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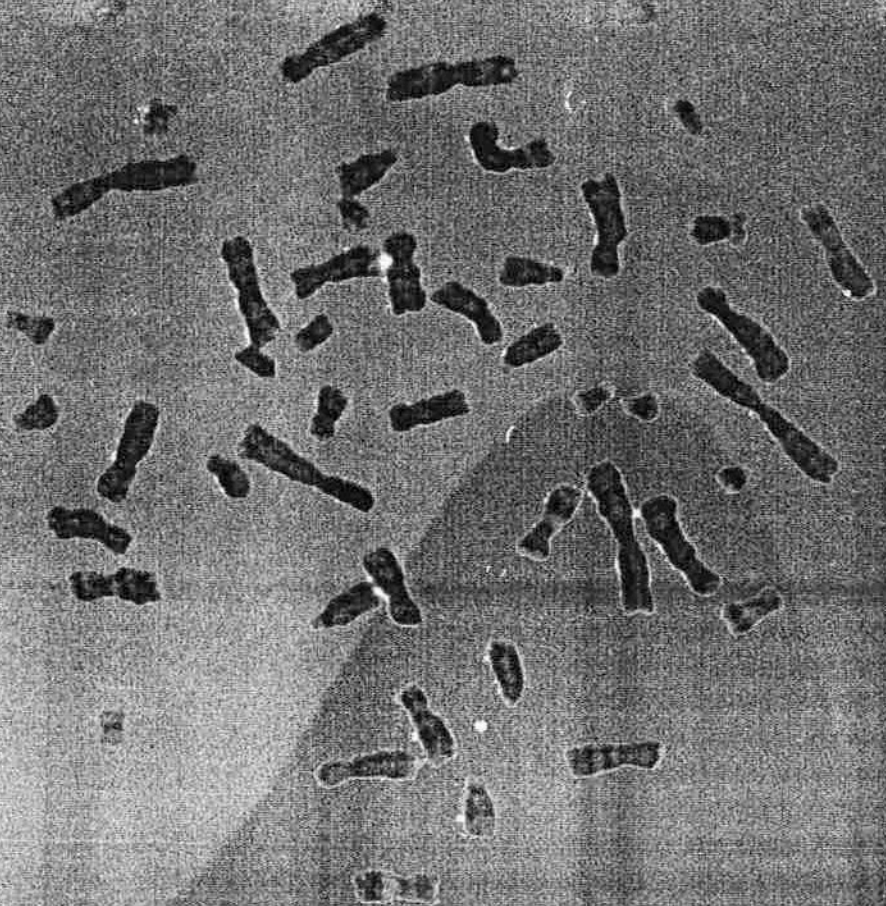
Laboratory Manual
and
Hand Book on
Recent Trends in Cytogenetics



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The Genetics Basis of Dilated Cardiomyopathy

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Purpose of review: - More than 40 different individual genes have been implicated in the inheritance of dilated cardiomyopathy. For a subset of these genes, mutations can lead to a spectrum of cardiomyopathy that extends to hypertrophic cardiomyopathy and left ventricular noncompaction. In nearly all cases, there is an increased risk of arrhythmias. With some genetic mutations, extracardiac manifestations are likely to be present. The precise genetic cause can usually not be discerned from the cardiac and/or extracardiac manifestations and requires molecular genetics diagnosis for prognostic determination and cardiac care.

Introduction: - Dilated cardiomyopathy (DCM) is characterized by left ventricular dilatation and impaired systolic function and is a leading cause of heart failure. DCM is considered idiopathic if no other discernable cause such as ischemia, valvular disease or hypertension is present. However, a multifactorial cause, such as hypertension in addition to a genetic defect, may lead to more severe disease with earlier onset. Idiopathic DCM is considered familial when more than one first-degree relative has been diagnosed with DCM or had a sudden cardiac death (SCD) at a young age. DCM is inherited in 20–50% of cases and abnormalities are frequently seen on echocardiogram in asymptomatic relatives. Inheritance for idiopathic DCM is primarily autosomal dominant, though other modes of inheritance occur. DCM can also occur secondarily in conjunction with systemic disease or syndromes. Determining the precise gene responsible for familial DCM impacts medical management and allows early identification of those at risk.

Till date, studies in this field have implicated defects in the transmission of contractile force as one mechanism for ventricular dilatation and dysfunction. To understand the pathology of DCM, we used genetic approaches to identify other inherited gene mutations that cause this disease.

The underlying causes of DCM are heterogeneous (1, 2), including myocarditis, drug toxicity (adriamycin), and ischemia-induced, metabolic, mitochondrial, and genetic abnormalities. A genetic cause of DCM is identified in approximately 30% of cases (3–4), with autosomal dominant inheritance being the most common (2). X linked, autosomal recessive, and mitochondrial inheritance have also been reported, albeit less frequently (5). In the past several years, the genetic basis of DCM has been sought, resulting in the identification of multiple genetic loci and five genes causing DCM to date. For X linked DCM, two genes have been identified, including *tafazzin* in cases of the infantile-onset DCM (Barthsyndrome) (6, 7) and isolated left ventricular noncompaction, and *dystrophin* in later-onset X linked Cardiomyopathy (XLCM) . In the more common autosomal dominant DCM, five loci have been mapped for pure DCM (1q32 [ref. 8], 2q31 [ref. 9], 9q13-q22 [ref. 10], 10q21-q23 [ref. 11], and 15q14 [ref.12]), and four loci have been mapped in families with DCM and associated with conduction disease (1p1-1q21 [ref. 13], 2q14-q22 [ref. 14], 2q35 [ref. 15], 3p25 p22 [ref. 16], and 6q23 [ref. 17]). Thus far, only the gene on chromosome 15q14 encoding *cardiac actin*, the gene on chromosome 2q35 encoding *desmin*, and the gene on chromosome 1p1-1q21 encoding *lamin A/C* have been identified and mutations characterized.

According to one study done by A Luk et al in the year 2008 Thirty per cent of patients with DCM either have a relative with the disease or show clinical evidence of left ventricular dysfunction or visible enlargement on two-dimensional echocardiography (18). Modes of inheritance include autosomal dominant (AD) with incomplete penetrance due to modifier genes and environmental factors, autosomal recessive (AR), and X-linked (19). Other genetic loci have been identified, but the specific genes are not yet known.