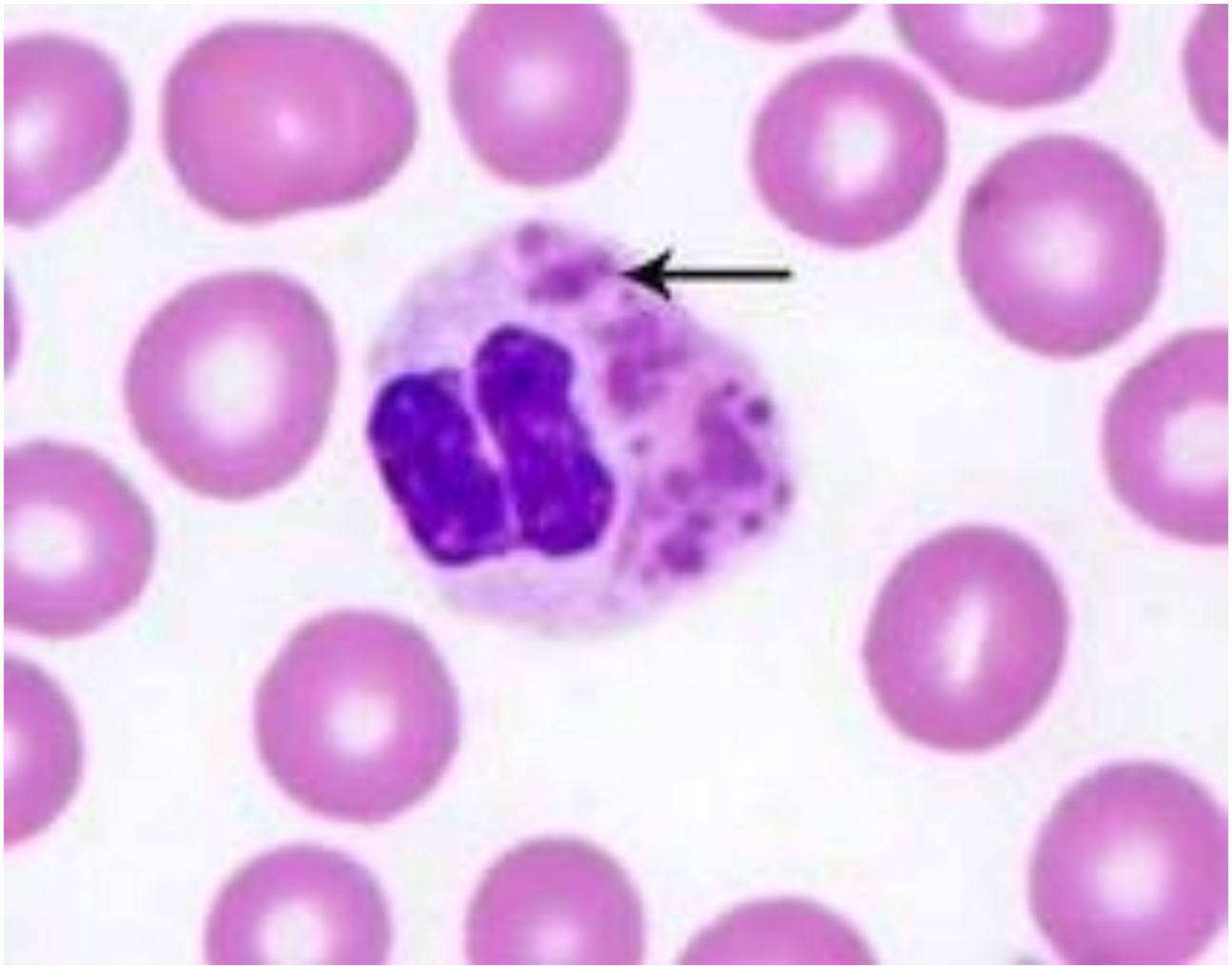
Ichthyosis, autosomal recessive type (left: gross appearance with goose-like skin, right: hyperkeratosis, H&E)

Autosomal recessive hereditary disorder-4



Abetalipoproteinemia, showing abnormal absorption of fat and fat-soluble vitamins, is caused by an autosomal recessive mutation in microsomal triglyceride transfer protein, resulting in deficiencies in the apolipoproteins. Duodenal biopsy reveals enterocytes with the clear cytoplasm accompanying lipid accumulation. H&E

Autosomal recessive hereditary disorder-5



Chediac-Higashi syndrome. An autosomal recessive disorder with a mutation of a lysosomal trafficking regulator protein. The decrease in phagocytosis results in recurrent pyogenic infections by *Staphylococcus aureus* and fungi, albinism and peripheral neuropathy. The neutrophil contains "giant inclusion bodies“ in the cytoplasm. Borrowed from PathPedia.com

Presentation of diseases with X-linked recessive inheritance

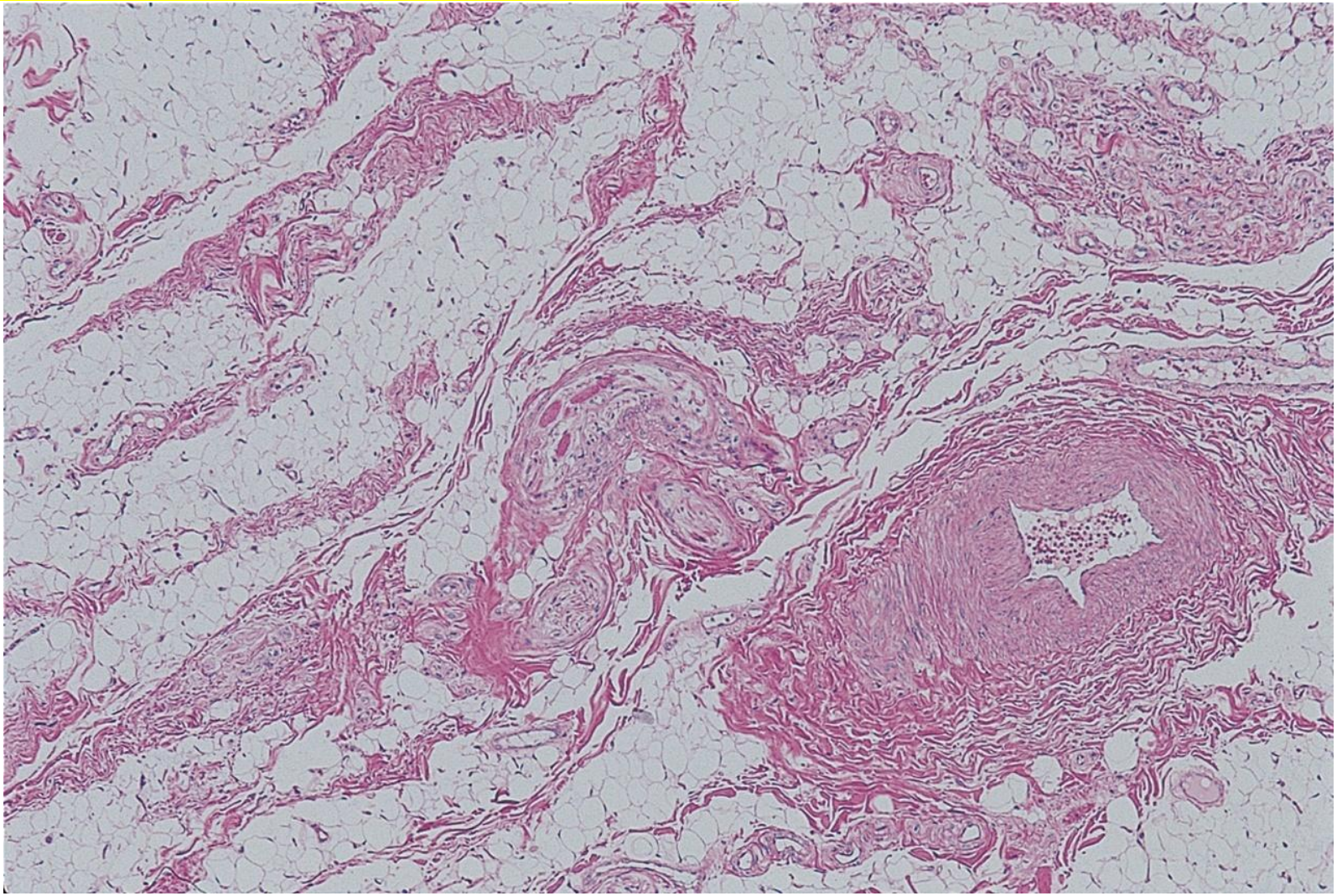
Duchenne type muscular dystrophy

Fabry disease

Hunter syndrome

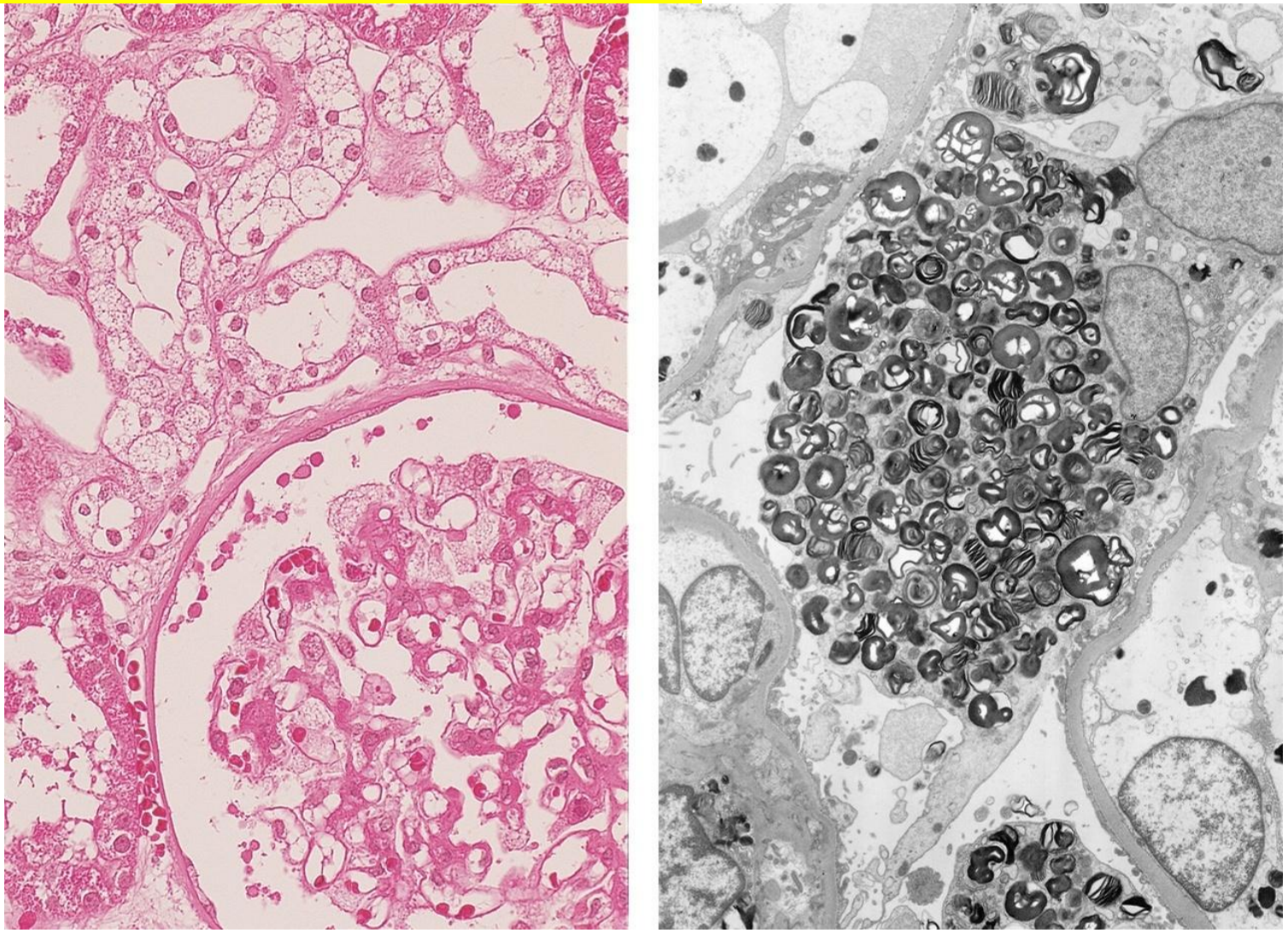
Chronic granulomatous disease

X-linked recessive hereditary disorder-1



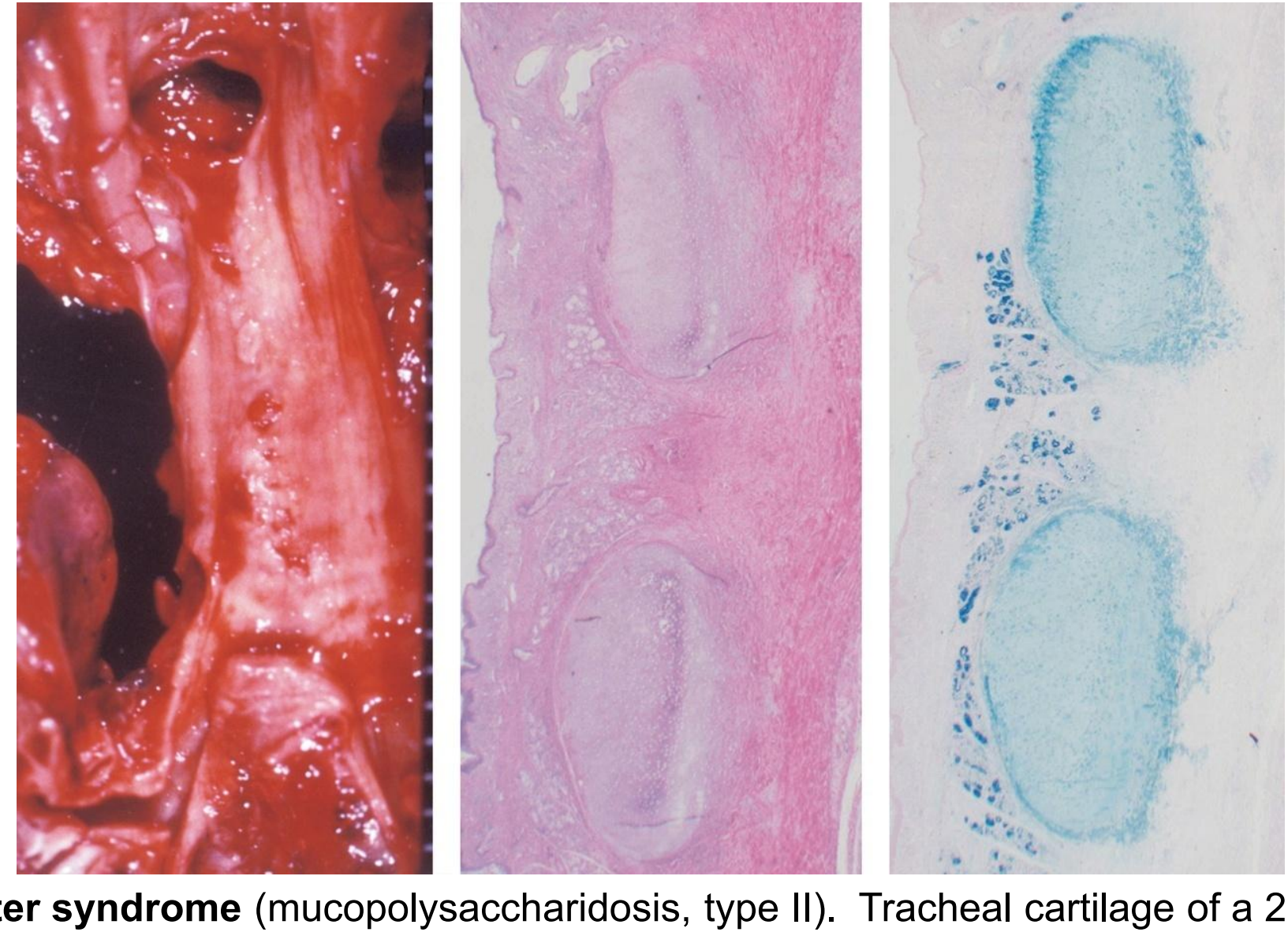
Duchenne type muscular dystrophy (H&E). Muscle biopsy from the thigh reveals severe loss of muscle fibers and marked stromal lipomatosis. Note a muscle spindle remains intact.

X-linked recessive hereditary disorder-2



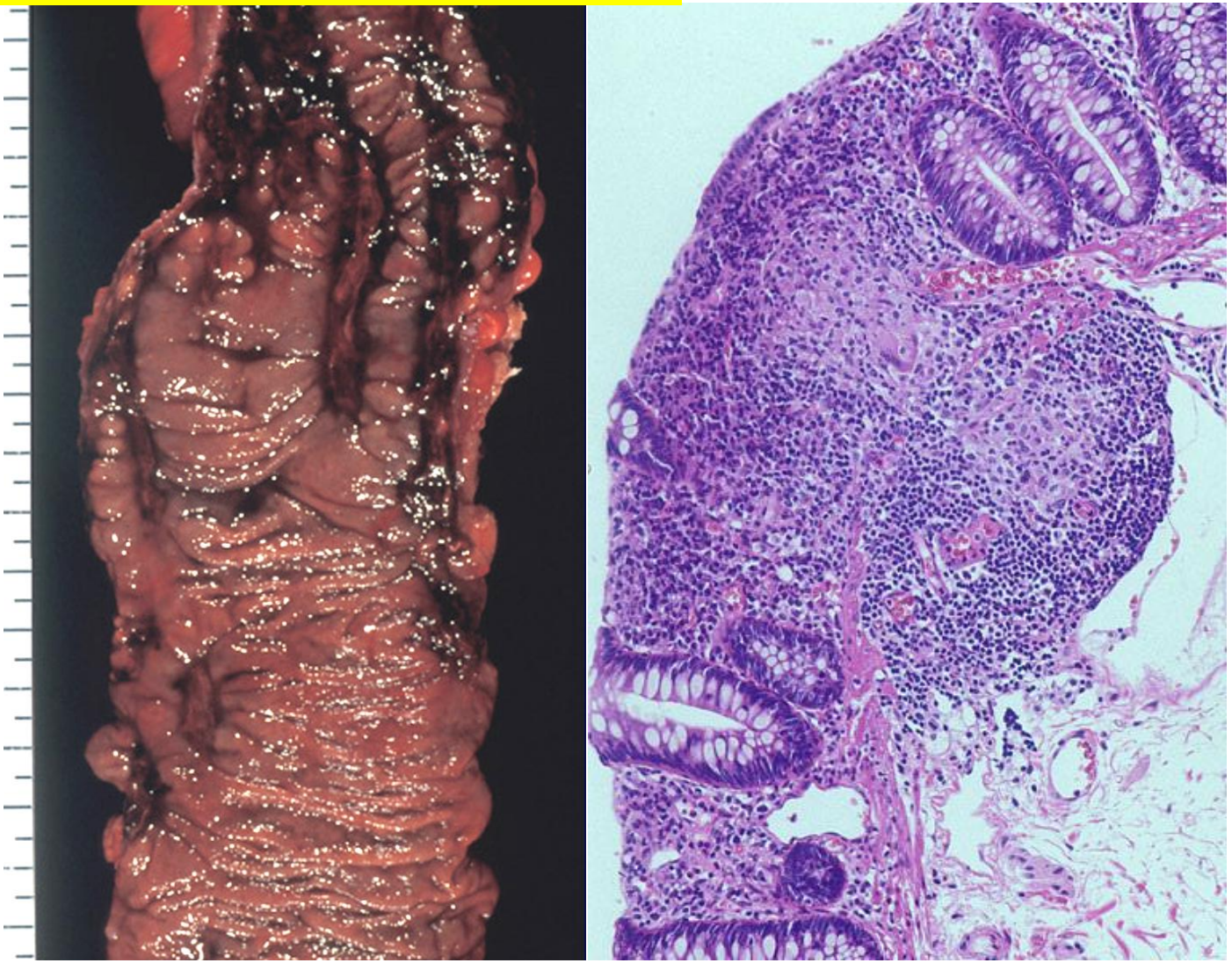
Fabry disease (renal biopsy: left: H&E, right: EM). Epithelial cells of the proximal renal tubules and glomeruli show foamy changes. Ultrastructurally, Zebra bodies composed of glycolipid (globotriaosylceramide) are deposited.

X-linked recessive hereditary disorder-3



Hunter syndrome (mucopolysaccharidosis, type II). Tracheal cartilage of a 20-year-old male patient is severely deformed to death. Left: gross appearance of the trachea, center: H&E, right: alcian blue. Deposition of acid mucosubstances is seen.

X-linked recessive hereditary disorder-4

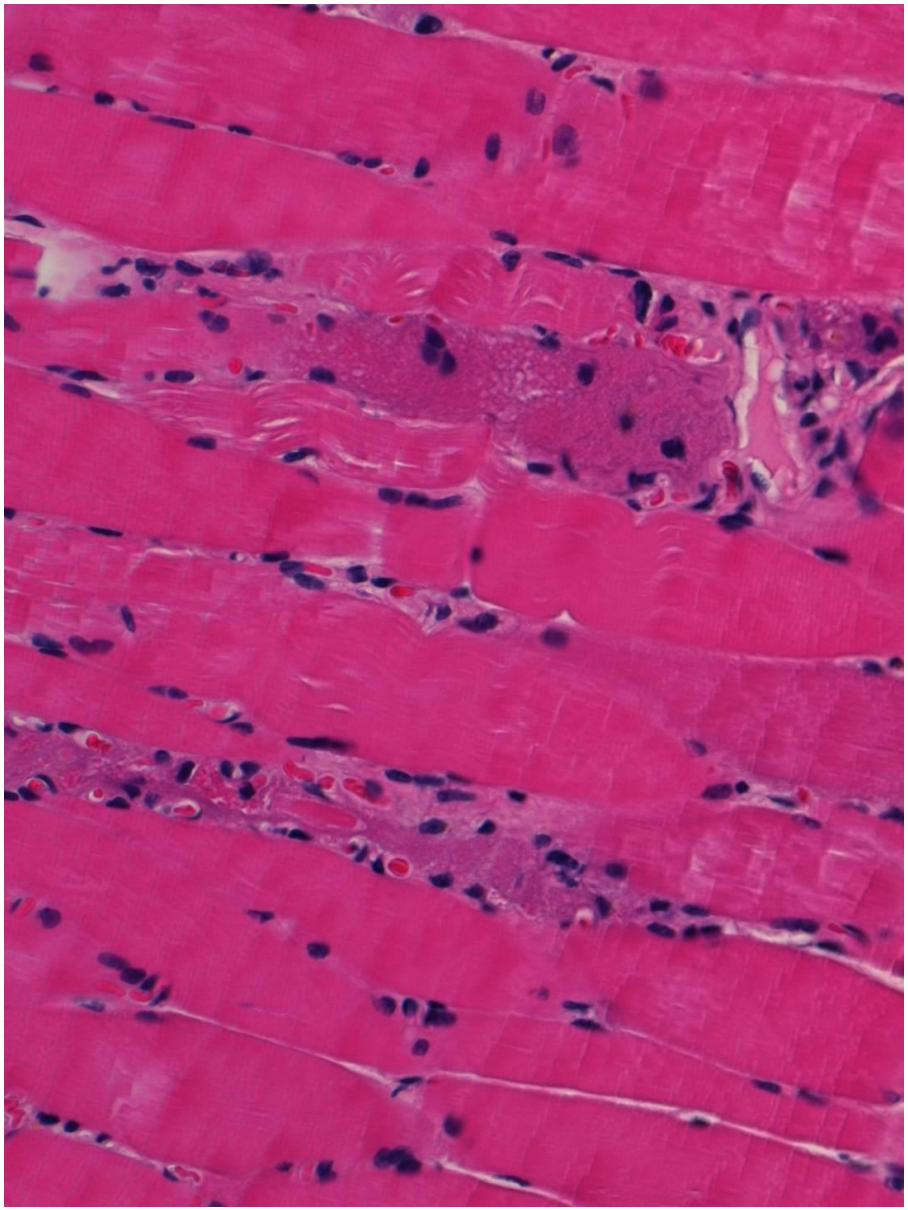


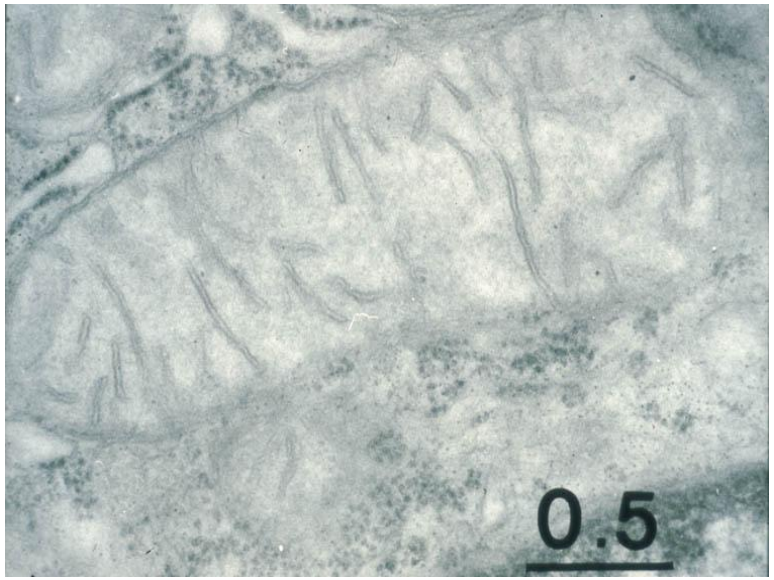
Chronic granulomatous disease with hereditary neutrophilic dysfunction. The surgically resected colon in an 8-year-old boy shows Crohn's disease-like longitudinal ulceration (left: gross). The defective neutrophils cannot digest catalase-producing microbes. Microscopically, non-caseous granuloma is seen in the gut wall (right: H&E).

Disorders with mitochondrial inheritance

MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes

Mitochondrial hereditary disorder-1



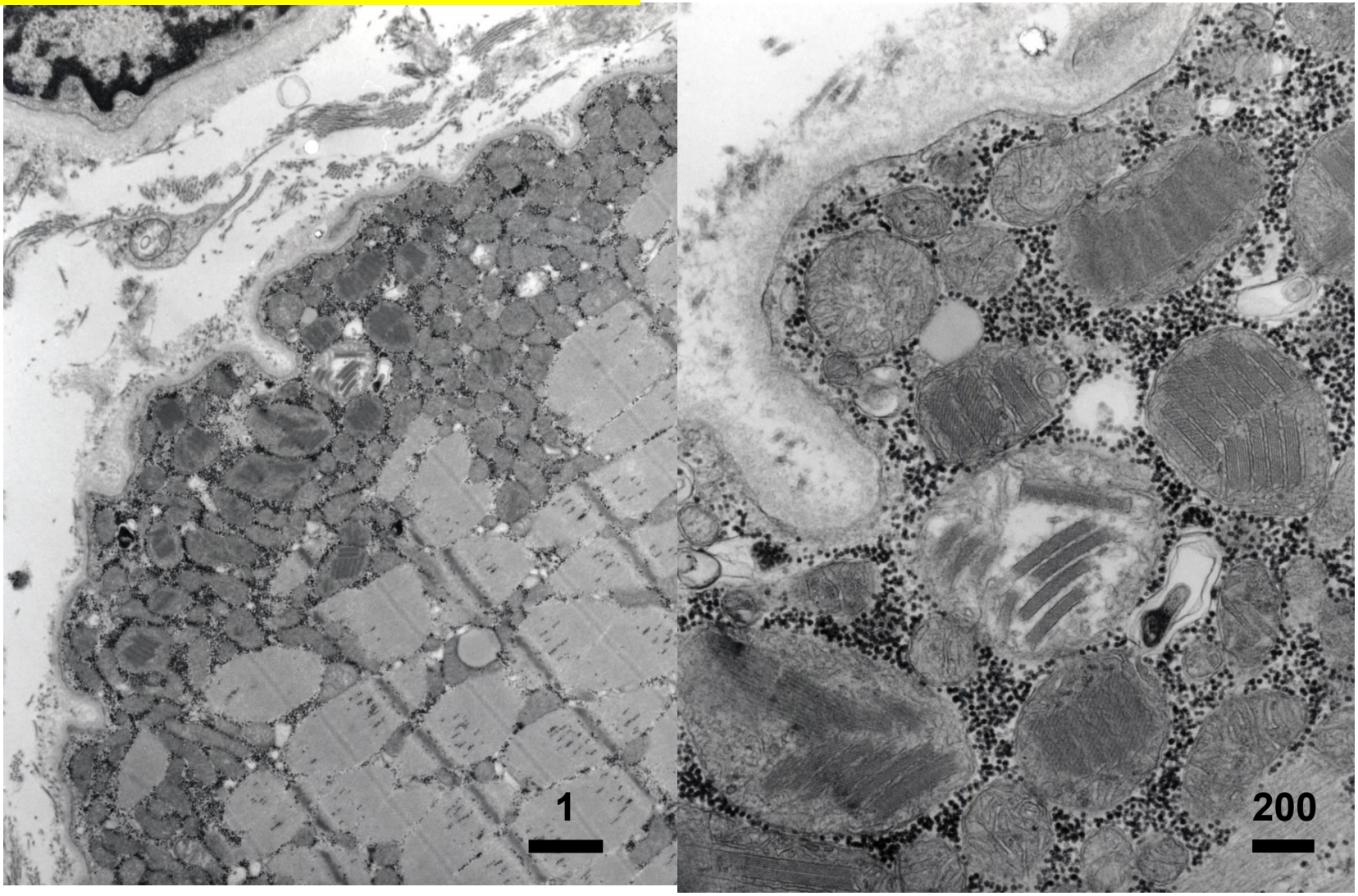


EM features of a mitochondrion in the normal hepatocyte

MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes

Striated muscle biopsy from a 36-year-old female patient (H&E). Accumulation of granular materials is noted.

Mitochondrial hereditary disorder-1



Ultrastructural features of MELAS (a 36-year-old female patient). Abnormal mitochondria are accumulated mainly in the peripheral cytoplasm of the myocyte. Crystalline deposition is evident in the mitochondrial matrix.

Polygenic disorders

Examples: Lifestyle diseases such as diabetes mellitus, essential hypertension and gout), cancer family, psychiatric disorders (schizophrenia and mood disorders), cleft palate, hearing loss

Multiple genes are involved in the pathogenesis.

Polygenic diseases are more frequently seen than single gene diseases

The more genes involved, the more severe clinically.

Environmental factors modify the disease.

Family agglomeration is seen to certain extent.

The genes involved are called "disease-susceptibility genes".

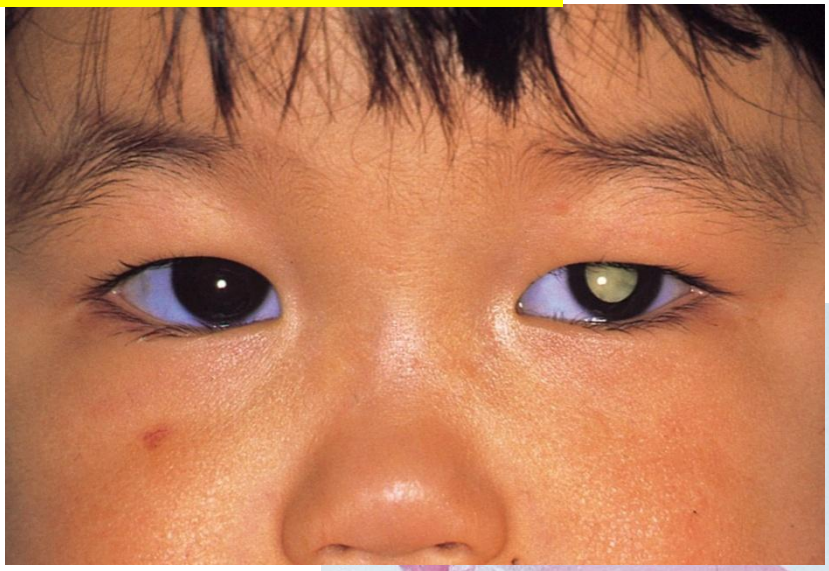
～The disease-susceptibility genes are generated by a combination of single-nucleotide polymorphism (SNP=snip), a germline substitution of a single nucleotide at a specific position in the genome～

Interactions of the disease-susceptibility genes make the constitution (physical makeups).

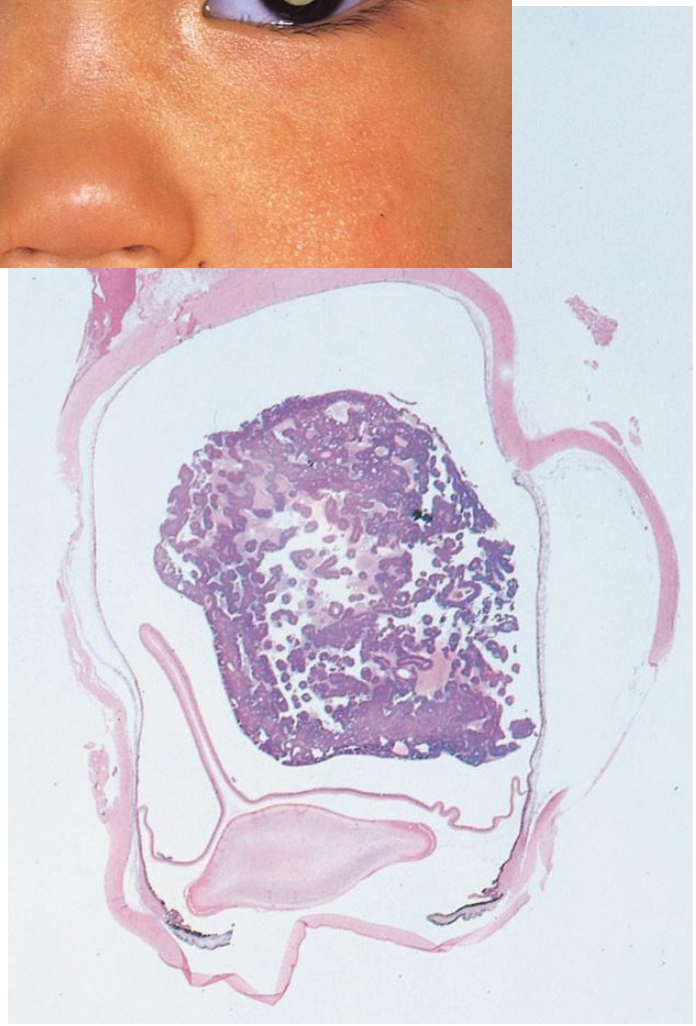
The pathogenic mechanisms of polygenic disorders have not been clarified yet.

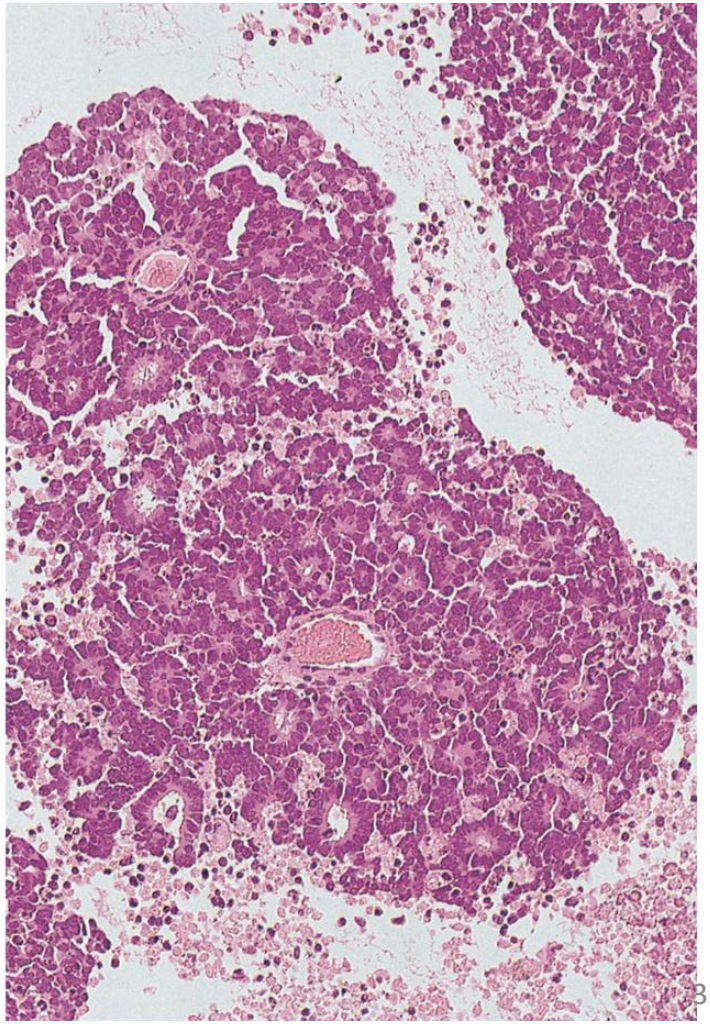
Hereditary neoplasms

- Retinoblastoma — Rb
- Wilms tumor (nephroblastoma) — WT
- Familial polyposis coli — APC
- Hereditary nonpolyposis colorectal cancer — DNA-repairing enzymes
- Multiple endocrine neoplasia type I (Wermer) — MEN1
- Multiple endocrine neoplasia type II (Sipple) — Ret
- von Recklinghausen disease (neurofibromatosis) — NF1
- Xeroderma pigmentosum — DNA-repairing enzymes
- Werner syndrome (progeria) — DNA helicase
- Cancer family (breast cancer: BRCA1, renal cell carcinoma: RCA1)

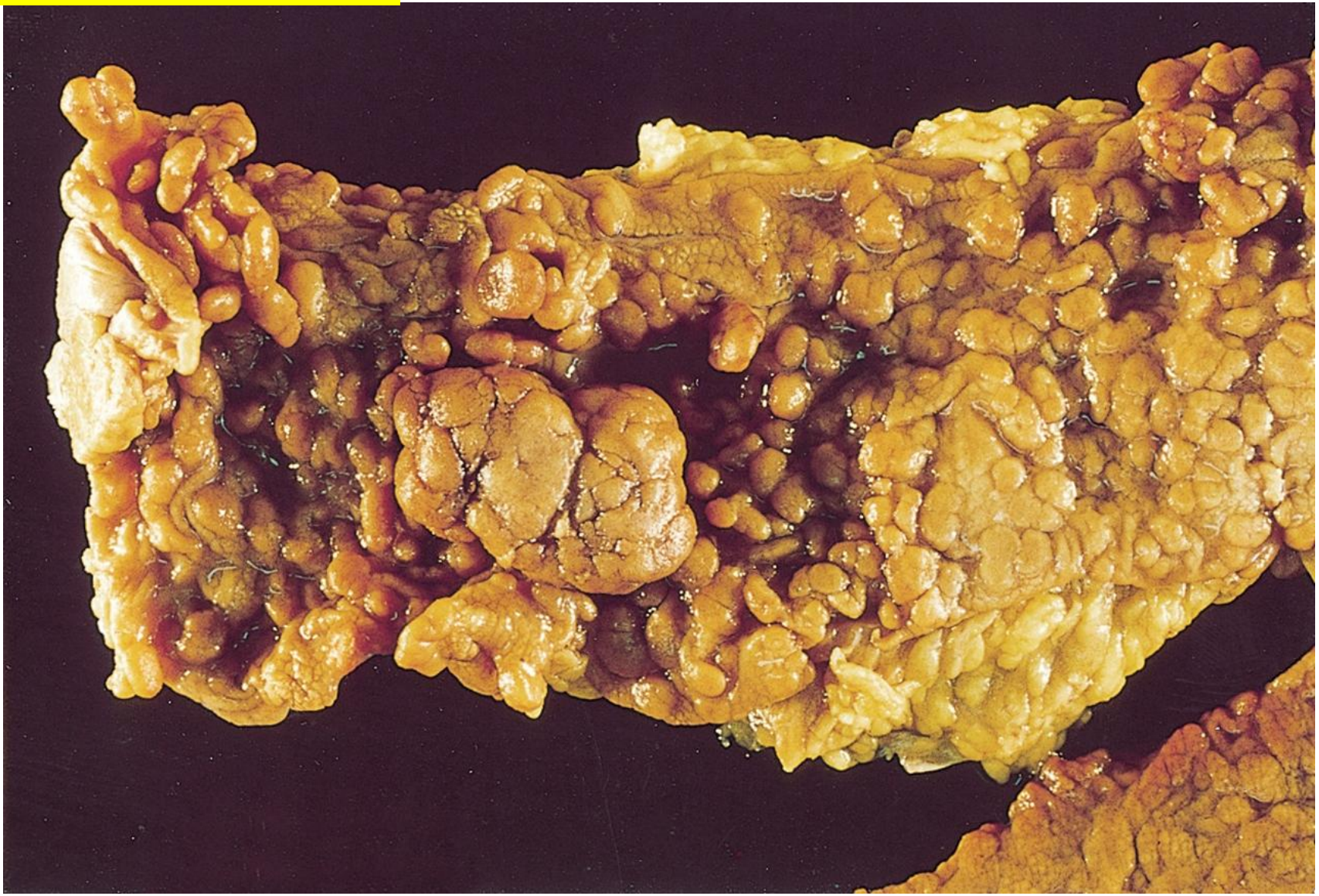


Retinoblastoma（leukocoria and rosette-forming blastic tumor cells, H&E)





Hereditary neoplasm-2



Familial polyposis coli: the surgical specimen after formalin fixation reveals numerous adenomas of varying sizes.

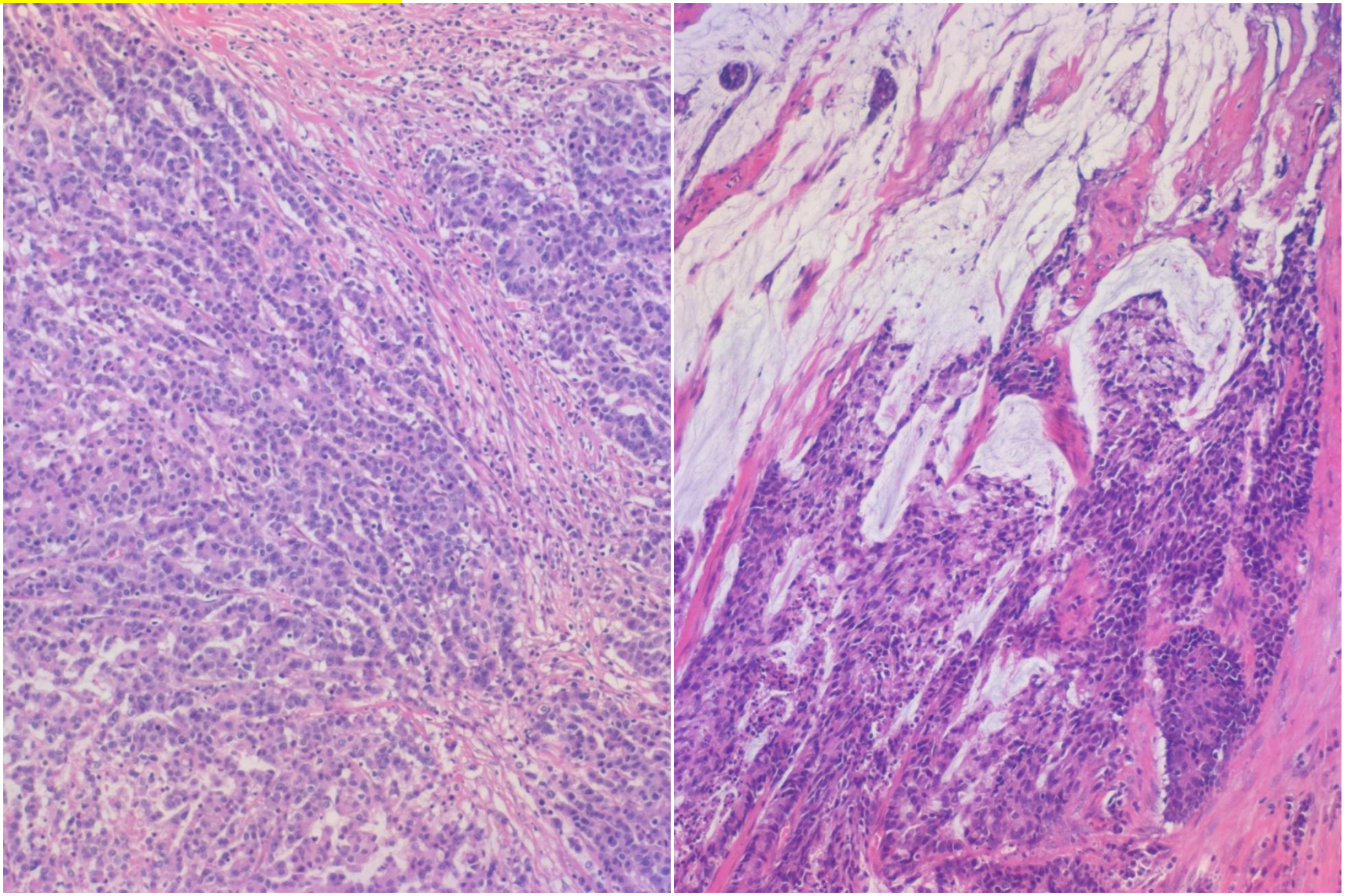
Lynch syndrome

Hereditary non-polyposis colorectal cancer (HNPCC)

Abnormalities of mismatch repairing enzymes are noted.

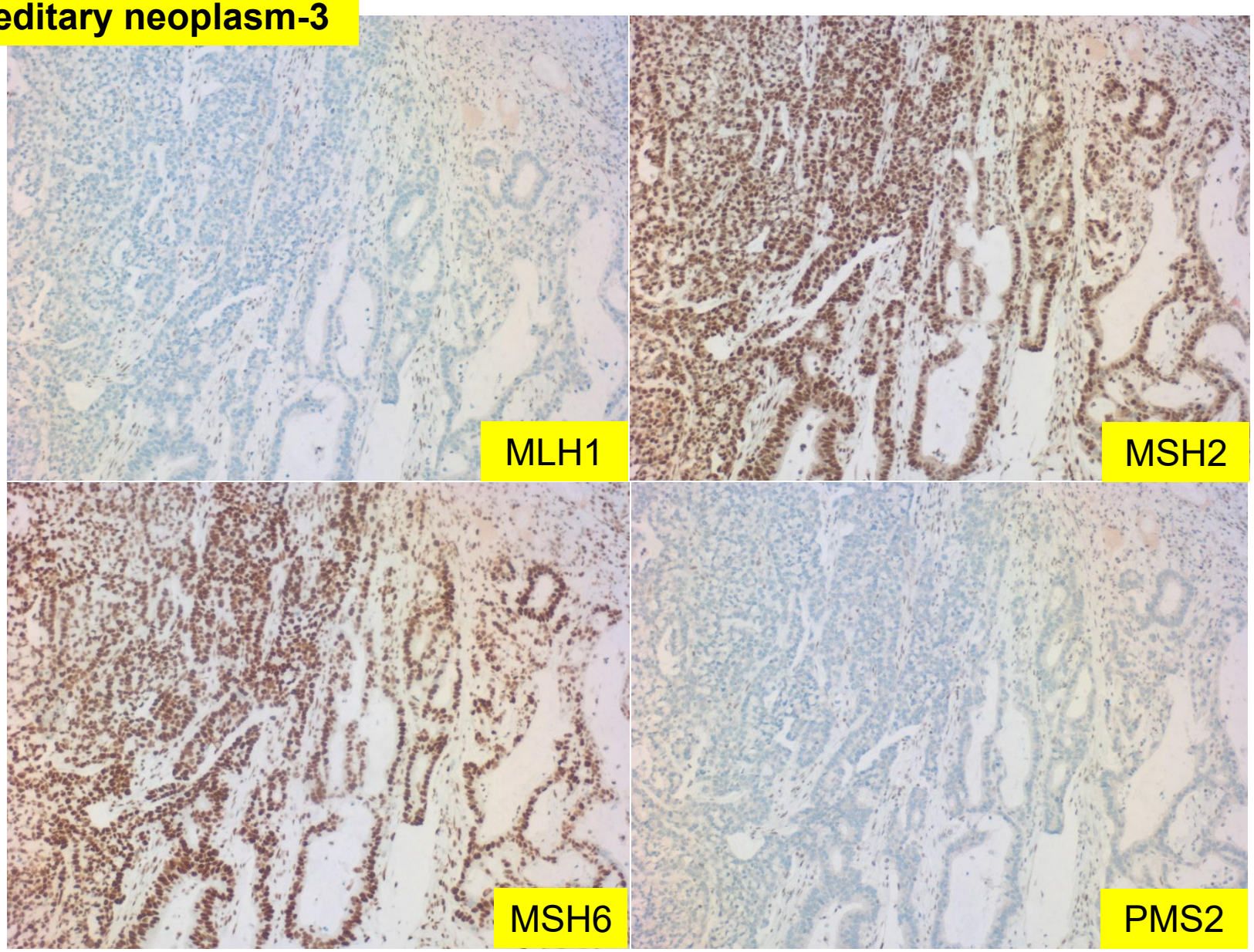
- Microsatellite instability (MSI) is associated.
- Mutations seen in either of **MLH1, MSH2,** PMS2 and MSH6.
- Colorectal cancer is frequently seen (2-5% of all colorectal cancer, 80% in individuals with abnormal genes)
- There is an increased risk of endometrial, ovarian, gastric, pancreatic, biliary and upper urological cancer.
- Autosomal dominant inheritance is proven.
- Juvenile-onset multifocal colorectal cancer with family history.
- Medullary carcinoma with lymphoid stroma or mucinous carcinoma.
- Immunostaining can identify the lack of enzyme expression in the nuclei.

Hereditary neoplasm-3



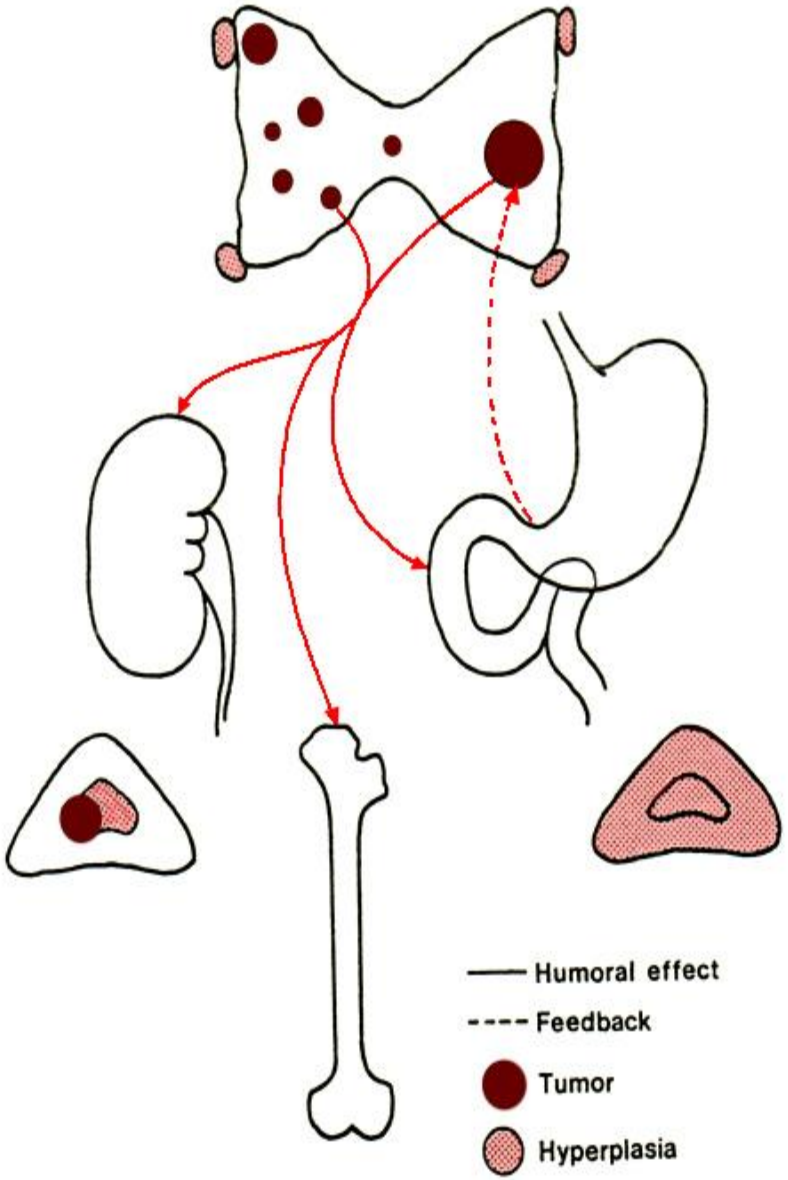
Lynch syndrome (HNPCC). Medullary carcinoma (left) or mucinous carcinoma (right) is common. Right-sided colon is the favorite site of occurrence. H&E

Hereditary neoplasm-3

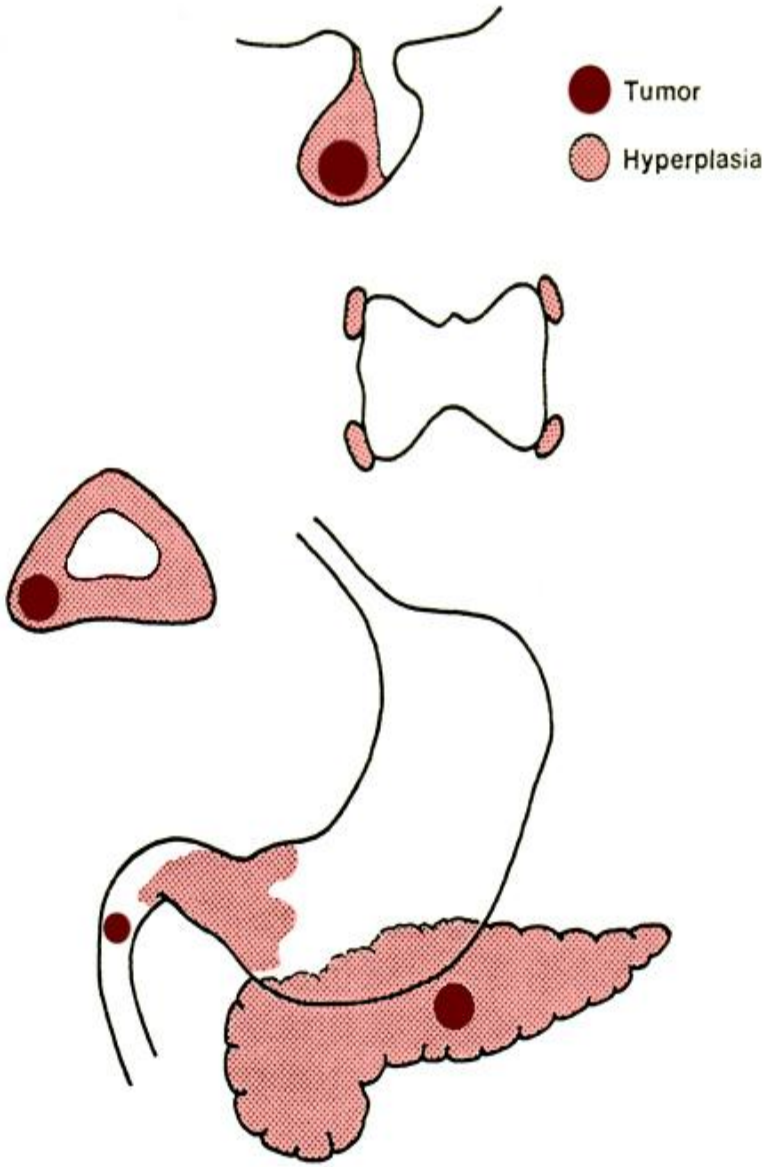


Medullary carcinoma in Lynch syndrome shows the lack of enzyme expression of MLH1 and PMS2. MSH2 and MSH6 are normally expressed in the nuclei. Immunostaining for mismatch repairing enzymes

Multiple endocrine neoplasia, type 2



Multiple endocrine neoplasia, type 1



MEN and genetic alterations

MEN1 (Wermer syndrome)

MEN1 gene (autosomal dominant trait)

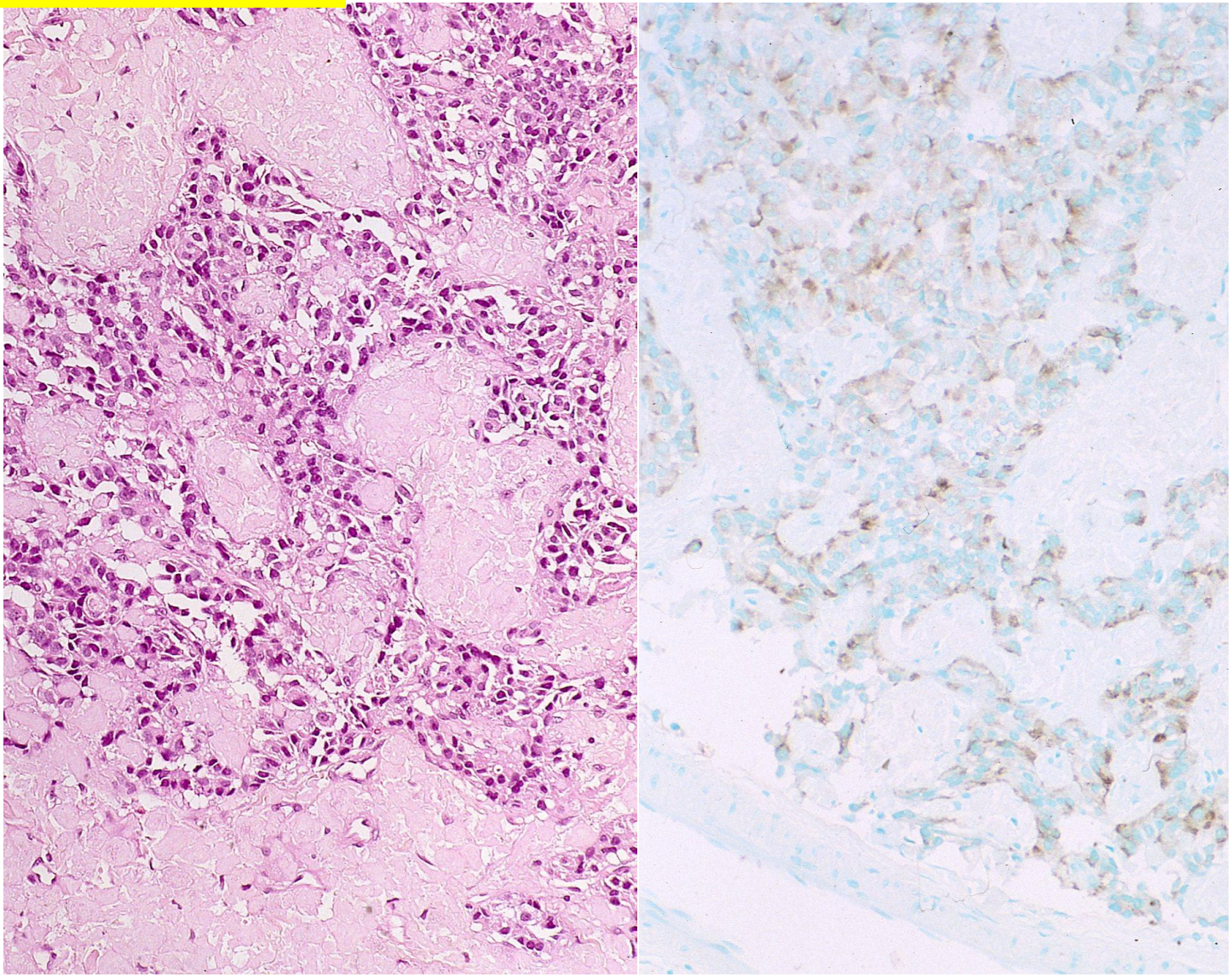
MEN2 (Sipple syndrome)

ret gene (autosomal dominant trait)

Ret gene-related disorders

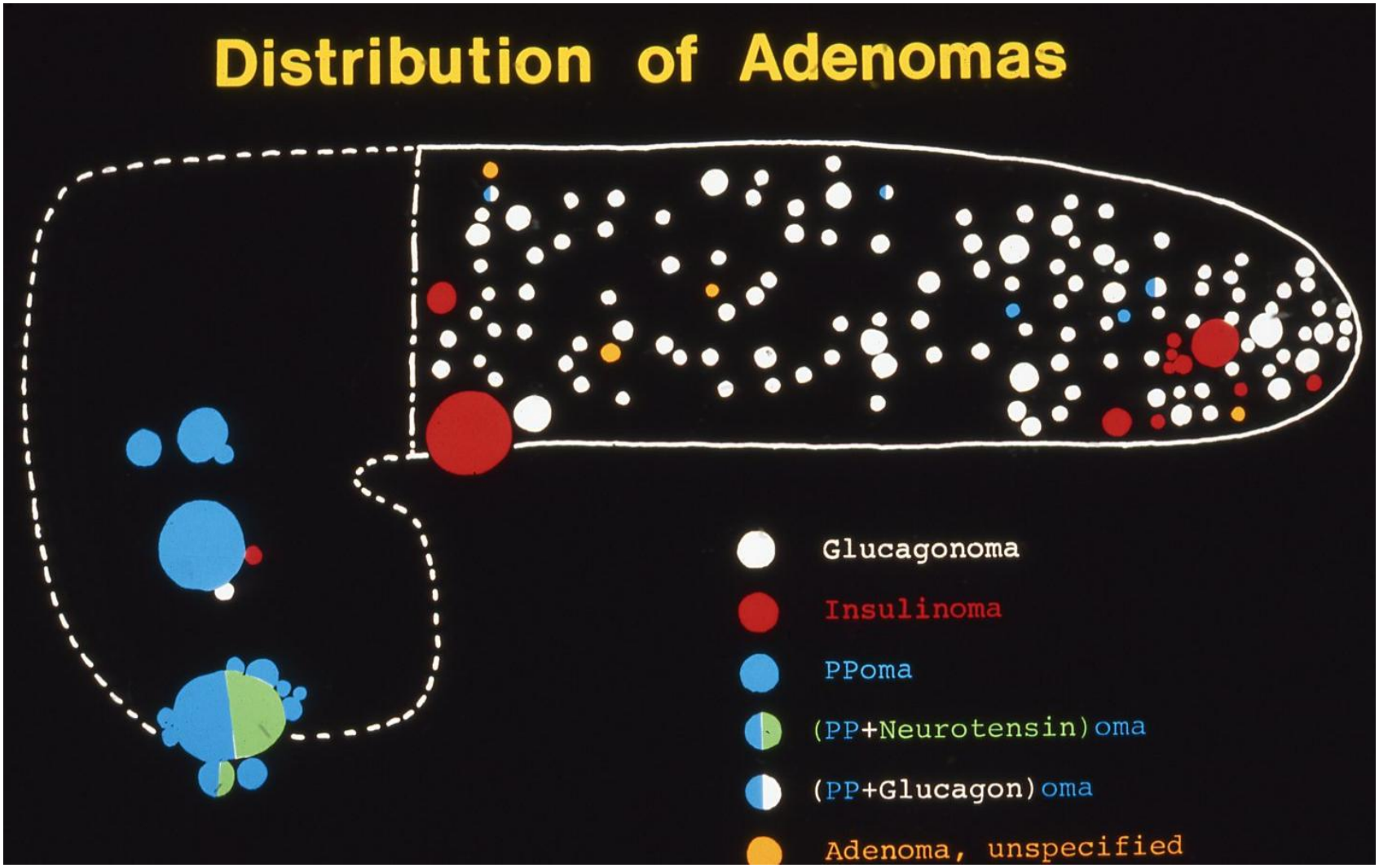
1) Point mutation causes MEN2A or MEN2B
2) Gene rearrangement (translocation) with ret/PTC chimeric genes causes papillary thyroid carcinoma
3) Gene deletion caused Hirschsprung disease (megacolon)

Hereditary neoplasm-4



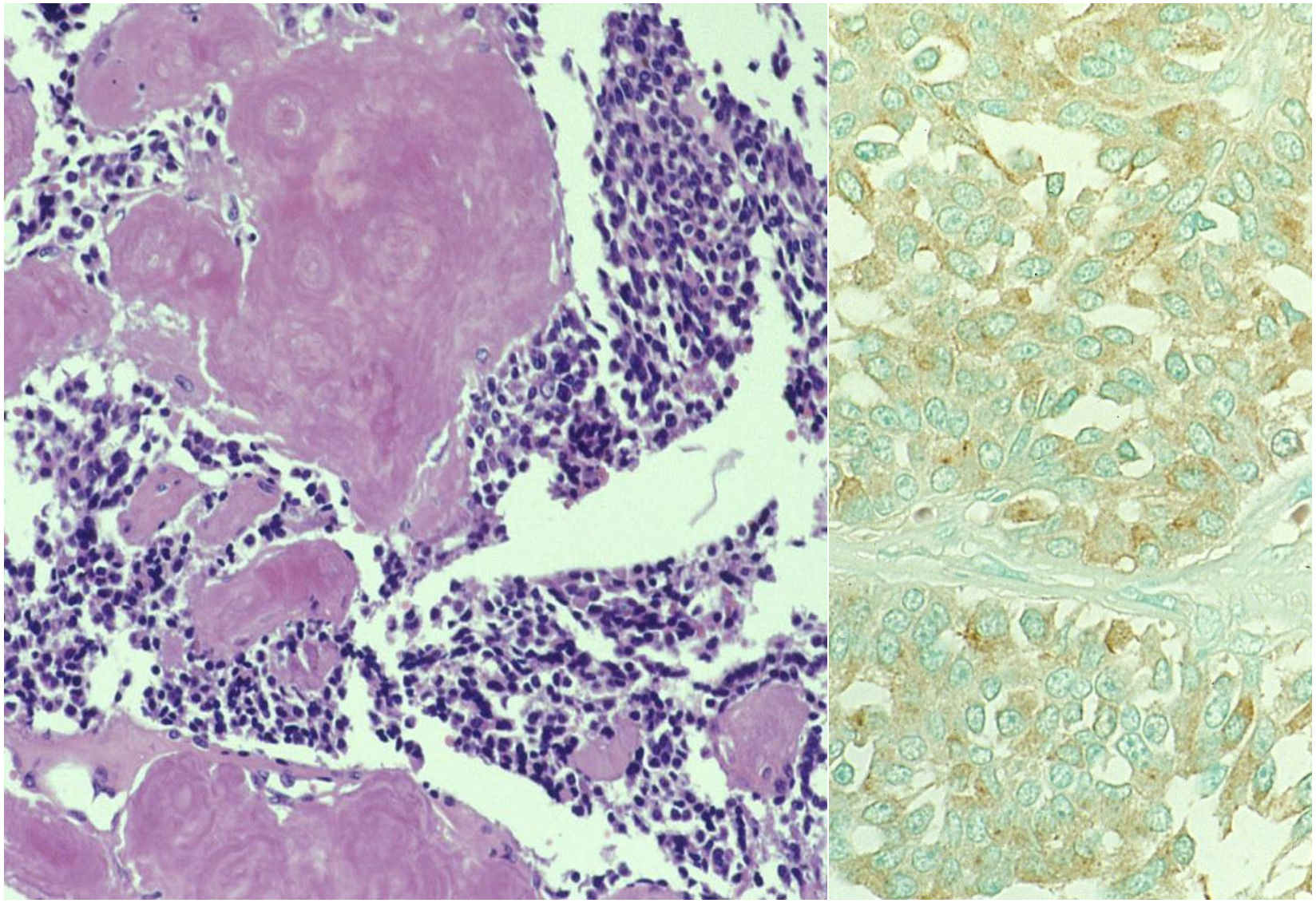
Multiple endocrine neoplasia, type I. A 42-year-old female patient with insulinoma syndrome underwent pancreatectomy. Insulinoma with amyloid deposition in the stroma is seen (left: H&E). Immunostaining for insulin is positive (right).

Hereditary neoplasm-4



Multiple endocrine neoplasia, type I. The 42-year-old female patient manifested insulinoma syndrome. The distribution of multiple benign islet cell tumors (glucagonoma, insulinoma, PPoma, etc) in the resected pancreas is illustrated. In MEN, multiple tumors are identified in the single organs.

Hereditary neoplasm-5



Multiple endocrine neoplasia, type II. A 51-year-old male patient with MEN2 shows multifocal medullary thyroid carcinoma with amyloid stroma (left: H&E). Immunostaining for calcitonin is positive (right).