Ancient skull spurs rift over hominid ties

A 9- to 10-million-year-old fossil skull unearthed last fall in Greece represents a direct ancestor of hominids — the evolutionary family that includes modern humans — and may even be the earliest known example of a hominid, its discoverers contend.

The controversial new specimen belongs to the species *Ouranopithecus macedoniensis,* previously known only from fragmentary remains. It possesses some facial features similar to those of several ancient apes considered ancestral to modern orangutans, reports a team led by Louis de Bonis of the University of Poitiers in France. But the size and shape of its teeth are closer to *Australopithecus afarensis,* the 3.5-million-year-old African hominid group that includes the remains of "Lucy," the French group maintains.

If *Ouranopithecus* is a direct forerunner of hominids, then it may have branched off from African gorillas and chimpanzees around 12 million years ago, the researchers suggest in the June 21 NATURE. In contrast, many scientists now hold that hominids diverged from African great apes between 5 million and 10 million years ago.

However, several paleoanthropologists familiar with the Greek skull doubt it is a hominid ancestor.

I'd be extremely surprised if de Bonis' interpretation is true," says Eric Delson of the City University of New York, who has seen photographs of the Greek find. "*Ouranopithecus* was probably on the orangutan lineage."

Jeffrey Schwartz of the University of Pittsburgh agrees. Much of the upper face of the *Ouranopithecus* specimen is orangutan-like, he notes. For instance, the steeply sloped floor of the nasal cavity and the wide space between oval eye sockets clearly link the skull to orangutans, Schwartz says. Moreover, dental features shared with *A. afarensis* are not highly specialized and also appear in other ancient ape species not directly linked to hominids, he maintains.

Remains of several ape genera dating to between 15 million and 7 million years ago have previously been found in Africa and Asia, but neither those animals nor *Ouranopithecus* display clear anatomical links to hominids, writes Peter Andrews of the Natural History Museum in London, England, in a commentary accompanying the research report.

The new specimen includes much of the face, part of the skull cap and the entire upper jaw with all its teeth save for one molar. Bones of ancient cattle, giraffes and mastodons found in the same sediment as the skull resemble animal remains at nearby sites dated at 9 million to 10 million years old.

The skull came from an adult male, de Bonis' group asserts. Its canines closely resemble *Ouranopithecus* canines previously identified as male, they point out. But canines in the new specimen are smaller than in any recent or ancient great ape and closer in size to those of *A. afarensis.* Round and swollen molar cusps and a brow ridge that does not project from the face also link *Ouranopithecus* to early hominids, the French scientists say.

Delson argues that assigning a sex to the Greek skull is difficult, considering the fragmentary nature of most *Ouranopithecus* remains. Round and swollen molar cusps — the product of extremely thick tooth enamel — characterize a wide range of ancient apes, not just *Ouranopithecus,* he adds.

From about 15 million to 7 million years ago, as many as five genera on the orangutan lineage lived throughout central Europe and Asia, including *Ouranopithecus, Sivapithecus* in south Asia and *Lufengpithecus* in China, Delson contends. Gorillas, chimpanzees and hominids probably originated in Africa, he says. Their evolutionary relationship to the 14-million-year-old African ape *Kenyapithecus* — known only from teeth and facial fragments — remains unclear, he adds.

— B. Bower

Computers shape AIDS-drug search

Using the rules of biochemistry, researchers over the years have developed hundreds of compounds to fight bacterial diseases. But attempts to expand the tiny arsenal of antiviral drugs pose greater challenges, in part because viruses — including the AIDS-causing HIV — replicate within the cells they infect. Rather than focusing on complex viral biochemistry, some scientists have turned to viral geometry — and tailor-made computer programs — to identify new antiviral weapons.

Last week, researchers described the first fruits of that approach as applied to HIV. Led by chemist Irwin D. Kuntz Jr. of the University of California, San Francisco, the team used specialized software to search a computer database depicting structural images of thousands of existing drugs, looking for molecules with just the right shape to bind and inhibit the activity of a key HIV enzyme.

Haloperidol — a long-established antipsychotic drug — turned up unexpectedly as the best fit.

The researchers then moved from the computer to the lab, showing that haloperidol indeed binds to purified HIV protease and, at high doses, slows HIV infection in cultured human lymphocytes. Kuntz reported the results at a research conference on AIDS held at the National Institutes of Health in Bethesda, Md.

This discovery offers no clinical benefit in itself, he emphasizes, because inhibiting the HIV enzyme would require 1,000 times the standard haloperidol dose — enough to kill any prospective patient. But the work does point to a new and relatively rapid method for identifying potential AIDS drugs, Kuntz says. If drug companies were to use specialized software to identify drug molecules with shapes that could lock onto the valleys, pockets and other surface peculiarities of HIV constituents, "all [they would] have to do is test the drugs to know quickly if any show promise of treating AIDS," he says.

To search for the perfect match between a drug and a targeted viral component, Kuntz's software system first constructs an inverse image of the target's shape. The surface of a drug molecule must match this inverse image in order to bind and inhibit the activity of the designated component.

The team targeted the viral enzyme known as HIV protease because other scientists had recently succeeded in crystallizing it, allowing detailed analysis of its structure. In addition, previous studies had shown that HIV, when replicating inside cells, relies on protease as a molecular scissors. The enzyme first snips itself from cellular material, then cuts out other proteins essential for development of the mature virus. Compounds that bind to HIV protease block the enzyme's activity, halting maturation of the next generation of viruses and leaving them vulnerable to immune attack.

A scan of three-dimensional computer images for 10,000 drugs revealed haloperidol's surprising potential. And unlike the easily digestible and short-lived peptide compounds already known to inhibit HIV protease, haloperidol's chemical structure may allow it to remain active far longer in the body, Kuntz notes.

"We got very excited," he says. "We realized we didn't have to change the structure from what we saw on the [computer] screen."

Kuntz told SCIENCE NEWS his group has developed a haloperidol derivative that blocks HIV protease at lower — but still lethally toxic — concentrations. The researchers are still struggling to modify the drug for safe use in AIDS patients. They have also begun work to identify and modify other potential weapons against HIV.

In a separate effort, Krzysztof Appelt of Agouron Pharmaceuticals Inc. in La Jolla, Calif., is using similar software to further expand the arsenal of nonpeptide compounds that inhibit HIV protease.

— R. Cowen