The Dystroglycanopathies:
2012 Patient and Family Conference

Deciphering the genetic basis of dystroglycanopathies: the beginning of the story.

SEN. PAUL D. WELLSTONE MD COOPERATIVE RESEARCH CENTER

LGMD2iFund
Limb Girdle Muscular Dystrophy 2I Research Fund

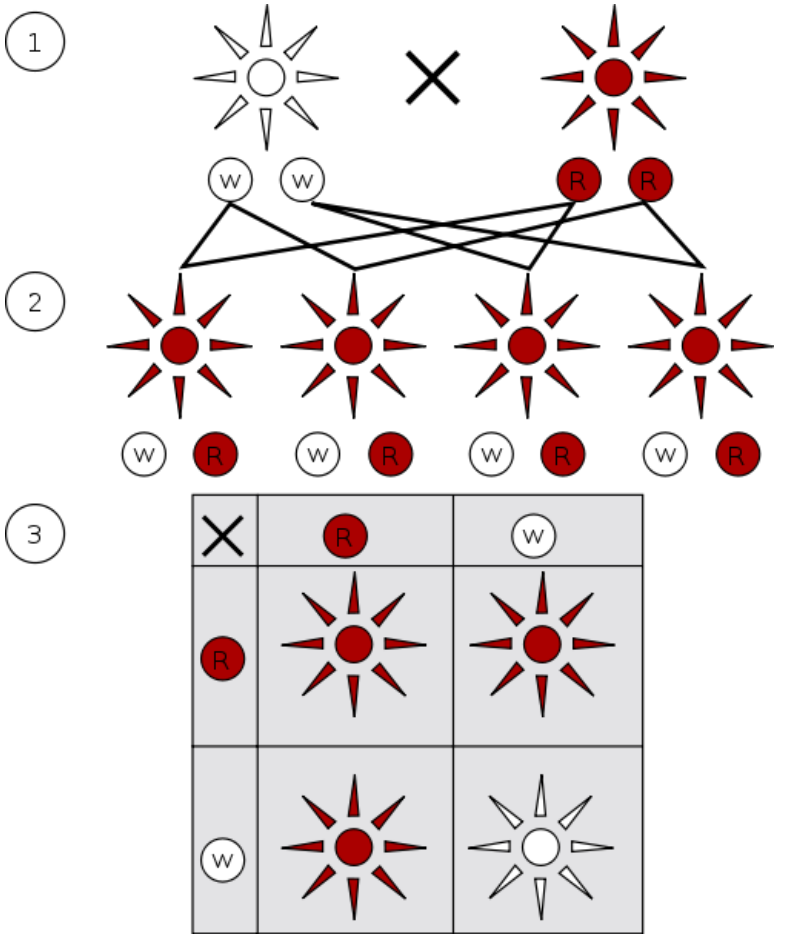
Genetics. The mendelian inheritance

Gregor Mendel 1865.

Between 1856 and 1863 he tested some 29,000 pea plants (*i.e., Pisum sativum*).

The three laws Mendel deduced seem common-sense now, but were radically new in his day:

1. **Law of Paired Factors**: Traits come in pairs (**alleles**), and each parent contributes just one of the alleles.
2. **Law of Dominance**: In a pair of genes (**genotype**), one allele will dominate the other and control the outward appearance (**phenotype**).
3. **Law of Segregation**: Traits are **inherited independently**.



Genetics. Mendel re-discovered

Gregor Mendel 1865. He was cited only 3 times in 35 years!!!

After Charles Darwin (On the Origin of Species, 1859).

Blending inheritance generally accepted.

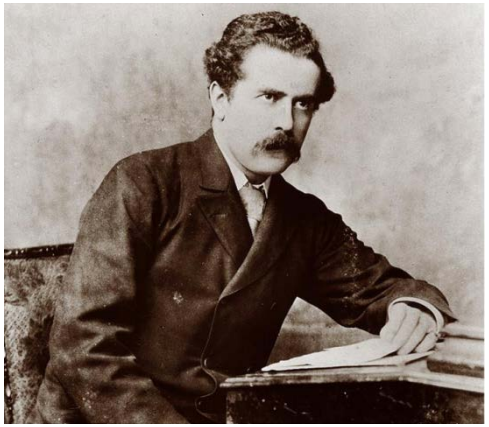
Saltationism vs Gradulamism.

By 1900, research aimed at finding a successful theory of discontinuous inheritance rather than blending inheritance led to independent duplication of his work by Hugo de Vries and Carl Correns, and the rediscovery of Mendel's writings and laws.

Willian Bateson begins to report a series of breeding experiments, conducted by his pupil, Miss E.R. Saunders, using the alpine brassica *Biscutella laevigata* in the Cambridge botanic gardens.

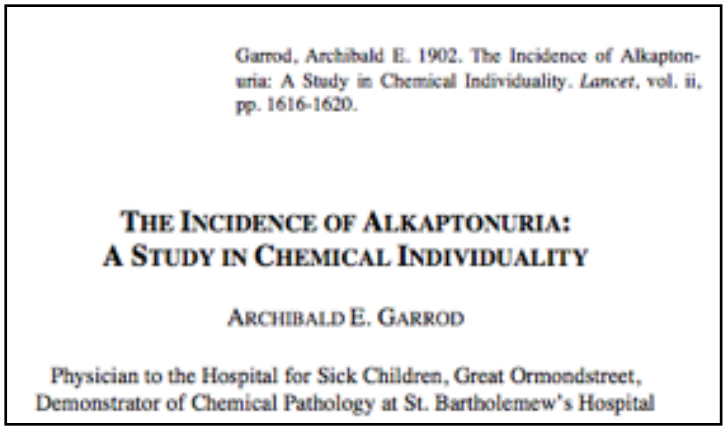
Bateson was the first to suggest the word "**genetics**" (from the Greek gennō, *γενώ*; *to give birth*) to describe the study of inheritance and the science of variation in a personal letter to Alan Sedgwick, dated April 18, 1905.

Garrod. Human genetics.



1898, a woman brought her newborn baby to his clinic. It seemed healthy, but she had noticed that its diapers turned an alarming black.

Garrod identified the condition as alkaptonuria, an exceedingly rare and essentially harmless condition believed at the time to be caused by a microbe.



Garrod, Archibald E. 1902. The Incidence of Alkaptonuria: A Study in Chemical Individuality. *Lancet*, vol. ii, pp. 1616-1620.

THE INCIDENCE OF ALKAPTONURIA:
A STUDY IN CHEMICAL INDIVIDUALITY

ARCHIBALD E. GARROD

Physician to the Hospital for Sick Children, Great Ormondstreet, Demonstrator of Chemical Pathology at St. Bartholemew's Hospital

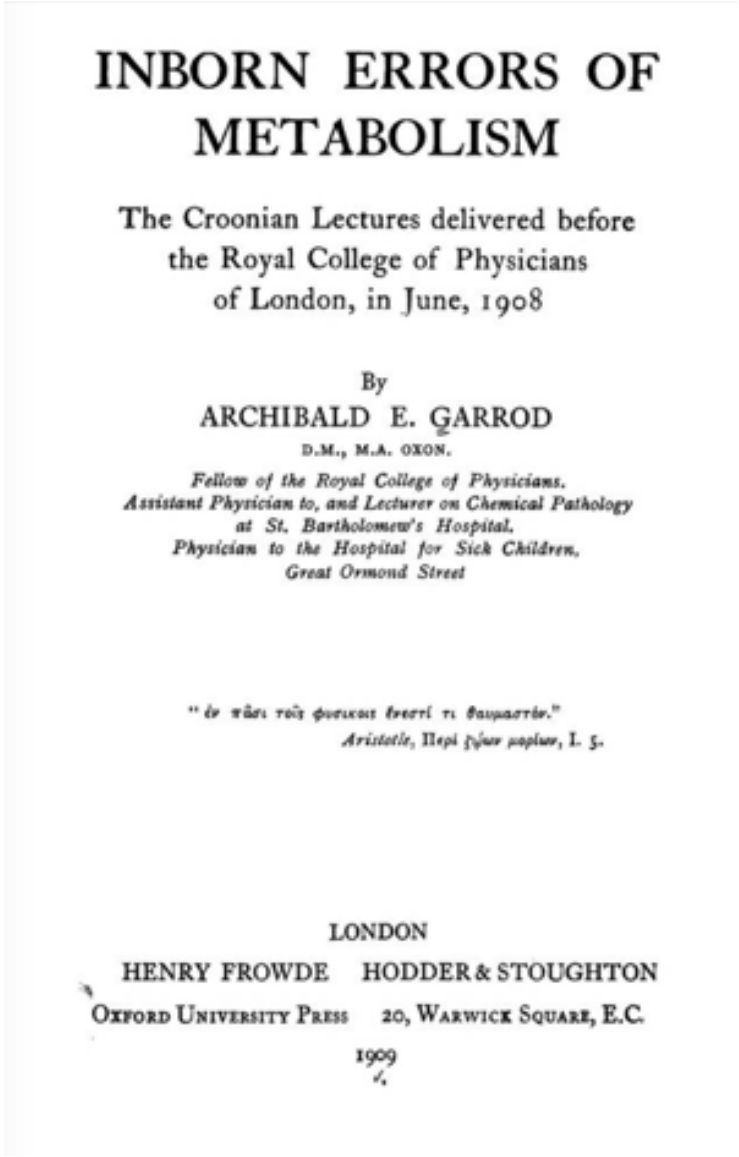
Garrod collected all the cases he could, mapped out pedigrees, and published a short note on it, suggesting that the high frequency within the families of his study could hardly be due to chance.

Bateson read his paper and collaborated with him.

Alkaptonuria was the frst human condition defined as a mendelian trait.

"There are good reasons for thinking that alkaptonuria is not the manifestation of a disease but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong."

Garrod. Human genetics.



INBORN ERRORS OF METABOLISM

The Croonian Lectures delivered before the Royal College of Physicians of London, in June, 1908

By

ARCHIBALD E. GARROD

D.M., M.A. OXON.

Fellow of the Royal College of Physicians.
Assistant Physician to, and Lecturer on Chemical Pathology at St. Bartholomew's Hospital.
Physician to the Hospital for Sick Children, Great Ormond Street

"ἐν πᾶσι τοῖς φυσικοῖς ἔνεστί τι θαυμαστόν."
Aristotle, Περὶ ζῴων μορίων, I. 5.

LONDON

HENRY FROWDE HODDER & STOUGHTON

OXFORD UNIVERSITY PRESS 20, WARWICK SQUARE, E.C.

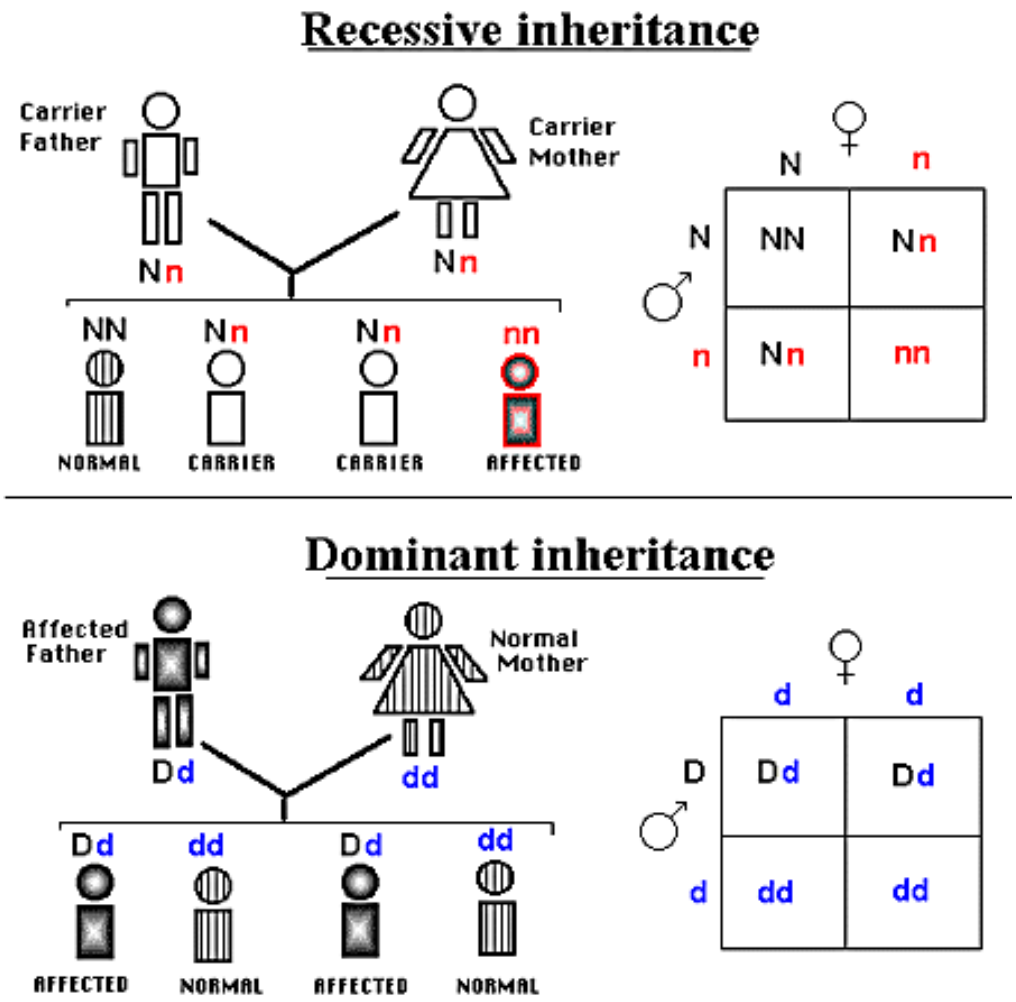
1909

Garrod's Tetrad:

- Alkaptonuria
- Cystinuria
- Pentosuria
- Albinism

personal examination. However, one point which stands out clearly is the remarkable similarity of the modes of incidence of alkaptonuria and albinism, which suggests that the manifestation of both is governed by the same laws. Both are apt to occur in several brothers and sisters of a family whose parents do not exhibit the anomaly, and direct transmission of either from parent to child is very rare. It has been repeatedly stated that a considerable proportion of human albinos are the offspring of consanguineous marriages. Thus

Garrod. Human genetics.

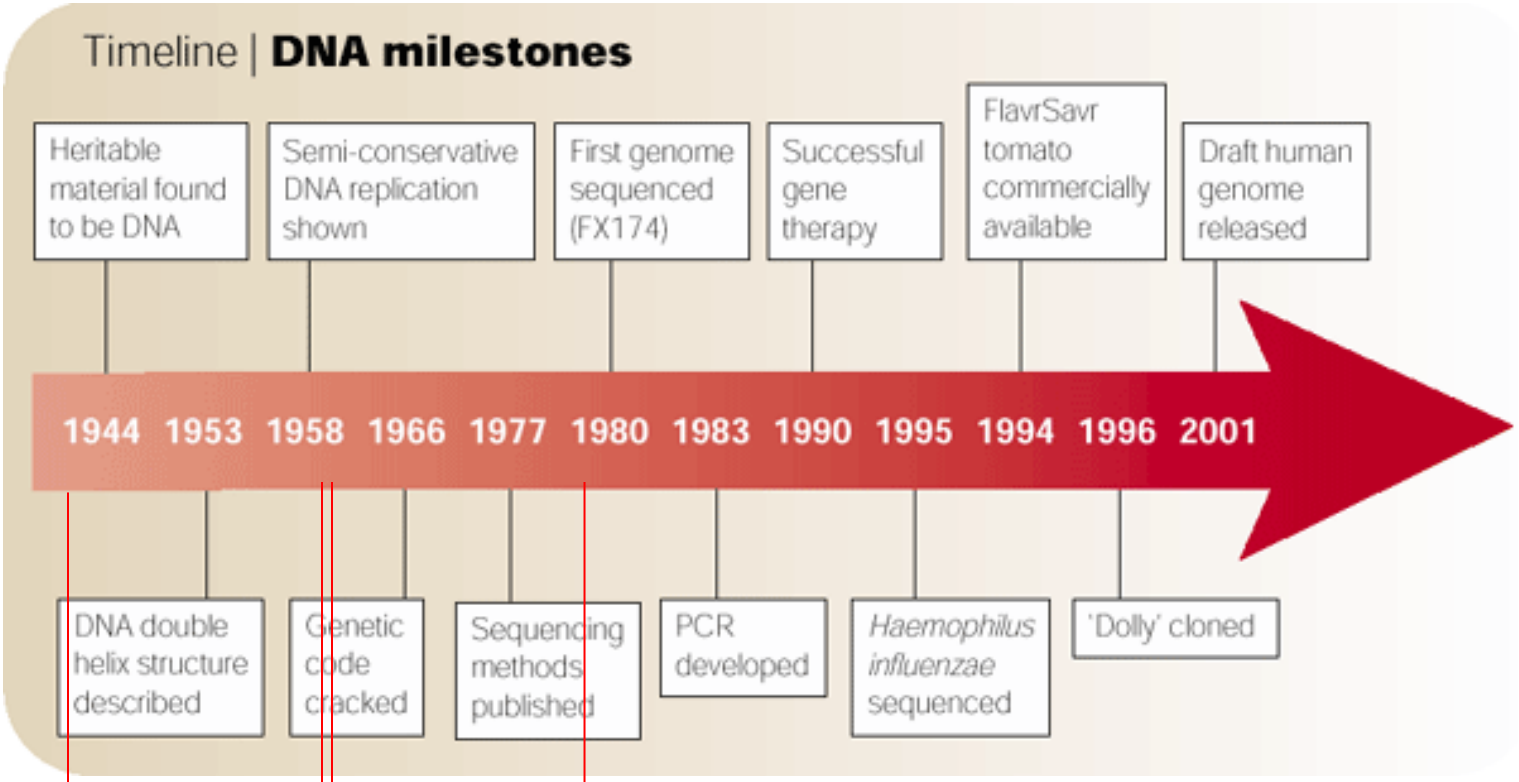


One congenital syndrome

One gene

One allele (recessive)

Human Molecular Genetics.



Walker 1942 **WWS**

Chung and Morton 1959 **LGMD**

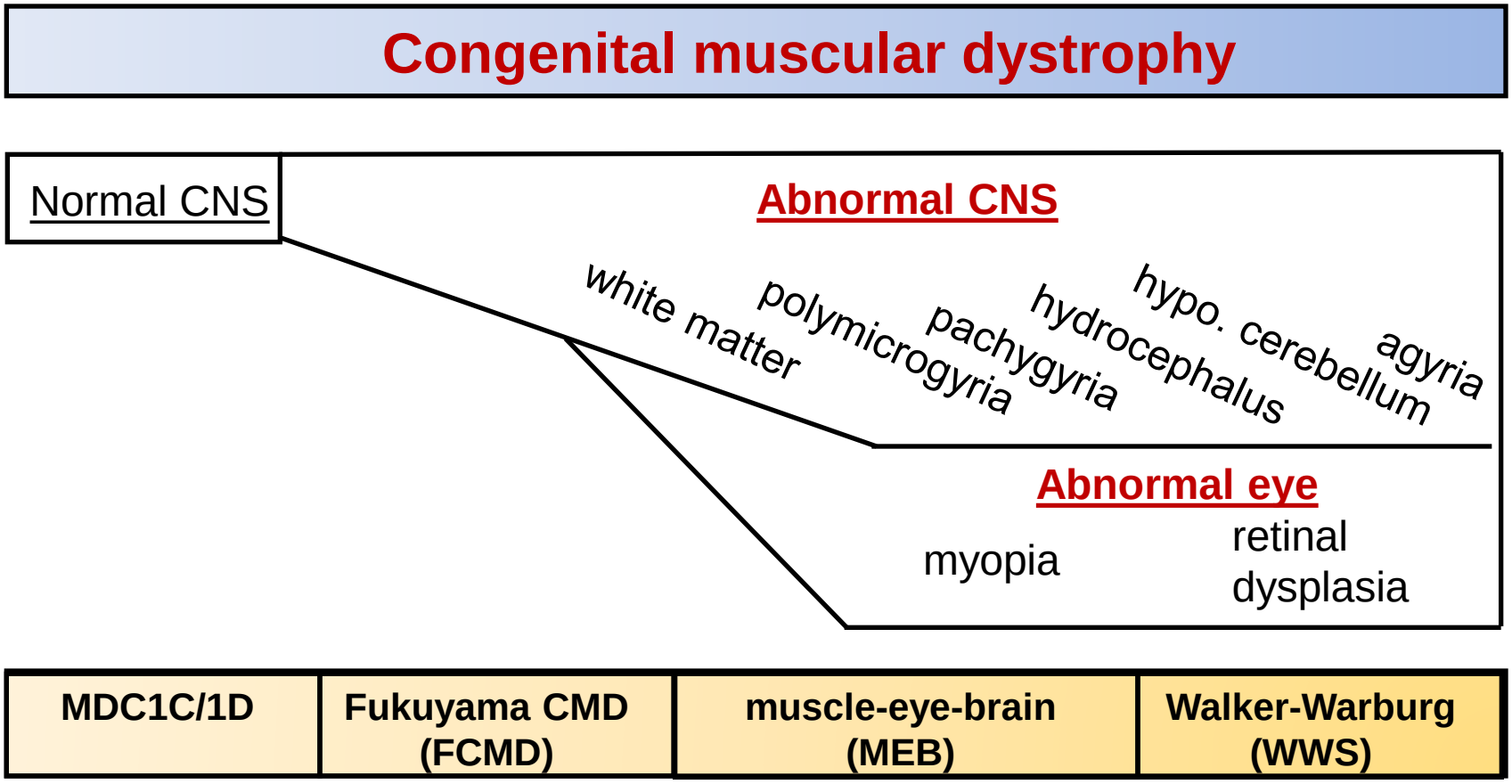
Fukuyama 1960 **FCMD**

Raitta et al 1978 **MEB**

Warburg 1978 **WWS**

Congenital Muscular Dystrophies

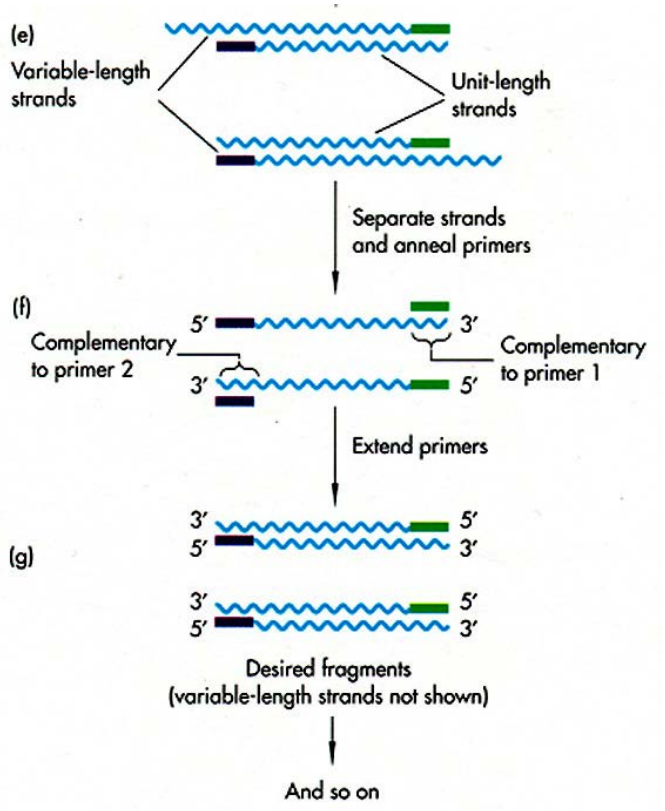
One gene, one syndrome dogma

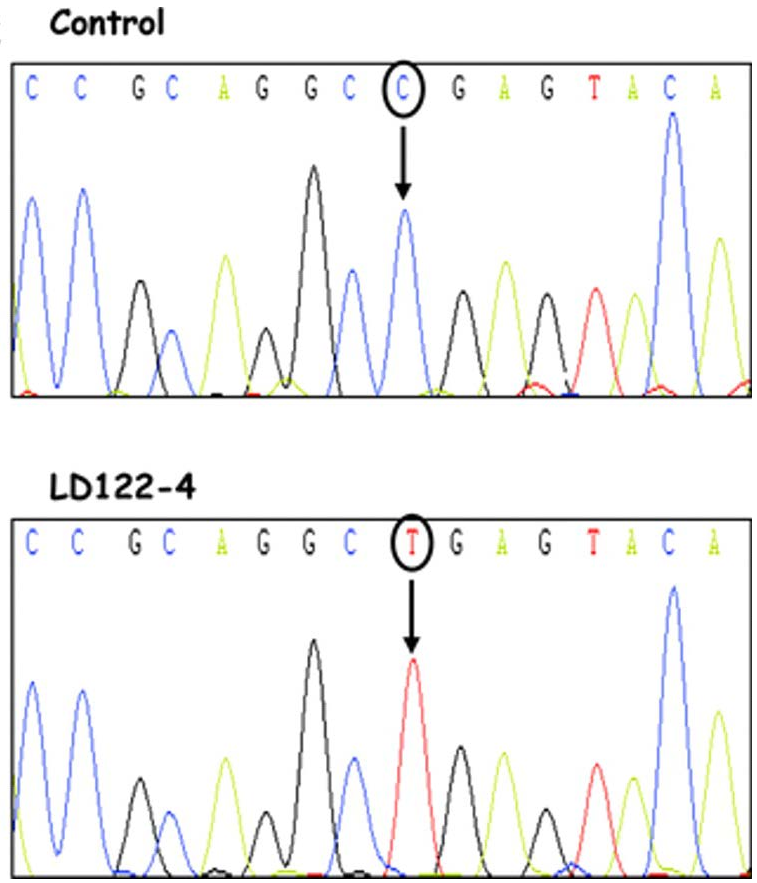


Tobias Willer (adapted from Yoshioka et al, 1997)

Mutations identification.

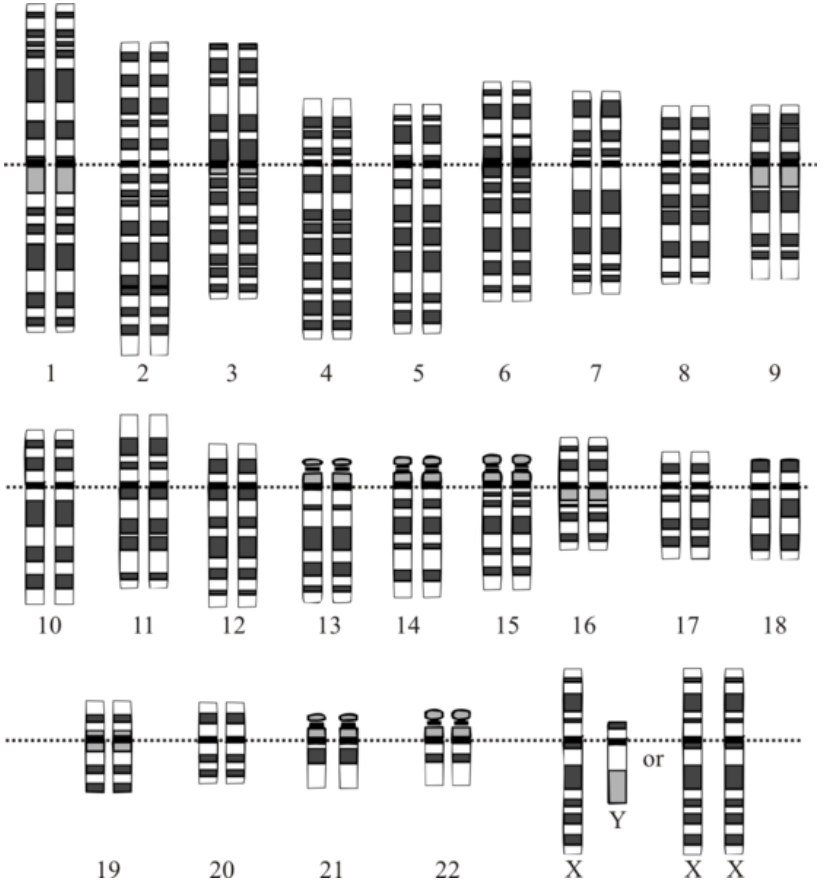
How do we identify the mutations?





The Human Genome.

The haploid human genome is 3.2 billion base pairs long and contains about 23,000 distinct protein-coding genes.



Only 1.5% of human genome codes for proteins,
the rest consists of:

- non-coding RNA genes,
- regulatory sequences,
- introns,
- and noncoding DNA (once known as "junk DNA").

Causative Gene Identification.

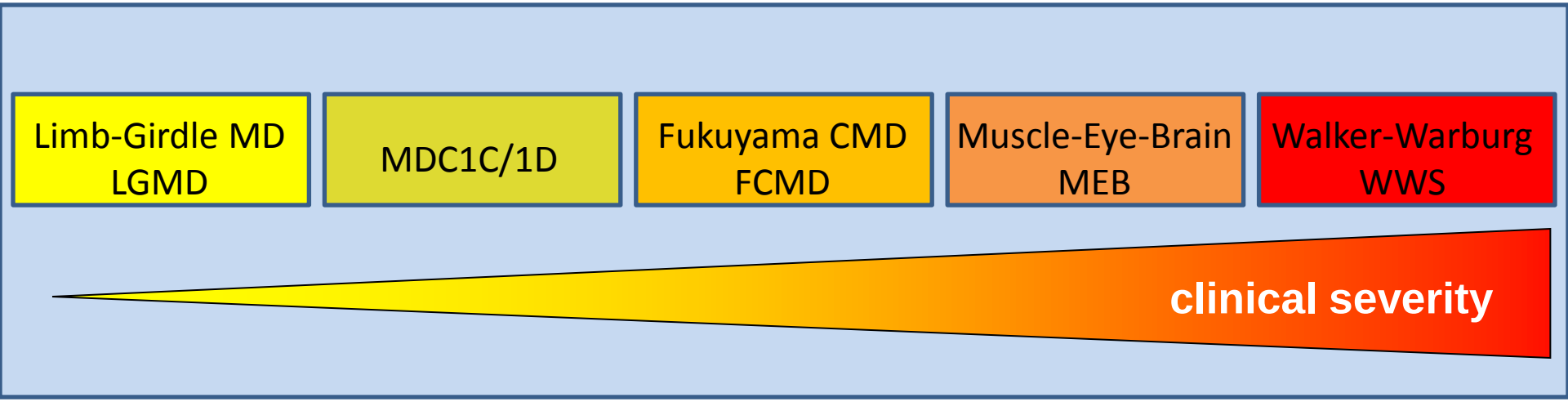
Candidate gene approach

FKRP
POMGnT1
POMT1
LARGE
POMT2
dystroglycan

Identification of the Human Gene Mutated

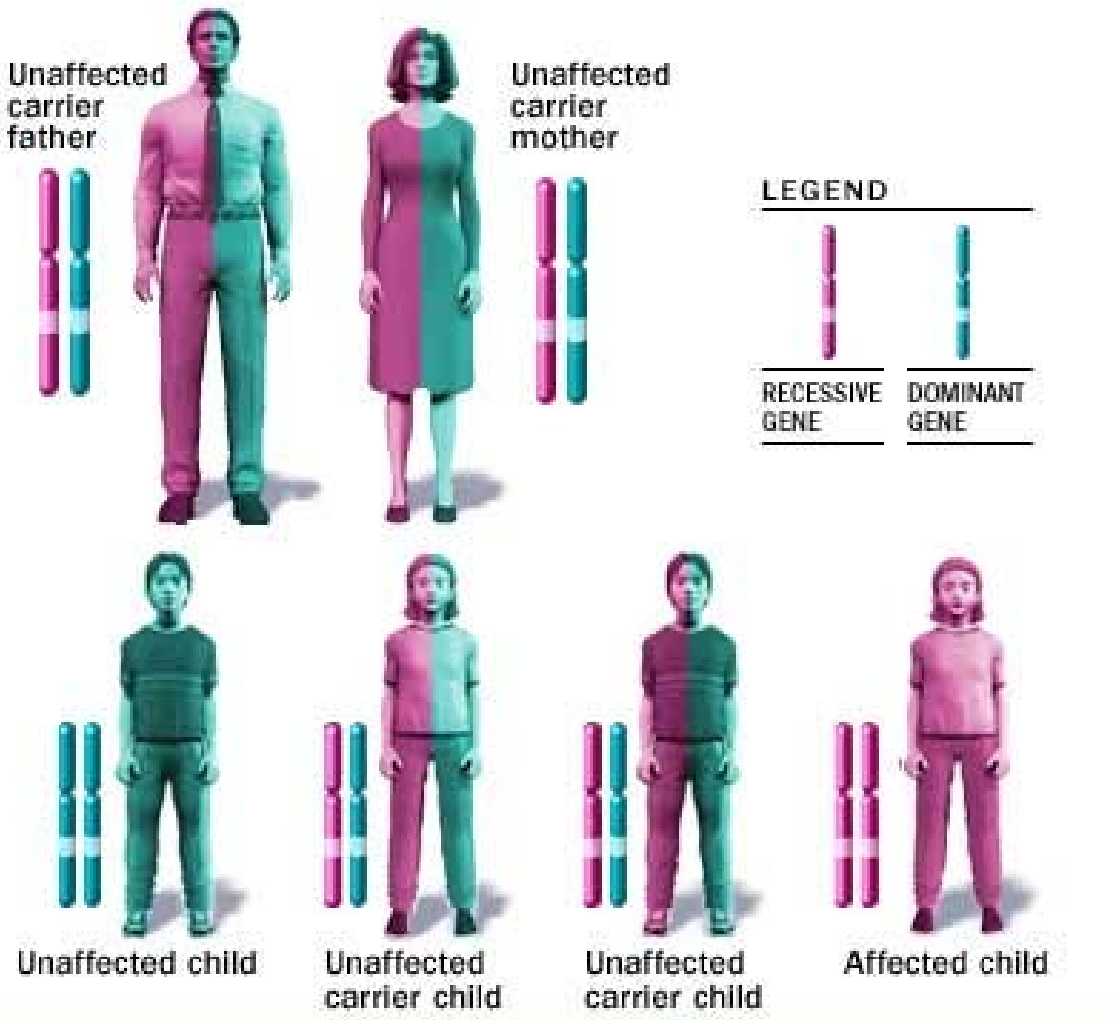
Fukutin
POMGnT1

Map the region that contains it



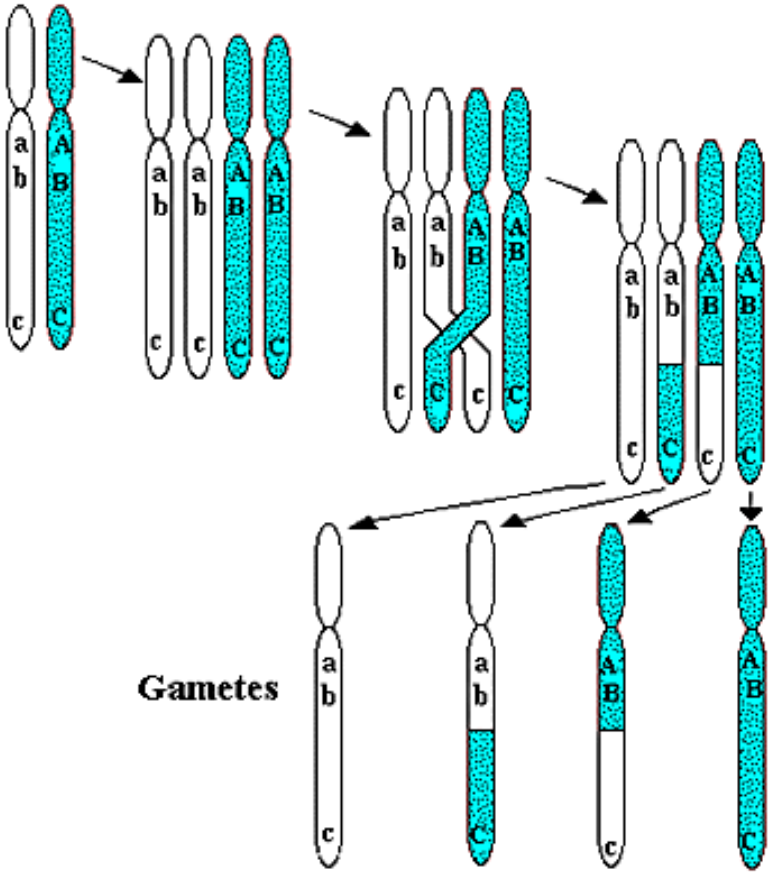
Recombination and positional cloning.

But…. how do we find them????



Recombination.

But…. how do we find them????

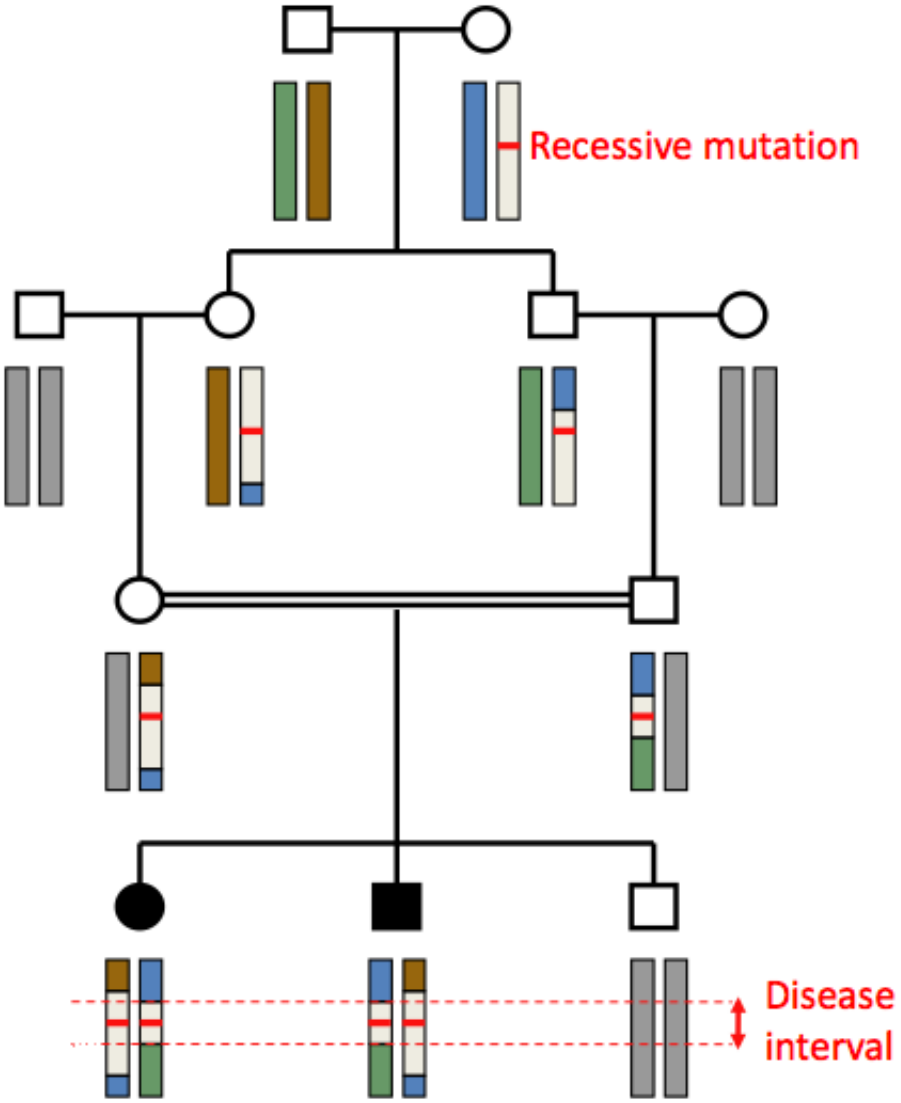


Crossing-over and recombination during meiosis

Let's play a game:

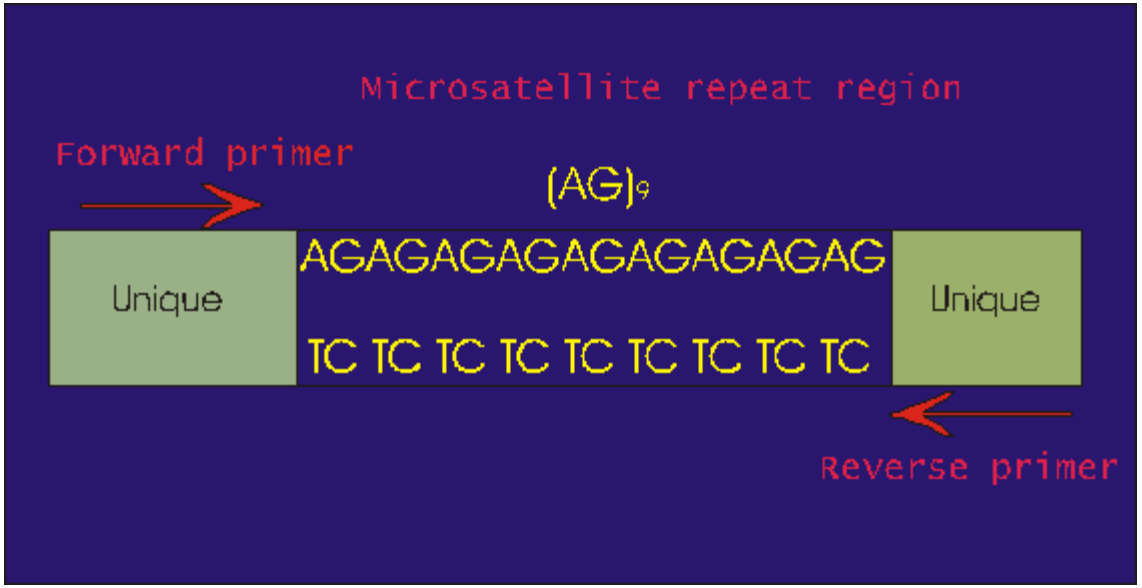
- Consanguineous family
- Recombination
- Positional cloning
- polymorphisms

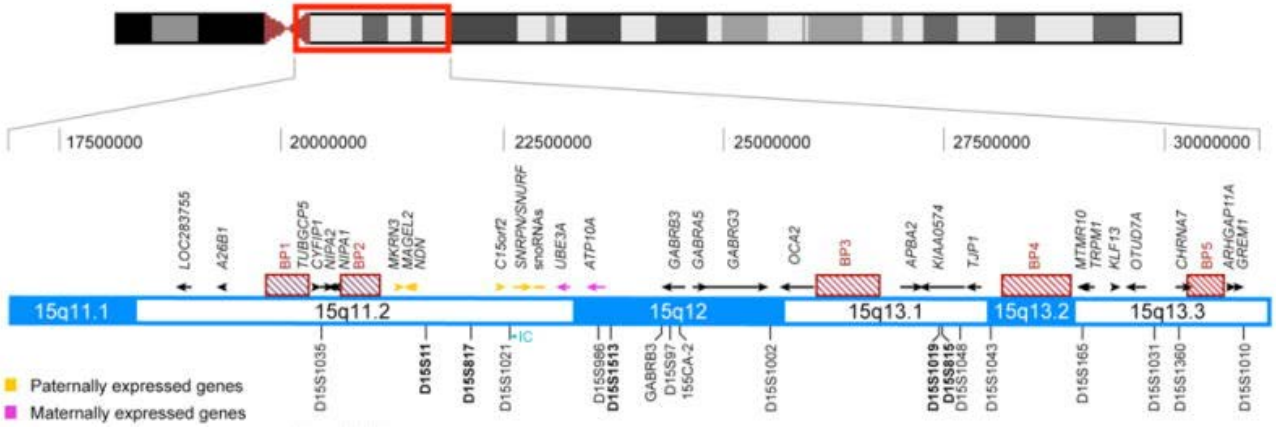
Positional cloning.



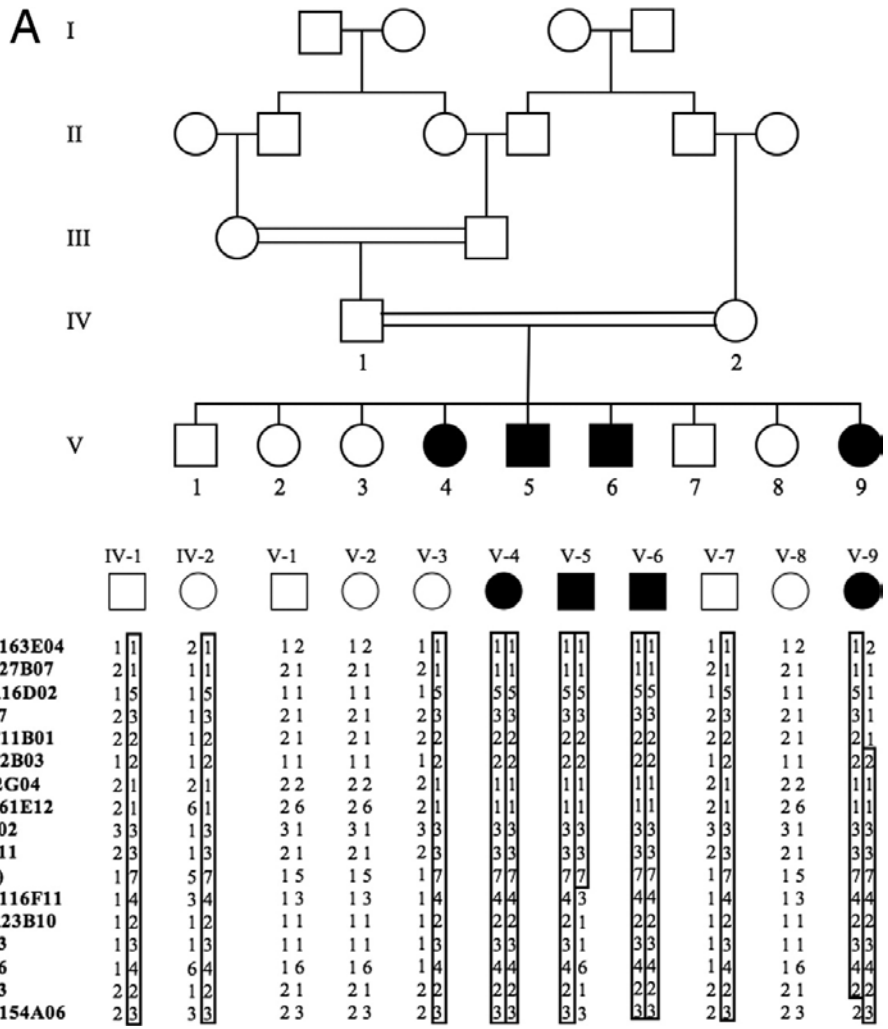
Positional cloning.

They are polymorphisms





Positional cloning.



BBS11 pedigree and shared haplotype.

Chiang A P et al. PNAS 2006;103:6287-6292

FCMD and Fukutin

article

Localization of a gene for Fukuyama type congenital muscular dystrophy to chromosome 9q31–33

T. Toda[1,2], M. Segawa[3], Y. Nomura[3], I. Nonaka[4], K. Masuda[5], T. Ishihara[6], M. Suzuki[7], I. Tomita[8], Y. Origuchi[9], K. Ohno[10], N. Misugi[11], Y. Sasaki[12], K. Takada[13], M. Kawai[14], K. Otani[15], T. Murakami[16], K. Saito[17], Y. Fukuyama[17], T. Shimizu[18], I. Kanazawa[2] & Y. Nakamura[1]

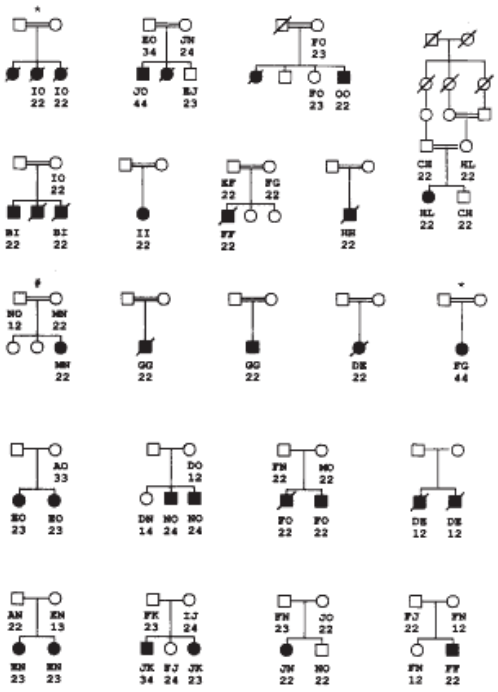
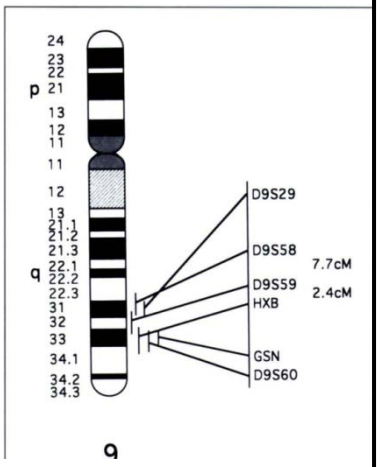


Fig. 2 Pedigrees of 21 FCMD families showing disease status and segregation of the two closest markers, *D9S58* (top) and *D9S59* (bottom). Alleles for *D9S58* are: A, 147 bp; B, 145 bp; C, 143 bp; D, 137 bp; E, 135 bp; F, 133 bp; G, 131 bp; H, 129 bp; I, 127 bp; J, 125 bp; K, 123 bp; L, 121 bp; M, 119 bp; N, 117 bp; O, 115 bp. Alleles for *D9S59* are: 1, 116 bp; 2, 114 bp; 3, 112 bp; 4, 96 bp. Solid symbols, affected subjects; slash, subject deceased. *, Second-cousin marriage; #, first and half-cousin marriage; other consanguineous marriages are first-cousins.



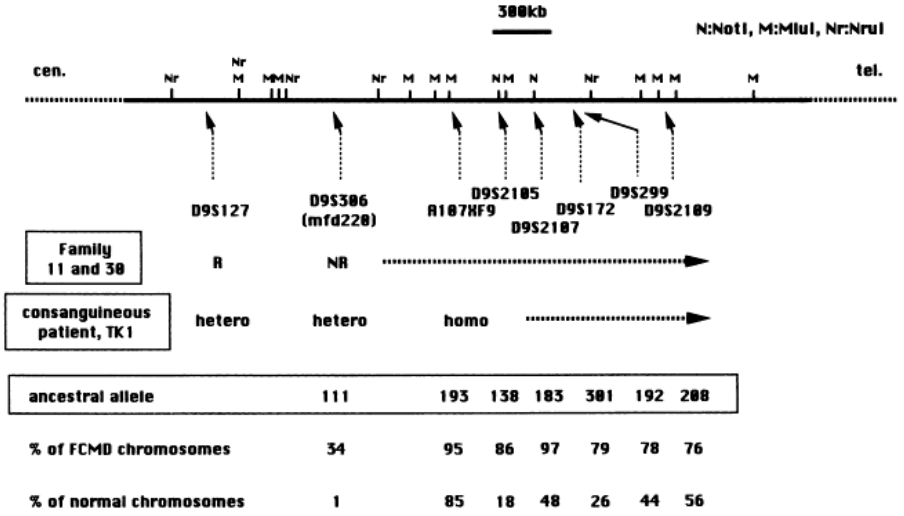
More than 500 genes

Am. J. Hum. Genet. 59:1313–1320, 1996

Linkage-Disequilibrium Mapping Narrows the Fukuyama-Type Congenital Muscular Dystrophy (FCMD) Candidate Region to <100 kb

Tatsushi Toda,[1] Masashi Miyake,[1] Kazuhiro Kobayashi,[1] Kunihiko Mizuno,[1] Kayoko Saito,[4] Makiko Osawa,[4] Yusuke Nakamura,[3] Ichiro Kanazawa,[2] Yasuo Nakagome,[1] Katsushi Tokunaga,[1] and Yutaka Nakahori[1]

Departments of [1]Human Genetics and [2]Neurology, University of Tokyo, and [3]Laboratory of Molecular Medicine, Institute of Medical Science, University of Tokyo, and [4]Department of Pediatrics, Tokyo Women's Medical College, Tokyo

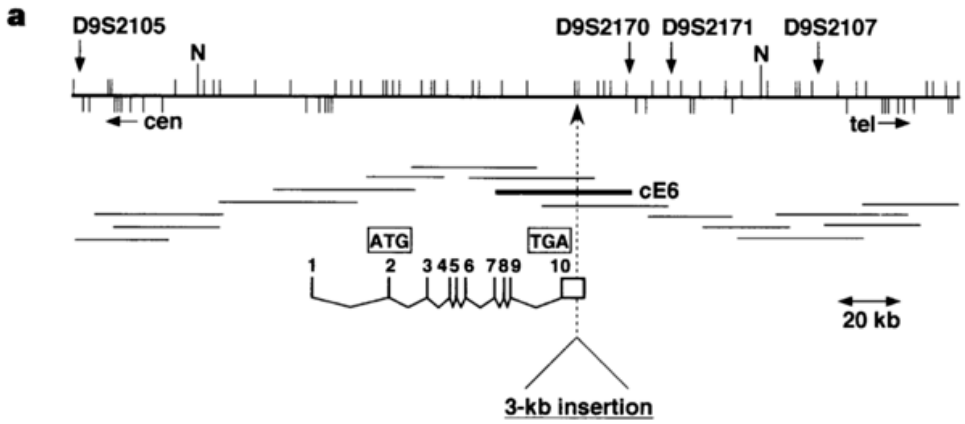


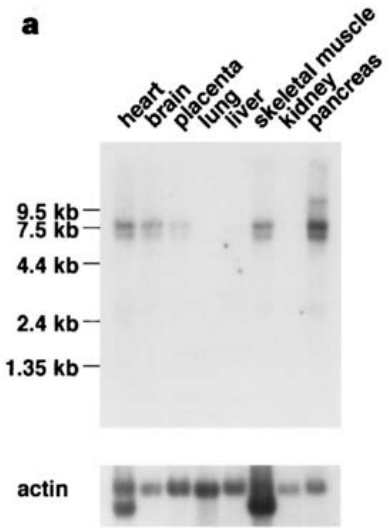
FCMD and Fukutin

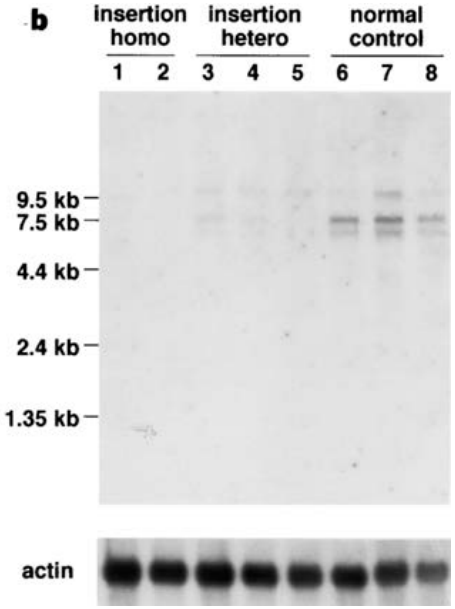
1998. Nature, 394:388-392.

An ancient retrotransposal insertion causes Fukuyama-type congenital muscular dystrophy

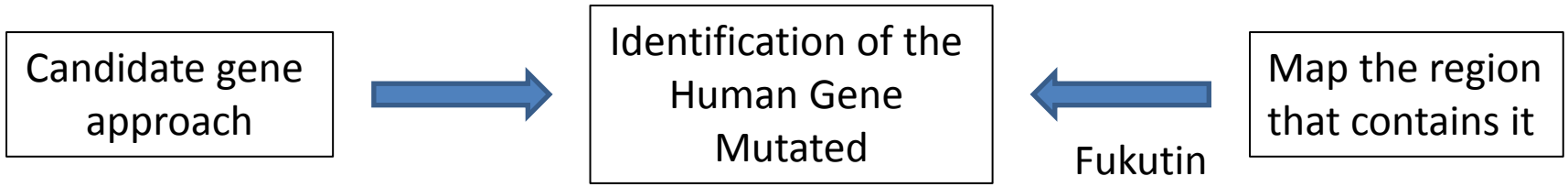
Kazuhiro Kobayashi*†, Yutaka Nakahori‡, Masashi Miyake†, Kiichiro Matsumura§, Eri Kondo-Iida*‖, Yoshiko Nomura¶, Masaya Segawa¶, Mieko Yoshioka#, Kayoko Saito‖, Makiko Osawa‖, Kenzo Hamano☆, Youichi Sakakihara**, Ikuya Nonaka††, Yasuo Nakagome†, Ichiro Kanazawa‡‡, Yusuke Nakamura§§, Katsushi Tokunaga† & Tatsushi Toda*

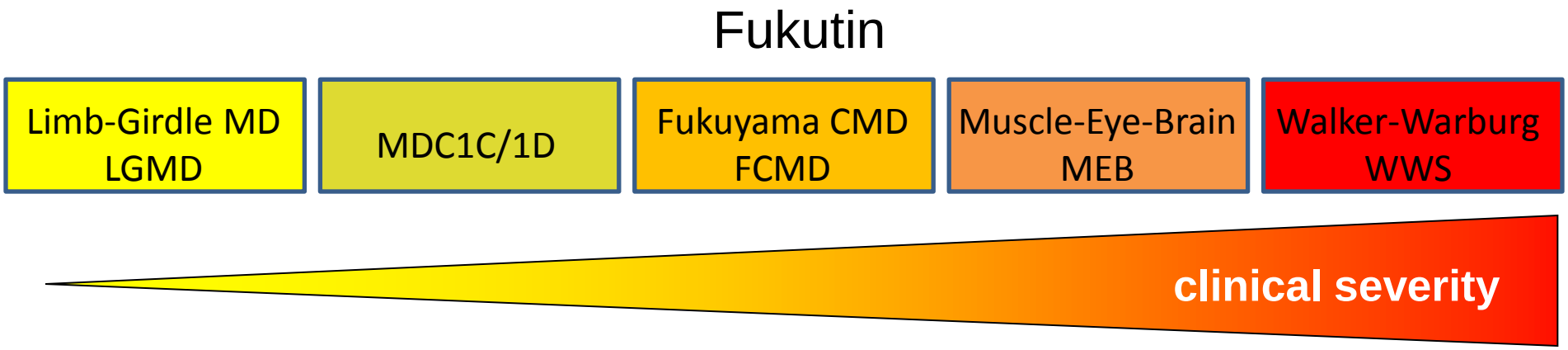






Causative Gene Identification.



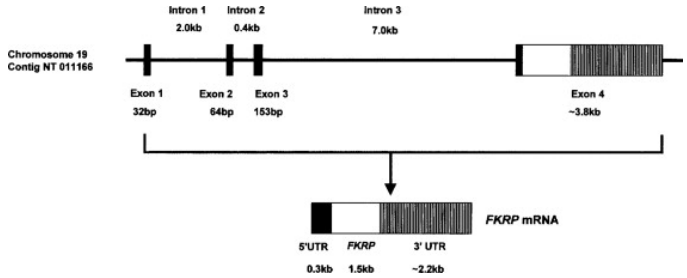


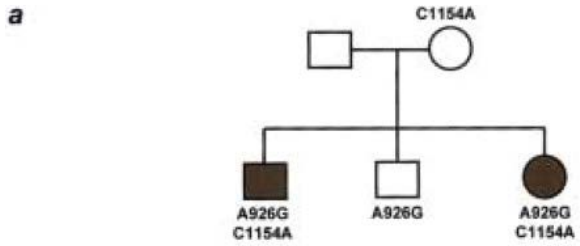
FKRP and CMD1D/LGMD

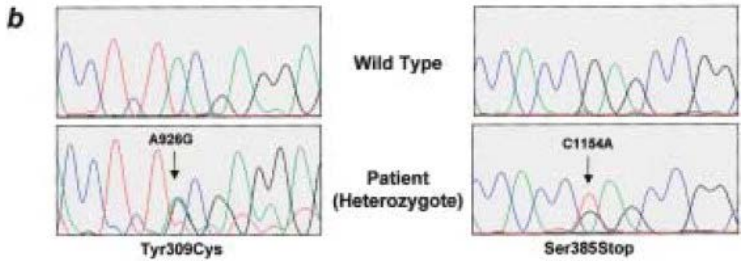
Am. J. Hum. Genet. 69:1198–1209, 2001

Mutations in the Fukutin-Related Protein Gene (*FKRP*) Cause a Form of Congenital Muscular Dystrophy with Secondary Laminin $\alpha 2$ Deficiency and Abnormal Glycosylation of α-Dystroglycan

Martin Brockington,[1,*] Derek J. Blake,[3,*] Paola Prandini,[1] Susan C. Brown,[1] Silvia Torelli,[1,4] Matthew A. Benson,[3] Chris P. Ponting,[2] Brigitte Estournet,[5] Norma B. Romero,[6] Eugenio Mercuri,[1] Thomas Voit,[7] Caroline A. Sewry,[1,8] Pascale Guicheney,[6] and Francesco Muntoni[1]





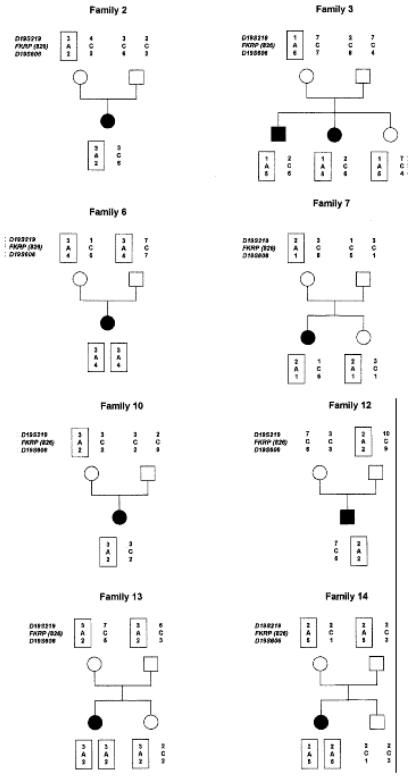


Human Molecular Genetics, 2001, Vol. 10, No. 25 2851–2859

ARTICLE

Mutations in the fukutin-related protein gene (*FKRP*) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C

Martin Brockington[1], Yeliz Yuva[1], Paola Prandini[1], Susan C. Brown[1], Silvia Torelli[1,2], Matthew A. Benson[3], Ralf Herrmann[4], Louise V.B. Anderson[5], Rumaisa Bashir[6], Jean-Marc Burgunder[7], Shari Fallet[8], Norma Romero[9], Michel Fardeau[9], Volker Straub[4], Gillian Storey[6], Christine Pollitt[5], Isabelle Richard[6], Caroline A. Sewry[1,10], Kate Bushby[5], Thomas Voit[4], Derek J. Blake[3] and Francesco Muntoni[1,*]



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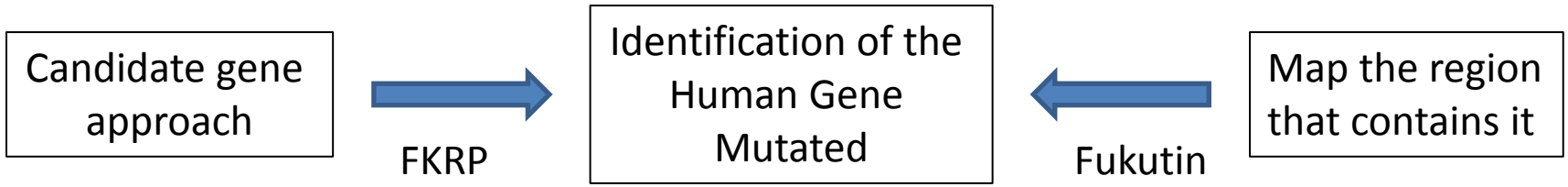
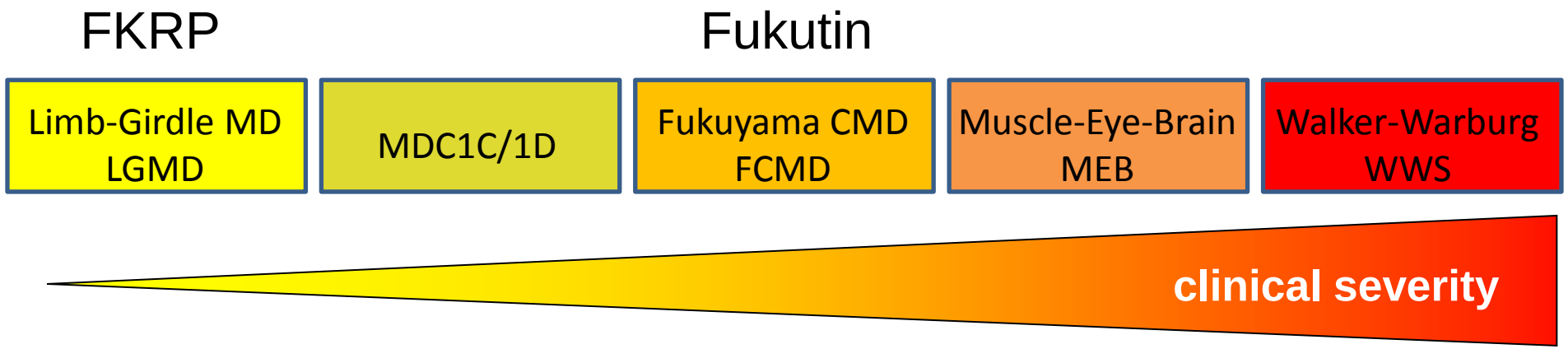
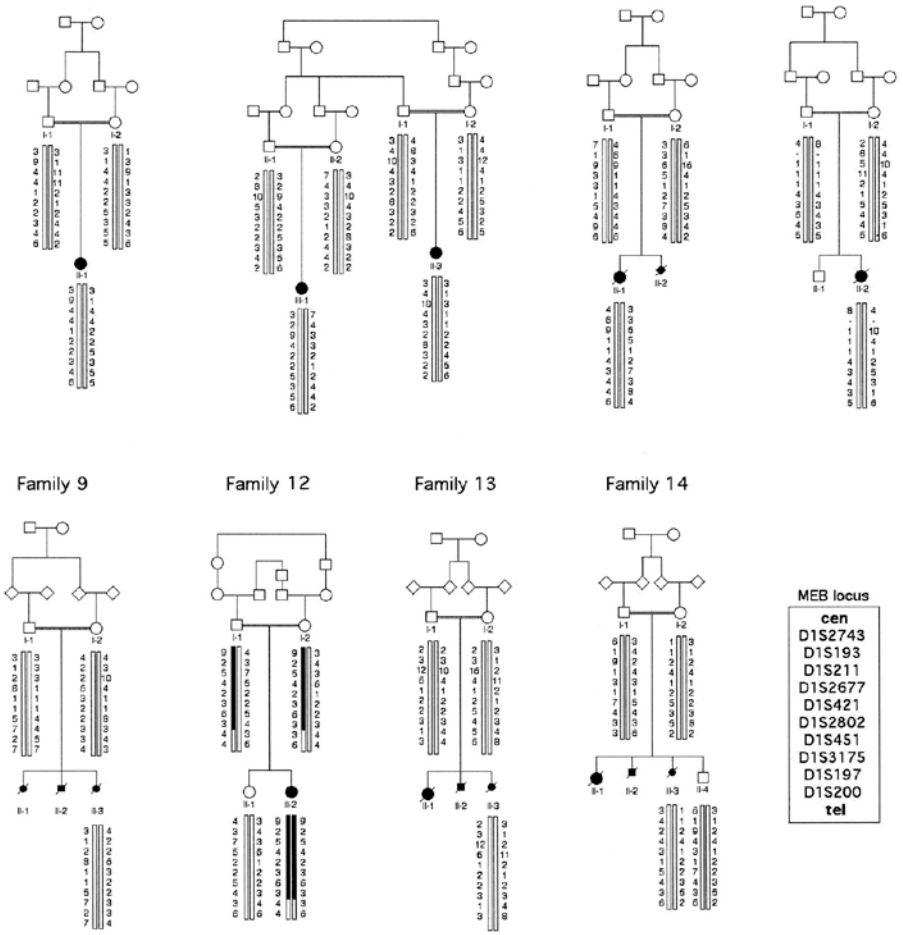




POMGnT1 and MEB

Clinical and genetic distinction between Walker–Warburg syndrome and muscle–eye–brain disease

B. Cormand, PhD; H. Pihko, MD, PhD; M. Bayés, PhD; L. Valanne, MD, PhD; P. Santavuori, MD, PhD; B. Talim, MD; R. Gershoni–Baruch, MD; A. Ahmad, MD; H. van Bokhoven, PhD; H.G. Brunner, MD, PhD; T. Voit, MD; H. Topaloglu, MD; W.B. Dobyns, MD; and A.–E. Lehesjoki, MD, PhD



Cormand B et al. Neurology 2001;56:1059-1069

POMGnT1 and MEB

Developmental Cell, Vol. 1, 717–724, November, 2001, Copyright ©2001 by Cell Press

Muscular Dystrophy and Neuronal Migration Disorder Caused by Mutations in a Glycosyltransferase, POMGnT1

Aruto Yoshida,[1,9] Kazuhiro Kobayashi,[2,9] Hiroshi Manya,[3] Kiyomi Taniguchi,[2] Hiroki Kano,[2] Mamoru Mizuno,[4] Toshiyuki Inazu,[4] Hideyo Mitsuhashi,[1] Seiichiro Takahashi,[3] Makoto Takeuchi,[1] Ralf Herrmann,[5] Volker Straub,[5] Beril Talim,[6] Thomas Voit,[5] Haluk Topaloglu,[7] Tatsushi Toda,[2,8,10] and Tamao Endo[3,8,10]

Introduction

Since the discovery of the Duchenne muscular dystrophy gene product dystrophin (Hoffman et al., 1987), many studies have focused on understanding the pathophysiology of muscular dystrophies and on developing therapeutic approaches. Dystroglycan is a component of the dystrophin-glycoprotein-complex (DGC) in skele-

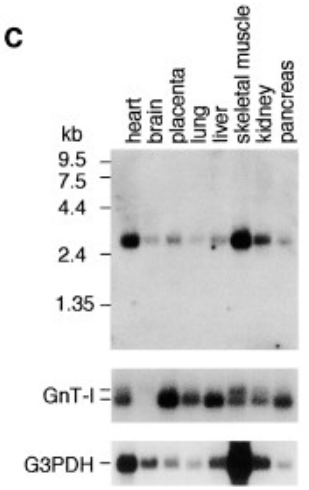
B

Acceptor Substrate Specificity of the Human POMGnT1 and GnT-I

Acceptors	Specific activity (pmol/h/μg protein) sPOMGnT1	sGnT-I
mannosylpeptide: Man | Ac-Ala-Ala-Pro-Thr-Pro-Val-Ala-Ala-Pro-NH_2	1.09	ND
M5-PA: Man α1→6 / Man α1→3 Man α1→6 / Man α1→3 Man β1→4GlcNAc β1→4GlcNAc–PA	ND	1.70
M3-PA: Man α1→6 / Man α1→3 Man β1→4GlcNAc β1→4GlcNAc–PA	ND	0.77

ND: not detected.

C



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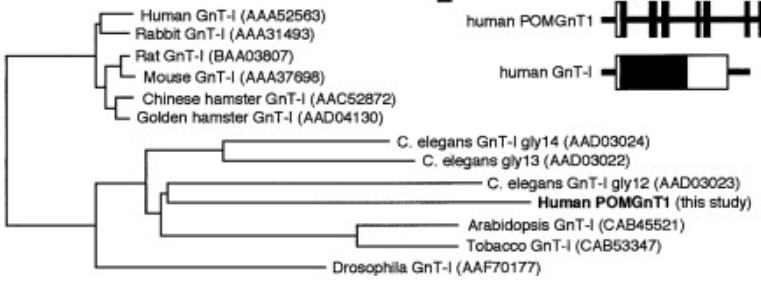
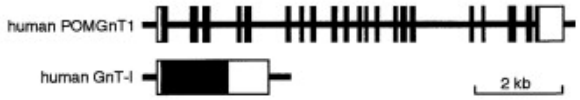


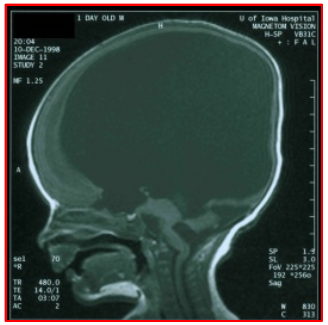
E



Causative Gene Identification.

One Gene – One Syndrome Dogma
One Syndrome – One Gene Dogma

Candidate gene approach → FKRP POMGnT1 → Identification of the Human Gene Mutated ← Fukutin POMGnT1 ← Map the region that contains it



FKRP		Fukutin	POMGnT1	
Limb-Girdle MD LGMD	MDC1C/1D	Fukuyama CMD FCMD	Muscle-Eye-Brain MEB	Walker-Warburg WWS

clinical severity

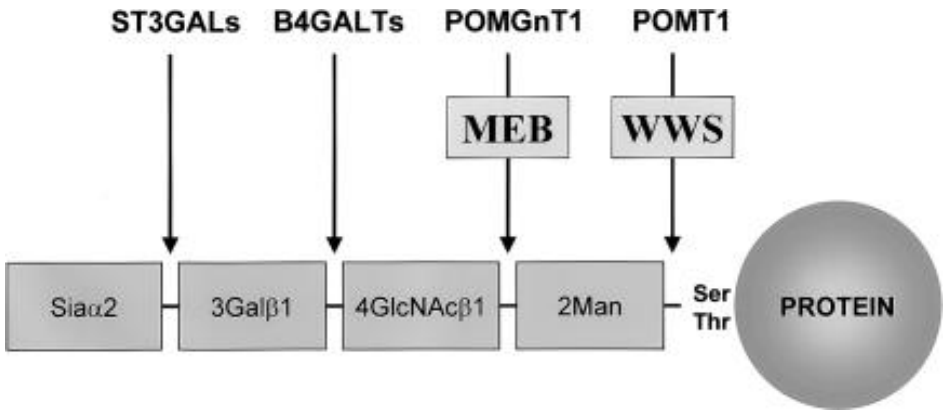
POMT1 and WWS

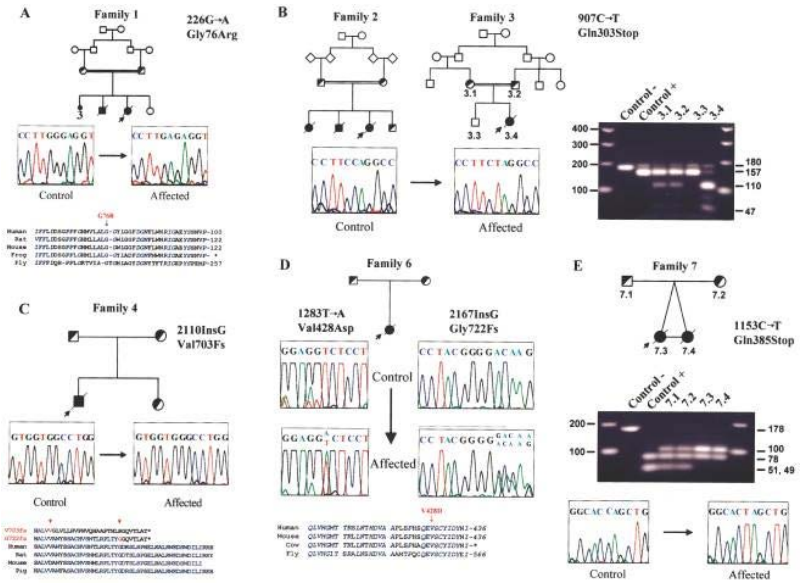
Am. J. Hum. Genet. 71:1033–1043, 2002

Mutations in the O-Mannosyltransferase Gene *POMT1* Give Rise to the Severe Neuronal Migration Disorder Walker-Warburg Syndrome

Daniel Beltrán-Valero de Bernabé,[1] Sophie Currier,[3] Alice Steinbrecher,[4,5] Jacopo Celli,[1] Ellen van Beusekom,[1] Bert van der Zwaag,[2] Hülya Kayserili,[6] Luciano Merlini,[7] David Chitayat,[8] William B. Dobyns,[9] Bru Cormand,[10] Ana-Elina Lehesjoki,[11] Jesús Cruces,[12] Thomas Voit,[5] Christopher A. Walsh,[3] Hans van Bokhoven,[1] and Han G. Brunner[1]

10 consanguineous families tested
More than one locus
More than 2 loci
Candidate gene approach





Causative Gene Identification.

One Syndrome – One Gene Dogma → WRONG!!
One Gene – One Syndrome Dogma ??

Candidate gene approach → FKRP, POMGnT1, POMT1 → Identification of the Human Gene Mutated ← Fukutin, POMGnT1 ← Map the region that contains it

FKRP		Fukutin	POMGnT1	POMT1
Limb-Girdle MD LGMD	MDC1C/1D	Fukuyama CMD FCMD	Muscle-Eye-Brain MEB	Walker-Warburg WWS

clinical severity

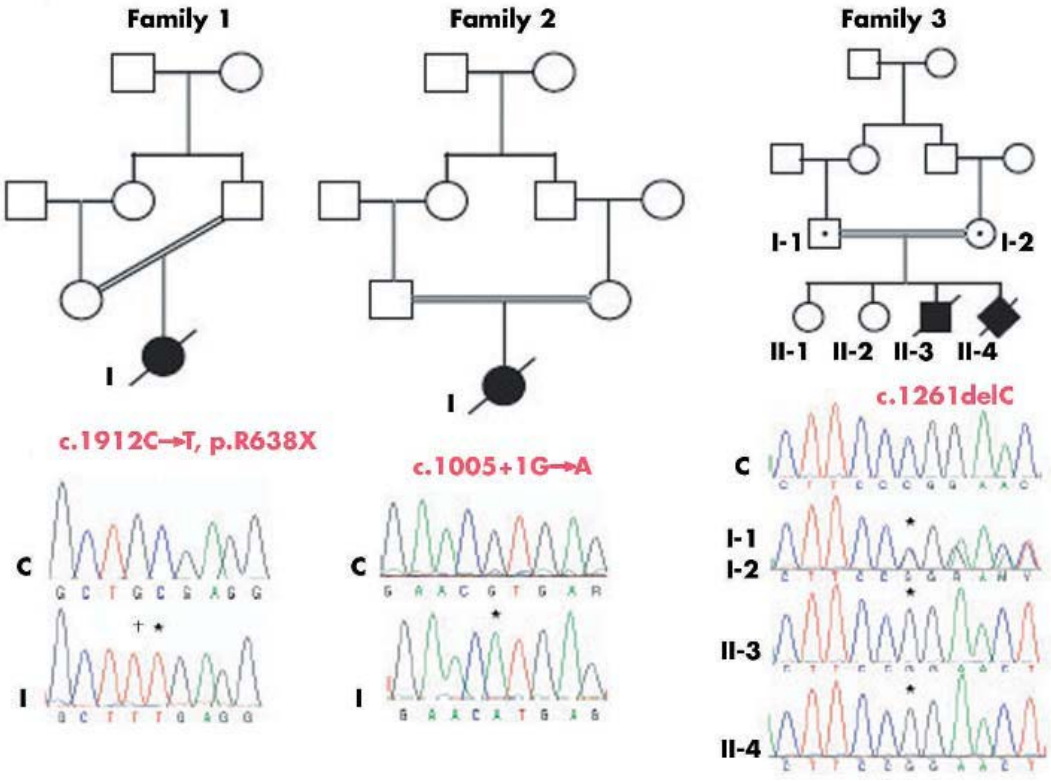
POMT2 and WWS

ORIGINAL ARTICLE

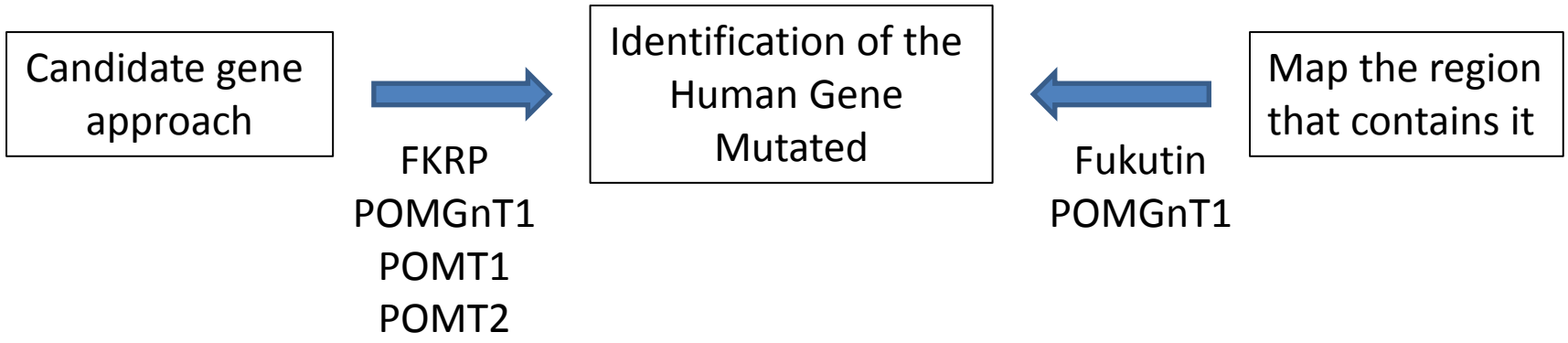
POMT2 mutations cause α-dystroglycan hypoglycosylation and Walker-Warburg syndrome

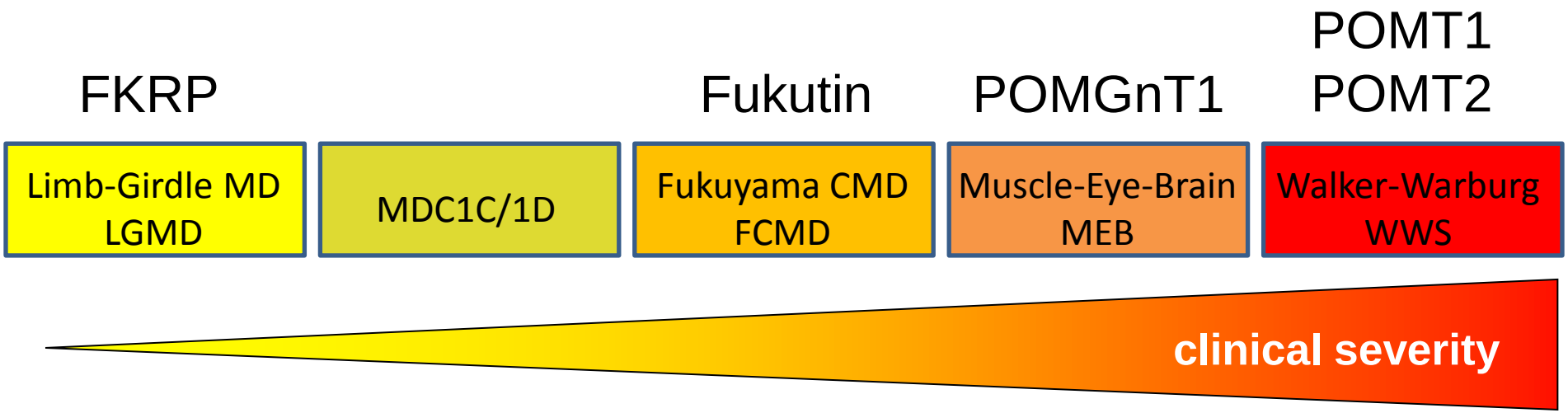
J van Reeuwijk, M Janssen, C van den Elzen, D Beltran-Valero de Bernabé, P Sabatelli, L Merlini, M Boon, H Scheffer, M Brockington, F Muntoni, M A Huynen, A Verrips, C A Walsh, P G Barth, H G Brunner, H van Bokhoven

J Med Genet 2005;**42**:907–912. doi: 10.1136/jmg.2005.031963



Causative Gene Identification.



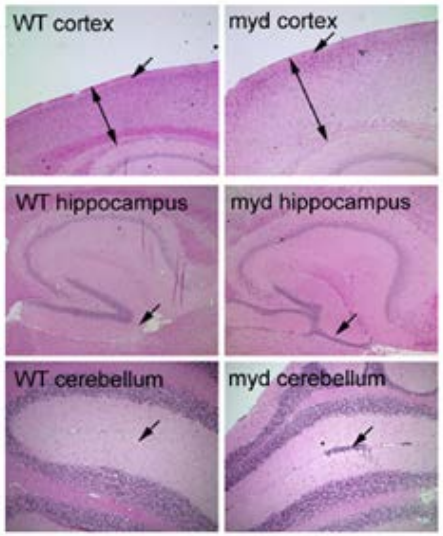


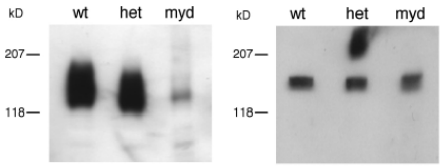
LARGE and MDC1D

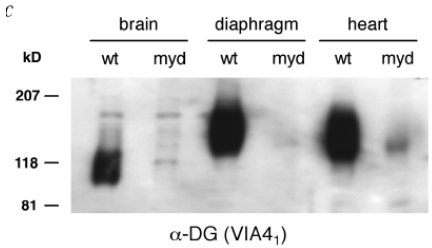
 letter

Mutant glycosyltransferase and altered glycosylation of α-dystroglycan in the myodystrophy mouse

Prabhjit K. Grewal[1], Paul J. Holzfeind[2], Reginald E. Bittner[2] & Jane E. Hewitt[1]



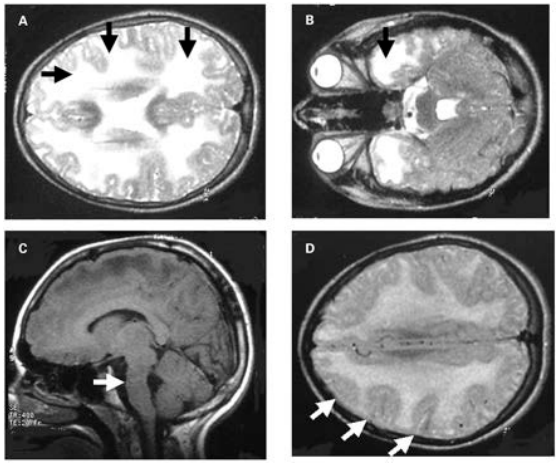


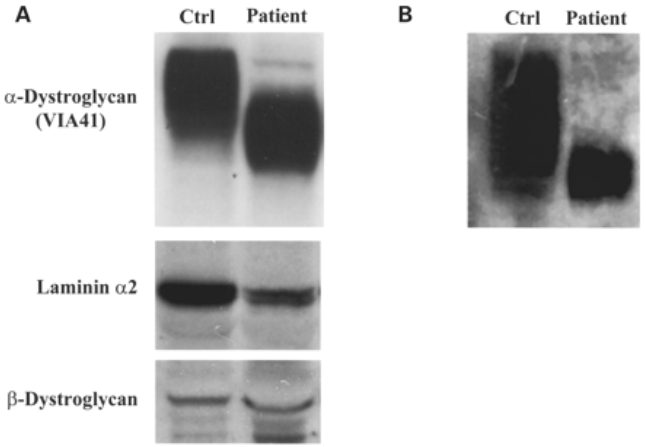


Human Molecular Genetics, 2003, Vol. 12, No. 21 2853–2861
DOI: 10.1093/hmg/ddg307

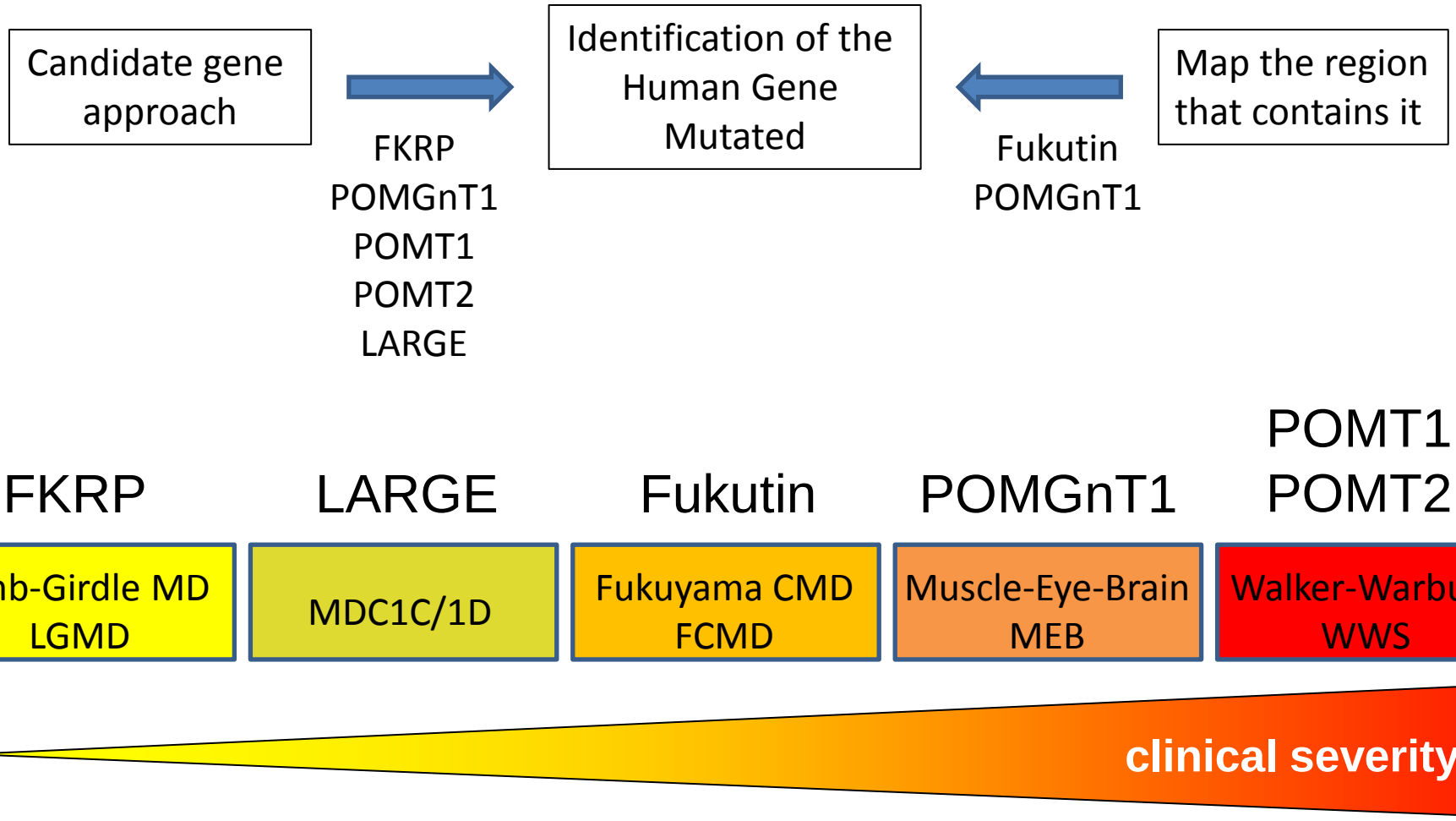
Mutations in the human *LARGE* gene cause MDC1D, a novel form of congenital muscular dystrophy with severe mental retardation and abnormal glycosylation of α-dystroglycan

Cheryl Longman[1,†], Martin Brockington[1,†], Silvia Torelli[1], Cecilia Jimenez-Mallebrera[1], Colin Kennedy[2], Nofal Khalil[3], Lucy Feng[1], Ravindra K. Saran[1,4], Thomas Voit[5], Luciano Merlini[6], Caroline A. Sewry[1,7], Susan C. Brown[1] and Francesco Muntoni[1,*]





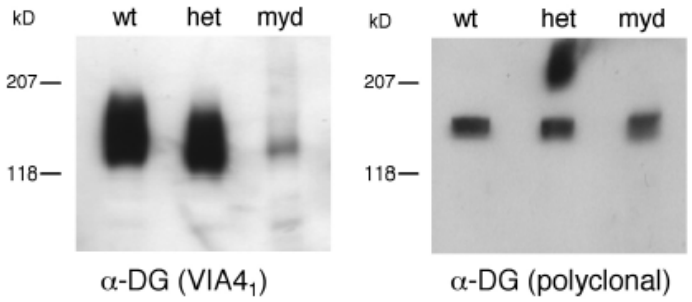
Causative Gene Identification.

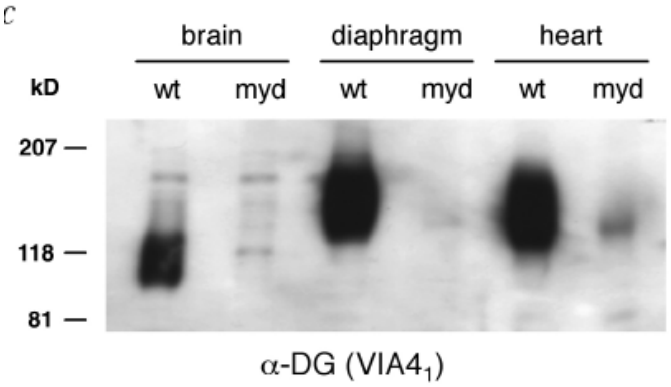


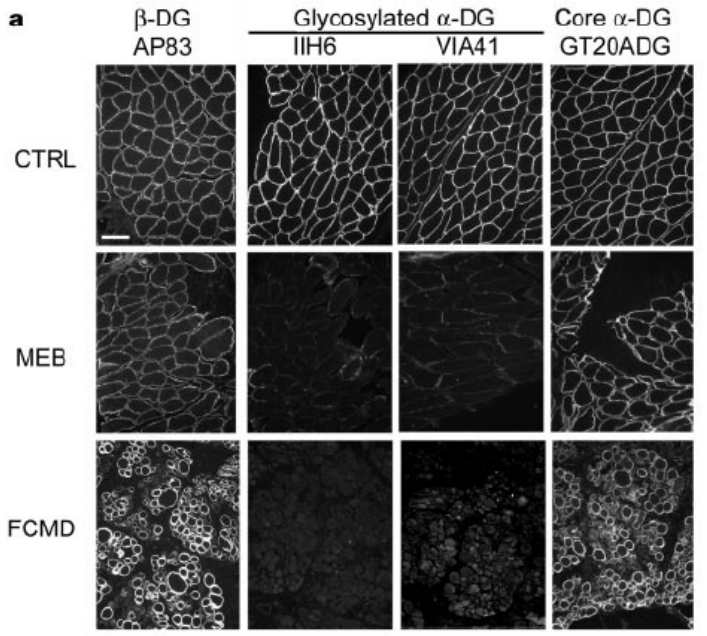
The common link. Dystroglycan glycosylation.

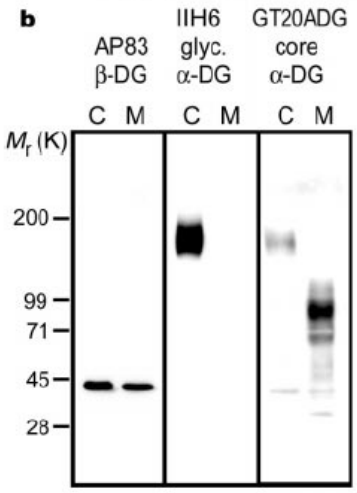
Post-translational disruption of dystroglycan–ligand interactions in congenital muscular dystrophies

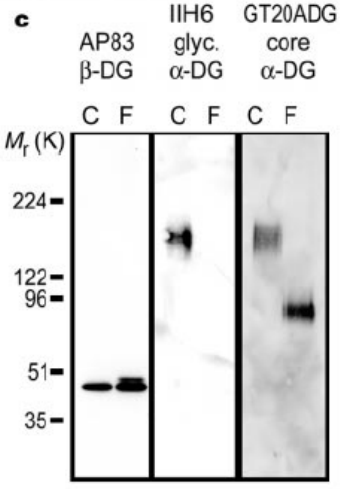
Daniel E. Michele*, Rita Barresi*, Motoi Kanagawa*, Fumiaki Saito*, Ronald D. Cohn*, Jakob S. Satz*, James Dollar†, Ichizo Nishino‡, Richard I. Kelley§, Hannu Somer||, Volker Straub*, Katherine D. Mathews¶, Steven A. Moore# & Kevin P. Campbell*



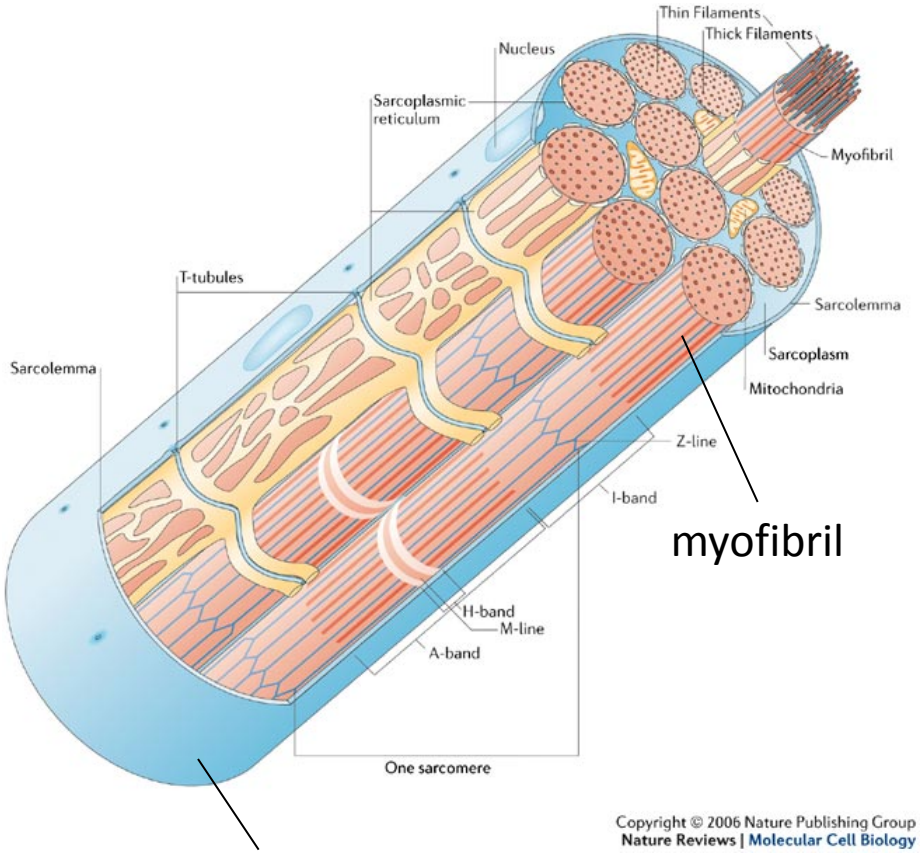








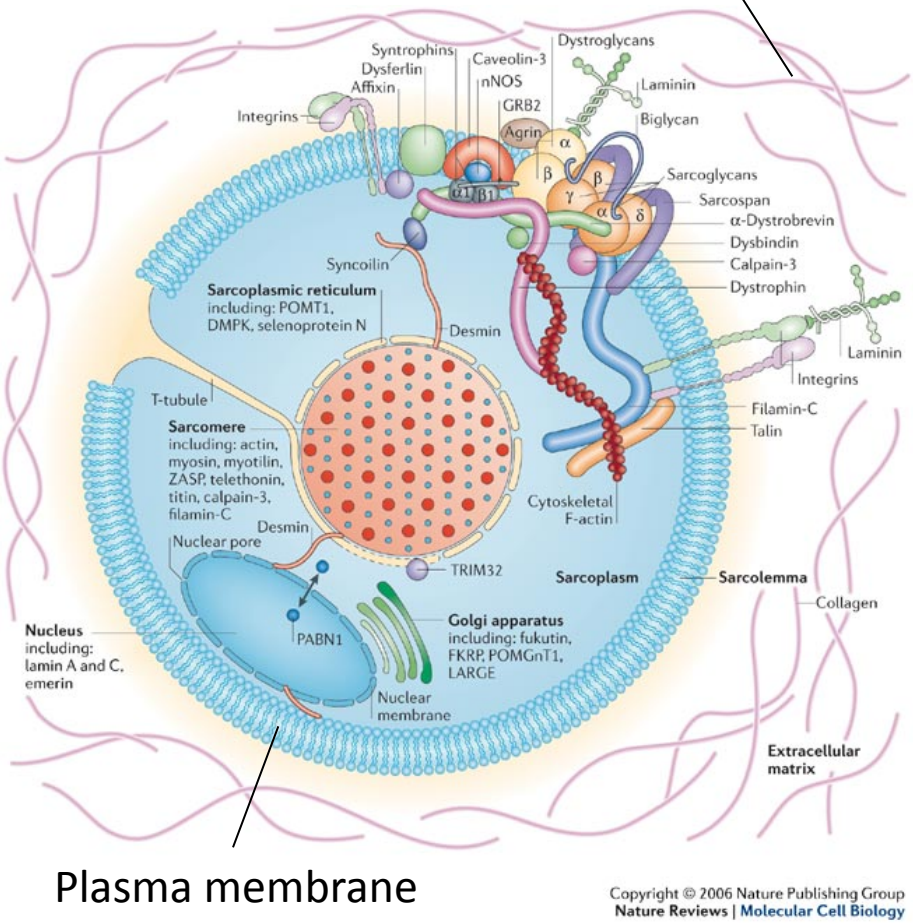
Dystroglycan function



myofibril

Plasma membrane
(Sarcolemma)

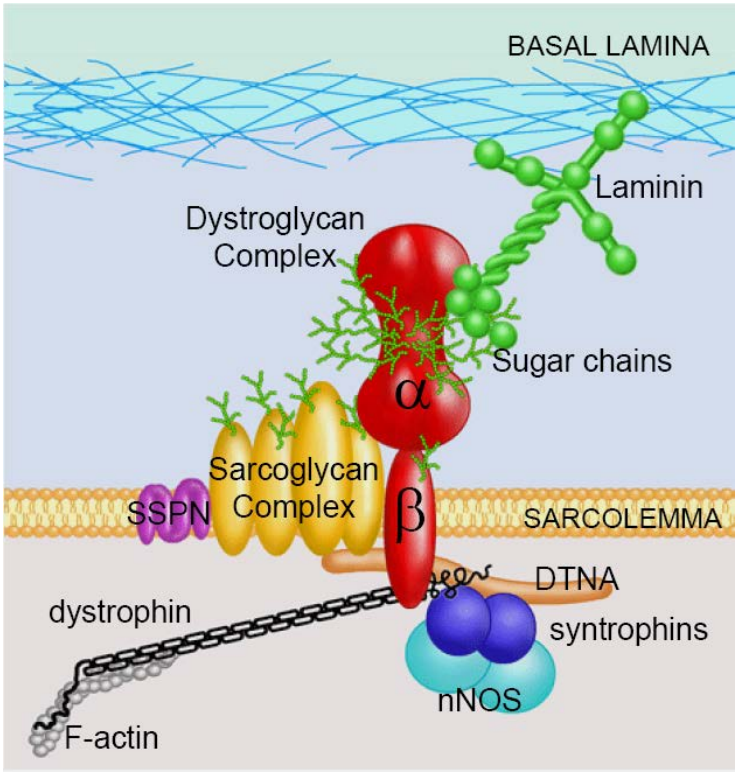
Extracellular matrix



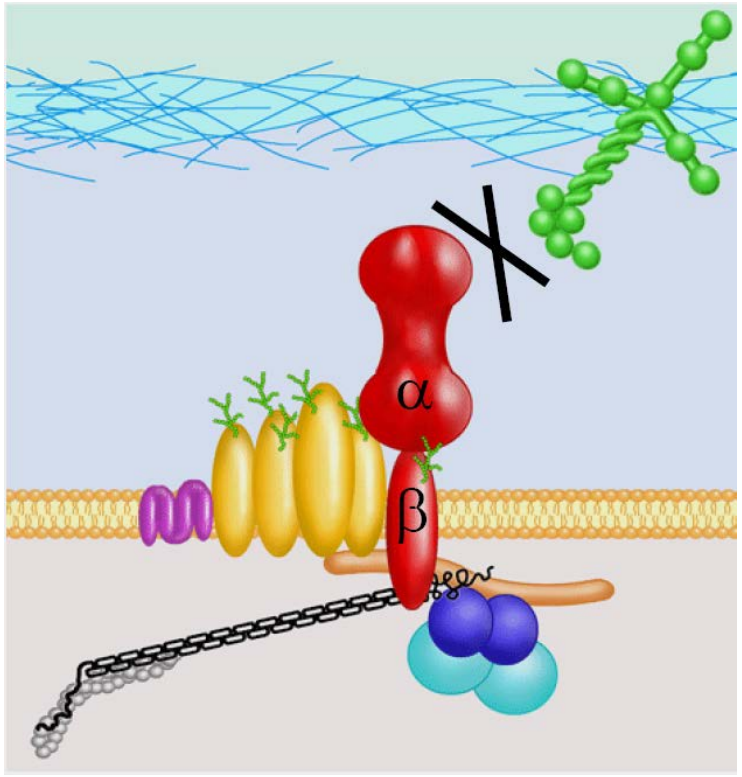
Plasma membrane
(Sarcolemma)

Nature Reviews Molecular Cell Biology **7**, 762–773 (2006)

Loss of α-Dystroglycan functional glycosylation results in congenital muscular dystrophy



Normal

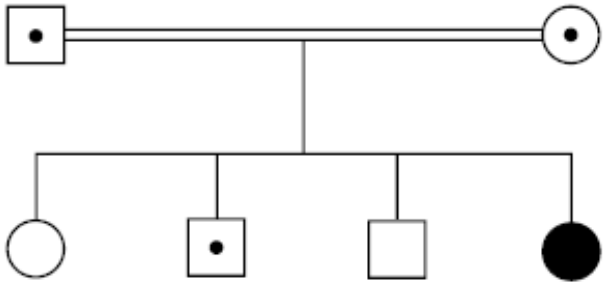


Walker-Warburg syndrome (WWS)
Muscle-eye-brain disease (MEB)
Fukuyama congenital muscular dystrophy (FCMD)
MDC1C/1D
Limb girdle muscular dystrophy (LGMD)2I/2K/2M/2N

Large^{myd} mouse

Figure generated by Tobias Willer

Dystroglycan and LGMD



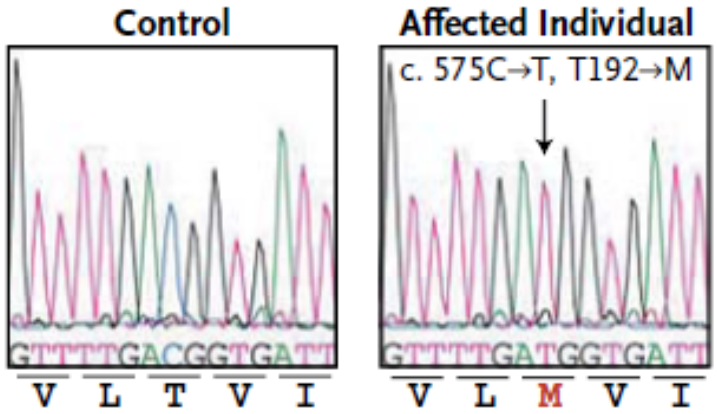
The NEW ENGLAND JOURNAL of MEDICINE

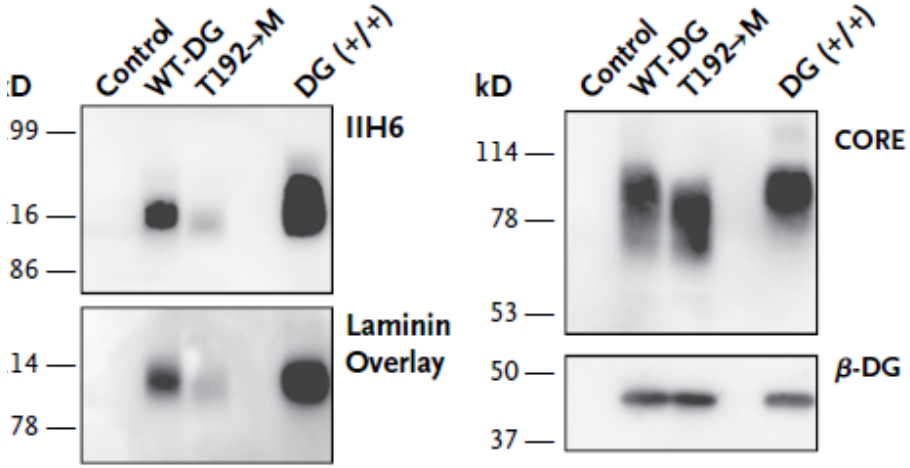
BRIEF REPORT

A Dystroglycan Mutation Associated with Limb-Girdle Muscular Dystrophy

Yuji Hara, Ph.D., Burcu Balci-Hayta, Ph.D., Takako Yoshida-Moriguchi, Ph.D., Motoi Kanagawa, Ph.D., Daniel Beltrán-Valero de Bernabé, Ph.D., Hülya Gündeşli, M.S., Tobias Willer, Ph.D., Jakob S. Satz, Ph.D., Robert W. Crawford, B.S., Steven J. Burden, Ph.D., Stefan Kunz, Ph.D., Michael B.A. Oldstone, M.D., Ph.D., Alessio Accardi, Ph.D., Beril Talim, M.D., Francesco Muntoni, M.D., Haluk Topaloğlu, M.D., Pervin Dinçer, Ph.D., and Kevin P. Campbell, Ph.D.

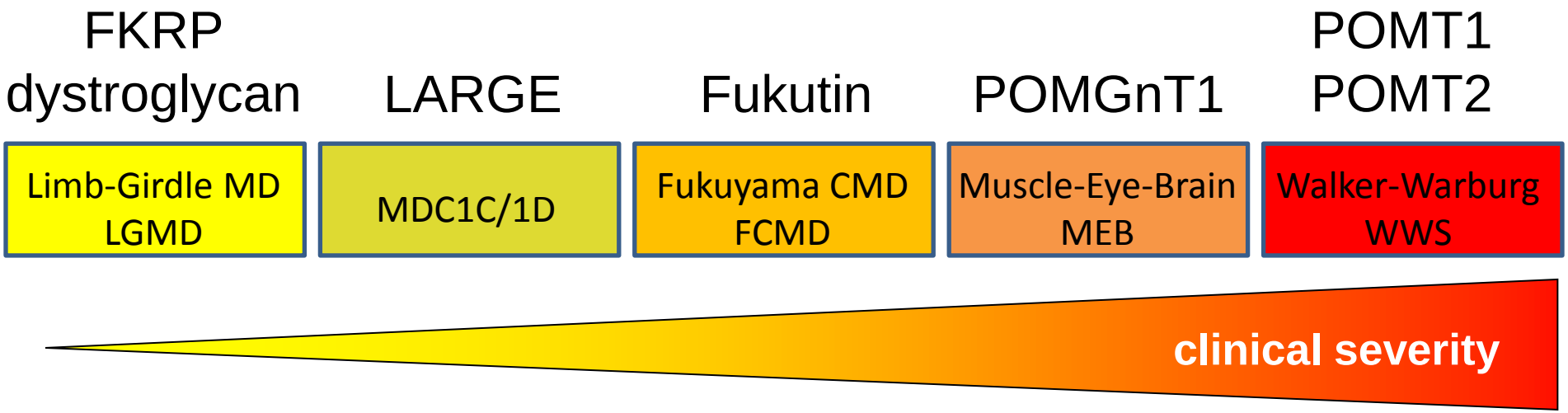
N Engl J Med 2011;364:939-46.





Causative Gene Identification.

Candidate gene approach → FKRP, POMGnT1, POMT1, POMT2, LARGE, dystroglycan → Identification of the Human Gene Mutated ← Fukutin, POMGnT1 ← Map the region that contains it



Phenotype / Genotype spectrum in Dystroglycanopathy patients

One Syndrome – One Gene Dogma → WRONG!!
One Gene – One Syndrome Dogma ??

LETTER TO JMG

A homozygous nonsense mutation in the *Fukutin* gene causes a Walker-Warburg syndrome phenotype

D Beltrán-Valero de Bernabé, H van Bokhoven, E van Beusekom, W Van den Akker, S Kant, W B Dobyns, B Cormand, S Currier, B Hamel, B Talim, H Topaloglu, H G Brunner

J Med Genet 2003;**40**:845–848

Hum Genet (2007) 121:685–690
DOI 10.1007/s00439-007-0362-y

ORIGINAL INVESTIGATION

Intragenic deletion in the *LARGE* gene causes Walker-Warburg syndrome

Jeroen van Reeuwijk · Prabhjit K. Grewal · Mustafa A. M. Salih · Daniel Beltrán-Valero de Bernabé · Jenny M. McLaughlan · Caroline B. Michielse · Ralf Herrmann · Jane E. Hewitt · Alice Steinbrecher · Mohamed Z. Seidahmed · Mohamed M. Shaheed · Abdullah Abomelha · Han G. Brunner · Hans van Bokhoven · Thomas Voit

ELECTRONIC LETTER

Mutations in the FKRP gene can cause muscle-eye-brain disease and Walker–Warburg syndrome

D Beltran-Valero de Bernabé, T Voit, C Longman, A Steinbrecher, V Straub, Y Yuva, R Herrmann, J Sperner, C Korenke, C Diesen, W B Dobyns, H G Brunner, H van Bokhoven, M Brockington, F Muntoni

J Med Genet 2004;**41**:e61 (http://www.jmedgenet.com/cgi/content/full/41/5/e61). doi: 10.1136/jmg.2003.013870

Phenotype / Genotype spectrum in Dystroglycanopathy patients

One Syndrome – One Gene Dogma → WRONG!!
One Gene – One Syndrome Dogma → WRONG!!

LGMD	CMD +/- brain involvement	muscle-eye-brain (MEB)	Walker-Warburg (WWS)
POMT1/2 (LGMD2K)	POMT1/2	POMT1/2	POMT1/2
POMGnT1 (LGMD2M)	POMGnT1	POMGnT1	?
Fukutin (LGMD2L)	Fukutin	Fukutin	Fukutin
FKRP (LGMD2I)	FKRP	FKRP	FKRP
	LARGE		LARGE

mild missense mutations — severe missense and nonsense mutations

LGMD — **WWS**

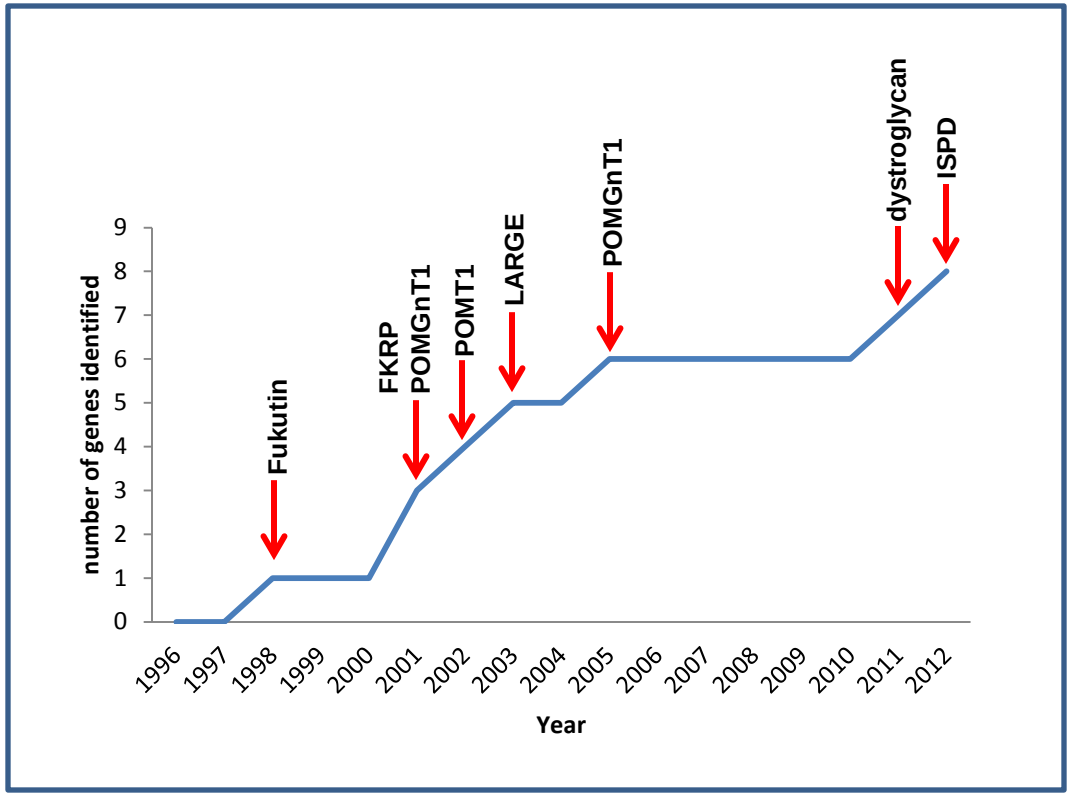
clinical severity

Figure generated by Tobias Willer

Walker-Warburg syndrome genes

6 known genes causing WWS:

- ***POMT1*** (9q34.1)
- ***POMT2*** (14q24.3)
- ***POMGnT1*** (1p34.1)
- ***FKRP*** (19q13.32)
- ***Fukutin*** (9q31)
- ***LARGE1*** (22q12.3)
- ***dystroglycan*** (3p21.31)
- ***ISPD*** (7p21.2)



Until 2012 only 50% of dystroglycanopathy patients can be explained with known genes and can be provided with genetic diagnosis.
Preliminary linkage data suggest ~ 5 additional candidate genes that still remain unidentified.

Figure generated by Tobias Willer

Classification of Congenital Muscular Dystrophy with Glycosylation Defects

Phenotype	Findings						
	Motor Function	Eye	Central Nervous System				Intellectual Disability / Epilepsy
			Cortex	Cerebellum	Brain Stem	Hydro-cephalus	
Walker-Warburg syndrome (WWS)	Absent psychomotor acquisitions	Severe [1]	Cobblestone lissencephaly	Very hypoplastic	Severely hypoplastic	Constant	Severe
Muscle-eye-brain (MEB) disease	Ambulation may be acquired	Common [2]	Frontoparietal pachygyria; polymicrogyria	Vermis hypoplasia, cyst, dysplastic	Usually hypoplastic	Common	Severe intellectual disability; refractory epilepsy; behavioral problems
Fukuyama CMD (FCMD)	Ambulation may be acquired	Variable / mild	Variable (from normal or only simplification of gyri to severe)	Hypoplasia, cysts, polymicrogyria	Usually normal	Rare	Moderate
Intermediate phenotypes (MDC1D, CRB-CMD)	Ambulation may be acquired	Rare / mild	Variable	Variable	Variable	Variable	Mild to moderate
CMD with intellectual disability	Ambulation may be acquired	Rare / mild	None	None	None	None	Mild to moderate
CMD no intellectual disability (MDC1C)	Ambulation may be acquired	None / mild	None	None	None	None	None

From Sparks *et al*. Gene Reviews 2012