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Opinion Article

Consequences of Human Genome Mutation

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DESCRIPTION

Chronic Granulomatous Disease (CGD) is an inherited innate immune system disorder marked by the impaired intracellular microbicidal activity of phagocytes. Mutations in one of four known nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components prevent the production of superoxide and other antimicrobial oxidants, resulting in the CGD phenotype. X-linked CGD is caused by mutations in the gp91-phox gene, which is encoded by the CYBB gene and is thought to account for approximately 65% of all CGD cases.CYBA, which encodes p22-phox, NCF2, which encodes p67-phox, NCF1, encodes p47-phox, and NCF4 and encodes p40-phox are the autosomal genes in CGD. These mutations inhibit oxidase activity and cause autosomal recessive chronic granulomatous disease (AR-CGD), which accounts for approximately 35% of all CGD cases. Specific mutations identified in CCD patients may help to explain some of the clinical severity variability seen in this disorder and demonstrate a genotype-phenotype correlation. X-CGD patients, on average, have a more severe clinical course than AR-CGD patients and show symptoms in their first years of life. AR-CGD patients, particularly those with p47-phox deficiency, have a milder clinical course and are most commonly seen in their first and second decades of life. Patients with AR-CGD who have missense mutations typically have a mild clinical course associated with residual p47-phox activity as well as p22 and p67-photos. However, the level of superoxide generation does not always correlate with the clinical course. Despite neutrophils with 10-20% normal oxidase activity, some patients have severe and recurring infections in our study of 40 AR-CGD families we were unable to establish a direct link between the molecular defect and the clinical course of the disease. Truncations nonsense and frame shift mutations or missense mutations could have influenced the phenotype significantly. CYBA is a gene cytochrome b alfa chain Cytochrome is made up of two chains, one light, and one heavy. The light, alpha subunit encoded by this gene has been proposed as a key component of the phagocyte's microbicidal oxidase system. AR-CGD is linked to mutations in this gene, which causes activated phagocytes to fail to generate superoxide, which is required for these cells' microbicidal activity. In about 5% of CGD patients, mutations in the cytochrome B alpha chain (CYBA) gene cause the disease.

The CYBA gene, which encodes p22-phox, is found on chromosome 16q24 and contains six exons as well as trans-membrane and proline-rich domains the CYBA gene, which encodes p22-phox, has more missense mutations than any other NADPH oxidase subunit gene, with 19 different missense mutations in 65 mutated alleles. P22-phox is important in the interaction of NADPH-oxidase subunits as well as any amino acid differences added to the pattern. The globular conformation of this phox protein may change due to differences in the electrophoretic properties of new amino acids, preventing complex formation with other subunits. Missense mutations in 19 different CYBA alleles in different NCFI alleles, 17 different NCR alleles, and one NCR allele cause changes in amino add patterns of NADPH oxidase subunits, resulting in AR-CGD. Missense mutations account for 11% of the total number of AR-CGD mutations. 70G>A in the CYBA gene is one of the most common missense mutations in AR-CO, causing p.GIy24Arg in p22-phox in 14 alleles from 9 families the first interaction between p22-phox and p67-phox occurs in the B domain of p22-phox, which is located between 81 and 91 amino acids. Four different missense mutations change the amino acid add (arginine) at position 90 (in 21 CYBA alleles). Any conformational changes that may prevent interaction with p67-phox are extremely dangerous in this position. The stability and function of p22-phox may be lost as a result of the change in the molecular structure of this part, and latent NADPH oxidase cannot be activated, resulting in AR-CGD. The missense mutations in P22-phox are the most diverse of any NADPH oxidase component. In the chain, the ratio of different missense mutations to amino additions is approximately 19/195 (%9.74). The different missense mutation to overall amino adds chain length in p67-phox is 17/526 (%3.23). In p47-phox, however, the ratio is 4/390 (%). This finding indicates that p67-phox has a threefold higher incidence of different missense mutations than p47-phox, and p22-phox has a tenfold higher incidence of different missense mutations than p47-phox. This finding indicates that in its primary amino acid structure, p67-phox has three times the frequency of different missense mutations as p47-phox, while p22-phox has approximately ten times the frequency. The underlying cause could be the highly specific interactionand function of p22-phlox, which is to change in protein globular structure.

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