PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Cholera takes a nasty turn

ArticleInfo		
ArticleID	:	4340
ArticleDOI	:	10.1186/gb-2002-3-5-reports0028
ArticleCitationID	:	reports0028
ArticleSequenceNumber	:	22
ArticleCategory	:	Paper report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2002–3–6 Received : 2002–3–6 OnlineDate : 2002–5–2
ArticleCopyright	:	BioMed Central Ltd2002
ArticleGrants	:	

ArticleContext	:	130593355

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Abstract

Genes encoding key factors that transform endemic *Vibrio cholerae* strains into pandemic ones have been identified

Significance and context

Throughout history, the pathogenic bacterium *Vibrio cholerae*, which causes severe diarrhea in humans, has been responsible for a number of cholera pandemics. Six were reported between 1817 and 1923, and were caused by strains of *V. cholerae* O1 serogroup. From 1961 onwards, strains of the biotype El Tor, which until then had only caused sporadic endemic outbreaks, were responsible for the seventh pandemic. The entire genome sequence of the *V. cholerae* El Tor O1 strain N16961 has been published recently and, as in this microarray-based study by Dziejman *et al*., is being used to study genes responsible for transforming *V. cholerae* strains that cause endemic disease into strains that cause pandemics.

Key results

A microarray was constructed containing gene-length PCR products made from the genomic sequence of *V. cholerae* El Tor O1 N16961, one of the strains responsible for the seventh cholera pandemic. Out of a total of approximately 3,890 open reading frames (ORFs), 3,632 were amplified and spotted on the microarray. Using this microarray, together with PCR and Southern hybridizations, it was shown that a pre-pandemic El Tor O1 strain isolated from Indonesia, a classical O1 strain isolated from India, and a seventh-pandemic strain isolated from Peru, lacked 49, 46, and 1 gene(s), respectively, compared with strain N16961. The missing genes were divided into four groups. Group I contained seven genes that were present in all El Tor strains but not in classical strains. Two of these genes encode proteins similar to acetyltransferases; two others were located in the region encoding the RTX toxin. Classical strains lack the *rtxC* gene, which encodes an acylation enzyme involved in activation of the RTX toxin. Another gene in the same neighborhood (encoding an unknown protein) was also absent from the classical strains. Group II contained genes that are present only in pandemic strains. Apart from genes encoding unknown proteins, this group includes the CTX bacteriophage genome involved in the production of the cholera toxin, and a gene encoding a DNA-repair protein. Group III comprises genes that are only present in the seventh-pandemic El Tor O1 strains. To this group belongs "*Vibrio* seventh-

pandemic island-I", a region with significantly lower G+C content than the overall content of the genome that was probably introduced by horizontal gene transfer. One gene in this island encodes a protein similar to deaminases that are involved in nucleotide scavenging or DNA uptake during competence. Another encodes a protein similar to phospholipases. Another region specific to seventh-pandemic strains contains eight genes with a low G+C content and was therefore named "*Vibrio* seventh-pandemic island-II". One gene in this region encodes a protein similar to a transcriptional regulator. Group IV contains genes uniquely absent from individual strains. One strain is missing two large regions, including genes that encode proteins required for the synthesis of the O-antigen capsule and the O139 lipopolysaccharide antigen, and genes encoding *N*-acetylneuraminate lyase and neuraminidase, proposed to be virulence factors involved in the cleavage of sialic acid residues from host-cell gangliosides, by which the sensitivity of the cell to cholera toxin is increased.

Links

The web page of John F. Heidelberg provides links to the *V. cholerae* genome database and to the web pages of other authors.

Conclusions

The close relationship of the strains tested in this study suggests that a small group of *V. cholerae* strains can become human pathogens after acquiring particular pathogenicity islands and the CTX bacteriophage genome. The genes on both *Vibrio* seventh-pandemic islands may be responsible for the unique characteristics of the seventh pandemic, providing a greater ability to adapt to, for instance, external chemical stresses, or to survive in aquatic environments, or improving survival in the human host.

Reporter's comments

>The microarray-based study by Dziejman *et al*. is an important contribution to our understanding of how *V. cholerae* evolved to cause pandemic cholera. It will be important to pinpoint the function of the proteins that are unique to the seventh-pandemic strains. Although we will not be able to prevent future changes in the genetic information of *V. cholerae*, this information will definitely be helpful in analyzing and assessing possible pandemic cholera outbreaks. Understanding how an endemic strain evolves into a pandemic strain may also be useful for developing drugs that specifically stop the spread of pandemic *V. cholerae* strains or treat patients infected with these strains.

Table of links

Proceedings of the National Academy of Sciences of the United States of America

The web page of John F. Heidelberg

References

1. Dziejman M, Balon E, Boyd D, Fraser CM, Heidelberg JF, Mekalanos JJ: Comparative genomic analysis of *Vibrio cholerae*: genes thatcorrelate with cholera endemic and pandemic disease. Proc Natl Acad Sci USA. 2002, 99: 1556-1561. 0027-8424