Journal Scan

De novo mutations in histone modifying genes in congenital heart disease

Congenital heart disease (CHD) is the most frequent birth defect, affecting 0.8% of live births. Many cases occur sporadically and impair reproductive fitness, suggesting a role for de novo mutations. By analysis of exome sequencing of parent-offspring trios, we compared the incidence of de novo mutations in 362 severe CHD cases and 264 controls. CHD cases showed a significant excess of protein-altering de novo mutations in genes expressed in the developing heart, with an odds ratio of 7.5 for damaging mutations. Similar odds ratios were seen across major classes of severe CHD. We found a marked excess of de novo mutations in genes involved in production, removal or reading of H3K4 methylation (H3K4me), or ubiquitination of H2BK120, which is required for H3K4 methylation. There were also two de novo mutations in SMAD2; SMAD2 signaling in the embryonic left-right organizer induces demethylation of H3K27me. H3K4me and H3K27me mark 'poised' promoters and enhancers that regulate expression of key developmental genes. These findings implicate de novo point mutations in several hundred genes that collectively contribute to ~10% of severe CHD.

Comment

De novo mutation means an alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself. Earlier researchers reported that MLL2, KDM6A, CHD7 genes involved in H3K4me pathway (production, removal or reading of methylation of histone H3, lysine 4) were associated in severe CHD. In this article, authors analysed exome sequence of parent-offspring trios and compared *de novo* mutations and predicted *de novo* mutations in genes involved in production of H3K4me. This study did not resolve the pathogenesis of most CHD cases. Rare and de novo copy number variants appear to account for a small fraction; rare or common transmitted variants are also expected to make significant contributions. Evidence of dosage sensitivity of many chromatin-modification genes raises the possibility that environmental perturbations of these pathways in critical developmental windows might phenocopy the effects of these mutations.

Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, Romano-Adesman A, Bjornson RD, Breitbart RE, Brown KK, Carriero NJ, Cheung YH, Deanfield J, DePalma S, Fakhro KA, Glessner J, Hakonarson H, Italia MJ, Kaltman JR, Kaski J, Kim R, Kline JK, Lee T, Leipzig J, Lopez A, Mane SM, Mitchell LE, Newburger JW, Parfenov M, Pe'er I, Porter G, Roberts AE, Sachidanandam R, Sanders SJ, Seiden HS, State MW, Subramanian S, Tikhonova IR, Wang W, Warburton D, White PS, Williams IA, Zhao H, Seidman JG, Brueckner M, Chung WK, Gelb BD, Goldmuntz E, Seidman CE, Lifton RP. De novo mutations in histone-modifying genes in congenital heart disease. Nature 2013 Jun 13;498(7453):220-3.

Emergence of Zaire Ebola virus disease in guinea — preliminary report

In March 2014, the World Health Organization was notified of an outbreak of a communicable disease characterized by fever, severe diarrhea, vomiting, and a high fatality rate in Guinea. Virologic investigation identified *Zaire ebolavirus* (EBOV) as the causative agent. Full-length genome

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http://svimstpt.ap.nic.in/jcsr/oct-dec14_files/js414.pdf

sequencing and phylogenetic analysis showed that EBOV from Guinea forms a separate clade in relationship to the known EBOV strains from the Democratic Republic of Congo and Gabon. Epidemiologic investigation linked the laboratory-confirmed cases with the presumed first fatality of the outbreak in December 2013. This study demonstrates the emergence of a new EBOV strain in Guinea.

Comment

Ebola virus was first identified in 1976 and the spread was in East and central Africa. The current outbreak of viral hemorrhagic fever is a tragic illustration in Africa. Recently the article entitled "Genomes reveal start of Ebola outbreak" was published in Science. In which fifty scientists were collaborators from four countries to develop diagnostic kit and vaccine candidate to Ebola virus. Five of the authors contracted Ebola virus disease themselves and died before the paper was published. Salutations from the scientific community to these dedicated, committed and devoted scientists. Jesse L. Goodman, have collected EBOV samples from 3 patients and complete sequencing was done followed by phylogenetic analysis of full length sequence. A few (6) polymorphisms were observed and among which three were synonymous. The phylogenetic analysis also revealed the emergence of new EBOV strain. The emergence of the virus in guinea highlights the risk of EBOV out breaks in the whole West African sub region.

Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, Soropogui B, Sow MS, Keïta S, De Clerck H, Tiffany A, Dominguez G, Loua M, Traoré A, Kolié M, Malano ER, Heleze E, Bocquin A, Mély S, Raoul H, Caro V, Cadar D, Gabriel M, Pahlmann M, Tappe D, Schmidt-Chanasit J, Impouma B, Diallo AK, Formenty P, Van Herp M, Günther S. Emergence of Zaire Ebola Virus Disease in Guinea - Preliminary Report. N Engl J Med 2014 Apr 16.

Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome

Abdominal infections are frequent causes of sepsis and septic shock in the intensive care unit (ICU) and are associated with adverse outcomes. The authors analyzed the characteristics, treatments and outcome of ICU patients with abdominal infections using data extracted from a one-day point prevalence study, the Extended Prevalence of Infection in the ICU (EPIC) II.

EPIC II included 13,796 adult patients from 1,265 ICUs in 75 countries. Infection was defined using the International Sepsis Forum criteria. Microbiological analyses were performed locally. Participating ICUs provided patient follow-up until hospital discharge or for 60 days. Of the 7,087 infected patients, 1,392 (19.6%) had an abdominal infection on the study day (60% male, mean age 62 ± 16 years, SAPS II score 39 ± 16, SOFA score 7.6 ± 4.6). Microbiological cultures were positive in 931 (67%) patients, most commonly Gram-negative bacteria (48.0%). Antibiotics were administered to 1366 (98.1%) patients. Patients who had been in the ICU for ≤ 2 days prior to the study day had more Escherichia coli, methicillin-sensitive Staphylococcus aureus and anaerobic isolates, and fewer enterococci than patients who had been in the ICU longer. ICU and hospital mortality rates were 29.4% and 36.3%, respectively. ICU mortality was higher in patients with abdominal infections than in those with other infections (29.4% vs. 24.4%, $p < 0.001$). In multivariable analysis, hematological malignancy, mechanical ventilation, cirrhosis, need for renal replacement therapy and SAPS II score were independently associated with increased mortality. The characteristics, microbiology and antibiotic treatment of abdominal infections in critically ill patients are diverse. Mortality in patients with isolated abdominal infections was higher than in those who had other infections.

Comment

This study is one of the first to look at abdominal infections in critically ill patients from a global prospective. Infections in the intensive care unit (ICU) are one of the major challenging tasks. Severe intra-abdominal infections are accompanied by septic shock and acute kidney injury. Diagnosis is crucial in the treatment of infectious diseases. So, Guidelines and recommendations were released by the infectious diseases society of America (IDSA) and the American society for Microbiology (ASM) to utilize the Microbiology laboratory for effective diagnosis of infectious diseases in the year 2013. The authors performed microbiological analysis and antibiotic treatment to 13,796 selected adult patients from 1,265 ICUs from 75 countries. They found that Gram negative bacteria were more prevalent than Gram positive bacteria and mortality rate was more for the patients with abdominal infections than other infections. Disease severity, need for organ support and presence of comorbidities were independently associated with mortality in this cohort.

De Waele J, Lipman J, Sakr Y, Marshall JC, Vanhems P, Barrera Groba C, Leone M, Vincent JL; EPIC II Investigators. Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. BMC Infect Dis 2014 Jul 29;14:420.

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