# Transposable elements and their involvement in several human muscular dystrophies

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## Introduction

Nearly **50% of the human genome is composed of transposable elements** (TEs) and, although they were initially called "junk DNA", they play an essential role in shaping the structure, variability and function of our genome.

TEs were successfully accumulated in the human genome throughout evolution. They are divided into two main classes: DNA transposons (3%) and retrotransposons (40%) Both classes are composed of different subgroups, but only **LINEs (17%)**, **SINEs (11%)** and **SVAs (0,2%)** elements (non-LTR retrotransposons) are actively mobilized in the human genome. LINE elements are autonomous retrotransposons but SINE and SVA elements need the enzymatic machinery of LINEs for their transposition.

Together, the transposable elements **L1, Alu and SVA are responsible for 0.27% of all human mutations** discovered to date. These elements are a source of genetic variability, and sometimes disease, by a wide range of molecular mechanisms.

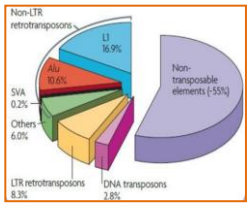


**Figure 1.** Distribution of TEs in the human genome.
Cordaux, R. et al, (2009)

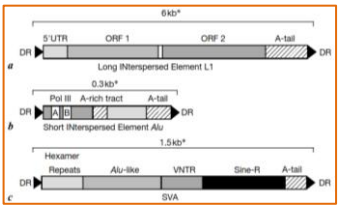


**Figure 2.** Active retrotransposons in the human genome.
Callinan, PA. et al, (2006)

## Objectives

- Generate knowledge about the huge source of genetic variability generated by TEs and about the importance of TEs in human genome evolution.
- Understand the importance of studying the different types of TEs and their involvement in different human muscular dystrophies.

## Methodology

Review of some human muscular dystrophies that are associated with the insertion of different transposable elements in important regions of the human genome.

- Articles
- Books
- Web resources

## Contribution of TEs in the development of human muscular dystrophies

### LINEs

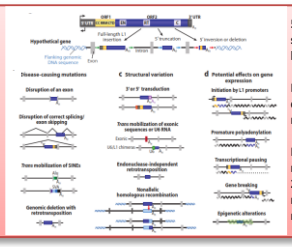

**Figure 3.** Various ways that L1-mediated retrotransposition events can impact the human genome.
Beck, C. et al, (2011)

**500,000 copies of L1 are scattered throughout the human genome.**

**L1 is actively mobilized by different mechanisms of retrotransposition.**

**L1 elements are directly responsible for less than 20% of human diseases related with events of retrotransposition.**

### SINEs

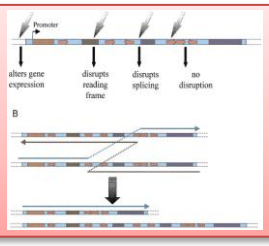


**Figure 5.** Various ways that Alu can induce DNA damage.
Deininger, P. et al, (1999)

**Alu elements present high levels of polymorphism in each individual.**

**The recent transposition of these elements is responsible for a significant number of human muscular dystrophies: French Walker Warburg syndrome, X-linked dilated cardiomyopathy or myotonic dystrophy.**

### SVAs

**The SVA elements are the least studied group of retrotransposons.**

**Haploid human genome has about 3,000 SVA elements.**

**SVAs have very low nucleotide divergence: recent origin and proliferation.**

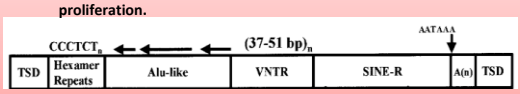


**Figure 7.** Structure of a full SVA element.
Ostertag, EM. et al, (2001)

## Examples

### DUCHENNE MUSCULAR DYSTROPHY

Serious disease caused by a deficiency of functional dystrophin.
Wide variety of mutations in the human dystrophin gene: deletions, duplications and point mutations.

Analysis of dystrophin gene in two Japanese brothers with DMD.

They found a **600 bp insertion into the 3' end of exon 44 of the DMD gene** → aberrant splicing → exon-skipping.

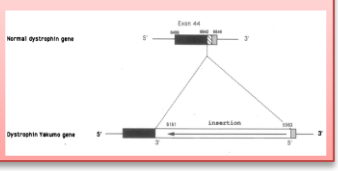


**Figure 4.** Scheme of insertion mutation into exon 44 of the dystrophin gene.
Narita, N. et al, (1993)

### FRENCH WALKER WARBURG SYNDROME

**Figure 6.** Patient with WWS syndrome.

Severe disorder associated with congenital muscular dystrophy and ocular abnormalities.

An analysis of five fetuses from three unrelated French families, found an **insertion of an Alu element with inverted DNA repeats in exon 3 of the POMT1 gene**.

### FUKUYAMA CONGENITAL MUSCULAR DYSTROPHY

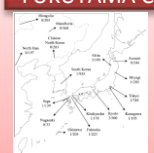

**Figure 8.** Geographical distribution of FCMD patients carrying the insertion.
Watanabe, M. et al, (2005)

FCMD is one of the most common autosomal recessive disorders in Japan. Associated with severe muscular dystrophy and brain malformations.

The **insertion of a 3 Kb SVA element in the 3 'UTR of fukutin gene** is responsible for an aberrant splicing → shorter transcript in FCMD patients. Most FCMD patients descend from a common ancestor (2,500 years ago) carrier of a SVA insertion element.

## Conclusions

There is widespread evidence that transposable elements play an important role in remodelling of the human genome. Science has come a long way since Barbara McClintock discovered the presence of transposable elements in maize more than fifty years ago.

**Personalized medicine**. In the future, it will be vital to take into account the profile of transposable elements in patients with some form of muscular dystrophy.
**One example of gene therapy**. Use of antisense oligonucleotides that block the aberrant splicing caused by the insertion of an intronic SVA element in FCMD.

Thanks to the optimization of the technological tools we will be able to identify a larger number of insertions of these elements and understand their role in the diversity of individual genomes, in different populations and in different human muscular dystrophies.

## REFERENCES

[1]. Ostertag, EM. *et al. SVA elements are nonautonomous retrotransposons that cause disease in humans*. Humane Genetics, (2003)
[2]. Callinan, P.A. and Batzer, M.A. *Retrotransposable elements and human disease*. Genome and disease, (2006)
[3]. Deininger, P. and Batzer, M.A. *Alu repeats and human disease*. Molecular Genetics and Metabolism, (1999)
[4]. Bouchet, C. *et al. Detection of an Alu insertion in the POMT1 gene from three French Walker Warburg syndrome families*. Molecular Genetics and Metabolism, (2007)4[13]. Beck, C. *et al. LINE1 elements in structural variation and disease*. Human Genetics, (2011)
[5]. Musova, Z. *et al. A novel insertion of a rearranged L1 element in exon 44 of the dystrophin gene: further evidence for possible bias in retroposon integration*. Elsevier, (2006)
[6]. Taniguchi-Ikeda, M. *et al. Pathogenic exon-trapping by SVA retrotransposon and rescue in Fukuyama muscular dystrophy*. Nature, (2012)
[7]. Watanabe, M. *et al. Founder SVA retrotransposal insertion in Fukuyama-type congenital muscular dystrophy and its origin in japanese and northeast asian populations*. American Journal of Medical Genetics, (2005)