PRIMEVIEW

CHROMOSOME INSTABILITY SYNDROMES

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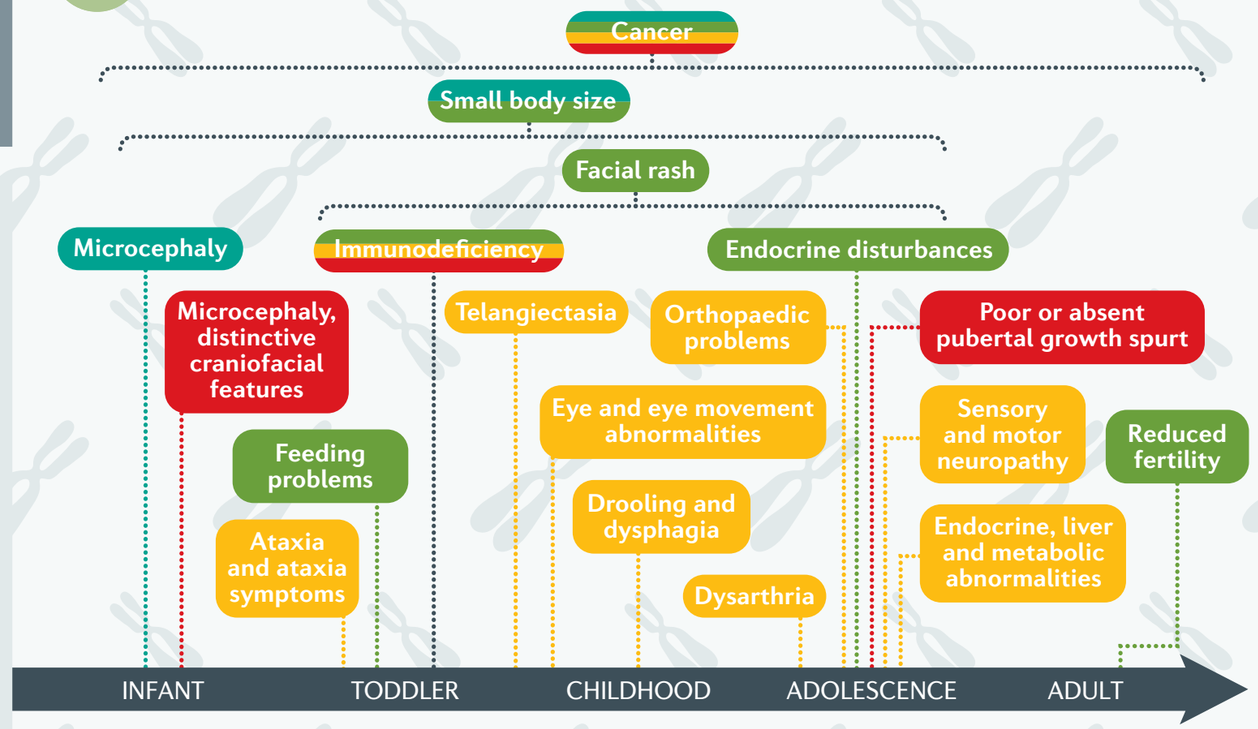
Fanconi anaemia (FA), ataxia telangiectasia (A-T), Nijmegen breakage syndrome (NBS) and Bloom syndrome (BS) are rare, clinically distinct, chromosome instability disorders that predispose to cancer.

MECHANISMS

Each condition has distinct molecular features. In FA, mutations in any of the 22 *FANC* genes affect the repair of DNA interstrand crosslinks. The inability to repair these crosslinks leads to stem cell failure (and, in turn, to developmental abnormalities and bone marrow failure) and genomic instability (leading to cancer). Mutations in *ATM* (in A-T) and *NBN* (in NBS) affect the resolution of DNA double-strand breaks and give rise to progressive cerebellar degeneration (in A-T) or microcephaly (in NBS), but the reasons underlying the different disease-associated neuropathology and how it is related to specific repair deficiencies are not well understood. In BS, mutations in *BLM* affect several aspects of homologous recombination pathways. Increased replication stress seems to lead to decreased cell proliferation rate and increased apoptosis, especially during embryonic and fetal development, contributing to small body size in patients. Closely associated disorders have also been documented. For example, mutations in *TOP3A*, *RMI1* and *RMI2* confer a BS-like phenotype.

QUALITY OF LIFE

The clinical features of all the chromosome instability disorders are quite distinct, often enabling a highly probable diagnosis based on clinical signs, symptoms and confirmed by routine laboratory testing



FANCONI ANAEMIA

The FA phenotype varies from severe (organ dysfunction and bone marrow failure) to a nearly normal life until the fourth decade

ATAXIA TELANGIECTASIA

Children with A-T experience impaired fine and gross motor coordination, delay in speech initiation and ocular problems that hamper reading and school life

NIJMEGEN BREAKAGE SYNDROME

Most children with NBS have striking psychomotor hyperactivity, and mild or moderate learning difficulties may be apparent as they grow

BLOOM SYNDROME

Day-to-day life of those with BS might not differ much from anyone else's except for accommodations needed for the sensitivity and small size

EPIDEMIOLOGY

As these syndromes are rare, and as management strategies improve, precise prevalence is difficult to ascertain. Mutations causing FA have been identified with an estimated average carrier frequency of 1 in 180 globally; of these mutations, >80% occur in *FANCA*, *FANCG* and *FANCC*. The estimated prevalence of A-T in the UK, Germany, France and Italy is ~3 per million population. A founder mutation in *NBN* has been identified with high prevalence in the Czech Republic (1 in 154), Ukraine (1 in 182) and Poland (1 in 190). BS is a particularly rare disorder, with <300 reported cases worldwide.

MANAGEMENT

A cancer diagnosis can be made at any age in those with FA, A-T or NBS and most frequently in early adulthood in those with BS. For example, although the risk of developing leukaemia can be reduced with haemopoietic stem cell transplantation in those with FA, the risk of squamous cell carcinoma in the aero-digestive and ano-genital regions increases with age. Typically, patients with FA with these cancers are difficult to treat because the disease can be multifocal and chemotherapies that crosslink DNA are very toxic for these patients. Accordingly, regular detailed inspection of the head and neck and ano-genital region and upper gastrointestinal endoscopy is important in patients with FA.

OUTLOOK

Owing to their rarity, there is much to learn and optimize in chromosome instability syndromes. For example, small animal models of A-T have not recapitulated the human neurological phenotype; a larger and longer lived A-T model is currently being studied and might provide some insight. Additionally, patients with A-T also have relevant respiratory conditions that require protocols for preventing decline in lung function. Furthermore, greater knowledge of the immunodeficiency in those with NBS is needed to understand the predisposition to lymphoma.

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