Allergy

PATHOPHYSIOLOGY

THE SEQUENCE OF THE HUMAN GENOME

Venter JC, and teams of scientists from Celera Genomics (Rockville, MD), GenetixXpress (Sydney, Australia), University of California-Berkeley, Penn State University, Case Western Reserve University, Johns Hopkins University, Rockefeller University, New England Biolabs (Beverly, MA), California Institute of Technology, Yale University, Applied Biosystems (Foster City, CA), The Center for Genome Research (Rockville, MD), Bar Ilan University (Ramat-Gan, Israel), and Universitat Pompeu Fabra (Barcelona, Spain). Science. 2001;291:1304–1351

Purpose of the Study. To determine the genetic sequence of the entire human genome.

Study Population. Five normal volunteers: 1 African American, 1 Asian-Chinese, 1 Hispanic-Mexican, and 2 Caucasians.

Methods. A 2.91-billion base pair (bp) consensus sequence of the human genome was generated. Two assembly strategies—a whole-genome assembly and a regional chromosome assembly—were used, each combining sequence data from Celera and the publicly funded genome effort.

Results. The 2 assembly strategies yielded very similar results that largely agree with independent mapping data. Analysis of the genome sequence revealed 26 588 genes for which there was strong corroborating evidence and an additional ~12,000 likely genes based on weaker evidence. Only 1.1% of the genome is spanned by exons (coding regions), whereas 24% is in introns (sequences within the coding region of the gene that are not translated into protein), and 75% of the genome is intergenic DNA. DNA sequence comparisons between the consensus sequence and publicly funded genome data provided locations of 2.1 million single-nucleotide polymorphisms (SNPs), and <1% of all SNPs resulted in variation in proteins.

Conclusions. The “shotgun” sequencing approach rapidly and accurately generated a nearly-complete (~95%) sequence of the human genome. Major surprises include the identification of a surprisingly low number of genes, estimated at 26 000 to 38 000, compared with previous estimates of up to 140 000. The polymorphisms that have so far been identified represent only a small fraction of the whole human population, and will be useful in both tracing human origins as well as identifying genetic variants that are associated with specific diseases. Analysis of the sequence data underscores previous findings that genetic differences between humans arise from only about 0.1% of the total sequence. Now that this “blueprint” of the human genome has been constructed, the next steps will be to identify genes and control elements, their functions, sequence variation among the human population, and the relationship between sequence variation and gene function.

Reviewer’s Comments. What a way to kick off the new millenium! Dual papers were published in Science and Nature (International Human Genome Sequencing Consortium, Nature 2001;409:860) to describe the efforts and results of the genome sequencing projects led by the private group at Celera and the public Human Genome Project respectively, and this entire issue of Science is devoted to the related scientific, ethical, and societal issues. There is no doubt that this is one of the landmarks of human achievement, but as the authors point out, this is only the beginning. The following quote by Eric Lander, who is the lead author of the Nature paper, helps to put things in perspective: “We’ve called the human genome the blueprint, the Holy Grail, all sorts of things. It’s a parts list. If I gave you the parts list for the Boeing 777 and it has 100 000 parts, I don’t think you could screw it together, and you certainly wouldn’t understand why it flew.” Given the apparent complexity of the genetics of allergy and asthma, it is likely that we will know that parts are broken before we truly understand the functional consequences.

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SECONDHAND SMOKE INDUCES ALLERGIC SENSITIZATION IN MICE


Purpose of the Study. Although there is evidence that environmental tobacco smoke (ETS) can exacerbate allergic responses, the role of ETS in primary allergic sensitization remains unclear. The objective of this study was to examine the influence of ETS on allergic sensitization in a mouse model.

Study Population. Female BALB/c and C57BL/6 mice.

Methods. The investigators exposed mice to either ovalbumin (OVA), saline, ETS, or OVA + ETS by nebulization. Total IgE and OVA-specific immunoglobulin E (IgE), IgG1, and IgG2a were quantified for each of the 4 exposure groups. Mice were reexposed to nebulized OVA 30 days after the initial exposure and cytokine levels in bronchoalveolar lavage (BAL) fluid were measured. Interleukin (IL)-2, IL-4, IL-5, IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) were measured to look for evidence of Th1 or Th2 skewed immune responses. Two strains of mice were studied, BALB/c, a high IgE producer, and C57BL/6, a low IgE producer.

Results. An allergic antibody response, as measured by total IgE and OVA-specific IgE and IgG1, was present in C57BL/6 mice exposed to OVA + ETS, but was not detectable in those exposed to saline, OVA alone, or ETS alone. The results were statistically significant. The allergic antibody response in the BALB/c mice was also most pronounced in the group exposed to OVA + ETS. As this strain more readily produces IgE, there was detectable total IgE as well as OVA-specific IgE and IgG1 in the group exposed to OVA alone, but levels of OVA-specific IgE and IgG1 were statistically significantly higher in the OVA + ETS group. BAL fluid was examined for eosinophilia after rechallenge with OVA in C57BL/6 mice. The OVA + ETS group had marked eosinophilia while the saline, OVA and ETS groups had no eosinophils. Cytokines were also quantified in BAL fluid. IFN-γ, a Th1-associated cytokine, was decreased in OVA + ETS mice as compared with the OVA-exposed group (P < .01), while IL-5, a Th2-associated cytokine, was increased as compared with the OVA-exposed group (P < .05).

Conclusion. ETS exposure appears to facilitate the primary allergic response in mice as measured by allergic antibody response and BAL cytokine response and eosinophilia.

Reviewers’ Comments. Although some evidence has been published regarding ETS and its role in exacerbating allergic responses, this is the first study demonstrating a significant role for ETS in primary allergic sensitization in
mice. Future studies will no doubt address the applicability of these findings to humans.

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ENVIRONMENTAL ALLERGENS

DISTRIBUTION AND REMOVAL OF CAT, DOG, AND MITE ALLERGENS ON SMOOTH SURFACES IN HOMES WITH AND WITHOUT PETS


Purpose of the Study. To characterize the distribution of dog (Can f 1), cat (Fel d 1), and mite (Der p 1 and Der f 1) allergens on hard surfaces in homes with and without pets and to evaluate the efficiency of removing allergen from hard surfaces by wiping with a dry dust cloth and by vacuum cleaning using the dust brush attachment.

Study Population. Dust samples were collected from 24 homes in Dayton, Ohio, that met the following criteria: 1 area with a large amount of smooth, hard-surfaced wall; 2 hard surface floors in 2 separate rooms; sufficient hard furniture surfaces; and lack of cleaning of floors, furniture, and walls for 7 days.

Methods. Two adjacent 1-square meter areas of smooth flooring in 2 separate rooms and a wall were selected and marked out for dust sampling. At each sampling area, half of the area was dusted by wiping with a Pledge Grab-It (SC Johnson, Racine, WI) dust cloth. The adjacent area was then dusted with a vacuum cleaner using the dust brush attachment. The concentrations of Der f 1, Der p 1, Fel d 1, and Can f 1 allergens were determined from each sample.

Results. Dust from hard surfaces and carpets in homes with pets had significantly (P < .05) more Fel d 1 than homes without cats. This is in contrast to the mean levels of Can f 1 on walls and furniture in homes without dogs, which was not significantly less (P < .05) than for homes with dogs. The levels of mite allergen detected on hard surfaces was very low, with 16, 21, and 17 of the 24 homes having no detectable Der f 1 or Der p 1 on smooth floors, walls, and furniture respectively. The mean total quantity of allergen collected by the Grab-It dust cloths was 1.05 to 3.4 times greater than the brush-vacuuming method.

Conclusions. As expected, significantly greater amounts of Fel d 1 were found in individual homes with cats compared with those without cats. A key finding in this study, however, was that detectable levels of dog allergen were present in all but one of the homes without dogs. Sixty-seven percent of homes without cats had measurable Fel d 1 levels present as well. This is postulated to be secondary to passive transfer of allergens from clothing, previous presence of a pet, or visitation by pets. From the data presented, carpeting was the major reservoir for pet allergen. Finally, dusting with a dust cloth was found to be a more effective method of removing allergen from hard surfaces than vacuum cleaning using a dust brush attachment.

Reviewers’ Comments. This article stresses the need for environmental control measures not only in homes with pets, but also in those without. We often must remind our patients, even those that live without pets, to clean their surroundings in an effective manner. This study also demonstrates that it is important to include cleaning walls, furniture, and smooth floors along with carpeting to reduce exposure to indoor allergens. This should greatly improve the quality of life for those that suffer from allergic disease.

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HOUSE DUST MITE, CAT, AND COCKROACH ALLERGEN CONCENTRATIONS IN DAY CARE CENTERS IN TAMPA, FLORIDA


Purpose of the Study. Indoor allergen exposure in early childhood is a known risk factor for allergic sensitization and the development of asthma. This study specifically seeks to determine the concentration of various indoor allergens in day care centers in a humid environment and compare them with their reported normal household levels.

Study Population. A total of 20 day care centers in Tampa, Florida, were surveyed for mite, cat, and cockroach allergens by collecting 1 dust and 2 air samples (1 during the day and 1 during the night).

Methods. Day care center selection was achieved by asking managers for permission to participate in the study and allow collection of dust and air samples. Questionnaires regarding building age, floor covering, and use of insecticide were obtained. Dust samples were collected from 1-sqare meter area for 2 minutes by a 1.7 peak horsepower vacuum cleaner. The filters were subsequently removed and transported to the laboratory in a sterile manner. Dust samples were extracted and specifically analyzed for mite (Der p 1 and Der f 1), cat (Fel d 1), and cockroach (Per a 1) allergens. Airborne mite concentrations were analyzed by radioallergosorbent test inhibition.

Results. Four day care centers were noted to have nicotine levels. The rest of the buildings had wall-to-wall carpeting. Mites were identified in dust samples 15 day care centers with allergen levels >2 µg/g of dust, the suggested threshold level for sensitization to group 1 mite allergens, in 40% of the centers. Cat allergen levels were detected in all centers, but were consistently below the suggested threshold sensitization level of 8 µg/g of Fel d 1 per gram of dust. Cockroach allergen was also found in all day care centers in variable quantity. Threshold levels for sensitization to Per a 1 have not been established, but the levels detected were similar to typical levels in homes in Tampa.

Conclusions. Dust mite, cat, and cockroach allergens were present in all day care centers in this humid environment. Mite allergen levels in dust exceeded levels associated with sensitization in 40% of the centers. Levels of cat allergen were noted to be lower than levels in homes with cats and were consistently less than known by pets. The concentrations for sensitization and symptoms. Cockroach allergen was detected in all day care centers in varying levels, similar to levels in local homes.

Reviewers’ Comments. As the authors note, the prevalence of asthma and sensitization to indoor allergens in children attending day care centers in the United States is unknown. Also unknown is the correlation between indoor air quality and respiratory symptoms in the preschool child. Asthma and allergic disease prevalence in the children attending the day care centers were not reported in this study. Allergen exposure in early childhood is a known risk factor for the development of asthma. And it has been documented that symptoms in children with
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Secondhand Smoke Induces Allergic Sensitization in Mice
Elizabeth Matsui and Robert A. Wood
Pediatrics 2002;110;429

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