Q5(e)

Single-gene mutation disorders in man.

UPSC Civil Services Mains 2024 · Anthropology GS 1 · 10 marks · Mendelian genetics in man-family study, single factor, multifactor, lethal, sub-lethal and polygenic inheritance in man.

9.2 Mendelian genetics in man-family study, single factor, multifactor, lethal, sub-lethal and polygenic inheritance in man.

Core demand of the question

- Define single-gene mutation disorders
- Classify them by Mendelian inheritance pattern
- Give accurate human examples and molecular mechanisms
- Add population-anthropological significance and limits of simple Mendelism

Revision summary

Single-gene disorders chiefly arise from a pathogenic variant at one locus.

Autosomal recessive examples include sickle-cell disease, PKU and cystic fibrosis.

Autosomal dominant examples include Huntington disease and achondroplasia.

Haemophilia A and Duchenne muscular dystrophy are X-linked recessive.

Allison linked sickle-cell carrier advantage with malaria.

Penetrance, expressivity, new mutations and environment prevent simplistic genetic determinism.

Introduction

A single-gene disorder arises mainly from a pathogenic variant at one locus and therefore tends to show a recognisable Mendelian pedigree. Its expression can still vary with penetrance, modifier genes, environment and reproductive fitness.

Body

Major inheritance patterns

• **Autosomal recessive:** disease usually appears in homozygotes while heterozygotes are carriers. Sickle-cell disease results from a missense variant in **HBB**; phenylketonuria commonly involves **PAH**; cystic fibrosis involves **CFTR**. Sickle-cell heterozygote advantage in malarial regions, identified by **A. C. Allison**, connects mutation to natural selection.

• **Autosomal dominant:** one altered allele can suffice. Huntington disease is caused by a CAG-repeat expansion in **HTT** and often appears after reproduction; achondroplasia commonly involves **FGFR3** and many cases are new mutations.

• **X-linked recessive:** males are more often affected because they have one X chromosome. Haemophilia A involves **F8**, and Duchenne muscular dystrophy involves **DMD**. Carrier mothers transmit risk; fathers do not pass X-linked traits to sons.

- **X-linked dominant and mitochondrial:** these are single-locus patterns too, though the latter is cytoplasmic. Mitochondrial disorders pass through mothers, not affected fathers.

Founder effect and endogamy can raise particular alleles in small populations, making community-sensitive screening useful in India. Yet "one gene" does not mean one fixed outcome: variable expressivity, incomplete penetrance and allelic heterogeneity complicate counselling. Chromosomal syndromes such as Down syndrome are not single-gene disorders.

Flow diagram

Single-gene mutation -> Autosomal recessive

Single-gene mutation -> Autosomal dominant

Single-gene mutation -> X-linked

Single-gene mutation -> Mitochondrial

Autosomal recessive -> Sickle cell / PKU

Autosomal dominant -> Huntington / achondroplasia

X-linked -> Haemophilia / DMD

Conclusion

Single-gene disorders make Mendelian rules visible in human pedigrees, while sickle cell demonstrates their evolutionary ecology. Diagnosis should combine pedigree and molecular evidence without converting communities into genetic stereotypes.

Facts & figures

Sickle-cell variant

A missense change in beta-globin produces HbS; homozygous disease and heterozygote malaria protection illustrate balanced polymorphism.

A. C. Allison

Established the classic link between sickle-cell trait frequencies and protection against severe falciparum malaria.

Huntington disease

An autosomal-dominant CAG-repeat expansion disorder with anticipation and commonly adult onset.

Haemophilia A

An X-linked recessive factor VIII disorder; an affected father does not transmit it to sons.