Researchers identify gene responsible for hypertension and brachydactyly

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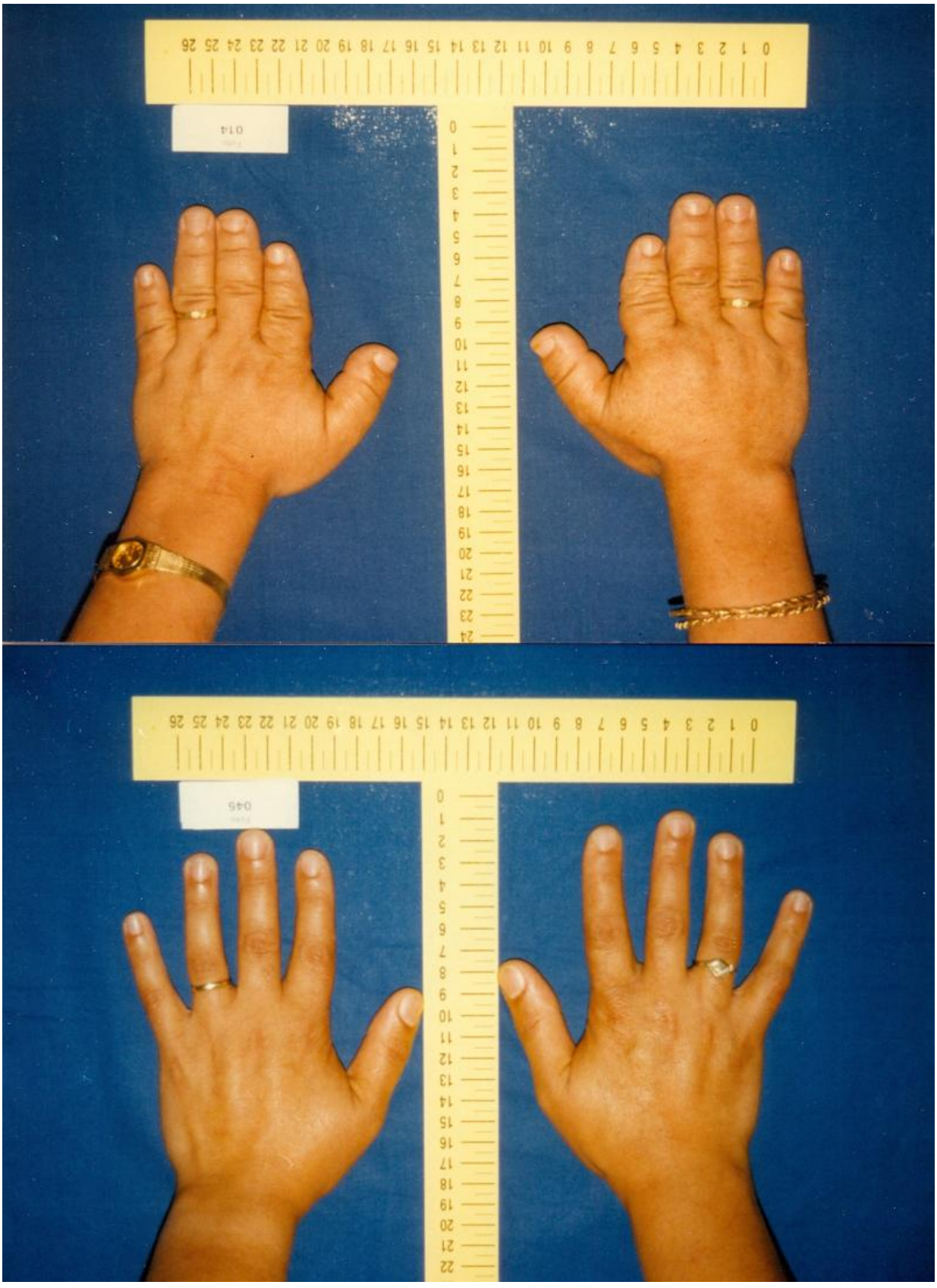

Shortened fingers, called brachydactyly, are a symptom by which members of a Turkish family can determine whether they will suffer from high blood pressure already at a young age. Brachydactyly is always inherited in this family in combination with hypertension. Above the hands of a woman with the disease, below the hands of a healthy woman as comparison.(Photo: Hakan Toka/ Copyright: MDC) Credit: Hakan Toka/ Copyright: MDC

Individuals with this altered gene have hereditary hypertension (high blood pressure) and at the same time a skeletal malformation called brachydactyly type E, which is characterized by unusually short fingers and toes. The effect on blood pressure is so serious that—if left untreated—it most often leads to death before age fifty. After more than 20 years of research, scientists of the Experimental and Clinical Research Center (ECRC), a joint cooperation between the MDC Max Delbrück Center for Molecular Medicine in the Helmholtz Association and the Charité—Universitätsmedizin Berlin have now identified the gene that causes this rare syndrome. In six families not related to each other they discovered different point mutations in the gene encoding phosphodiesterase-3A (PDE3A). These mutations always lead to high blood pressure and shortened bones of the extremities, particularly the metacarpal and metatarsal bones. This syndrome is the first Mendelian hypertension form (salt-resistant) not based on salt reabsorption but instead is more directly related to resistance in small blood vessels ().

"In 1994, when we began with the study of this disease and examined the largest of the affected families in Turkey for the first time, modern DNA sequencing methods did not yet exist. Extensive gene databases to facilitate the search for the cause of this genetic disease were also lacking back then," said PD Dr. Sylvia Bähring, senior author of the research group's publication headed by Professor Friedrich C. Luft.

"Veritable treasure trove for genetics"

In 1996, the research group succeeded in comparing the genetic material of healthy and diseased family members in order to localize the chromosome region where this disease gene must reside. The region they detected was on a segment of chromosome 12 and was an estimated 10 million base pairs in size. "Ultimately however," said Dr. Bähring, "a 16-year-old Turkish boy helped us to pinpoint this gene. He is a veritable treasure trove for the field of genetics." He also has severe high blood pressure—like all other test subjects he is being treated anti-hypertensive drugs—but his hands are nearly normal. Only the metacarpal bones of his little fingers are slightly shortened.

Whole-genome sequencing of the DNA from several people with the syndrome recently enabled Dr. Philipp G. Maass, Dr. Atakan Aydin, Professor Luft, Dr. Okan Toka (formerly MDC/Charité, now the University of Erlangen), Dr. Carolin Schächterle (MDC research group Dr. Enno Klußmann) and Dr. Bähring to identify the gene and six different point mutations in a total of six families from around the world. It is the gene PDE3A, which contains the blueprint for the enzyme, phosphodiesterase 3A. The six different point mutations, which the researchers pinpointed in the PDE3A gene, lead to the exchange of a single DNA building block that is different in each family. In each case, one amino acid of the enzyme is exchanged.

One gene—two different syndromes

But how can one mutated gene cause two quite different diseases such as hypertension and brachydactyly? The ECRC researchers also provide the explanation for this in their study. The task of the phosphodiesterase encoded by the PDE3A gene is to control the quantity of the two secondary messenger proteins present in each cell, cAMP (cyclic

adenosine monophosphate) and cGMP (cyclic guanosine monophosphate), and thus to regulate the duration of their activity.

The mutations in the gene PDE3A, however, cause the enzyme phosphodiesterase to be overexpressed. Thus, it modulates too much of the secondary messenger protein cAMP (cyclic adenosine monophosphate) into AMP (adenosine monophosphate). As a result, the cell has less cAMP at its disposal. The consequence is that, in the affected family members, the smooth muscle cells of the vascular wall of small arteries divide to a greater extent. This proliferation leads to a thickening of the vascular muscle layer, and the blood vessels narrow and stiffen, resulting in high blood pressure. Furthermore, a too low cAMP level in the vascular muscle cells also leads to increased narrowing of the blood vessels.

But what effect do the lowered cAMP levels have on the development of the bones of the extremities? The gene that elicits the skeletal malformation brachydactyly type E is PTHLH (parathyroid hormone-like hormone). In the cartilage cells, a transcription factor (CREB), activated by cAMP, binds in the control region of the gene. This factor ensures that the gene is transcribed and can affect the growth of the cartilage. If there is less cAMP in the cartilage cell, this mechanism is disturbed. This situation then leads to the shortening of the metacarpals and metatarsals, namely the fingers and toes. Thus, by varying the cellular signal transduction, one point mutation can elicit two different characteristics in one and the same person.

New perspectives on hypertension development

The researchers point out that hypertension in the families they examined is not linked to dietary salt intake. The consensus of researchers so far has been that too much salt in the diet damages the kidneys and drives blood pressure up. "We have shown in our study that

for the development of the inheritable form of hypertension only the blood vessels are of significance and not directly the kidneys," said Dr. Bähring, stressing the importance of this study.

First description of the disease in 1973

In 1973, the Turkish physician, Professor Nihat Bilginturan, of the Haceteppe University in Ankara, Turkey first described the disease whose genetic cause has now been elucidated by the researchers in Berlin. Dr Bilginturan noted that in an extended family living on the coast of the Black Sea several family members had shortened fingers and toes - the medical term for this syndrome is brachydactyly (from Greek: brachus for short and daktylos for finger). Remarkably, the affected family members also had severe high blood pressure from youth on and died at a relatively young age. Untreated, their blood pressure exceeded the normal level of 140/90 mm Hg by an average of 50 mm Hg, leading to death before the age of 50, usually due to stroke. The geneticist Professor Thomas Wienker (formerly of the MDC and the University of Bonn, now at the Max Planck Institute for Molecular Genetics, Berlin) discovered Bilginturan's publication and set the wheels of research in motion.

More information: PDE3A mutations cause autosomal-dominant hypertension with brachydactyly, *Nature Genetics* online, DOI: 10.1038/ng.3302

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