Carvajal/Naxos syndrome secondary to Desmoplakin-dominant mutation is associated with dilated cardiomyopathy, wolly hair, palmoplantar keratoderma and hypo/oligodontia

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Introduction :
Carvajal is a syndrome associating curly, fair and fine hair (woolly hair), thickening of skin with fissures on hands palms and feet soles, left or biventricular heart dilatation and decreased contractility. Naxos syndrome associates the same hair and skin signs but is associated with fibrofatty tissue replacement of the right ventricular walls. Naxos disease is autosomal recessive and the causal gene encodes plakoglobin. Plakoglobin and desmoplakin are components of desmosomes. Desmosomes are cell-cell junctions responsible for maintaining the structural integrity of tissues by resisting to shear forces. There is accumulating evidence that Carvajal and Naxos syndromes are variable expressions of the same syndrome secondary to mutations in Plakoglobin or Desmoplakin.

Here, we report on family members affected by Carvajal/Naxos disease. In addition to woolly hair, palmoplantar keratoderma and dilated cardiomyopathy, affected family members had teeth agenesis ranging from missing a single second mandibulary molar to 11 absent teeth (not including third molars).

Materials and Methods:

Enrollment of human subjects
Family history and examinations were performed in the usual frame of genetic and cardiac consultations at the University Hospital of Lyon. Informed consent was obtained before blood drawing.

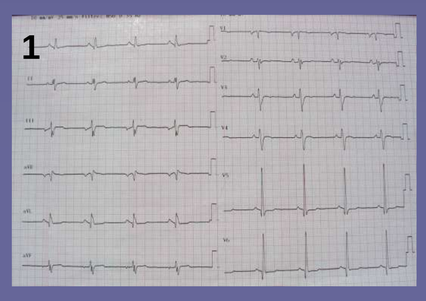
Molecular genetic analysis
Genomic DNA from each family member was used to screen for mutation in the desmoplakin (DSP) and plakoglobin (JUP) genes. Oligonucleotide primers for DSP (24 coding exons) and JUP (16 coding exons) were used to amplify and Sanger sequence DNAs.

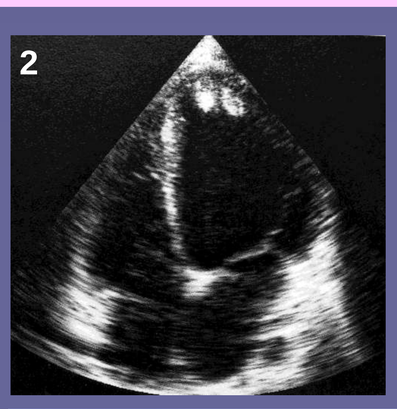
Histology
The heart of the graft recipient was process for macroscopic and microscopic examination. Samples from the posterior and anterior walls of the right and left ventricle and the interventricular septum were fixed in APS, embedded in paraffin. Sections 10 micrometers thick were obtained, deparaffinized, rehydrated and stained by the Masson trichrome method.

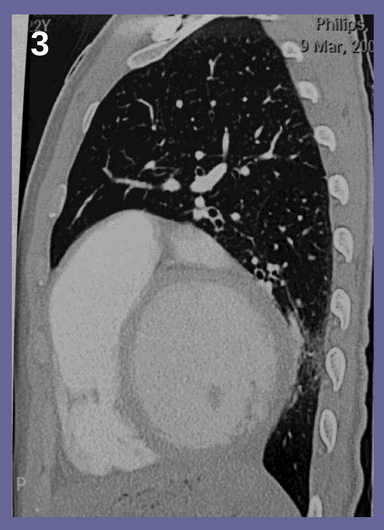
Results:

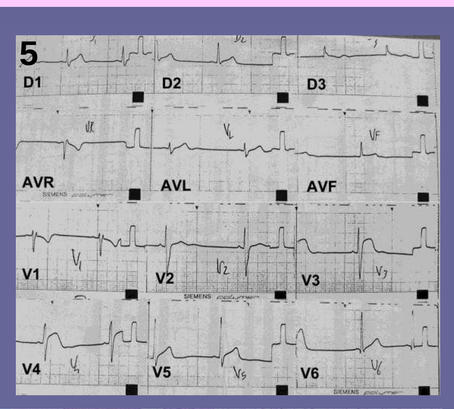
Clinical description: *a family with autosomal dominant dilated cardiomyopathy*

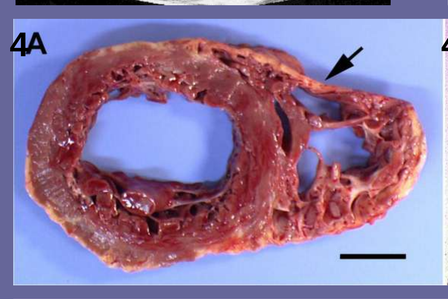
The proband had a membraneous VSD in the neonatal period that closed spontaneously. As he was 17 years old, he had 3 fainting episodes . He had an iRBBB (**Fig. 1**) and an dilated left ventricle (60 mm of diameter at end-diastole) with normokinetics (**Fig. 2 and 3**). At age 21, he became limited in his daily activity due to a shortness of breath. His left ventricle was enlarged to 70 mm with a decrease of contractility (bidimensional ejection EF 20%). An ambulatory ECG evidenced numerous ventricular premature contractions, doublets and triplets. Despite medical therapy, his hemodynamic state deteriorated. Moreover, he experienced a non-sustained ventricular tachycardia. A coronarography showed absence of arterial lesion. He received a heart graft less than 6 months after he started to suffer from shortness of breath.
Macroscopic examination showed an enlarged LV with abnormal thinning of the anterior wall of the RV (**Fig. 4A and B**).











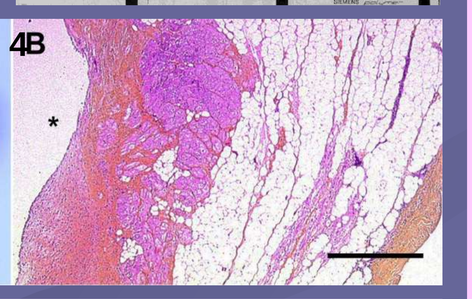


Fig. 1: proband's ECG; **Fig. 2** and **3**: 2D-echo and MRI of proband;
Fig. 4A and **B**: proband's heart showing fibrofatty replacement;
Fig. 5: ECG of the oldest brother during chest pain.

The oldest brother had 3 episodes of chest pain as he was 15, 16 and 27 with an elevated ST segment (**Fig. 5**) and a mild rise of troponin. His LV was dilated (60 mm) but normocontractile (EF 59%). Coronarography was normal
He had spontaneous supraventricular and ventricular premature beats disappearing during physical excercise.

The father had also a dilated cardiomyopathy (LV 60 mm, EF 55%) with prolonged QRS duration.

No **other family member** had any cardiopathy.

Extra-cardiac symptoms make a difference:

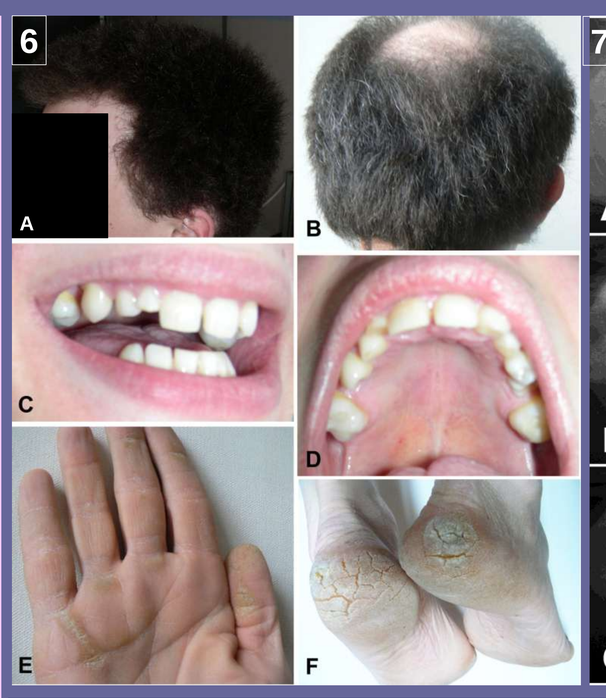
Hair: The proband had curly, fair and fine hair mimicking wool (***wooly hair***) (**Fig. 6A**). The oldest brother and the father (**Fig. 6B**) had also wooly hair.

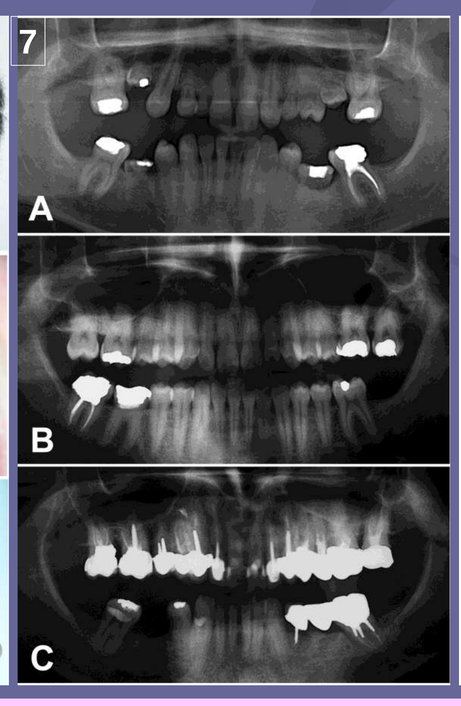
Skin: The skin of proband's hands palms and feet soles was abnormally thick with fissures as shown in the father (**Fig. 6E** and **F**) (***palmoplantar keratoderma***).

Teeth: The proband had only 4 permanent molars and several persisting primary teeth (**Fig. 6C, D** and **7A**). The oldest brother was missing the left mandibular 2nd molar and all 3rd molars (**Fig. 7B**). The father was missing several premolars and molars (**Fig. 7C**) (***hypo/oligodontia***)**.**

No other family members had wooly hair, palmoplantar keratoderma and hypo/oligodontia (**Fig. 8A**).

An heterozygous missense mutation was found in the Desmoplakin gene in the all affected family members but not in any unaffected family members.





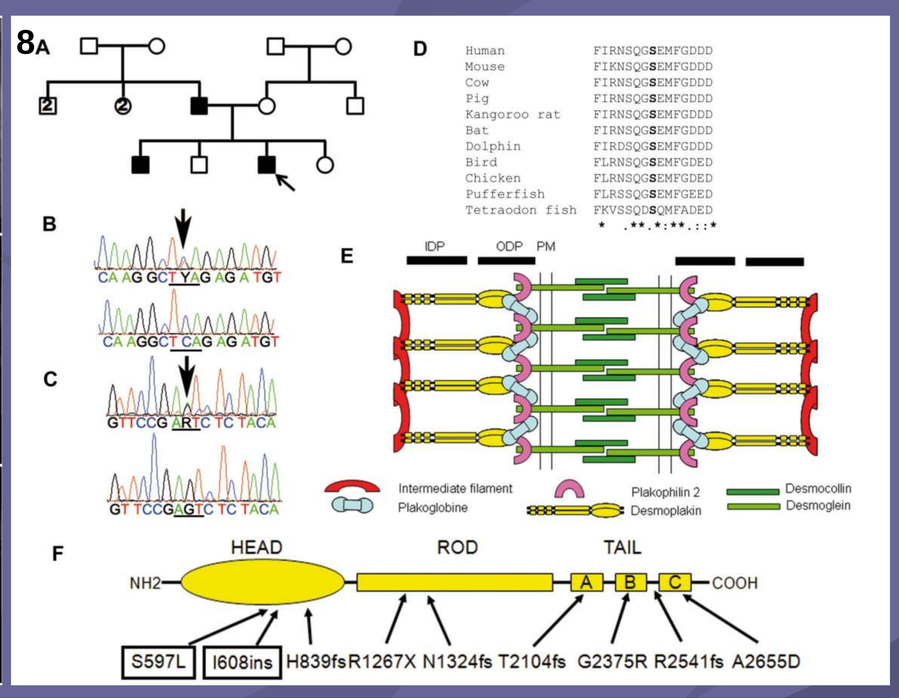


Fig. 6A and B: wooly hair of the proband and his father, respectively; **C** and **D**: images of proband teeth; **E** and **F**: keratoderma of palms and soles of proband's father. Note the fissures of the back part of the heels.

Fig. 7A: proband's panorex radiograph: all second pre-molars, all second and third molars are missing. In addition, the 2 upper lateral incisors and the upper right first pre-molars are missing. Several deciduous teeth are persisting; **B**: brother's panorex. The mandibular left second molar is missing. All 4 third molars are absent; **C**: the father has absent first or second premolars, and second and third molars on the mandibule.

Fig. 8A: pedigree tree of the family. The arrow points to the proband. Filled symbols: affected, empty symbols: unaffected; **B** and **C**: sense and antisense electrophoregrams of proband and control DNA, respectively. The arrow points to the heterozygous mutation; **D**: peptide alignment of the Desmoplakin in the region of the mutation. The serine residue is highly conserved; **E**: schematic presentation of a desmosomal plaque. IDP, inner dense plaque; ODP, outer dense plaque; PM, plasma membrane; **F**: desmoplakin protein. A-C are plakin repeat domains. Reported mutations are indicated. Mutations with dominant inheritance and dental agenesis are boxed.

<u>Conclusion</u>: Pediatric and adult cardiologists should be aware that wooly hair, thickening and fissures of palms and soles or hypo/oligodontia in the setting of a dilated cardiomyopathy suggest a Carvajal/Naxos disease resulting from desmosomal anomalies (Chalabreysse et al., J Dental Res, 2011, 90: 58-64).