# APPLYING GENOMICS TO BIOMEDICINE
# DIAGNOSIS OF ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

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## INTRODUCTION

The arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited heart disease. It is characterized by death of myocytes in the right ventricle and their replacement by fibro-fatty tissue. Major genetic defects are found in desmosomes whose function is cell adhesion. Sudden cardiac death (SCD) is the main problem of ARVD; around of 20% of SCD are involved by ARVD (table 1). 50% of cases have familial distribution with at least one affected patient. The pattern of inheritance is AD and the prevalence range is 1:2500, but varies between populations.

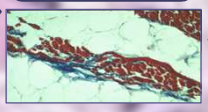
**TABLE 1: CAUSES OF SUDDEN CARDIAC DEATH (%) IN PEOPLE UNDER 35 YEARS OLD. Corrado et al. (1998)**

| CAUSES | ATHLETES | NO ATHLETES | TOTAL |
|---|---|---|---|
| Arrhythmogenic right ventricular dysplasia | 22,4 | 8,2 | 10,8 |
| Coronary arteriosclerosis | 18,4 | 16,4 | 16,7 |
| Anomalous coronary arteries | 12,2 | 0,5 | 2,6 |
| Conduction system disease | 8,2 | 9,1 | 8,9 |
| Mitral valve prolapse | 10,2 | 9,5 | 9,7 |

## OBJECTIVES

The main objective is to discuss the possibility of applying genomics to biomedicine as a genetic test for a long-term disease, for example in ARVD; extrapolating this use in many diseases such as cancer and cardiomyopathies. In particular, presentation of all features of ARVD: clinical characteristics, genetic causes, genetic testing and genetic counseling. Also, introducing a real case to explain improvement of applying genomic testing.

**DESMOSOMES: CELL ADHESION** → HAVE GENETIC ALTERATIONS → **DEATH OF MYOCYTES** → **FIBRO-FATTY INFILTRATION**



**SYMPTOMS:** (figure 1)
Palpitations and syncopes
Advanced phase: RV failure and LV involvement
Sudden Cardiac Death (SCD)

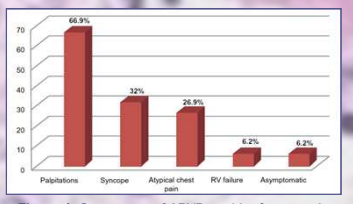
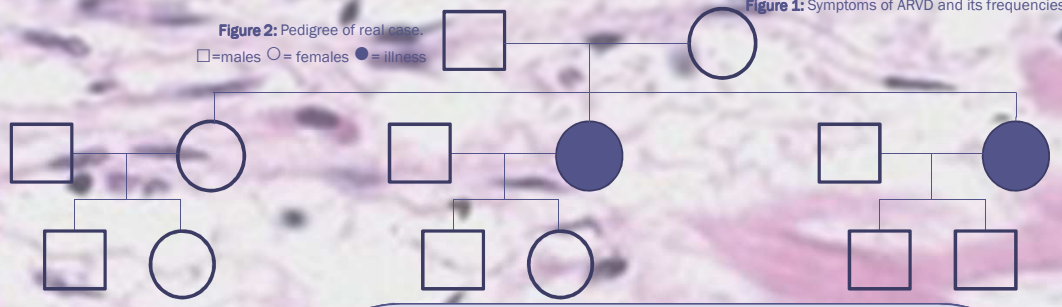



**Figure 1:** Symptoms of ARVD and its frequencies.

## REAL CASE

To introduce genetic testing in ARVD, here it is presented a familiar with two affected females (figure 2). They were diagnosed when they were 30-35 years old.
Any genetic test hasn't been done and any mutation hasn't been found. Also, sons and daughters are too young to present any clinical symptoms. The possible genetic diagnostic is explained in this work.

**Figure 2:** Pedigree of real case.
□=males ○= females ●= illness



## GENETIC CAUSES

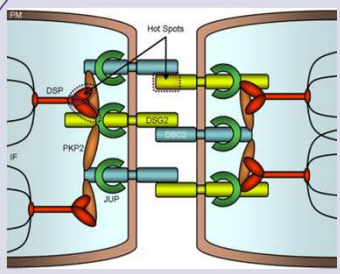



**Figure 3:** Molecular model of desmosomes. Genes are *PKP2, DSC2, DSG2, DSP* and *JUP*.

**TABLE 2: GENES ASSOCIATED WITH ARVD.**

| GENE | LOCUS | PROTEIN |
|---|---|---|
| CTNNA3 | 10q21.3 | αT-catenin |
| DES | 2q35 | Desmin |
| DSC2 | 18q21 | Desmocollin-2 |
| DSG2 | 18q12.1 | Desmoglein-2 |
| DSP | 6p24 | Desmoplakin |
| JUP | 17q21 | Junction plakoglobin |
| LMNA | 1q22 | Lamin A/C |
| PKP2 | 12p11 | Plakophilin-2 |
| PLN | 6q22.1 | Phospholamban |
| TGFβ3 | 14q24.3 | Transforming growth factor β 3 |
| TMEM43 | 3p25.1 | Transmembrane protein 43 |
| TTN | 2q31.2 | Titin |

***PKP2:*** is the most prevalent gene affected in ARVD. There are more than 150 pathogenic mutations identified only in *PKP2* that represent 35-40% of total ARVD cases. A lot of types of mutations have been detected (CNV, splicing, missense, nonsense and frameshift).

***DSC2***, ***DSG2***, ***DSP*** and ***JUP*** are genes that encodes desmosomes, too (table 2 and figure 3). More than 200 mutations have been found in this four genes. Majority of variations are punctual changes as missense mutations. All types of mutations may be detect.

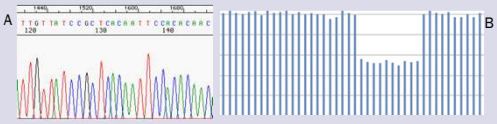
Non-desmosomal genes: recent genes have been discovered, these could relate with cases of misdiagnosis and are important in genetic test; their prevalence is low (10%). These genes are: ***DES***, ***TGFβ3***, ***TMEM43***, ***LMNA***, ***TTN*** and ***PLN*** (table 2). They encode, mainly, intermediate filaments or regulatory elements.

In *ARVD/C Genetic Variants Database,* it is possible to find all variants in this 12 genes with all important information. For that is a good tool for genetic diagnostic.

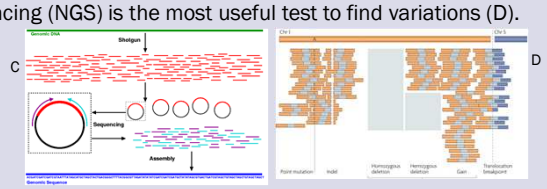
## GENETIC TESTING

The major diagnosed people has a mutation in PKP2 (40%), around 40% people is not diagnosed and other 20% is affected different other genes.

oThere are techniques used to find variations only in one sequence of the genome: Sanger sequencing (A) and MLPA (B). Usually, are the first steps to look for a mutation in *PKP2.*




oMore genetic causes in different chromosomes, it would be more efficient to use a whole-genome technique (C). Next Generation Sequencing (NGS) is the most useful test to find variations (D).




oIdentifying variations in *ARVD/C Genetic Variants Database* (E) to know all information of this variant.

E

| Gene | Mutation | DNA change | Protein change | Exon | Locus | Type | Reported Classification | Grantham Score | SIFT | PolyPhen | Domain | Notes | LOVD ID |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PKP2 | Del exon 1-4 | c.1-?_542+?del | - | | 1 | 12p11 | Deletion | Pathogenic | | | | | |

Clinical reports of this mutation in patients and controls

| Article | Article details | Controls | Patient | # Affected Relatives | Notes |
|---|---|---|---|---|---|
| Cox et al. Circulation 2011;123:2690-2700. | Article details | 0/400 | TFC+ | 1 | |

## ETHICAL QUESTIONS

Key information and suggestions that cardiologists should know:
➢Genetic testing in patients and relatives (al least two diagnosed in a family)
•Interpretation of the results: mode of inheritance and risk recurrence, molecular genetics, penetrance and natural history and variable expressivity.
•Organization of genetic counselling, principles of bioethics.
➢Possible prenatal or preimplantation diagnostic if variations have been found.

## CONCLUSIONS

▪ARVD is a polygenic disease and can evolve to a SCD (20%) or other malignant symptoms.
▪Applying genomics to biomedicine may help as a good tool in some complicated diseases as cardiomyopathies or cancer.
▪Whole-genome testing will be important in research and diagnostic to these diseases.
▪Genetic causes and diagnostic of ARVD have been explained to solve real cases of affected families and the manner to help to improve their life.

## REFERENCES

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