

Repository of the Max Delbrück Center for Molecular Medicine (MDC)
in the Helmholtz Association

<http://edoc.mdc-berlin.de/16008>

The Case : a handful of hypertension

van den Born, B.J.H., Oskam, L.C., Zidane, M., Schaechterle, C., Klusmann, E., Baehring, S., Luft, F.C.

NOTICE: this is the author's version of a work that was accepted for publication in *Kidney International*. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in:

Kidney International
2016 OCT ; 90(4): 911-913
2016 SEP 13 (first published online)
doi: [10.1016/j.kint.2016.03.037](https://doi.org/10.1016/j.kint.2016.03.037)
Publisher: [Elsevier](http://www.elsevier.com)



Make your diagnosis

The case | A Handful of Hypertension

Bert-Jan van den Born MD¹, Louise C Oskam MD¹, Majida Zidane MD, PhD²,
Carolin Schächterle PhD³, Enno Klussmann PhD³, Sylvia Bähring PhD⁴,
Friedrich C. Luft MD^{3,4}

¹Departments of Internal and Vascular Medicine Academic Medical Centre, Amsterdam, the Netherlands. b.j.vandenborn@amc.uva.nl; l.c.oskam@amc.uva.nl

²Department of Internal Medicine, Rode Kruis Ziekenhuis, Beverwijk, the Netherlands. mzidane@rkz.nl

³Max-Delbrück Center for Molecular Medicine, Berlin, Germany. enno.klussmann@mdc-berlin.de, Carolin.Schaechterle@mdc-berlin.de

⁴Experimental and Clinical Research Centre (ECRC), a joint cooperation between the Medical Faculty of the Charité and the Max-Delbrück Centre for Molecular Medicine, Berlin, Germany sylvia.baehring@charite.de, friedrich.luft@charite.de

Correspondence:

Friedrich C. Luft

ECRC

Lindenbergerweg 80

13125 Berlin, Germany

Text: 440 words

Figure legend: 165 words

A 37 year-old woman was referred to our clinic with difficult-to-control hypertension since age 12 years. At 18 years, enalapril was administered. One year before referral to our department, she was admitted with a left-sided hemiparesis and pressure values $>200/120$ mm Hg. Thereafter, blood pressure lowering treatment was intensified and a *statin* was begun. The patient is a short-statured ballet dancer (her height is 143 cm). Physical examination was otherwise devoid of target-organ damage. There was no evidence of left ventricular hypertrophy. Laboratory tests including electrolytes, acid-base balance, and renal function were normal. Both her brother and mother also had hypertension at a young age. A plain roentgenogram of her hand was revealing (Figure 1).



What is your diagnosis?

The diagnosis: HTNB (OMIM 112410)

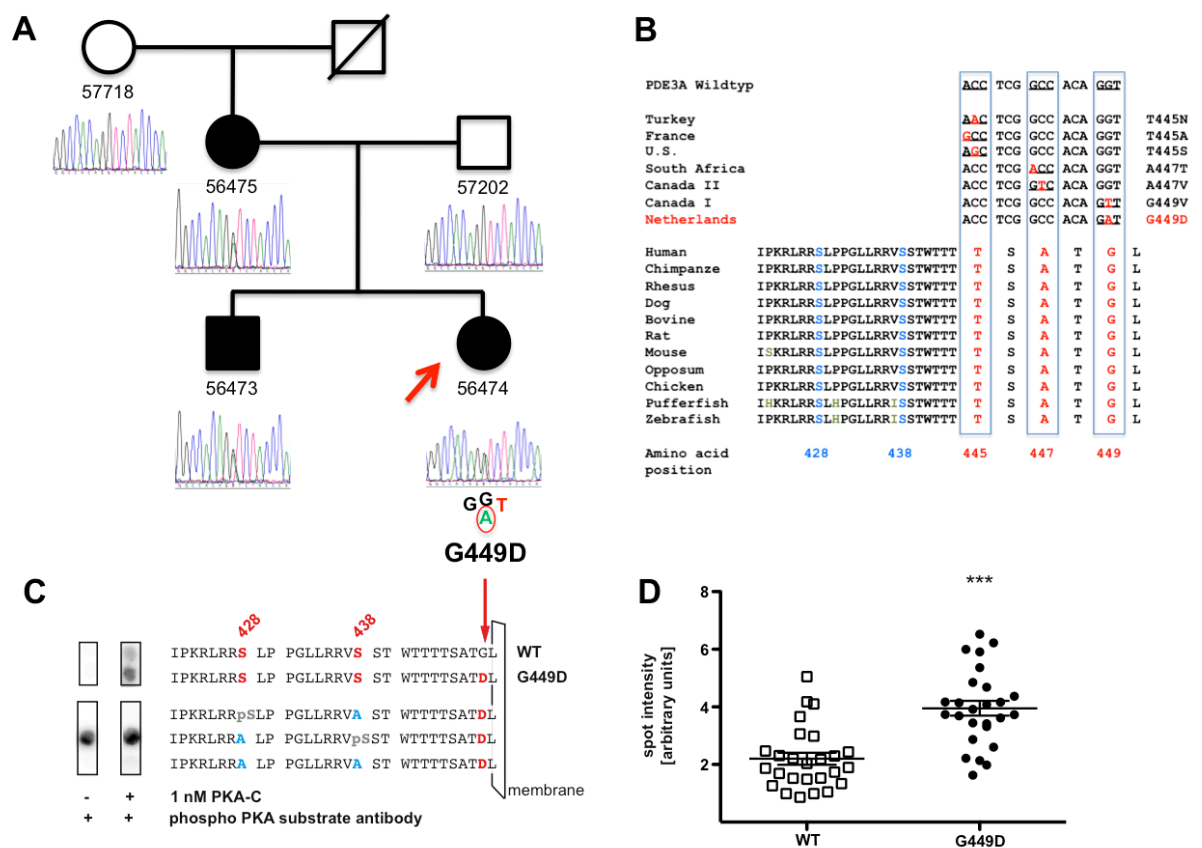
The patient has a Mendelian form of hypertension, autosomal-dominant hypertension with type E brachydactyly (HTNB). The family was aware of the diagnosis from the OMIM (112410) database (figure 2A). HTNB is a non-salt sensitive form of hypertension featuring a remarkable increase in blood pressure with increasing age amounting to about 50 mm Hg by age 50 years.¹ Untreated, HTNB results in stroke before age 50 years. Heart failure and renal failure are not common.

Gain-of-function mutations in the gene encoding phosphodiesterase 3A (PDE3A) were recently shown to cause HTNB.¹ The mutated enzyme has an enhanced cAMP-hydrolytic activity due to increased phosphorylation of two serines at positions 428 and 438 in close proximity to the mutations. We screened the highly conserved area in exon 4 of PDE3A and found that our affected family members had a mutation at glycine 449 (figure 2A). A Canadian family had a valine substitution at this point (figure 2B), whereas our family here has a novel aspartic acid substitution at this same site (p.G449D). To prove that this novel mutation also causes hyperphosphorylation we relied on a peptide SPOT assay of the PDE3A Gly449Asp mutant. Compared to wildtype peptide the mutation leads to a significantly enhanced phosphorylation at the PDE3A Ser438 residue, as we showed earlier (figure 2C and 2D).¹

HTNB was initially described in a Turkish kindred; phenotyping showed that the hypertension resembles essential hypertension, as opposed to all other Mendelian hypertensive syndromes described to date that feature increased sodium reabsorption in the distal nephron. Blood pressure lowering generally requires 2-3 different drug classes to avoid premature stroke, as underscored by our patient. Other target organs such as eye, kidney, coronaries, and heart are less affected.² Neurovascular contact at the rostral ventrolateral medulla and faulty baroreceptor reflex regulation are also described. Renin-angiotensin-

catecholamine values, acid-base regulation, and responses to provocative manoeuvres are normal in HTNB.²

We believe that the HTNB findings are relevant to essential hypertension. First, a linkage analysis led to this locus in Chinese families with essential hypertension without a skeletal phenotype.^{1,2} Second, two separate genome-wide association studies have identified PDE3A in cohorts with essential hypertension.^{2,3} Third, the PDE3 inhibitor milrinone lowers blood pressure both systemically and in the pulmonary circulation. More modest PDE3A variation could contribute to essential hypertension. The enzyme is an attractive drug target since it is inhibited by increasing cyclic GMP and could also be addressed by specific protein-protein interactions functioning at intracellular microdomains.² Physicians treating hypertension should be familiar with this syndrome.



References

1. Maass PG, Aydin A, Luft FC et al. PDE3A mutations cause autosomal dominant hypertension with brachydactyly. *Nat Genet.* 2015;47:647-53.
2. Toka O, Tank J, Schächterle C, et al. Clinical effects of phosphodiesterase 3A mutations in inherited hypertension with brachydactyly. *Hypertension.* 2015;66:800-8.
3. Kato N, Loh M, Takeuchi F et al. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. *Nat Genet.* 2015;47:1282-93.

Figure 1. Shortened metacarpals and cone-shaped epiphyses feature brachydactyly type E.

Figure 2. HTNB in a Dutch kindred.

(A) The family tree shows the affected mother and two offspring, including our patient. We identified a novel missense mutation (c.1346 G>A; NM_000921) in *PDE3A* resulting in a glycine for aspartic acid substitution at protein position 449. (B) The sites of mutations we have identified to date are given, as is the conserved nature of the protein. (C) We performed Phosphokinase A (PKA) phosphorylation of SPOT-synthesized peptides. The principle is based on comparing the signal intensity of different peptide sequences after *in-vitro* phosphorylation with PKA catalytic subunit at the corresponding phosphosite S438. Without incubation of PKA catalytic subunit only spotted phosphoserine at position 438 can be detected by PKA phosphosubstrate antibody. A phosphoserine substitution at S428 and an alanine substitution at both S428 and S438 confirmed the specificity of the antibody. Upon incubation with PKA catalytic subunit spotted serine at position 438 was phosphorylated (WT and G449D sequence). (D) Densitometric quantification of chemoluminescence signals reveal a significantly increased phosphorylation of S438 of the G449D mutation (mean \pm s.e.m.; biological replicates, $n = 26$; two-tailed students t-test, $***P < 0.001$).

Disclosures

None

Work distribution

Bert-Jan van den Born, Louise C Oskam, and Majida Zidane' cared for the patient, referred the patient for additional evaluation, and suggested a genetic diagnosis. Carolin Schächterle and Enno Klussmann delineated the functional relevance of the mutation, Sylvia

Bähring identified the mutation, Bert-Jan van den Born and Friedrich C. Luft focused on preparing the report.