ST-akademin VT 2022
Kardiogenetik

Genetik och genetisk vägledning

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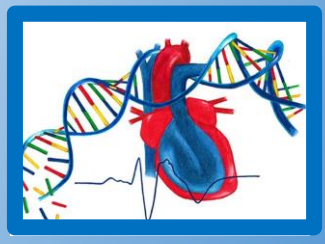

Tänk om…

Du vet att det i din familj förekommer en ärftlig hjärtsjukdom. Alla drabbas inte, men det har förekommit ett par dödsfall i tidig medelålder som man tror kanske har med sjukdomen att göra.

Nu har man funnit en sjukdomsorsakande genetisk variant i familjen, och frågan kommer om du vill göra en genetisk analys.

Brainstorming – vad vill du veta för att kunna fatta beslut?

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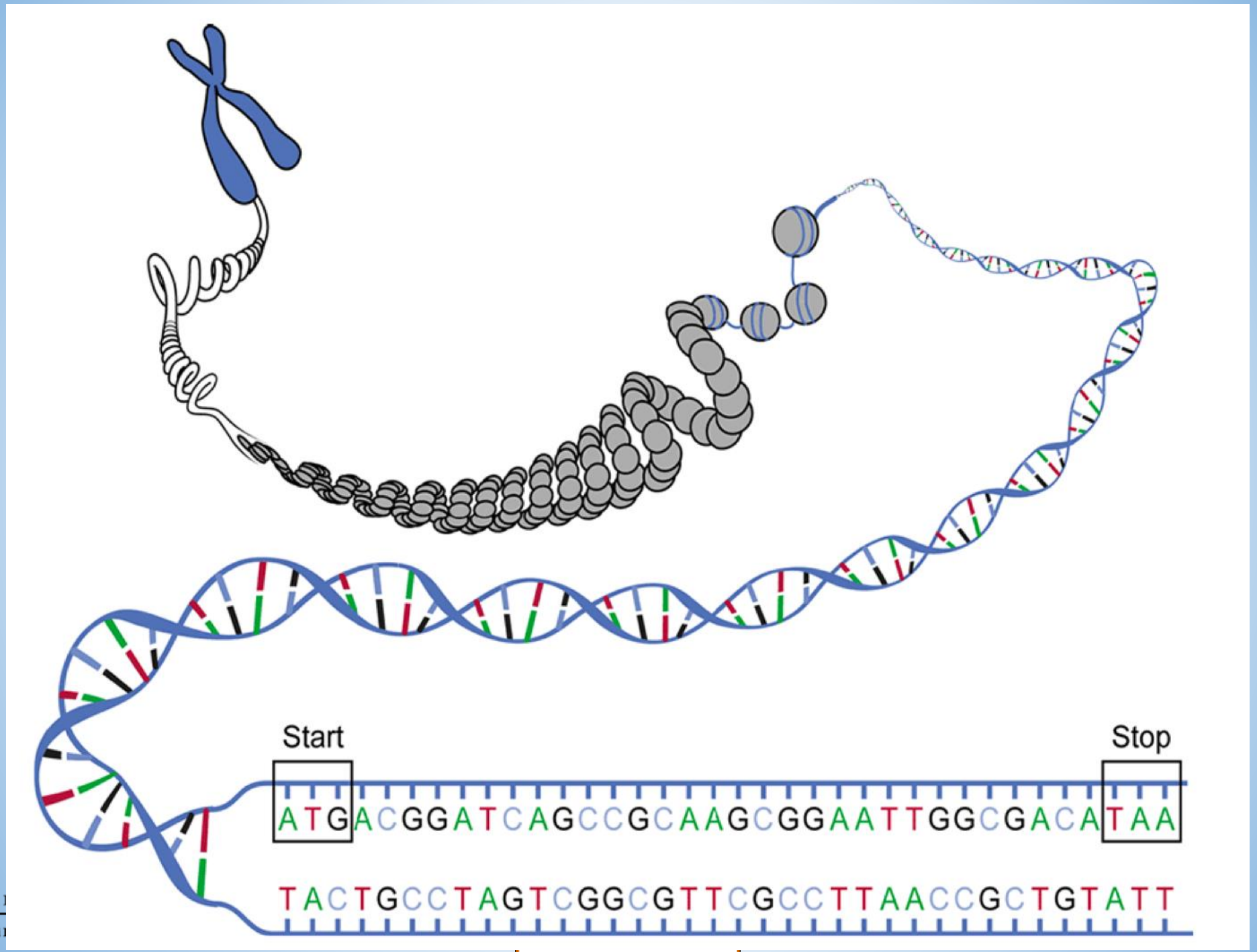
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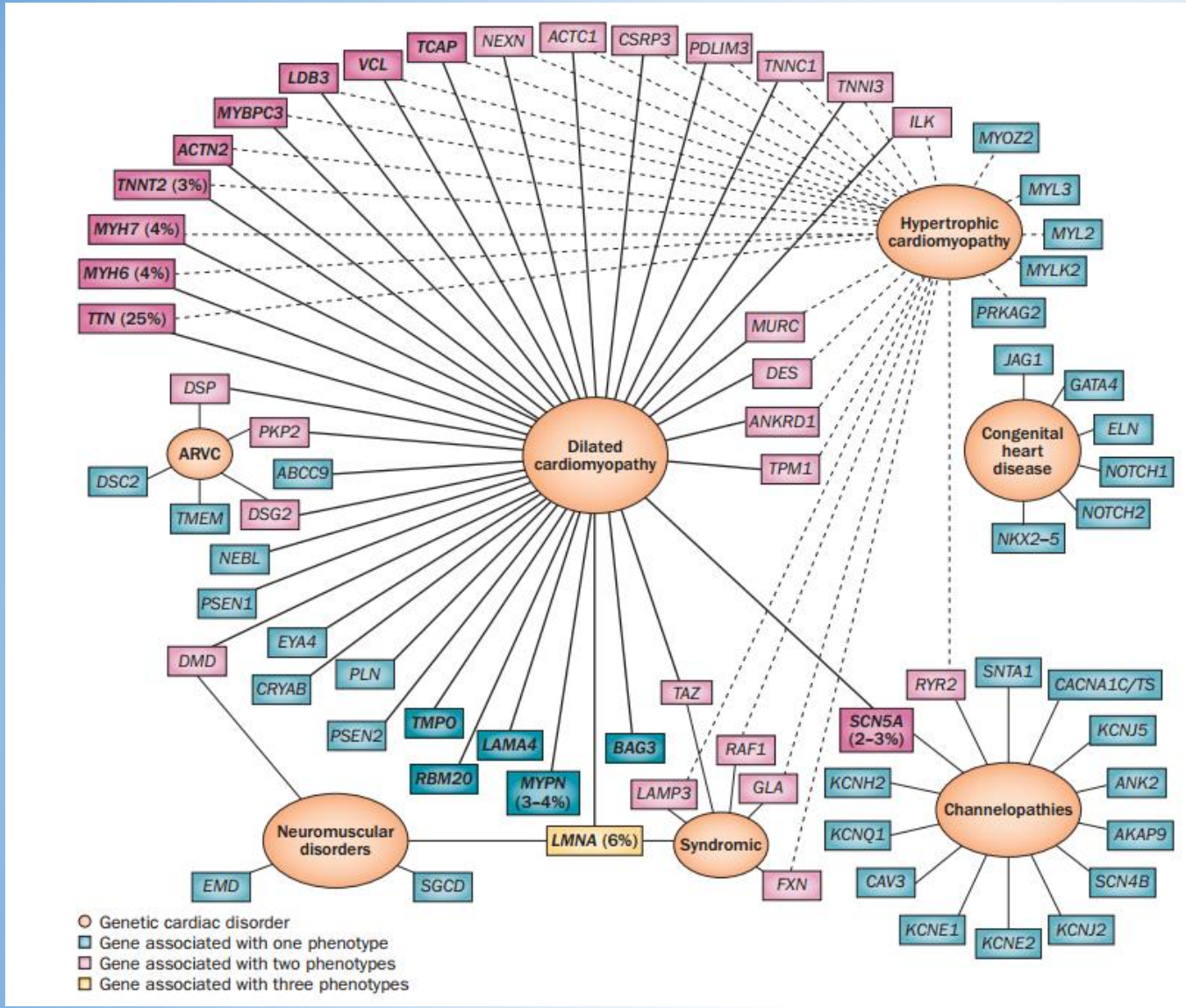
Kardiogenetiska sjukdomar

Prevalens

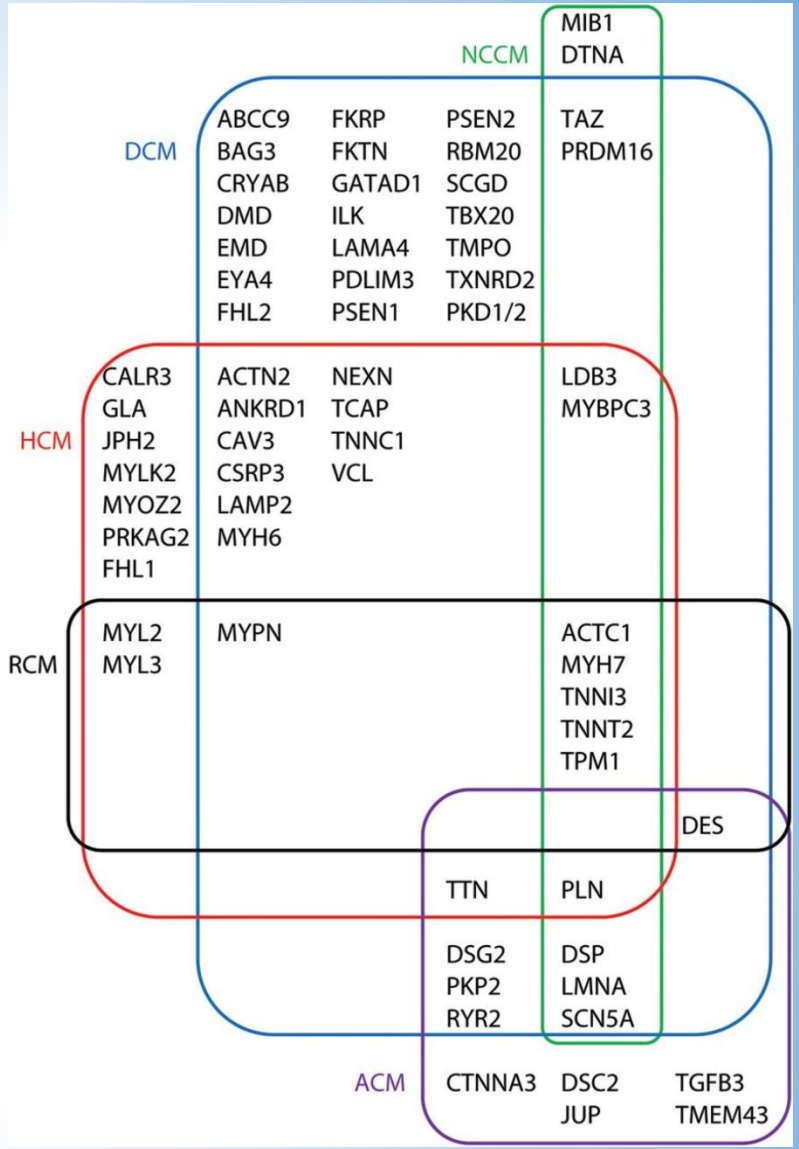
- 0.5% FH (familjär hyperkolesterolemi)
- 0.4% DCM (dilaterad kardiomyopati)
- 0.2 % HCM (hypertrof kardiomyopati)
- 0.05% LQTS (långt QT-syndrom)
- 0.02% ARVC (arytmogen högerkammarkardiomyopati)
- 0.02% Marfans syndrom

Utveckling eller inveckling…?

- “En gen – en sjukdom”
  - I begynnelsen av kardiovaskulär genetik - 1989
- “En sjukdom – många olika gener”
  - “the final common pathway hypothesis” ang kardiomyopatier
- “En gen – många olika sjukdomar”



Nat Rev Cardiol 2013;10:531-547



Cardiovasc Research 2014;101:571-578

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Involverade proteiner

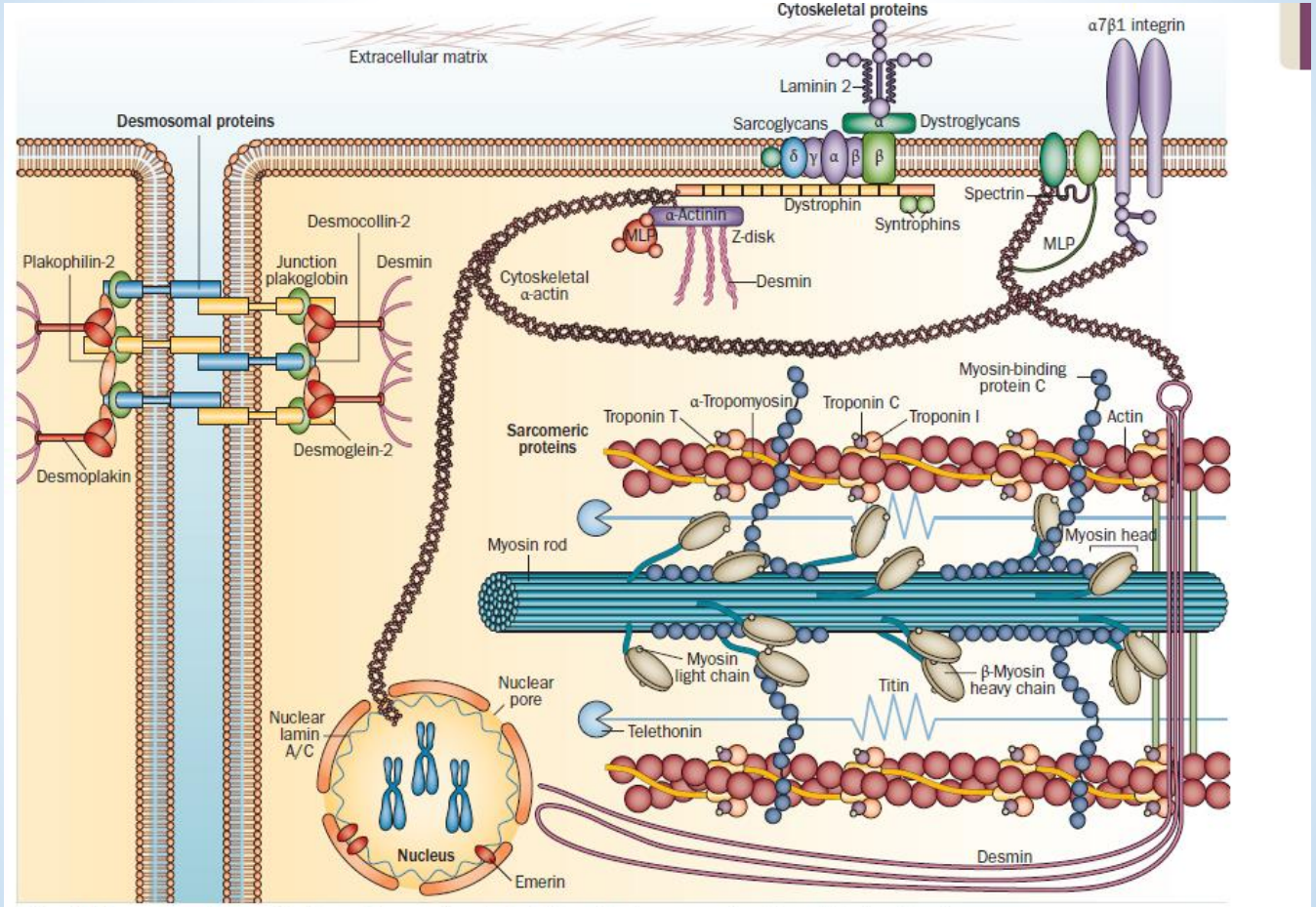
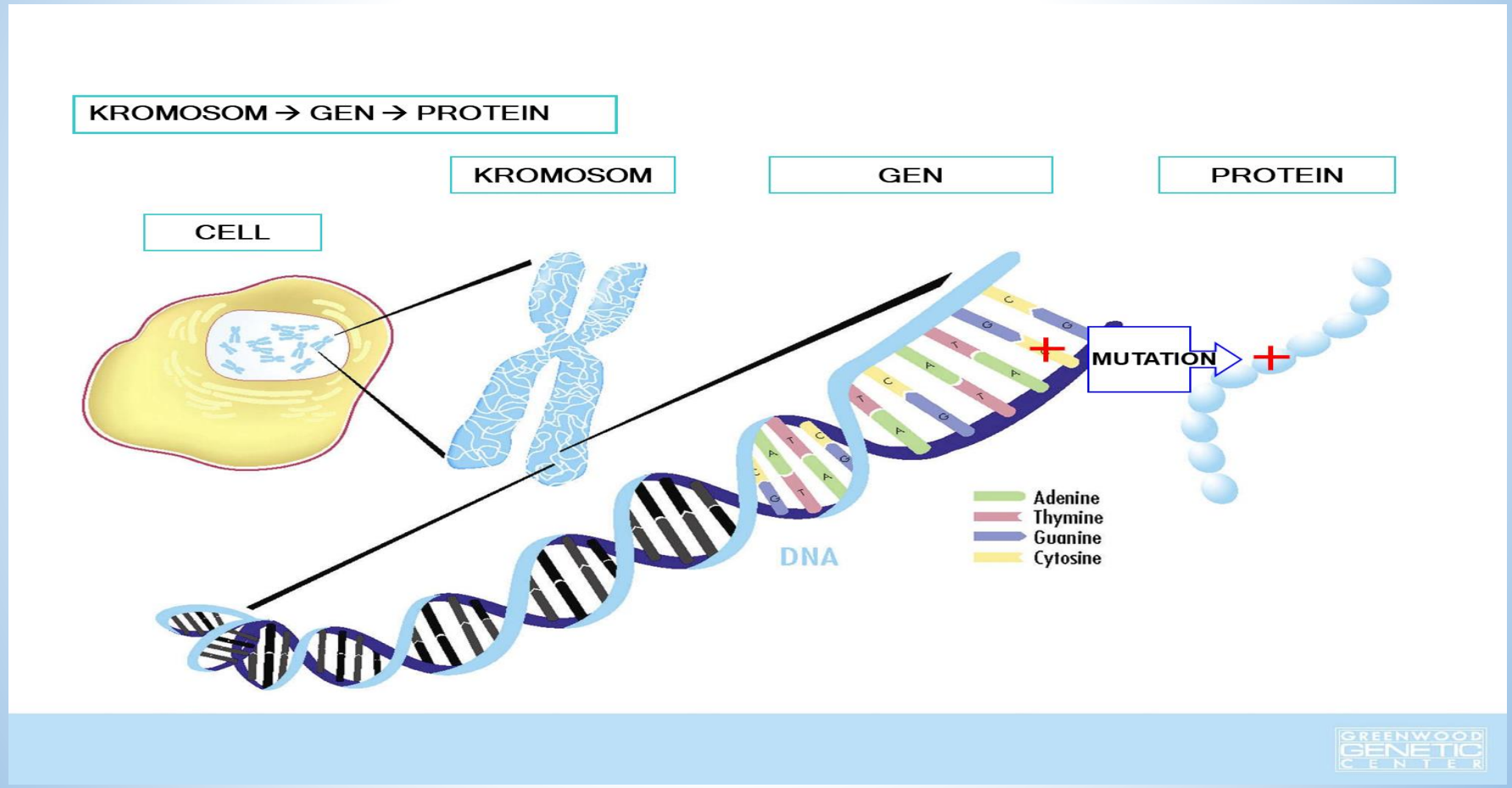


Figure 4 | The main proteins involved in cardiomyopathies. Indicated are the desmosomal proteins, which form the desmosome and connect one cell to another; the sarcomeric proteins, which form the contractile apparatus; the cytoskeletal proteins, which connect the extracellular matrix to the cells, and connect various transmembrane proteins to the sarcomere and the nucleus; and the nuclear envelope proteins. Mutations in the encoding genes lead to aberrant function of the respective proteins and to one of the cardiomyopathies (Table 1). Abbreviation: MLP, cysteine and glycine-rich protein 3 (also known as muscle LIM protein).

Wilde, A. A. M. & Behr, E. R. *Nat. Rev. Cardiol.* **10**, 571–583 (2013);

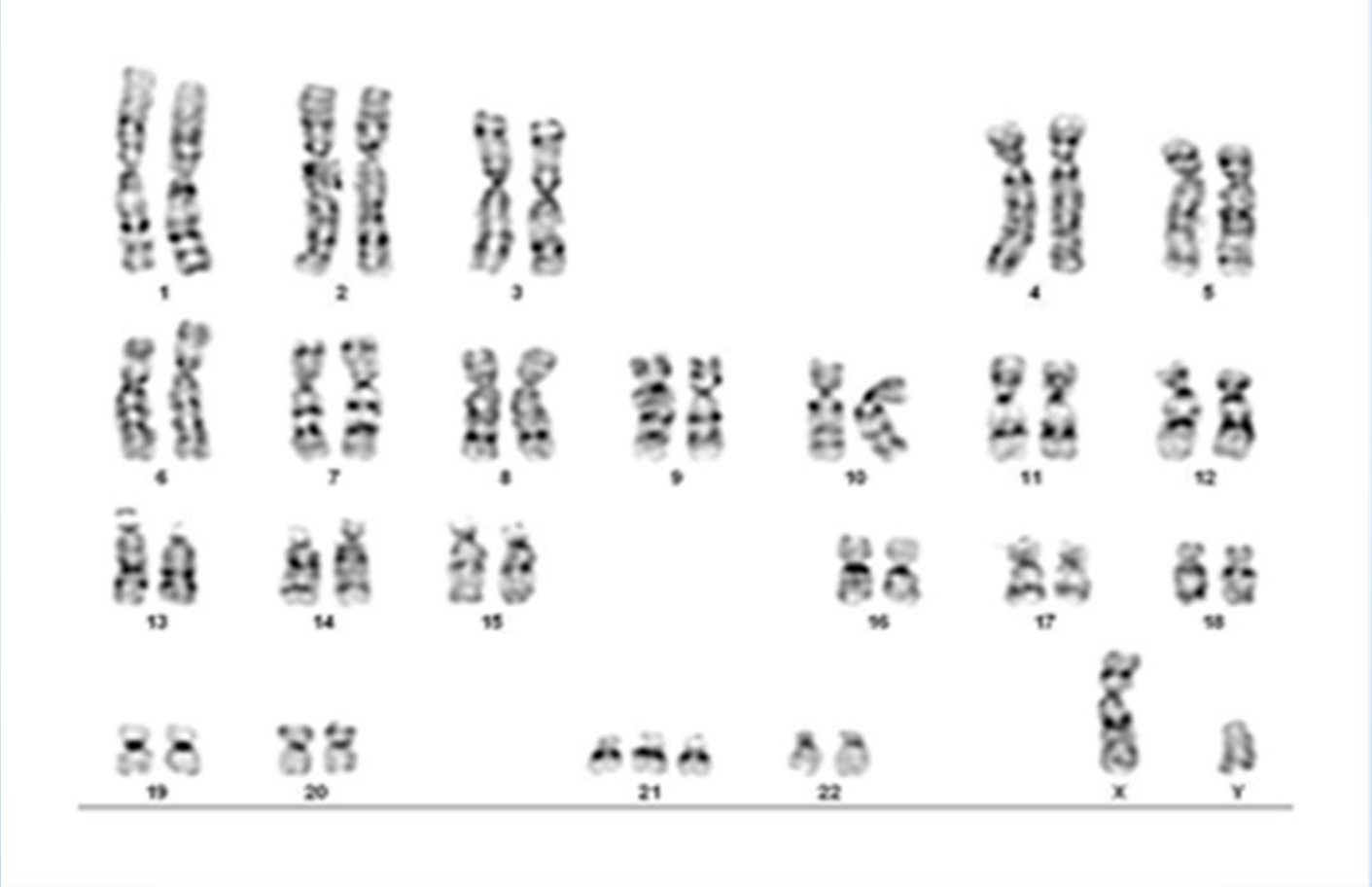
Basal genetik



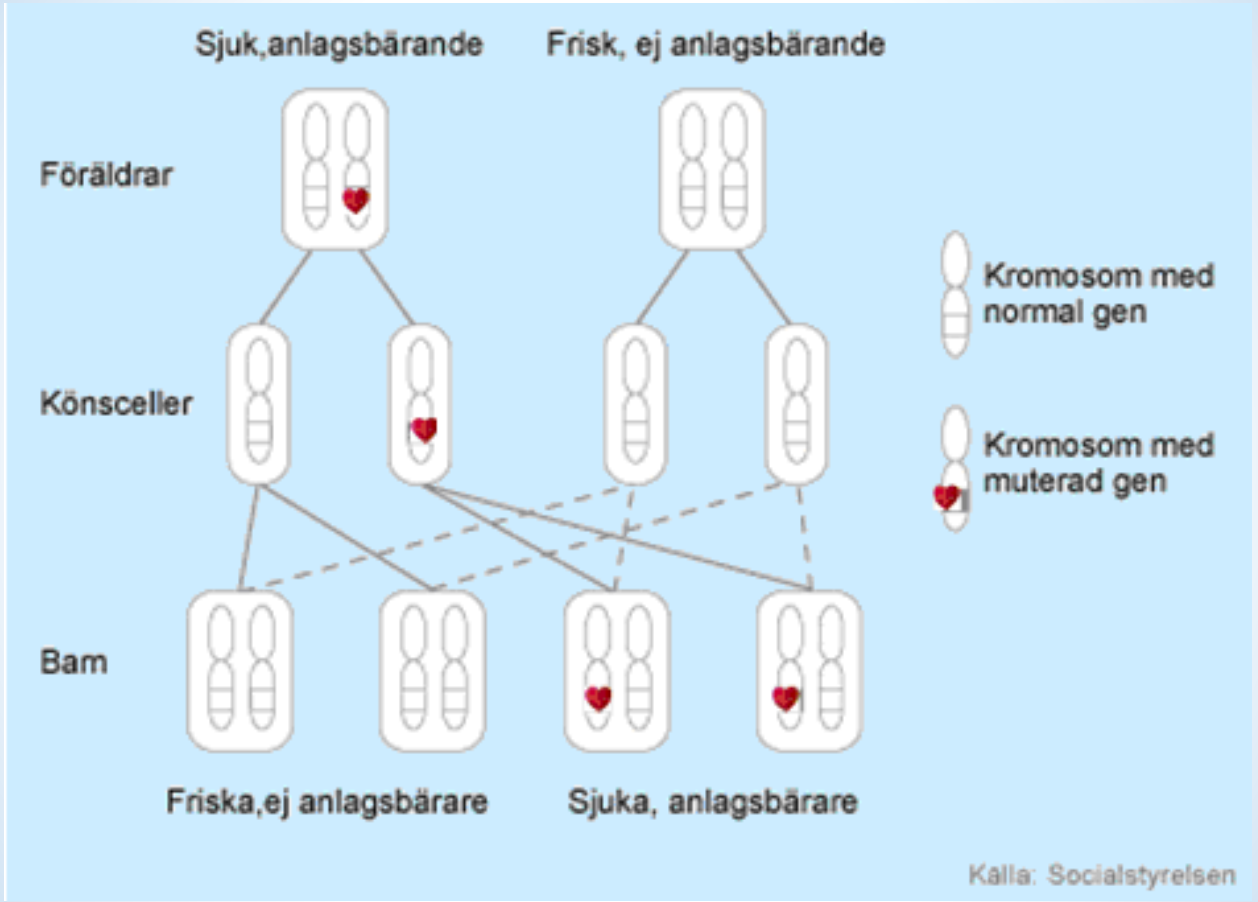
SNPs

- Single nucleotide polymorphisms (SNPs)
- Populationsfrekvens >1%
- Adderande riskfaktor till sjukdomar
- Stora populationsstudier använder SNPs – association med hypertension?
- Genome-wide association studies (GWAS)

Kromosomavvikelser



Autosomalt dominant nedärvning

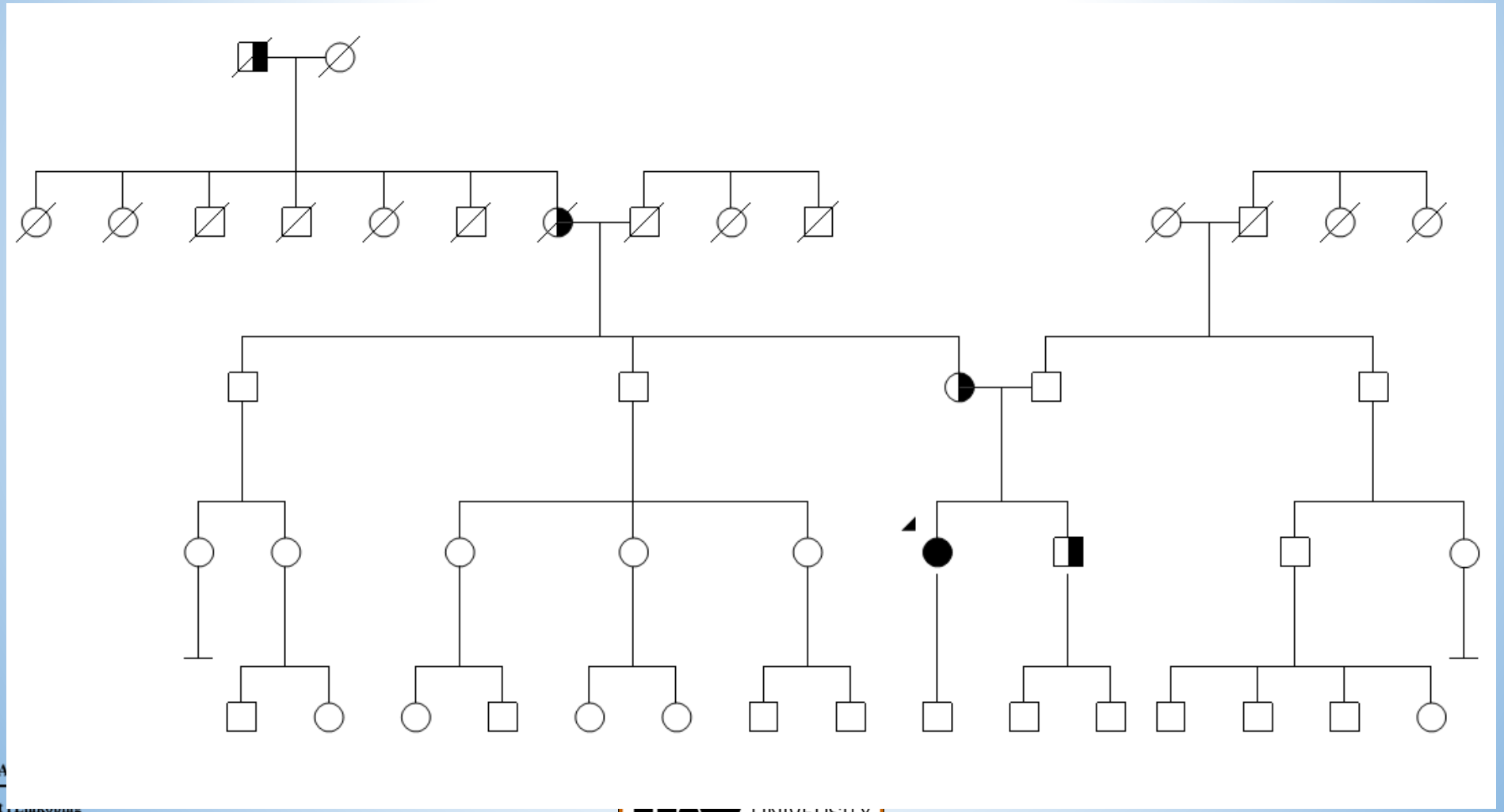


Nedärvningsrisk 50% för varje individ

Typer av testning

- Diagnostisk testning
- Presymtomatisk / anlagsbärartestning
- Prenatal

Pedigree



Genetisk analys = entydigt svar?

- Till exempel c.76A>C (nukleotid 76 ska vara ett A men är i stället ett C)
  - Hur kan vi tolka dess betydelse för fenotypen?
  - Tidigare känd?
  - Sjukdomsorsakande?
- 3 alternativ:
  - Sjukdomsorsakande genetisk variant
  - Oklar variant
  - Normalvariation

Genetisk analys = ”lätta” svar?

- Information om för- och nackdelar samt testets begränsningar
- Testet går inte att göra ogjort – måste vara medveten om vad det kan innebära

- Ovetande – jag tar det om/när det kommer
- Få besked – men kanske leva med vetskapen

- Skuldkänslor
  - Varför jag? Varför inte jag? Vad har jag kanske orsakat?

Kaskadscreening

- Familjeutredning
  - Genotyp pos / fenotyp pos = patient
  - Genotyp pos / fenotyp neg = skall följas
  - Genotyp neg = frisk
- Genetisk variant ≠ sjukdom (men ibland diagnos)
- Stor variation i uttryck såväl mellan som inom samma familj

Diagnostic yield beror på diagnos och urval

Disease	Diagnostic	Prognostic	Therapeutic	Yield[a]
LQTS	+++	+++	+++	±60–70%
CPVT	+++	+	–	±60%
SQTS	+	–	–	±30%
Brugada syndrome	+	+	+	±20–30%
CCD	+	–	–	Low
ERS	–	–	–	Low
Atrial fibrillation	–	–	–	Low
HCM	+++	+	+	±60%
DCM with CDD	+++	++	++	±70%
DCM without CCD	++	++	+	±30%
ARVC	++	++	++	±60%
RCM	+	–	–	?
NCCM	+	–	–	±30%

LQTS long QT syndrome, *CPVT* catecholaminergic polymorphic VT/VF, *SQTS* short QT syndrome, *CCD* cardiac conduction disease, *ERS* early repolarisation syndrome, *HCM* hypertrophic cardiomyopathy, *DCM* dilated cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *RCM* restrictive cardiomyopathy, *NCCM* non-compaction cardiomyopathy

Cardiogenetics, 25 years a growing subspecialism

A. A. M. Wilde · E. Nannenberg · C. van der Werf

Neth Heart J (2020) 28 (Suppl 1):S39–S43
https://doi.org/10.1007/s12471-020-01444-8

Användbarhet för genetiska fynd

Table 5 Impact of genetic testing for the proband

Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	–	+	–
Atrial fibrillation	–	+	–
Early repolarization syndrome	–	–	–
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic cardiomyopathy	+++	++	++
Left ventricular non-compaction	+	+	–
Restrictive cardiomyopathy	+	+	+
Congenital heart disease			
Syndromic CHD	+++	+	–
Non-syndromic CHD	+	–	–
Familial CHD	++	–	–

+++ : is recommended/is indicated or useful.
++ : can be recommended/can be useful.
+ : may be considered/may be useful.
– : is not recommended/is not indicated nor useful.

PGL 5.6.0 DTD ■ HRTHM9355_proof ■ 15 April 2022 ■ 9:12 pm ■ ce

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the Q2Q1 State of Genetic Testing for Cardiac Diseases. Wilde et al. 2022

När ska vem testas och för vad?

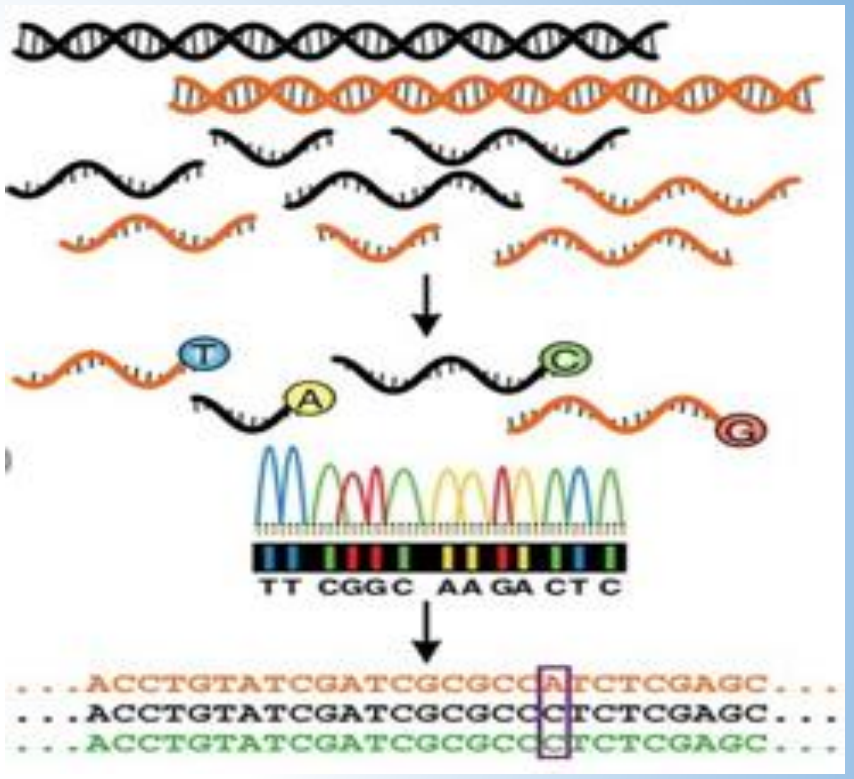
- Om sjukdomsorsakande variant är identifierad i släkt
  - inhämta provsvar
  - bekräfta/bedöm svaret
  - om bedömningen kvarstår erbjuds släktingar test för endast denna gen/variant

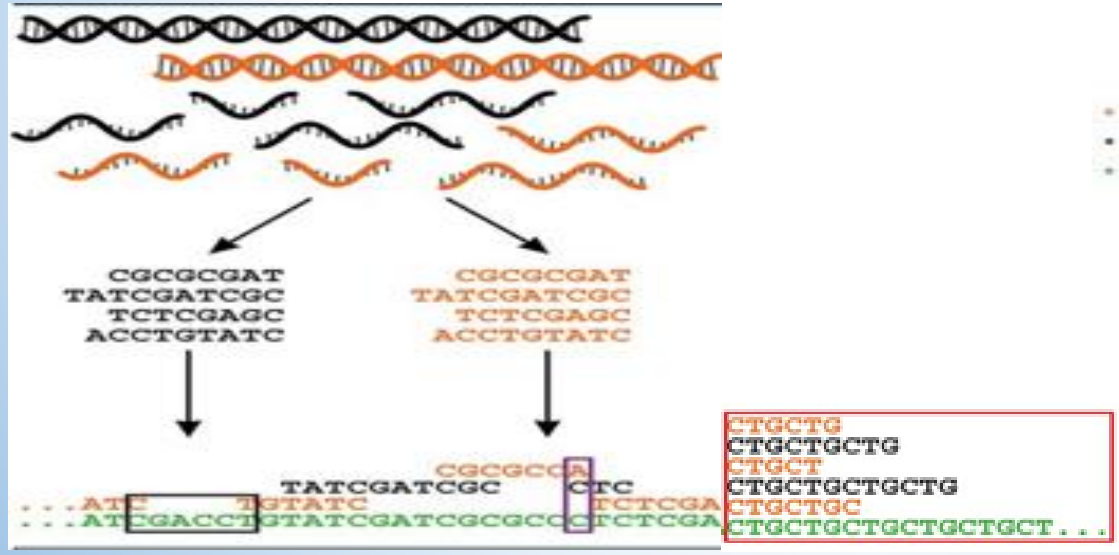
- Tidigare ej utförd genetisk testning i familjen:
  - beställ genpanel utifrån symtombild och klinisk diagnos
  - beskriv ev släktanamnes i remiss

- Genpanel: Innehåll varierar över tid, lab, teknik mm.
- Osäker? Konsultera före – klinisk genetiker tillgänglig kontorstid via växeln

Analys

- Sangersekvensering – en gen
- NGS – flera gener samtidigt



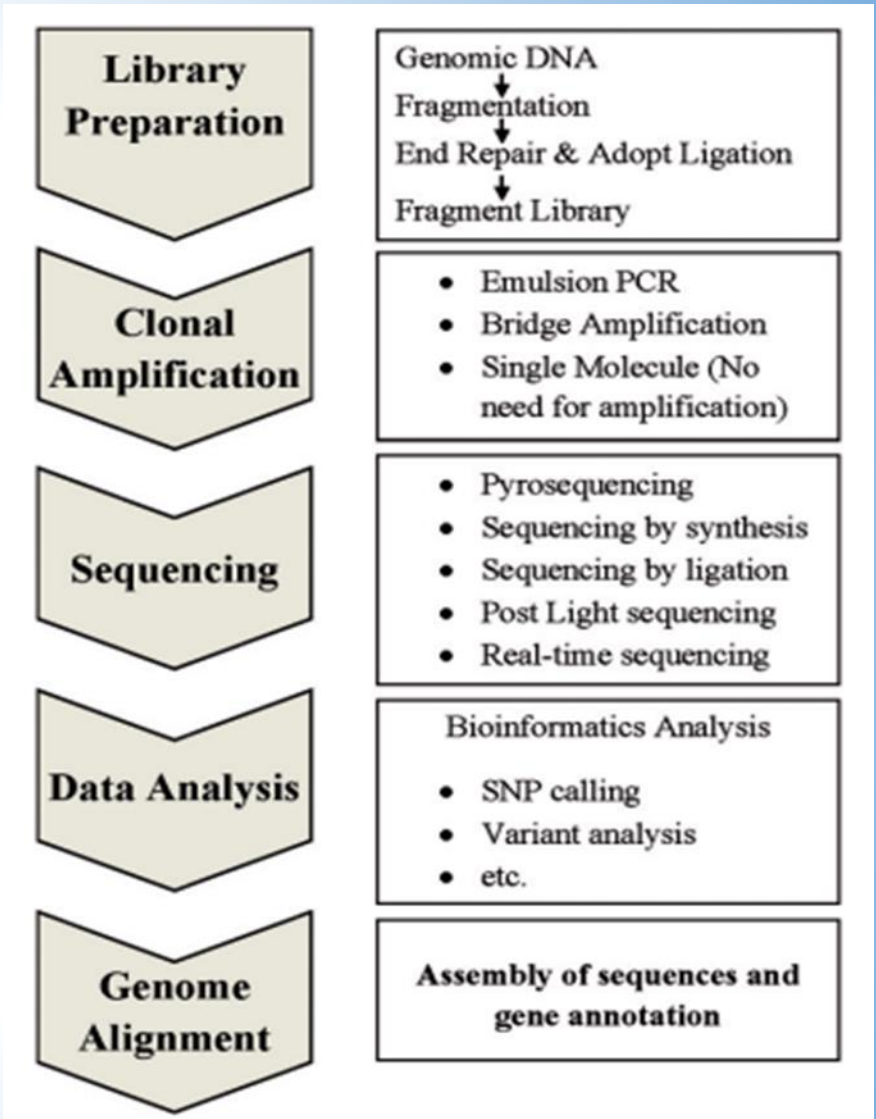


NGS

- Bioinformatik

- Alla kliniskt relevanta gener (ca 20.000) sekvenseras,
  men utifrån beställd analys
  ”plockas fram” relevanta gener (genpanel)
  eller gener från symtom (WES), trio …

- Tolkning av varianter



Genetiskt provsvar – vad står i rapporten?

- The American College of Medical Genetics and Genomics guidelines (2015)
- I rapporten:
  - varianter påvisade
  - associerad sjukdom
  - nedärvningsmönster

  - Tolkning
  - hur varianten klassificerats och varför
  - förväntad effekt

  - Ev rekommendationer på vidare genetisk utredning.

Klassificering av varianter

- Patogen
- Troligen patogen
- VUS (variant of unknown significance)
- Likely benign
- Benign

Konserverad, djur och lab-studier, databaser av friska/sjuka individer, segregationsanalyser, data-förutsägningar (proteinförändringar struktur/funktion), tidigare publicerade/databaser osv.
Sammanvägd ”poäng”

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
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Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

Bra artiklar

ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–17
https://doi.org/10.1093/eurheartj/ehab895

SPECIAL ARTICLE

Interpretation and actionability of genetic variants in cardiomyopathies: a position statement from the European Society of Cardiology Council on cardiovascular genomics

Eloisa Arbustini [1]*, Elijah R. Behr [2], Lucie Carrier [3,4], Cornelia van Duijn [5], Paul Evans[6], Valentina Favalli[7], Pim van der Harst [8], Kristina Hermann Haugaa [9,10], Guillaume Jondeau [11,12,13]†, Stefan Kääb[14,15], Juan Pablo Kaski [16,17], Maryam Kavousi[18], Bart Loeys [19,20], Antonis Pantazis[21], Yigal Pinto[22], Heribert Schunkert[23,24], Alessandro Di Toro [1], Thomas Thum [25,26], Mario Urtis [1], Johannes Waltenberger [27,28], and Perry Elliott [29,30]

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases

Arthur A.M. Wilde (EHRA Chair),[1,†,‡,¶] Christopher Semsarian (APHRS Co-Chair),[2,†] Manlio F. Márquez (LAHRS Co-Chair),[3,†] Alireza Sepehri Shamloo,[4] Michael J. Ackerman,[5] Euan A. Ashley,[6] Eduardo Back Sternick,[7] Héctor Barajas-Martinez,[8] Elijah R. Behr,[9,¶] Connie R. Bezzina,[11,‡] Jeroen Breckpot,[12,‡] Philippe Charron,[13,‡] Priya Chockalingam,[14] Lia Crotti,[15,16,17,‡,¶] Michael H. Gollob,[18] Steven Lubitz,[19] Naomasa Makita,[20] Seiko Ohno,[21] Martín Ortiz-Genga,[22] Luciana Sacilotto,[23] Eric Schulze-Bahr,[24,‡,¶] Wataru Shimizu,[25] Nona Sotoodehnia,[26] Rafik Tadros,[27] James S. Ware,[28,29] David S. Winlaw,[30] Elizabeth S. Kaufman (HRS Co-Chair)[31,†]

VUS

- Utmaning!!
- Ska ej påverka kliniska handläggningen

- Ev analys av släktingar endast (!) för att se om segregerar med sjukdom, eller i andra specifika ärenden. Gärna kontakt före med klin gen/kollega.

- Rekommendation vanligen; Återkom om 3-5 år för ny bedömning

I fall där genetisk orsak inte påvisas

- Utesluter inte ärftlighet

- Ställningstagande till ev kontrollprogram, finns på Svenska Kardiologföreningens hemsida under rubriken ”Riktlinjer”
- utredning-av-anhoriga-vid-familjar-sjukdom-utan-kand-genetisk-orsak-200305.pdf (sls.se)

- Familjebrev ”utan mutation”

Utredning av anhöriga vid familjär sjukdom utan känd genetisk orsak

Rekommendationer och arbetssätt bland medlemmar i Svenskt Kardiogenetiskt nätverk

sammanställt av

Anneli Svensson, överläkare
ansvarig för Kardiogenetisk verksamhet, Universitetssjuk
Ordförande i Svenska Nationella Kardiogenetik

Pia Dahlberg, överläkare
ansvarig för Kardiogenetisk verksamhet, Sahlgrenska Universit
Vice ordförande i Svenska Nationella Kardiogenet

Sjukdomsgrupper

Jonkanalsjukdomar:

- Långt QT-syndrom (LQTS)
- Kort QT-tids syndrom (SQTS)
- Brugadas Syndrom (BS)
- Katekolaminerg Polymorf Ventrikel Takykardi (CPVT)

Kardiomyopatier:

- Hypertrofisk kardiomyopati (HCM)
- Arytmogen högerkammar-kardiomyopati (ARVC)
- Dilaterad kardiomyopati (DCM)

Plötslig hjärtdöd / SCD

indexfall med neg obduktion inkl genetisk analys

- Vem: alla FGS
  - ingen formell åldersgräns hos indexfallet för utredning av släktingar
  - i danska riktlinjer anges under 50 års ålder
- Vad: anamnes + kliniskt status + EKG + UKG + arbetsprov
- Start: ingen åldersgräns
- Hur ofta: upprepa i regel efter 4–5 år, speciellt om den primära screeningen var före 18 års ålder
- Stopp: initial samt en uppföljande undersökning, sedan stopp
  - ev ytterligare undersökningar även i frånvaro av fynd, beroende på individens/familjens inställning och önskemål

Mars 2020 A Svensson/P Dahlberg

Take home message; vi behöver hjälpas åt!