LES NOUVEAUX TROUBLES DE CONDUCTION HEREDITAIRES

Alban Baruteau

L’institut du thorax, INSERM 1087 – CNRS 6291
 IRS – Université de Nantes

Centre Chirurgical Marie Lannelongue – M3C
Université Paris Sud – Le Kremlin Bicêtre

Reims – 11 septembre 2014
**INTRODUCTION**

**Definition**

unexplained progressive conduction abnormalities  
early onset < 50 years old  
especially if family history of PCCD  
in the absence of skeletal myopathies

Priori S et al. Heart Rhythm 2013
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IS AN INHERITED DISORDER

Genetic epidemiological approach of PCCD

n=6600 pts
French social security number → city of birth
Mapping of the frequency of PM implantations 0.21% to 2.28% in specific parishes
Identification of 5 large families with PCCD

Strong genetic background in PCCD

Gourraud JB et al. Heart 2012
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IS AN INHERITED DISORDER

Genetic epidemiological approach of PCCD

1980-2009 retrospective study, 13 centers
141 children - pediatric idiopathic heart block

- 42 incomplete AV block at diagnosis
- 70% progressed to a permanent complete AV block

Postnatal degenerative process of the specialized conduction tissue?

ECG screening – 130 asymptomatic parents
130 matched healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Parents</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction disorders</td>
<td>6 (4.6%)</td>
<td>66 (50.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1st degree AVB</td>
<td>0 (0%)</td>
<td>24 (18.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBBB</td>
<td>2 (1.5%)</td>
<td>51 (39.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBBB</td>
<td>4 (3.1%)</td>
<td>20 (15.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Heritability = 0.91

Baruteau AE et al. Circulation 2012
Baruteau AE et al. Eur Heart J 2012
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

Etiology

- genetically mediated
- autosomal dominant mode of inheritance
- age-dependent penetrance
- variable expressivity

Giudicessi A et al. Transl Res 2013
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

Etiology

Structurally normal heart

Primary electrical diseases
SCN5A
SCN5A overlap syndromes
SCN1B
SCN10A
Connexins
TRPM4
KCNK17

Structurally abnormal heart

Congenital heart disease
NMX2.5
TBX5 and TBX3
Dilated cardiomyopathy
LMNA gene
Hypertrophic cardiomyopathy
PRKAG2
Glycogen storage diseases

PCCD IS AN INHERITED DISORDER
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IS AN INHERITED DISORDER

Etiology

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**Structurally normal heart**

Primary electrical diseases
- SCN5A
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**Structurally abnormal heart**

Congenital heart disease
- NKX2.5
- TBX5 and TBX3

Dilated cardiomyopathy
- LMNA gene

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INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IS AN INHERITED DISORDER

Structurally normal heart

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Structurally abnormal heart

- Congenital heart disease
  - Nkx2.5
  - Tbx5 and Tbx3
- Dilated cardiomyopathy
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- Glycogen storage diseases
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

Lydia DeWitt’s - 1909

Abriel H. Gene 2013
Munshi N. Circ Res 2012

- Currents
  - Na⁺ current
  - Ca²⁺ current
  - I₉ current
  - IKs current
  - IKr current

- Channels
  - Na₉,5, sodium
  - Ca₉,2, calcium
  - K₉,3 potassium
  - KCNQ1 – K₉,7,1 potassium
  - hERG – K₉,11,1 potassium

- Genes
  - SCN5A
  - CACNA1C
  - KCND3
  - KCNQ1
  - KCNH2

Progression of cardiac impulse
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

SCN5A - locus 3p21
Cardiac voltage-gated sodium channel Nav1.5
Loss of function mutations

Probst V et al. J Am Coll Cardiol 2002
Schott JJ et al. Nat Genet 1999
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

SCN5A overlap syndromes

SCN5A mutations

- a broad phenotypic spectrum from asymptomatic carriers...
- to lethal arrhythmias

Congenital sick sinus syndrome
Atrial standstill
Familial atrial fibrillation
Cardiac conduction disease – AV block
Brugada syndrome
Congenital long-QT syndrome type 3
Dilated cardiomyopathy
Sudden infant death syndrome

Remme CA. J Physiol 2013
Kanter R et al. Circulation 2012
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

SCN1B - locus 19q13

Beta 1 subunit of the voltage-gated sodium channel Nav1.5 modulate expression and function of the sodium channel

Loss of function mutations

Watanabe H. J Clin Invest 2008
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

SCN10A - 3p22

Voltage-gated sodium channel Nav1.8
Late sodium current

Genome-wide association study on 28,517 pts

SCN10A found to be associated with AV conduction

Nav1.8 activates more slowly and at more positive potentials than Nav1.5

Pfeufer A et al. Nat Genet 2010
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

CONNEXINS - locus 1q21
Cardiac gap junctions
Electrical coupling – intercellular communication
Low resistance channels – 4 Cx isoforms

Temple I et al. Heart Rhythm 2013
Makita N et al. Circ Arrhythmia Electrophysiol 2012

156 probands with familial AV block
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

CONNXINS - locus 1q21
Cardiac gap junctions
Electrical coupling – intercellular communication
Low resistance channels – 4 Cx isoforms

GJ plaque formation

Makita N et al. Circ Arrhythmia Electrophysiol 2012
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

TRPM4 - locus 19q13

Transient receptor potential cation channel, Subfamily M, Member 4
Gain of function mutations by altered deSUMOylation
Impair endocytosis and stabilize the mutant channels at the cell surface

May reduce the number of available sodium channels
by cell membrane depolarization in the conduction system

Stallmeyer B et al. Hum Mutat 2011
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN STRUCTURALLY NORMAL HEARTS

KCNK17 - locus 6p21
Potassium channel Task-4
Gain of function mutation
Purkinje cells

Ventricular Tachycardia
1st degree AV block + RBBB

Digenic mutation SCN5A + KCNK17

Gain of function in presence of a normal cellular distribution and cell surface expression

May reduce the number of available sodium channels by cell membrane depolarization in the conduction system

Friedrich C et al. EMBO Mol Med 2014
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

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Hypertrophic cardiomyopathy
- PRKAG2

Glycogen storage diseases
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD ASSOCIATED WITH CONGENITAL HEART DISEASES

Bruneau B. Nature 2008

Tbx5 expression

NKX2.5 expression

Overlap
Tbx5 + NKX2.5 expression

Atrial septation

Ventricular septation + AV cushion formation

Great vessel formation + valvulogenesis

ASD: NKX2-5
GATA4
TBX20
MYH6
TBX5

VSD: NKX2-5
GATA4
TBX20
TBX1
TBX5

AVSD: PTPN11
KRAS
SOS1
RAF1
CRELD1

Ebstein’s, TA: NKX2-5

DORV, TGA: NKX2-5
THRAP2
PTA: TBX1
TGA: NKX2-5,
NOTCH1
TBX1
JAG1
NOTCH2

AS and AC: NOTCH1
PTPN11
PS: PTPN11
JAG1
NOTCH2

BAV: NOTCH1
HLHS: NOTCH1
PDA: TCFP2B
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD ASSOCIATED WITH CONGENITAL HEART DISEASES

Core transcription factors for both cardiac chamber formation and conduction system development

Bruneau B. Nature 2008
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD ASSOCIATED WITH CONGENITAL HEART DISEASES

NKX2.5 - locus 5q34
Cardiac specific homeobox transcription factor

Wild-type embryos

NKX2.5 knockout embryos

INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD ASSOCIATED WITH CONGENITAL HEART DISEASES

NKX2.5 - locus 5q34
Cardiac specific homeobox transcription factor

AV conduction disorders
Sudden death

... and Congenital heart diseases
  Secundum ASD
  Tetralogy of Fallot
  Truncus arteriosus
  Double-outlet right ventricle
  L-transposition of great arteries
  Interrupted aortic arch
  Hypoplastic left heart syndrome
  Ventricular noncompaction

McElhinney DB et al. J Am Coll Cardiol 2003
Schott JJ et al. Science 1998
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD ASSOCIATED WITH CONGENITAL HEART DISEASES

TBX5 - locus 12q24
T-box transcription factor

Holt-Oram syndrome
The « heart and hand syndrome »

Cardiac conduction disorders
- Sinus bradycardia
- AV block
- even in the absence of overt CHD

... and Congenital heart diseases
- Secundum ASD
- Muscular VSD
- AV septal defect
- Aortic coarctation

... and Radial ray upper limb abnormalities

Basson CT et al. Nat Genet 1997
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD ASSOCIATED WITH CONGENITAL HEART DISEASES

TBX3 and TBX5 - locus 12q24

T-box transcription factors

12q24

TBX5

↓

Holt-Oram syndrome

TBX3

Ulnar-mammary syndrome

Ulnar ray UL abnormalities

Mammary gland hypoplasia

Genital defects

## Diagnosis

### Clinical data

<table>
<thead>
<tr>
<th>History</th>
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<tbody>
<tr>
<td><strong>Family history</strong></td>
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<tr>
<td>conduction abnormalities</td>
</tr>
<tr>
<td>pacemaker implantation</td>
</tr>
<tr>
<td>sudden death</td>
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### 12-lead ECG

### Underlying CHD?

<table>
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<tr>
<th>Clinical exam</th>
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<tr>
<td>2D echocardiography</td>
</tr>
<tr>
<td>± Cardiac MRI</td>
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Priori S et al. Heart Rhythm 2013
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN ROUTINE PRACTICE

**Diagnosis**

**Clinical data**

- History
  - Family history: conduction abnormalities, pacemaker implantation, sudden death
- 12-lead ECG

**Underlying CHD?**

- Clinical exam
- 2D echocardiography
- ± Cardiac MRI

**Positive family history**

**Early-onset conduction disorders**

Targeted genetic testing may be considered

Priori S et al. Heart Rhythm 2013
INHERITED PROGRESSIVE CARDIAC CONDUCTION DISORDERS

PCCD IN ROUTINE PRACTICE

Risk stratification

No genotype-based risk stratification

Clinical risk stratification

- 12-lead ECG
- Holter ECG
- 2D echocardiography

Independent of symptom status

Low threshold for EP study

Epstein A et al. Circulation 2013
Priori S et al. Heart Rhythm 2013
Management

1. General measures
   - Restriction of medications with conduction-slowing properties
   - Active treatment of fever in SCN5A mutation carriers

Epstein A et al. Circulation 2013
Priori S et al. Heart Rhythm 2013
Ackerman M et al. Heart Rhythm 2011
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2. Pacemaker implantation
   - is recommended if
     a) Intermittent or permanent third-degree or high-grade AV block
     b) Symptomatic Mobitz I or II second-degree AV block
   - can be useful if
     bifascicular block with or without first-degree AV block

Epstein A et al. Circulation 2013
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   - *can be useful* if
     - Bifascicular block with or without first-degree AV block

3. Family screening of first-degree relatives
   - Clinical, ECG, TTE screening
   - Targeted-genetic testing in family with mutation-positive PCCD
   - Prospective follow-up of asymptomatic mutation carriers

References:
- Epstein A et al. Circulation 2013
- Priori S et al. Heart Rhythm 2013
- Ackerman M et al. Heart Rhythm 2011
CONCLUSION

A genetic origin for unexplained progressive conduction abnormalities in the young

A complex physiopathological process
With mutations in gene encoding cardiac ion channels
ion channels interacting proteins
cardiac transcription factors

A promising future
Genetic analysis part of the clinical routine work-up?
Preventive strategies in mutation carriers?
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