Published in final edited form as:

J Clin Immunol. 2013 May ; 33(4): 725–730. doi:10.1007/s10875-013-9871-8.

Diabetes, Renal and Cardiovascular Disease in p47^{phox}–/– Chronic Granulomatous Disease

Jennifer W. Leiding,

Laboratories of Clinical Infectious Diseases, National Institutes of Health, CRC B3-4141 MSC
1684, Bethesda, MD 20892-1684, USA

Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology, University of
South Florida, St. Petersburg, FL, USA

Beatriz E. Marciano,

Laboratories of Clinical Infectious Diseases, National Institutes of Health, CRC B3-4141 MSC
1684, Bethesda, MD 20892-1684, USA

Christa S. Zerbe,

Laboratories of Clinical Infectious Diseases, National Institutes of Health, CRC B3-4141 MSC
1684, Bethesda, MD 20892-1684, USA

Suk See DeRavin,

Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health,
Bethesda, MD, USA

Harry L. Malech, and

Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health,
Bethesda, MD, USA

Steven M. Holland

Laboratories of Clinical Infectious Diseases, National Institutes of Health, CRC B3-4141 MSC
1684, Bethesda, MD 20892-1684, USA

Steven M. Holland: smh@nih.gov

Abstract

Chronic granulomatous disease is a rare immunodeficiency due to defects in the phagocyte NADPH oxidase. The X-linked form (gp91^{phox} deficiency) accounts for about 70 % of cases; autosomal recessive p47^{phox} deficiency accounts for about 25 % of cases. We identified a 10 % incidence of diabetes in p47^{phox} deficient CGD, but none in X-linked CGD. Renal and cardiovascular diseases were also higher in p47^{phox} deficiency. p47^{phox} deficient CGD has noninfectious morbidities distinct from those in X-linked CGD.

Keywords

Chronic granulomatous disease; p47^{phox}; diabetes; kidney; renal

Introduction

Chronic granulomatous disease (CGD) is a rare immunodeficiency caused by mutations in the subunits of the phagocyte NADPH oxidase; gp91^{phox} and p22^{phox} are membrane bound, while p47^{phox}, p40^{phox}, and p67^{phox} are cytosolic. Mutations in any of the five genes of the NADPH oxidase result in failure to produce superoxide and downstream antimicrobial oxidants leading to infections, granulomatous lesions, and hyperinflammation. Mutations in the X linked gp91^{phox} account for about 70 % of cases; autosomal recessive p47^{phox} deficiency causes about 25 % of cases, and the remainder are divided between p67^{phox} and p22^{phox} [1]. There is one reported case of p40^{phox} deficiency [2]. gp91^{phox} is most abundant in phagocytes while the other components are expressed in phagocytes and elsewhere, including vascular endothelium, the heart and renal epithelium [3] (Tables I and II).

Overall survival in CGD is around 90 % stretching into early adulthood. Multiple factors influence this rate including age at diagnosis, history of infections, co-morbidities, and access to care. p47^{phox} CGD has a significantly better prognosis than X-linked disease [4, 5]. Infections and granuloma formation are less frequent and severe in p47^{phox} CGD, supposedly because they have higher residual superoxide production than those with X-linked CGD. Specific mutations in gp91^{phox} predict the presence or absence of residual phagocyte superoxide production and correlate strongly with overall survival [6]. In contrast, almost all patients with p47^{phox} production and good overall survival.

Despite the overall better survival in p47^{phox} deficient CGD, we recently recognized p47^{phox} deficient CGD patients with diabetes mellitus, with or without cardiovascular and renal disease. Having not seen similar events in X-linked CGD, we examined our entire population of CGD patients to understand the frequency of diabetes, renal and coronary artery disease.

Methods

Charts of all 229 CGD patients followed at the NIH were reviewed for CGD genotype, diabetes mellitus, insulin requirement, renal parameters, and symptomatic cardiovascular disease. Where available, laboratories, imaging and pathology were reviewed. All patients were consented to approved protocols of the National Institute of Allergy and Infectious Diseases.

Patient 1

A 17y African American girl was identified with p47^{phox} deficient CGD at age 3 through family screening. She had multiple pneumonias including *Burkholderia cepacia*, *Trichosporin inkin* [7] and *Serratia marcesens*; pancreatitis of unknown etiology which spontaneously resolved; hydradenitis suppurativa; and ichthyosis vulgaris. At age 12, she was evaluated by endocrinology for weight 70.4 kg and acanthosis nigricans. Her hemoglobin A1C was 6.6 % (normal range 4.8–6.4), fasting glucose 90 mg/dL, glucose tolerance test within normal limits and low fasting insulin levels (32.4 uU/ml). She has been successfully managed with dietary modifications alone.

Patient 2

A 30 year old Caucasian woman was diagnosed with p47^{phox} deficient CGD as a child due to chronic otitis media. She had a brother with CGD who died at age 12 of *Chromobacterium violaceum* sepsis and a sister with CGD who is alive. She had multiple pneumonias including *Mucor* as well as cellulitis and colitis. Juvenile rheumatoid arthritis was diagnosed as a child and discoid lupus as an adult. At age 28, and weighing 60.2 kg, she presented with a hemoglobin A1C of 7.3 % (4.8–6.4). Her C-peptide was low at 0.2 ng/ml (0.9–7.1), pro-insulin was normal at 12 pmol/ml [3–20], and insulin like growth factor was low at 76 ng/ml (117–329). Anti-islet, -insulin and, -GAD-65 antibodies were negative. Urine microalbumin/creatinine was normal at 8.1 ug/g (<17). She was started on metformin but required insulin replacement within a year. Complications of diabetes have included lower extremity neuropathy, and microalbuminuria with a microalbumin/creatinine 87.3 ug/g. An episode of diabetic ketoacidosis (DKA) around *Mucor* pneumonia led to complete right pneumonectomy, following which her diabetes has been more manageable.

Patient 3

Patient 3 is a 44 year old African American woman diagnosed with p47^{phox} deficient CGD at age 7 because of cervical lymphadenitis. Both of her siblings have p47^{phox} deficient CGD as well. She has had multiple pneumonias including *Aspergillus* and *Burkholderia cepacia* complex, as well as bronchiectasis, restrictive and obstructive lung disease, recurrent soft tissue abscesses, liver abscess, and osteomyelitis. She also has schizophrenia and hypertension. At age 30 weighing 79.9 kg, she developed insulin dependent diabetes. Eight years later she developed proteinuria with membranous features on kidney biopsy.

Patient 4

Patient 4, the twin sister of patient 3, was a 36 year old African American woman diagnosed with p47^{phox} deficient CGD at age 12 because of a liver abscess. She has had multiple pneumonias including *Aspergillus*, *Nocardia*, *Burkholderia*, and the dematiaceous mold, *Wangiella*; *Staphylococcus aureus* osteomyelitis; hydradenitis suppurativa; *Actinomyces* encephalitis; and recurrent skin abscesses. Hypertension and chronic renal failure were thought to be due to nephrotoxic antimicrobial exposure. At age 26 and weight 75.6 kg, she was diagnosed with type 2 diabetes mellitus with elevated blood glucose levels and HbA1C 10.6 %. Despite glyburide and dietary modification her diabetes was complicated by retinopathy. Dialysis began at age 29. At age 36 after 7 years of hemodialysis she developed fatal sepsis thought to be from her long-term central dialysis catheter.

Patient 5

Patient 5 is a 47 year old African American man diagnosed with p47^{phox} deficient CGD at age 29 because of *Aspergillus* pneumonia and staphylococcal osteomyelitis of the sternum requiring partial sternectomy. He is the brother of Patients 3 and 4. He has had fungal and bacterial pneumonias including *Basidiomycete* species and *Staphylococcus aureus*. At age 34 he developed renal insufficiency that progressed to end stage renal disease requiring hemodialysis. The etiology was presumed to be previous amphotericin B therapy for his fungal infections. At age 44 he underwent cadaveric kidney transplant, complicated by mild

acute and chronic rejection and he remains on steroids, mycophenolate mofetil, and FK-506 for immunosuppression. Steroid induced diabetes has been managed with insulin.

Patient 6

A 64 year old Caucasian man was diagnosed with CGD at age 38 because of *Pseudomonas* pneumonia complicated by respiratory failure with prolonged intubation and ventilatory support [8]. He had *E. coli* liver abscess as a younger man and mulch pneumonitis at 63 years (patient 5 in Siddiqui et al [9]). He also had chronic ichthyosis and Melkersson-Rosenthal syndrome [8]. At age 31 he developed type 1 diabetes and required insulin within the year. Retinopathy and neuropathy were typical of diabetes. Multiple myocardial infarctions led to coronary artery bypass graft surgery of 5 vessels at age 55. He died at 64 years following his mulch pneumonitis with cardiac and renal failure.

Patient 7

A 46 year old Caucasian man was diagnosed with p47^{phox} deficient CGD at age 12 because of recurrent skin and soft tissue abscesses. He had smoked since age 9. He had multiple pneumonias and liver abscesses with multiple resections. Brain aneurysms were found as part of family screening. At age 43 he had an abnormal stress test and had stent placed in left anterior descending coronary artery. Another stent was placed subsequently in the distal circumflex coronary artery. At age 45 and weight 80 kg, he was diagnosed with diabetes and is now managed with glipizide, sitagliptin, and insulin.

Patient 8

A 27 year old Mexican man was diagnosed with p47^{phox} deficient CGD at age 25 because of *Nocardia otitidiscavarium* osteomyelitis of the scapula that required extensive debridement and radical scapulectomy. A few years preceding his diagnosis, and before receiving any antimicrobials he developed hypertension that was difficult to control. He never received nephrotoxic agents. Renal biopsy showed focal segmental glomerulosclerosis.

Patient 9

Patient 9 was a 28 year old man diagnosed with p47^{phox} deficient CGD at 10 months due to *Aspergillus* and *Nocardia* pneumonias. He had *Paecilomyces variottii* pneumonia at age 12 requiring left pneumonectomy and recurrent *Aspergillus fumigatus* pneumonia, during both of which amphotericin B was given in high dose. Recurrent cellulitis, hydradenitis suppurativa, vancomycin resistant *Enterococcus faecium*, *Saccharomyces cerevisiae* subhepatic abscess, and aseptic meningitis were other complications. At age 15, he developed nephrotic range proteinuria. Renal biopsy was consistent with focal segmental glomerulosclerosis with tubulointerstitial nephritis, moderate arteriosclerosis, and severe nephrocalcinosis. Peritoneal dialysis began at age 19. Secondary hyperparathyroidism required total parathyroidectomy and autotransplantation. At age 21, a living unrelated donor kidney transplant (patient 1 in [10]) was complicated by several episodes of acute rejection, eventually returning to hemodialysis for ESRD at age 27. Shortly after returning to hemodialysis, he developed a chronic exudative pleural effusion. Echocardiogram showed mitral and aortic valve calcifications and regurgitation as well as mild pulmonary

hypertension. Sudden death at 28 years was attributed to arrhythmogenic cardiomyopathy. Autopsy findings included cardiomegaly (weight 820 g) with left ventricular hypertrophy and right ventricular dilation; the coronary arteries showed no atheromata or stenosis. The renal parenchyma was replaced with fatty tissue and renal pelvices and calyces were dilated. The pancreas was normal.

Results and Discussion

Of 64 patients with $p47^{phox}$ deficient CGD followed at the National Institutes of Health, 6 (9.4 %) developed type 1-like diabetes mellitus and 5 (7.8 %) developed kidney disease, 3 of whom developed ESRD. Several developed severe cardiovascular disease, as well. Of the diabetic patients, 3 were mildly obese, 1 was overweight, and 2 were normal weight based on body mass index (BMI) criteria. All patients presented with diabetes at a relatively young age (ages 12–45), a feature more consistent with type 1 diabetes. The three patients with higher BMI's (30.1–32.7 kg/m²) were the eldest at presentation and 2 had dyslipidemia, placing them at higher risk for metabolic syndrome and type 2 diabetes. However, 2 mildly obese and 2 normal BMI patients required insulin replacement within 6 months of diagnosis after failing insulin sparing medications. Diabetes was complicated by proteinuria in 3, neuropathy in 2, and retinopathy in 2. In contrast to the 9.4 % of $p47^{phox}$ deficient patients with diabetes, none of the 165 patients with X-linked CGD followed at the NIH have developed diabetes independent of specific mutation or residual superoxide production ($p = 0.0004$). Approximately one third of X-linked CGD patients followed at the NIH have missense mutations in *CYBB* allowing for low-level residual superoxide production similar to that seen in $p47^{phox}$ deficiency [6]. Female carriers of X-linked CGD also have low level to normal levels of superoxide production based on degree of Lyonization. Diabetes had not occurred in any female carriers to the best of our knowledge, but we have not systematically explored this aspect of X-linked carriage. Also, no patients with other forms of autosomal recessive CGD (6 with $p67^{phox}$ deficiency, 8 with $p22^{phox}$ deficiency, and 1 with $p40^{phox}$ deficiency) have developed diabetes.

Renal pathology included membranous glomerulonephropathy, focal segmental glomerulosclerosis, and nephrocalcinosis. Four patients had received nephrotoxic agents and 2 have not developed end stage renal disease. Cardiovascular diseases include hypertension in 2, coronary artery disease in 2, and cerebral aneurysms in 1. One patient's coronary artery disease was complicated by fatal congestive heart failure. Two patients had severe vascular disease requiring extensive corrective surgery. Approximately 51 % of X linked and 42 % of $p47^{phox}$ deficient patients had fungal infections that were treated to some degree with nephrotoxic agents. Fourteen (8.5 %) X linked CGD patients developed acute renal failure during their treatment and 4 (2.4 %) developed chronic renal failure that progressed to end stage renal disease. One $p22^{phox}$ deficient patient developed chronic renal failure associated with nephrotoxic antimicrobial use. Two $p47^{phox}$ deficient patients have developed acute renal failure and 3 have developed ESRD, 2 going on to receive kidney transplants. Despite equal frequency of nephrotoxic agent use in these two populations, a larger proportion of $p47^{phox}$ deficient patients developed chronic kidney disease.

Of the 60 patients with CGD reported by Walther et al in 1962, 7 had elevated creatinine, 3 were X-linked, 3 were due to p47^{phox} deficiency, and 1 was due to p22^{phox} deficiency [11]. Amphotericin use was associated in 4 cases, ureteral obstruction in 2, and both in 1. Interestingly, obstructive lesions occurred nearly 8 times more frequently in those with X-linked than p47^{phox} deficient CGD, whereas renal insufficiency was equal between those with p47^{phox} deficiency and X-linked CGD [11]. Primary renal disorders also appear more common in p47^{phox} deficient than in X-linked CGD. Interstitial nephritis [11–13], ESRD due to Henoch-Schonlein nephritis and associated 18q syndrome [14], immune complex glomerulonephritis associated with staphylococcal liver abscess [11, 15], FSGS [16, 10], papillary necrosis [11, 16, 17], nephrocalcinosis [10], and renal amyloidosis [18–21] have all been reported with most occurring in those with p47^{phox} deficiency [14–16, 22]. Renal transplant has also been successful in p47^{phox} deficient CGD patients with ESRD [10].

Autoimmune disorders are relatively common in CGD. Discoid lupus is more common in X-linked female carriers [23], while idiopathic thrombocytopenic purpura, juvenile idiopathic arthritis, autoimmune pulmonary disease, myasthenia gravis, IgA nephropathy, antiphospholipid syndrome, and recurrent pericardial effusions have also been reported [5, 24]. The p47^{phox} deficient CGD mouse model suggests that reactive oxygen species (ROS) are critical for the development of insulin-dependent diabetes, since CGD mice are protected [25]. In contrast, our patients with p47^{phox} deficiency and impaired superoxide production were much more prone to diabetes than either X-linked CGD patients or normals, suggesting markedly distinct roles for p47^{phox} in humans and mice.

Nuclear cytosolic factor 1 (*NCF1*) encodes p47^{phox} located on chromosome 7q11.23. The vast majority of mutations in *NCF1* are due to the same homozygous mutation, a GT deletion (GT) at the beginning of exon 2 causing a frame shift and premature stop codon at amino acid 51 [6, 26]. The GT allele is the most common CGD-causing allele in the population, with a carrier frequency of 1:250. This high frequency is attributed to the two *NCF1* pseudogenes carrying the GT that flank the functional allele [27]. Recombination events between *NCF1* and these pseudogenes lead to the incorporation of GT into *NCF1*. It has also been shown that the pseudogenes are transcriptionally active, although their function, if any, is unclear [28]. It is theoretically possible that some of the manifestations of p47^{phox}-deficient CGD could in fact be due to aberrant expression of a pseudogene, but this possibility would be very difficult to explore.

Increased production of ROS has been viewed as contributing to multiple different cardiovascular diseases. Therefore, mutations in any of the subunits of the NADPH oxidase should theoretically be protective against development of cardiovascular disease. In agreement with this assumption, patients with CGD have been shown to have decreased platelet recruitment to agonist induced thrombus formation in vitro [29] and enhanced arterial dilation following induced shear stress [30] with reduced injury following ischemia/reperfusion injury [31] in vivo. However, under physiologic conditions, ROS help regulate vascular tone and intracellular signaling pathways involving proliferation, migration, and differentiation. Although still abnormal, patients with p47^{phox} deficiency do have some residual superoxide production, which likely contributes to their improved survival as compared to those with X-linked CGD [6]. However, whether these low amounts of

superoxide, which are higher than those in typical X-linked CGD, are both protective against CGD mortality while at the same time contributing to the development of diabetes and cardiovascular pathology, remains unclear.

Diabetes, renal and cardiovascular diseases occur more often and with greater severity in p47^{phox} deficient CGD than in gp91^{phox} deficient CGD, indicating distinct features to p47^{phox} CGD, likely beyond the generation of superoxide alone.

Acknowledgments

This work supported by the Division of Intramural Research, NIAID, NIH.

References

- Holland SM. Chronic granulomatous disease. *Clin Rev Allergy Immunol*. 2010; 38(1):3–10. [PubMed: 19504359]
- Matute JD, Arias AA, Wright NA, Wrobel I, Waterhouse CC, Li XJ, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. *Blood*. 2009; 114(15):3309–3315. Epub 2009/08/21. [PubMed: 19692703]
- Ushio-Fukai M. Localizing NADPH oxidase-derived ROS. *Sci STKE*. 2006; 2006(349):re8. Epub 2006/08/24. [PubMed: 16926363]
- Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. *Clin Immunol*. 2008; 126(2):155–164. Epub 2007/11/27. [PubMed: 18037347]
- Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)*. 2000; 79(3):155–169. Epub 2000/06/09. [PubMed: 10844935]
- Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. *N Engl J Med*. 2010; 363(27):2600–2610. Epub 2010/12/31. [PubMed: 21190454]
- Wynne SM, Kwon-Chung KJ, Shea YR, Filie AC, Varma A, Lupo P, et al. Invasive infection with *Trichosporon inkin* in 2 siblings with chronic granulomatous disease. *J Allergy Clin Immunol*. 2004; 114(6):1418–1424. Epub 2004/12/04. [PubMed: 15577847]
- Nerurkar LS, Jacob A, Zeligs B, Walser J, Yeager H Jr, Bellanti JA. Chronic granulomatous disease in an adult. *South Med J*. 1987; 80(10):1296–1302. Epub 1987/10/01. [PubMed: 3660045]
- Siddiqui S, Anderson VL, Hilligoss DM, Abinun M, Kuijpers TW, Masur H, et al. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. *Clin Infect Dis*. 2007; 45(6):673–681. Epub 2007/08/23. [PubMed: 17712749]
- Bolanowski A, Mannon RB, Holland SM, Malech HL, Aschan J, Palmblad J, et al. Successful renal transplantation in patients with chronic granulomatous disease. *Am J Transplant*. 2006; 6(3):636–639. Epub 2006/02/14. [PubMed: 16468977]
- Walther MM, Malech H, Berman A, Choyke P, Venzon DJ, Linehan WM, et al. The urological manifestations of chronic granulomatous disease. *J Urol*. 1992; 147(5):1314–1318. Epub 1992/05/01. [PubMed: 1569675]
- Carson MJ, Chadwick DL, Brubaker CA, Cleland RS, Landing BH. Thirteen boys with progressive septic granulomatosis. *Pediatrics*. 1965; 35:405–412. Epub 1965/03/01. [PubMed: 14258653]
- Dilworth JA, Mandell GL. Adults with chronic granulomatous disease of “childhood”. *Am J Med*. 1977; 63(2):233–243. Epub 1977/08/01. [PubMed: 407791]
- Kimpen J, Van Damme-Lombaerts R, Van den Berghe G, Proesmans W. Autosomal recessive chronic granulomatous disease associated with 18q-syndrome and end-stage renal failure due to

- Henoch-Schonlein nephritis. *Eur J Pediatr*. 1991; 150(5):325–326. Epub 1991/03/01. [PubMed: 2044603]
15. van Rhenen DJ, Koolen MI, Feltkamp-Vroom TM, Weening RS. Immune complex glomerulonephritis in chronic granulomatous disease. Case report of an eighteen-year-old girl. *Acta Med Scand*. 1979; 206(3):233–237. Epub 1979/01/01. [PubMed: 495232]
 16. Frifelt JJ, Schonheyder H, Valerius NH, Strate M, Starklint H. Chronic granulomatous disease associated with chronic glomerulonephritis. *Acta Paediatr Scand*. 1985; 74(1):152–157. Epub 1985/01/01. [PubMed: 3984721]
 17. Forbes GS, Hartman GW, Burke EC, Segura JW. Genitourinary involvement in chronic granulomatous disease of childhood. *AJR Am J Roentgenol*. 1976; 127(4):683–686. Epub 1976/10/01. [PubMed: 970547]
 18. De Seigneux R, Kanfer A, Terrioux P, Sraer JD, Whitworth JA. Letter: Renal amyloidosis in chronic granulomatous disease. *Br Med J*. 1974; 4(5938):230. Epub 1974/10/26. [PubMed: 4472747]
 19. Dechelette E, Rossignol AM, Gout JP, Poirot P, Frappat P, Bost M. [Renal amylosis and chronic septic granulomatosis. Apropos of a case]. *Pediatric*. 1977; 32(6) UNKNOWN. Epub 1977/09/01. Amylose renale et granulomatoses septique chronique. A propos d'une observation.
 20. Kaltenis P, Mudeniene V, Maknavicius S, Seinins D. Renal amyloidosis in a child with chronic granulomatous disease and invasive aspergillosis. *Pediatr Nephrol*. 2008; 23(5):831–834. Epub 2008/01/12. [PubMed: 18188609]
 21. Peces R, Ablanado P, Seco M. [Amyloidosis associated with chronic granulomatous disease in a patient with a renal transplant and recurrent urinary tract infections]. *Nefrologia*. 2002; 22(5):486–491. Epub 2002/12/25. Amiloidosis asociada a enfermedad granulomatosa cronica en una paciente con un trasplante renal e infecciones urinarias de repeticion. [PubMed: 12497752]
 22. Yamazaki H, Nishi S, Chou T, Nakagawa Y, Shimada H, Nunoi H, et al. Two brothers with p47-phox-deficient chronic granulomatous disease associated with end-stage renal failure. *Nephrol Dial Transplant*. 1995; 10(12):2334–2336. Epub 1995/12/01. [PubMed: 8808236]
 23. Hafner J, Enderlin A, Seger RA, Wuthrich B, Bruckner-Tudermann L, Panizzoni P, et al. Discoid lupus erythematosus-like lesions in carriers of X-linked chronic granulomatous disease. *Br J Dermatol*. 1992; 127(4):446–447. Epub 1992/10/01. [PubMed: 1419770]
 24. De Ravin SS, Naumann N, Cowen EW, Friend J, Hilligoss D, Marquesen M, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. *J Allergy Clin Immunol*. 2008; 122(6):1097–1103. [PubMed: 18823651]
 25. Tse HM, Thayer TC, Steele C, Cuda CM, Morel L, Piganelli JD, et al. NADPH oxidase deficiency regulates Th lineage commitment and modulates autoimmunity. *J Immunol*. 2010; 185(9):5247–5258. Epub 2010/10/01. [PubMed: 20881184]
 26. Roos D, Kuhns DB, Maddalena A, Bustamante J, Kannengiesser C, de Boer M, et al. Hematologically important mutations: the autosomal recessive forms of chronic granulomatous disease (second update). *Blood Cells Mol Dis*. 2010; 44(4):291–299. Epub 2010/02/20. [PubMed: 20167518]
 27. Gorlach A, Lee PL, Roesler J, Hopkins PJ, Christensen B, Green ED, et al. A p47-phox pseudogene carries the most common mutation causing p47-phoxdeficient chronic granulomatous disease. *J Clin Invest*. 1997; 100(8):1907–1918. Epub 1997/10/23. [PubMed: 9329953]
 28. Brunson T, Wang Q, Chambers I, Song Q. A copy number variation in human NCF1 and its pseudogenes. *BMC Genet*. 2010; 11:13. Epub 2010/02/25. [PubMed: 20178640]
 29. Pignatelli P, Carnevale R, Di Santo S, Bartimoccia S, Sanguigni V, Lenti L, et al. Inherited human gp91phox deficiency is associated with impaired isoprostane formation and platelet dysfunction. *Arterioscler Thromb Vasc Biol*. 2011; 31(2):423–434. Epub 2010/11/13. [PubMed: 21071703]
 30. Violi F, Sanguigni V, Carnevale R, Plebani A, Rossi P, Finocchi A, et al. Hereditary deficiency of gp91(phox) is associated with enhanced arterial dilatation: results of a multicenter study. *Circulation*. 2009; 120(16):1616–1622. Epub 2009/10/07. [PubMed: 19805647]
 31. Loukogeorgakis SP, van den Berg MJ, Sofat R, Nitsch D, Charakida M, Haiyee B, et al. Role of NADPH oxidase in endothelial ischemia/ reperfusion injury in humans. *Circulation*. 2010; 121(21):2310–2316. Epub 2010/05/19. [PubMed: 20479156]

Table 1

Characteristics of p47^{phox}−/− patients with diabetes, renal, and cardiovascular disease

Patient	DHR (>225 AU)	Age/Sex	Age at DM dx	BMI (kg/m ²) at DM diagnosis	Age at CV disease diagnosis	Dyslipidemia	Smoker	CV disease	Renal disease	Sequelae
1	539	17 years F	12 years	28.8		LDL above optimal	−	−	−	−
2	2068	30 years F	28 years	23.1		↓ HDL	+	−	−	Neuropathy Microalbuminuria
3	484	44 years F	30 years	32.8		↓ HDL	−	−	*Membranous kidney disease HTN	−
4	NA	36 years F				26 years 32.7	−	−	§ESRD	Retinopathy Died due to catheter related sepsis
5	432	47 years M	§40's	25.4		↓ TG borderline	−	−	*ESR D FSGS	−
6	NA	64 years M	16 years	NA	55 years	↓ HDL	+	CAD CABG × 5 CA stent placement Multiple MI's CHF	−	Retinopathy Neuropathy Died of CHF
7	203	46 years M	45 years	30.1	43 years	↓ LDL ↓ HDL	+	CAD CA stents Cerebral aneurysms	−	Neuropathy Microalbuminuria
8	1107	27 years M	24.4		↓ HDL	−	−	−	HTN FSG S	−
9	1327	28 years M	29.3	27 years	−	−	−	MR, AR, Pulm HTN	*ESRD FSGS Interstitialnephritis	−

DHR dihydrorhodamine assay; AU arbitrary units; DM diabetes mellitus; BMI body mass index (kg/m²) <18.5 underweight, 18.5–24.9 normal, 25–29.9 overweight, 30 obese; CV cardiovascular; NA not available; High density lipoprotein (HDL) mg/dL <40 low (high risk), 60 high (low risk); Low density lipoprotein (LDL) mg/dL <100 optimal, 100–129 near or above optimal, 130–159 borderline high, 160–189 high, 190; Total cholesterol (TC) mg/dL <200 desirable, 200–239 borderline, 240 high risk; Triglyceride (TG) mg/dL <150 normal, 150–199 borderline, 200–499 high, >500 very high; HTN hypertension; ESRD end stage renal disease; FSGS focal segmental glomerulosclerosis; CAD coronary artery disease; CABG coronary artery bypass graft; CA coronary artery; MI, myocardial infarction; CHF congestive heart failure; MR mitral regurgitation; AR, aortic regurgitation

* All 3 patients were exposed to nephrotoxic antimicrobials

§ Steroid induced diabetes

Patients 3 and 4 are twin sisters. Patient 5 is the brother of patients 3 and 4

Table IINumber of X-linked and p47^{p_{hox}-/-} CGD patients with diabetes

CGD mutation	Diabetes	No Diabetes
gp91 ^{p_{hox}} (X-linked)	0	165
p47 ^{p_{hox}} (Autosomal recessive)	6	58

 $p=0.0004$