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CASE REPORT
Adult congenital heart disease

Genetic variant in the *BRAF* gene compatible with Noonan spectrum disorders in an adult Fontan patient with refractory protein losing enteropathy: a follow-up report

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Background Patients with a univentricular heart form a morphological heterogenous group of patients at the most severe end of the congenital heart disease (CHD) spectrum. Over the past decades, more awareness and knowledge has been raised on the genetic contributions to CHD. To date, only a limited number of genes have been identified in the hypoplastic heart, mainly in left-sided hypoplasia. There is still much more to be elucidated in this field.

Case summary Here, we present a follow-up report of a case of an adult patient after Fontan palliation, born with a.o. tricuspid atresia with hypoplastic right ventricle and pulmonary stenosis. This patient encountered a myriad of late sequalae involving multiple organ systems during the course of his young adult life, including refractory protein losing enteropathy (PLE). Concomitant extracardiac anomalies, in addition to the complex CHD and its complications, prompted for genetic evaluation. Whole exome sequencing showed a variant of uncertain significance in the *BRAF* gene [NM_004333.4:c.1897T > C p.(Tyr633His)], associated with Noonan spectrum disorders, that is also infamous for lymphoedema and PLE. The variant regards an evolutionarily highly conserved amino acid and is assumed pathogenic according to all prediction programmes. The mutation was most likely *de novo*.

Discussion Genetic screening can provide new insights in the complex and varied phenotype of the (adult) Fontan patient and in the myriad of complications encountered. Adult CHD cardiologists should be aware of genetic syndromes underlying a CHD, concomitant extracardiac anomalies, and a complex clinical course with a broad spectrum of late sequelae.

Keywords Case report • Congenital heart disease • Fontan circulation • Univentricular heart • Long term complications • Genetic disorder • Noonan spectrum

ESC Curriculum 9.7 Adult congenital heart disease • 4.9 Multivalvular disease

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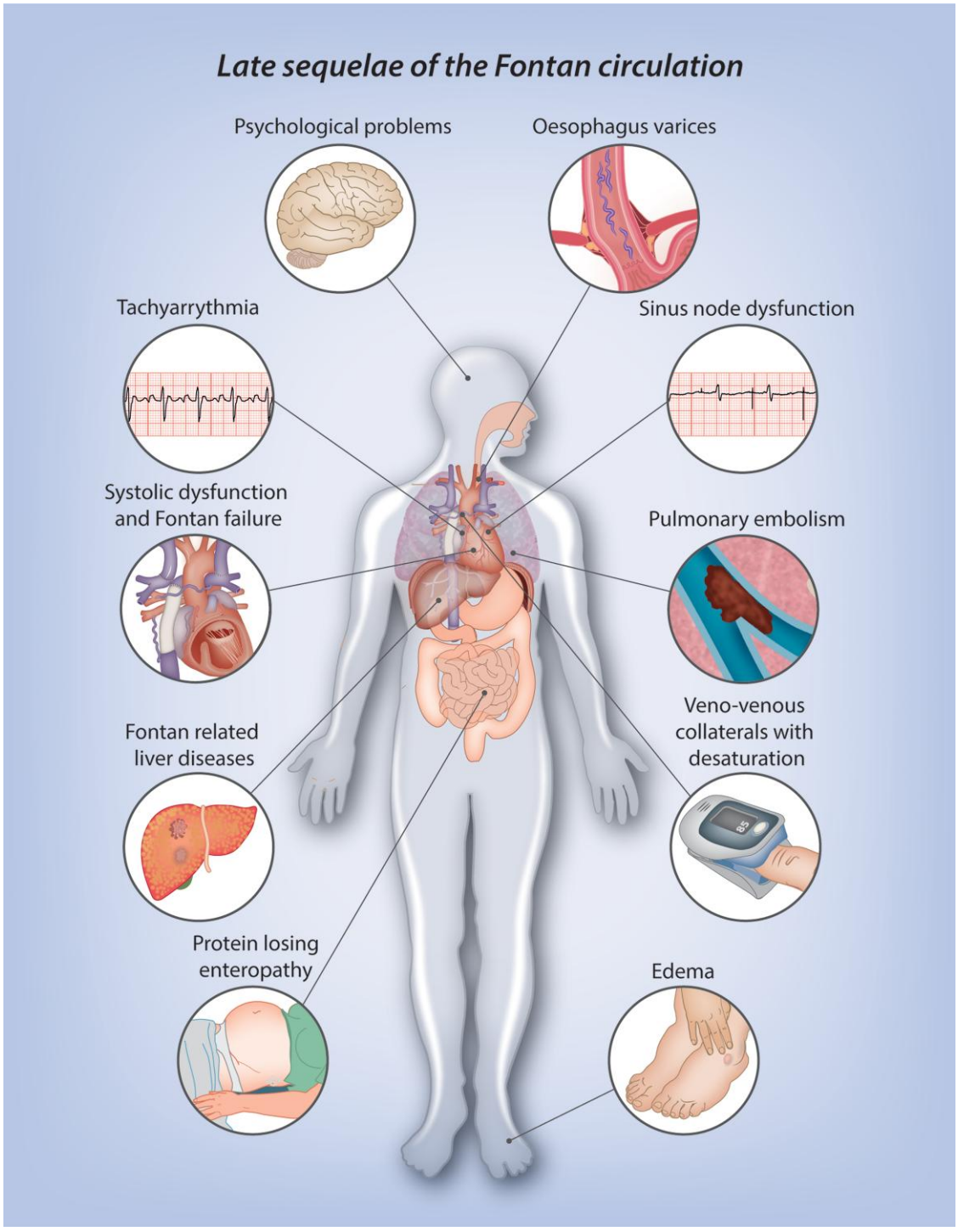

Figure 1 Case summary of the patient with univentricular physiology palliated by the Fontan circulation and the broad spectrum of encountered late complications.

Case recap

We previously described the case of an adult patient with extensive late complications after Fontan palliation.[1] The patient was born with tricuspid atresia with hypoplastic right ventricle, pulmonary stenosis, persisting left superior vena cava, and atrial and ventricular septal defects. After multiple consecutive operations, the patient was eventually palliated with an extracardiac total cavopulmonary connection. The case was illustrative of the complex clinical course and the broad spectrum of complications that can be encountered during follow-up, including, yet not limited to, Fontan failure, arrhythmias, Fontan-related liver diseases, and protein losing enteropathy (PLE), summarized in *Figure 1*.

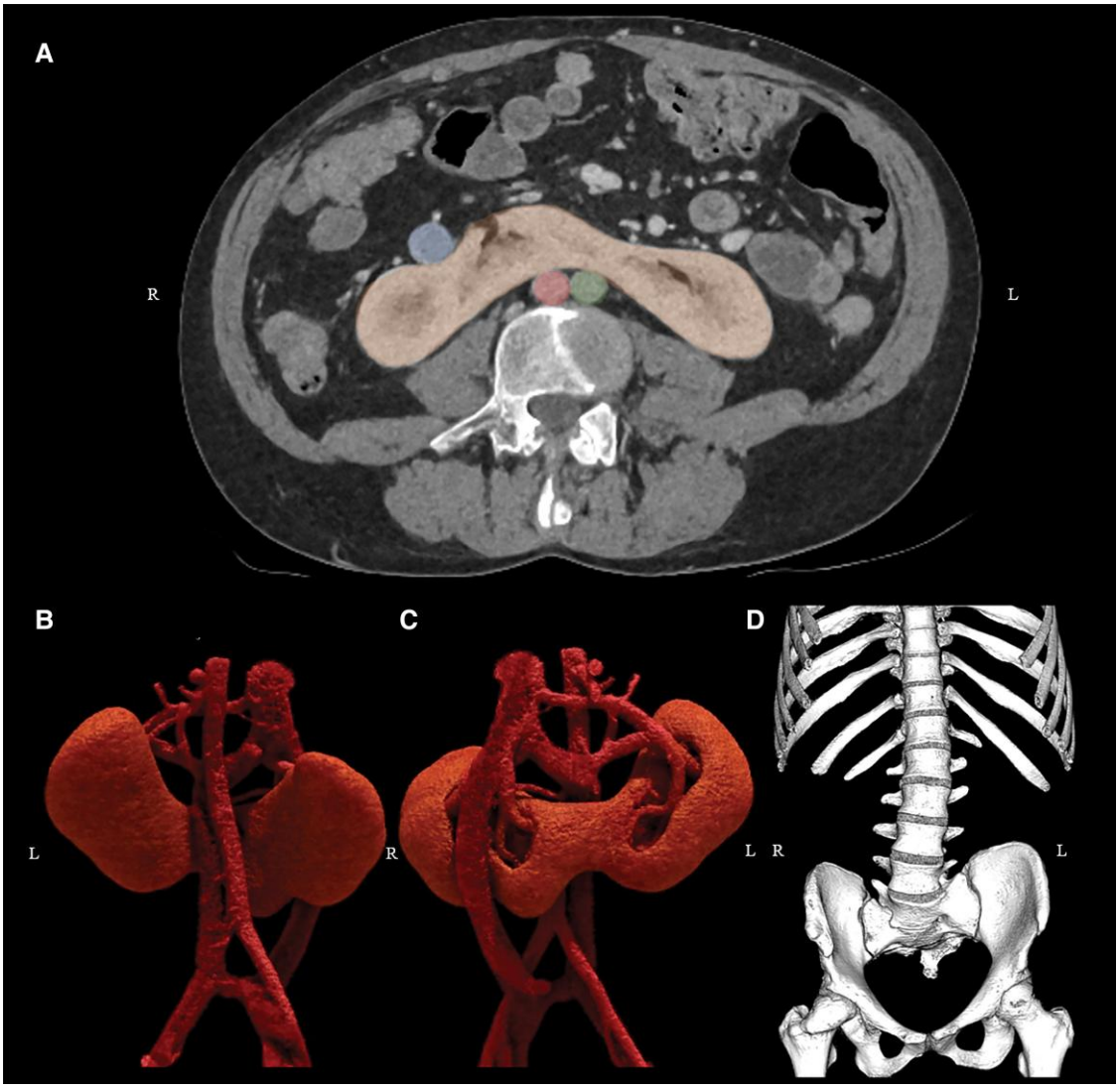

Figure 2 Computed tomography visualizing extracardiac abnormalities. (*A*) Transversal plane showing the horseshoe kidney (orange), the aorta (red), the inferior vena cava (blue), and the persisting left inferior vena cava (green). Three-dimensional reconstruction illustrating the relationship and the course of the horseshoe kidney, vena cava inferior, persisting left inferior vena cava, and the aorta in the posterior (*B*) and anterior (*C*) view. (*D*) Three-dimensional reconstruction of the skeleton illustrating deformation of the right femoral head and acetabulum with consequent misalignment, hypoplasia of the sacrum, and a mild scoliosis.

This emphasized the need for a multidisciplinary approach in the clinical care for these patients.

Further follow-up

The patient experienced worsening episodes of PLE during follow-up, which instigated further analysis. This revealed several other extracardiac anomalies, including high myopia, a horseshoe kidney situated dorsally from a displaced inferior vena cava, a persisting left inferior vena cava draining in the left renal vein, sacral hypoplasia, and signs of right hip dysplasia and secondary arthrosis (*Figure 2*, Supplementary material online, *Videos S1* and *S2*). In conjunction with the complex congenital heart disease (CHD), these abnormalities prompted a clinical genetics referral. Physical examination denoted several dysmorphic features, including woolly hair, ptosis of the right eye, sparse eyelashes, a broad flat philtrum, widely spaced nipples, a bulging abdomen, thin limbs with long thin fingers and elongated first digits of both feet, keratosis pilaris on upper legs, and signs of venous insufficiency on lower legs (*Figure 3*). Whole exome sequencing showed a variant of uncertain significance [NM_004333.4:c.1897T > C p.(Tyr633His)] in the *BRAF* gene, a gene that is associated with Noonan spectrum disorders (see Supplementary material online, *Figure S1*). This variant has not been described previously in medical literature or the gnomAD database.[2] It concerns an evolutionarily highly conserved amino acid and is deemed pathogenic according to all prediction programmes. Although parental DNA could not be obtained, *BRAF* pathogenic variants most likely arise as *de novo* mutations. Although the Noonan spectrum disorders overlap phenotypically, *BRAF* pathogenic variants are often found in patients with cardiofaciocutaneous (CFC) syndrome (OMIM 115150). Our patient's cardiac-, facial-, and cutaneous features, specifically the ectodermal-derived findings, support this diagnosis and help to differentiate it from other disorders in the Noonan spectrum. Not in favour of the diagnosis is this patients'

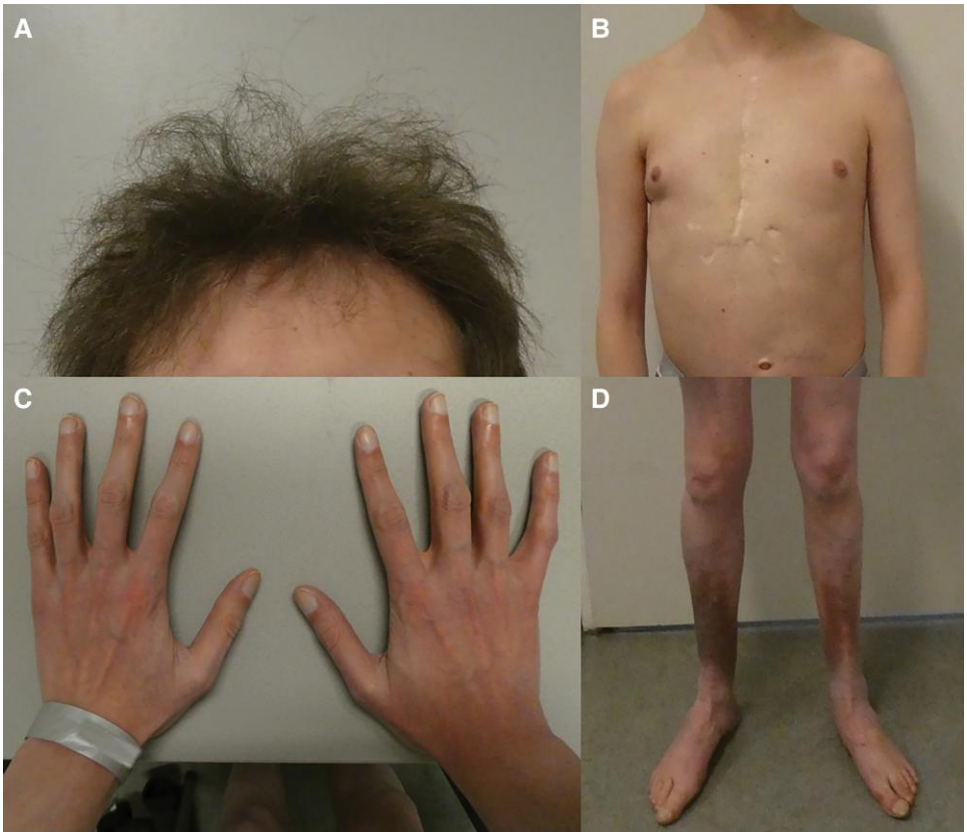

Figure 3 Patient demonstrating (*A*) the woolly hair, (*B*) the widely-spaced nipples, bulging abdomen, and thin limbs, (*C*) the long thin fingers, and (*D*) bilaterally elongated first digit of the foot and signs of lower leg venous insufficiency.

high intellectual performance, as usual some form of neurological or cognitive delay is reported in CFC patients.

Discussion

Patients with a univentricular heart form a morphologically heterogenous cohort at the most severe end of the CHD spectrum. Over the last decades, more awareness and knowledge has been raised on the genetic contributions to CHD. To date, only a limited number of genes have been identified in hypoplastic heart disease, mainly concerning left-sided hypoplasia.[3] According to a recent expert consensus statement on genetic testing for cardiac diseases, genetic testing for CHD is indicated in case of concomitant extracardiac anomalies.[4] Even though genetic diagnosis has limited impact on CHD management strategies, it does help to differentiate syndromic from non-syndromic CHD and may thereby assist in risk stratification and prognostication.[4]

The variant found in this patient was located in the *BRAF* gene, which is a protein coding gene involved in the Ras/mitogen-activated protein kinase (MAPK; RAS–MAP kinase) pathway. This signal transduction pathway sends extracellular signals to the cell nucleus where specific genes are activated to regulate cell division, growth, and differentiation. Additionally, this pathway is involved in angiogenesis, cell cycle regulation, as well as in wound and tissue repair.[5] *BRAF* variants are generally related to CFC but have also been described in patients with Noonan syndrome with and without multiple lentigines. Concomitant CHD is frequently encountered, pulmonary valve stenosis being the most prevalent.[6] Hypoplastic right heart disease has not previously been associated with this variant. Notably, lymphatic disorders are described in the Noonan spectrum, with up to 50% prevalence of any form of lymphoedema, both chronic and intermittent in nature.[7] More often it presents as lymphoedema of the genitals and lower limbs, yet systemic involvement is also common. Intestinal lymphangiectasia is responsible for PLE, and although the true prevalence is unknown, it was described in 5 of 11 cases (45%) described with lymphatic involvement in Noonan and CFC syndrome.[8] In comparison, the incidence of PLE in the Fontan population is 5–12%. Prognosis differs greatly with reported 5-year survival rates varying from <50 to 88%.[9,10] It may be speculated that the underlying genetic variant contributes to the severity of the phenotype of refractory PLE as late sequel in this patient.

In conclusion, genetic screening can provide new insights into the complex and varying phenotype of the Fontan patient and accompanying complications. Adult CHD cardiologists should be aware of genetic syndromes underlying CHD and concomitant extracardiac anomalies. Although more explorative studies are required to unravel the role of genetics in the broad morphological range of complex CHD underlying univentricular heart phenotypes, we advocate considering genetic screening as part of the multidisciplinary management of Fontan patients.

Lead author biography

Marieke Nederend (1993) is currently a PhD candidate and junior doctor in (congenital) Cardiology at the Leiden University Medical Center, the Netherlands. After graduating summa cum laude in Medicine at the Leiden University, she started her career at the Leiden University Medical Center. Her thesis focuses on addressing late complications in adults with complex congenital heart disease, with a focus on the systemic right ventricle and the Fontan circulation. She will start residency training in Cardiology after finishing her PhD.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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Consent: All procedures performed involving the human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards. The patient provided written consent for publication in compliance with COPE guidelines.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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