**Critical Micellar Concentration**

**Definition**
Critical micellar concentration characterizes a concentration at which detergent molecules assemble spontaneously into micelles to bury the hydrophobic moiety in a hydrophobic core.

▶Two-dimensional Crystallization of Membrane Proteins

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**Crk**

**Definition**
Crk stands for Chicken retroviral kinase. It is the protein product of the **crk** gene from chicken retroviruses CT10 and ASV–1. The cellular homologues, the Crk adapters, mediate different cytoplasmic signals.

▶Signal Transduction: Integrin-Mediated Pathways
▶Tyrosine Kinases

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**cRNA**

**Definition**
cRNA stands for complementary RNA. It is an RNA that is synthesized from a cDNA template by *in vitro* transcription.

▶DNA Microarrays/DNA Arrays

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**Crohn Disease**

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**Synonyms**
Crohn disease is a heterogeneous syndrome that belongs to the group of inflammatory bowel disease 1 (OMIM 266600; IBD 1). Crohn disease can be differentiated from ulcerative colitis (OMIM 191390) by clinical, endoscopic, radiological and histopathological parameters.

**Definition**
Typical presentation of Crohn disease includes inflammation in the terminal ileum. However, this typical presentation with ileitis is seen only in 70% of cases. 25% of patients present with disease confined only to the colon (Crohn colitis) and in 5% exclusive involvement of the upper gastrointestinal tract is seen. The diagnosis is mostly based on a suggestive clinical course, a typical distribution of affected areas throughout the gastrointestinal tract ("skip lesions") and a typical type of endoscopic lesions (Fig. 1). Histological characteristics (i.e. granuloma formation) are only seen in a minority of the patients.

**Characteristics**
Crohn disease was first described as a clinical entity in 1920. It is a chronic relapsing complex disease, that can present with diarrhoea, right lower quadrant pain, weight loss, malaise, fever and a host of extraintestinal manifestations in joints (arthralgia, arthritis), skin (pyoderma gangrenosum), vessels (erythema nodosum), liver (autoimmune hepatitis, rarely primary sclerosing cholangitis), eyes (uveitis, episcleritis), pancreas (hyperamylasemia and pancreatitis), lung (pneumonitis) and heart (rarely myocarditis). Complications include the development of intestinal strictures, fistula, osteoporosis and an increased risk for colonic cancer. Since the second World War a growing incidence of cases was observed in Western civilisations but is now also observed in Asian countries.
including Japan, Korea and China. “Hot spots” of incidence and prevalence have been described in Western Canada and Iceland. Lifetime prevalence in Northern countries has been estimated at up to 0.5%. Typical age of onset peaks in the 2nd and 3rd decades of life, but the disease can also manifest in young children or in the elderly. Genetic anticipation has been proposed in Crohn disease. However, large epidemiologic studies suggest that the increase in incidence since World War II due to an accumulation of confounders has been confused with genetic anticipation.

Epidemiological studies have identified a significant genetic contribution to the aetiology of inflammatory bowel disease. Familial clustering is seen, with estimates of sibling relative risk ($\lambda_s$) ranging from 15 to 35 for Crohn disease and 5 to 17 for ulcerative colitis. Simple Mendelian models of inheritance are not supported by segregation analyses of inflammatory bowel disease. Concordance of Crohn disease in identical twins is seen in up to 56% in comparison with 4% in dizygotic twins. Therefore, disease concordance data in monozygotic and dizygotic twins suggest that both genetic and environmental factors are involved. Disease characteristics (subphenotypes) cluster in families and show concordance in identical twins, too. These observations support a complex immunogenetic model for inflammatory bowel disease, whereby genetically susceptible individuals harbour an aberrant response to yet unidentified environmental influences that most likely are included in the life-style of industrialized societies.

**Cellular and Molecular Regulation**

Attempts to localise susceptibility genes for inflammatory bowel disease through genome-wide linkage studies have identified putative loci on many human chromosomes with eight of them having been listed in OMIM thus far (chromosomes 16p, 16q, 12, 6p, 14q11/12, 5q31, 19p13, 1q36 – Table 1); the original finding of the linkage on chromosome 16 has been replicated in several independent populations and by the IBD International Genetics Consortium. Recently three groups showed that sequence variations within the CARD15 (NOD2) gene (OMIM 605956) on chromosome 16q12, were strongly associated with susceptibility to Crohn disease but not to ulcerative colitis. P268S, R702W and 3020insC (Fig. 2) were found as the main disease associated variations with an ODDS ratio for the development of CD ranging between 2.4 (homozygotes) and 40 (compound heterozygotes and homozygotes). The three main variations (P268S, R702W, 3020insC) result in amino acid exchanges or in a truncation, respectively, of leucine rich repeats at the C-terminal part of the CARD15 protein. A series of additional “private” mutations has been found in patients with Crohn disease in this part of the gene. Taken together it appears that variants in the CARD15 gene alone could explain the risk for development of Crohn disease in up to 15% of cases (compound heterozygotes and homozygotes) and may contribute to another 15% in concert with other disease genes (homozygotes).

CARD15 is a member of a family of genes (Apaf-1, Ced-4, CARD-4/NOD1) implicated in activation of NFκB, pro-inflammatory cytokine induction and apoptosis. They represent regulatory proteins with a central nucleotide-binding oligomerization domain (NOD) and N-terminal caspase recruitment domains (CARD) that are involved in programmed cell death and immune responses. A high degree of homology is apparent to a group of disease resistance (R) genes in plants that encode cytosolic and membrane-bound proteins mediating recognition of pathogens. Membrane-bound R proteins are homologous to

**Table 1 Susceptibility loci for Crohn disease**

<table>
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<td></td>
<td>1p36</td>
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<td>Chop PNAS 1998, Cho Hum Mol Gen 2000</td>
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toll-like receptors (TLRs) because they contain leucine-rich repeats (LRR) and recognize pathogenic components at the cell surface. 

CARD15 is expressed in monocytes, B-cells and activated epithelial cells. It encodes the protein NOD2 that demonstrates a strictly intracellular distribution. Expression of CARD15 mRNA and protein is regulated synergistically by TNF and interferon-γ. Preliminary functional evidence for CARD15 as a susceptibility gene for Crohn disease was suggested by its ability to activate NFκB following exposure to bacterial lipopolysaccharides (probably more specifically muramyl dipeptide). Most importantly, activation of NFκB was impaired in cells transfected with CARD15 constructs carrying the disease-associated variations. It is therefore currently assumed that CARD15 variations may impair intestinal barrier function and lead to a defect in epithelial defence against the commensal flora. In support of the hypothesis, an increased presence of intracellular E. coli has been described earlier in colonic epithelial cells of patients with Crohn disease. A more detailed molecular definition of the role of CARD15 in mucosal barrier function remains to be established.

The disease susceptibility locus on chromosome 5q31 could be resolved to a disease-associated haplotype called “IBD5”. An interaction between CARD15 and IBD5 in the risk for Crohn disease has been suggested. An independent association between ulcerative colitis and IBD5 was described recently in a large series of patients. However, identification of putatively causative variants in a disease gene is still pending in this (IBD5) and other chromosomal regions. Hierarchical mapping using the TDT in European CD patients identified a disease-associated haplotype block in the suggestive linkage region on chromosome 10q. This block contained exactly one gene, DLG5, which led to the conclusion that it represented a susceptibility gene for inflammatory bowel disease. This association has recently been replicated in Japanese CD patients albeit with different susceptibility alleles from those in European populations. Further replication in populations of European descent will be necessary. In contrast to the strong genetic effect of NOD2, where the associated variant confers a relative risk greater than 40 for homozygotes and compound heterozygotes, the risk of DLG5 appears to be much smaller, with observed odds ratios of approximately 1.5. DLG5 that codes for a protein involved in cell-cell contacts, is a disease gene that could be easily integrated into a hypothetical mechanism of a defect in barrier integrity as a main cause for Crohn disease. The haplotype structure of 5q31 has rendered the identification of the respective disease gene more problematic than on 10q and 16q. A strong linkage signal on 5q31 led to the identification of a large haplotype block that could not be resolved further by means of genetic epidemiological methods. Instead, Peltekova and colleagues used (7) a combination of functional and genetic evidence to implicate variants...
around the SLC22A4 and SLC22A5 genes in the etiology of Crohn disease. Although the identification of the disease-associated variants in these genes has evoked clear functional consequences, the exact mechanism by which alteration of the encoded transporter proteins OCTN1/2 contribute to disease is still unknown.

**Clinical Relevance**

Disease-associated variants in the CARD15 gene are associated with development of a particular subphenotype of Crohn disease. In particular, homozygosity or compound heterozygosity of 3020insC is associated with the “typical” presentation of the disease with ileal inflammation. It also appears that Crohn disease manifests at a younger age in patients presenting with a combination of CARD15 variants and the IBD5 haplotype.

The example of CARD15 also shows the heterogeneity of population from different ethnicities but also within the European white population. It underlines the importance of population representative assessment (i.e. through biobanks). The haplotypes and causative variants that are strongly associated with Crohn disease in white populations of European descent are completely absent in Asian populations and almost absent in African Americans. Even within Europe a great variation is seen as to the population frequencies and to the relative risk for carriers. Any future concept for a medical use must therefore take the specific population background into account.

Crohn disease is a chronic relapsing disorder. On average 40% of patients in remission relapse during 12 month of follow up. In some cases primary chronic active disease is developed despite adequate therapy. Short-term therapy with glucocorticoids is a hallmark of anti-inflammatory management of acute disease. However, it leads in 30% of cases to glucocorticoid-refractory or -dependent chronic active disease with additional complications through the long-term use of glucocorticoids. To date only azathioprine, methotrexate and infliximab (i.e. a monoclonal antibody directed against \(\text{TNF-alpha}\)) are effective for remission maintenance.

Outlet of a therapy with infliximab has raised particularly interest in pharmacogenetic explorations. The targeted intervention (infusion of a monoclonal antibody which is directed against TNF) induces remission in approximately 40% of patients with active Crohn disease, while improvement is seen in another 20% and no response in the remainder. The availability of several large trials that were conducted for approval of the drug in the EU and in the USA facilitated a pharmacogenetic investigation with a design characterized by a high statistical power. Unfortunately neither variants in the TNF/TNF-receptor system nor variants of the CARD15 gene were associated with therapeutic outcome to anti-TNF therapy with infliximab.

**References**


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**Cross-Bridge**

**Definition**

The term cross-bridge is used to characterize the pear-shaped motor domain of myosin projecting in regular spacings from the thick filament. These domains interact with the actin of the thin filaments during muscle contraction.

**Muscle Contraction**

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**Cross-Fostering Studies**

**Definition**

Cross-fostering studies compare the risk of the disorder in adoptees who have affected biological parents but
unaffected adopting parents, and in adoptees with unaffected biological parents but affected adopting parents.

**Schizophrenia Genetics**

**Crossing-Over**

**Definition**
Crossing-over refers to a reciprocal exchange (recombination) between non-sister chromatids of a pair of homologous chromosomes and involves breakage and reunion of chromatids.

**Chromosomal Instability Syndromes**

**Genetic Epidemiology**

**Meiosis and Meiotic Recombination**

**Cross-Linking Patterns**

**Definition**
Cross-linking patterns denote the pattern of proteins that are observed on a polyacrylamide gel after treatment with a cross-linking reagent.

**Protein Interaction Analysis: Chemical Cross-Linking**

**Cross-Linking Reagents**

**Definition**
Cross-linking reagents are chemical compounds that are used to covalently couple two or more molecules.

**Protein Interaction Analysis: Chemical Cross-Linking**

**Cross-Talk**

**Definition**
Cross-talk refers to the functional interaction between individual signal transduction pathways or cascades which may affect signalling positively or negatively.

**Ras Signalling**

**Crossvalidation**

**Definition**
Crossvalidation is a method for the evaluation of classification techniques: the study data are split into several subsets; each is used in turn as a test set for a classifier trained on the other data sets.

**Computational Diagnostics**

**CRP**

**C-Reactive Protein**

**Cryo Electron Crystallography**

**Definition**
Cryo electron crystallography uses electrons for diffraction. Since electrons are diffracted much stronger than X-rays, very tiny crystals can be studied. Accordingly, cryo electron crystallography has been applied to extremely thin, so-called two-dimensional crystals, composed of membrane-bound proteins. However, the experimental requirements for this method are more demanding than for usual protein crystallography, and only limited resolution of the structures can be obtained.

**Structure-Based Drug Design**

**Cryo-Electron Microscopy: Single-Particle Reconstruction**

**Definition**
Cryo-electron microscopy (cryo-EM) in combination with single-particle reconstruction refers to the combined application of two methods used for...