



Journée AChro-Puce
26 novembre 2025

Guide du réseau AChro-Puce pour l'interprétation des CNVs

Mise à jour 2025

Matthieu EGOFF – **Céline Pebrel-Richard**
Poitiers *Clermont-Ferrand*

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Journée AChro-Puce
26 novembre 2025

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Guide du réseau AChro-Puce

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Interprétation des CNVs

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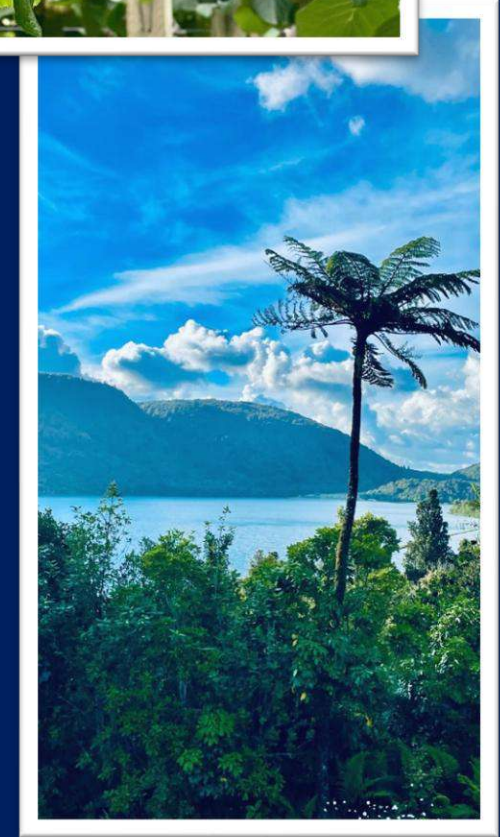
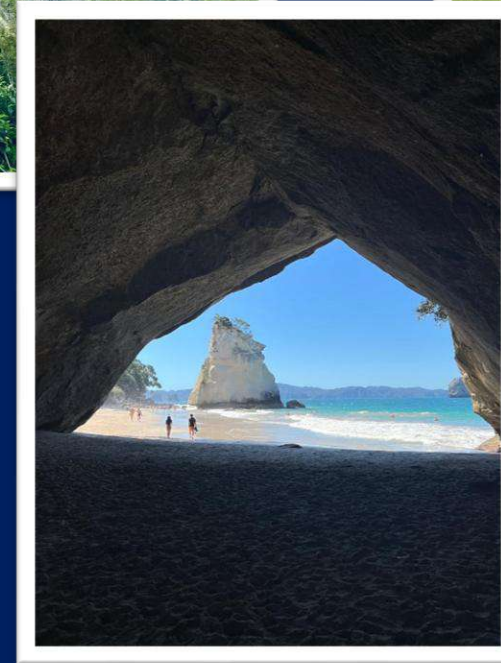
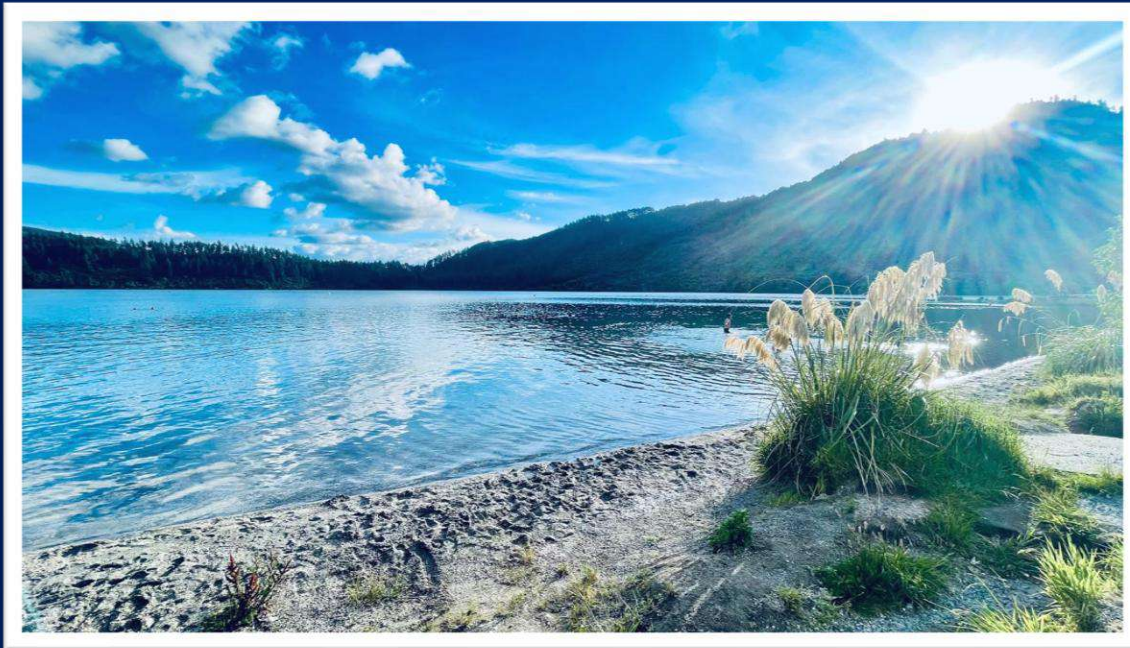
Salut Céline
Je suis à la journée Achro-Puce, on t'attend
pour commencer ?
Où es-tu ?

mise à jour 2025

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Matthieu EGOFF – Céline Pebrel-Richard

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Céline Pebrel-Richard

Contexte

Guide et recommandations pour aider à la standardisation de la **classification** et de **l'interprétation** des CNVs

Groupe de travail Achro-Puce : première version en juin 2019

Objectif : **homogénéiser les pratiques** au niveau national

Création de la nouvelle classe « PIEV » (dès 2019) :

CNVs récurrents de susceptibilité aux TNDs

Pénétrance **I**ncomplète

Expressivité **V**ariable

Souvent hérités d'un parent sain

Surreprésentation dans cohortes patients

NB : existe sous une forme plus ou moins similaire dans d'autres pays

Contexte



<https://acpa-achropuce.com/diagnostic-postnatal/>

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Mises à jour 2025

Critères de classification :

Pas de modification depuis 2022 (sauf bases de données, outils d'aide automatique...)

Classifications des CNVs récurrents proposée par le réseau :

Modifications en 2023 :

Dup 17q12 (*HNF1B*) = ~~PIEV~~ -> VSI

Dup Xp22.33 (*STS*) = ~~PIEV~~ -> VSI

Dup 22q11.2 (*TBX1*) = PIEV

Modifications en 2025 :

~~Del~~ 15q11.2 BP1-BP2 (*NIPA1/TUBGCP5*) : ~~PIEV~~ -> **VSI**

Dup 16p11.2 distale BP2-BP3 (*SH2B1*) : ~~PIEV~~ -> **VSI**

~~Del~~ 16p11.2 distale BP2-BP3 (*SH2B1*) : **classe 5 pour obésité** (reste PIEV TNDs)

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Guide du réseau Achro-Puce
pour l'interprétation des CNVs

Publication du guide



26 nov.
2025

Clinical Genetics

WILEY

ORIGINAL ARTICLE

CLINICAL
GENETICS

French Guidelines of the AchroPuce Network for the Interpretation and Reporting of Constitutional Copy Number Variants

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Guide du réseau Achro-Puce
pour l'interprétation des CNVs

Publication du guide

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ORIGINAL ARTICLE

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GENETICS

French Guidelines of the AchroPuce Network for the Interpretation of Constitutional Copy Number Variants

ABSTRACT

Over the past 15 years, the field of constitutional copy number variants (CNVs) has evolved significantly, becoming integral to routine genetic diagnostics. The clinical implications of CNVs, both benign and pathogenic, are particularly important as sources of neurodevelopmental disorders (NDDs). To address these challenges, the French AchroPuce Network has developed a novel classification termed “PIEV,” referring to CNVs with pathogenicity and variable expressivity. This category complements the existing ACMG classification and aims to harmonize practice through standardized French interpretation precision. Distinguishing clearly pathogenic CNVs from benign variants independently of the clinical context requires a multidisciplinary clinical approach. The AchroPuce Network provides consensus recommendations with a customized interpretation tool to enhance national consistency in CNVs reporting.



...evolved significantly, becoming integral to routine genetic diagnostics. The clinical implications of CNVs, both benign and pathogenic, are particularly important as sources of neurodevelopmental disorders (NDDs). To address these challenges, the French AchroPuce Network has developed a novel classification termed “PIEV,” referring to CNVs with pathogenicity and variable expressivity. This category complements the existing ACMG classification and aims to harmonize practice through standardized French interpretation precision. Distinguishing clearly pathogenic CNVs from benign variants independently of the clinical context requires a multidisciplinary clinical approach. The AchroPuce Network provides consensus recommendations with a customized

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Guide du réseau Achro-Puce
pour l'interprétation des CNVs

TABLE 1 | French guidelines by the AchroPuce Network for the interpretation and reporting of constitutional Copy Number Variants.

Class 5: Pathogenic CNVs

Necessary and sufficient evidence: the CNV is well documented as clinically significant in multiple peer-reviewed publications and patients databases

Class 4: Likely pathogenic CNV

Two major evidences or one major and two minor evidences must be provided to belong to class 4

Major evidences:

• Medical literature:

- In case of non-specific phenotype (e.g., intellectual disease (ID), autism spectrum disease (ASD)): CNV is described in the literature in at least one patient with a concordant phenotype
- In case of specific phenotype: CNV is described in the literature in at least one patient with only a few common phenotypic criteria with the carrier patient

• Parental Inheritance:

- CNV occurred *de novo*

- CNV is inherited from an affected parent
- CNV is inherited from a parent with mosaic CNV

• Gene content:

- The genes contained in the CNV have been associated with a concordant phenotype in the literature or there are strong functional data: studies in cells and/or animal models which may provide relevant information about its potential pathogenicity
- The CNV corresponds to a region close to a candidate gene for the disease characterized by a specific phenotype
- The CNV is a deletion involving the 5' region with additional coding sequence of an established haploinsufficient gene.

• Nature:

- CNV is a homozygous deletion
- CNV corresponds to a triplication or amplification referenced in curated databases as a common polymorphism

Class 3: VUS

Necessary and sufficient evidence: the CNV does not have sufficient evidence to be classified as pathogenic or benign

Minor evidences:

• Epidemiology:

- In ID: CNV is identified more frequently in ID patients than in controls in Coe et al. study [23]
- CNV is absent from control databases

• Gene content:

- CNV partially overlaps with CNVs identified as pathogenic in OMIM or ClinGen Curated Pathogenic without a clearly identified candidate gene

• Size:

- > 1Mb

TABLE 1 | (Continued)

Class 2: likely benign

Two major evidences or one major and two minor evidences must be provided to belong to class 2.

Major evidences:

• Epidemiology:

- CNV is often reported in healthy population but not enough to be considered as a polymorphism (< 1%)
- CNV is reported at least once in the GnomAD and/or DGV-gold polymorphic variant databases with an overlap of 80%.

• Inheritance:

- CNV is inherited from a healthy parent or does not segregate with the phenotype within family

• Gene content:

- CNV contains no genes or contains only repeats/pseudogenes/segmental duplications
- CNV contains only genes without argument for a role in human pathology (unknown function, patterns of expression, low pLI and high LOEUF...)

Class 1: Benign CNV

Necessary and sufficient evidence: There are sufficient evidences in multiple peer-reviewed publications or in curated databases to consider them as benign variants

Minor evidences:

• Epidemiology:

- In ID: CNV is identified with the same or lower frequency in ID patients compared to controls
- CNV is reported at least once in the ExAC/DGV-gold polymorphic variant databases but with a threshold of overlap between 50% and 80%

• Gene content:

- No gene contained in the CNV has been associated with the same phenotype in the literature or there is no argument for the role of one or more genes included in the CNV in the pathology presented by the patient

• Size:

- Not exceeding 500 kb

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Guide du réseau Achro-Puce pour l'interprétation des CNVs

Classe 1 : bénin

Un critère nécessaire et suffisant

Classe 5 : pathogène

Un critère nécessaire et suffisant

Classe 2 : prob^t bénin

Au moins 2 critères majeurs
ou 1 critère majeur et 2 mineurs

Classe 4 : prob^t patho

Au moins 2 critères majeurs
ou 1 critère majeur et 2 mineurs

Classe 3 : VOUS

Un critère nécessaire et suffisant

PIEV : susceptibilité aux TND

Critères détaillés en français dans le guide, sur le site du réseau Achro-Puce

<https://acpa-achropuce.com/diagnostic-postnatal/>

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Guide du réseau Achro-Puce
pour l'interprétation des CNVs

Classe 1 : bénin

Un critère nécessaire et suffisant

Classe 5 : pathogène

Un critère nécessaire et suffisant

Classe 2 : prob^t bénin

Au moins 2 critères majeurs
ou 1 critère majeur et 2 mineurs

Classe 4 : prob^t patho

Au moins 2 critères majeurs
ou 1 critère majeur et 2 mineurs

Classe 3 : VOUS

Un critère nécessaire et suffisant

PIEV : susceptibilité aux TND

Critères détaillés en français dans le guide, sur le site du réseau Achro-Puce

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Guide du réseau Achro-Puce
pour l'interprétation des CNVs

TABLE 2 | Classification of recurrent CNVs.

CNV	Genomic coordinates	Candidate genes	Variation	Classification
Proximal 1q21.1 (BP2-BP3)	<i>GRCh37: chr1:145386507-145748064</i> <i>GRCh38: chr1:145686999-146048495</i>	RBM8A	Del	Class 3: VOUS
			Dup	Class 3: VOUS
Distal 1q21.1 (BP3-BP4)	<i>GRCh37: chr1:146577486-147394506</i> <i>GRCh38: chr1: 147105904-147917509</i>	GJA5, GJA8	Del	PIEV (high penetrance)
			Dup	PIEV (low penetrance)
2q11.2	<i>GRCh37: chr2:96739012-97671429</i> <i>GRCh38: chr2:96073264-97005692</i>	ARID5A, KANSL3, TMEM127	Del	Class 3: VOUS
			Dup	Class 3: VOUS
2q13	<i>GRCh37: chr2:111392193-113104742</i> <i>GRCh38: chr2:110634616-112347165</i>	BUB1, BCL2L11	Del	PIEV (low penetrance)
			Dup	Class 3: VOUS
3q29	<i>GRCh37: chr3:195756054-197344662</i> <i>GRCh38: chr3:196029183-197617791</i>	DLG1, BDH1	Del	PIEV (high penetrance)
			Dup	Class 3: VOUS
10q11.21q11.23 (LCRC-D)	<i>GRCh37: chr10:49389703-51053583</i> <i>GRCh38: chr10:48181660-49845537</i>	CHAT, SLC18A3	Del	PIEV (low penetrance)
			Dup	Class 3: VOUS
15q11.2 (BP1-BP2)	<i>GRCh37: chr15:22832519-23090897</i> <i>GRCh38: chr15: 22782170-23040134</i>	NIPA1, NIPA2	Del	Class 3: VOUS
			Dup	Class 1: Benign
15q13.3 (BP4-BP5)	<i>GRCh37: chr15:31192889-32445405</i> <i>GRCh38: chr15:30900686-32153204</i>	CHRNA7, TRPM1, OTUD7A	Del	PIEV (high penetrance)
			Dup	Class 3: VOUS
15q13.3 (D-CHRNA7 to BP5)	<i>GRCh37: chr15:3201962132445405</i> <i>GRCh38: chr15:31727418-32153204</i>	CHRNA7, OTUD7A	Del	PIEV (high penetrance)
			Dup	Class 1: Benign
16p13.11	<i>GRCh37: chr16:15511711-16292265</i> <i>GRCh38: chr16:15417854-16198408</i>	NDE1, MYH11	Del	PIEV (low penetrance)
			Dup	Class 3: VOUS
16p12.2	<i>GRCh37: chr16:21948445-22430804</i> <i>GRCh38: chr16:2193712422419483</i>	EEF2K, POLR3E, CDR2	Del	PIEV (low penetrance)
			Dup	Class 3: VOUS
Distal 16p11.2 (BP2-BP3)	<i>GRCh37: chr16:28822635-29046499</i> <i>GRCh38: chr16:28811314-29035178</i>	SH2B1	Del	PIEV (high penetrance) Class 5: Pathogenic in case of obesity
			Dup	Class 3: VOUS
Proximal 16p11.2 (BP4-BP5)	<i>GRCh37: chr16:29649997-30199852</i> <i>GRCh38: chr16:29638676-30188531</i>	TBX6, KCTD13, PRRT2	Del	PIEV (high penetrance)
			Dup	PIEV (high penetrance)

(Continues)

TABLE 2 | (Continued)

CNV	Genomic coordinates	Candidate genes	Variation	Classification
17q12	<i>GRCh37: chr17:34815072-36192489</i> <i>GRCh38: chr17:36458167-37854616</i>	<i>HNFB1B</i>	Del	PIEV (low penetrance) Class 5: Pathogenic in case of renal and pancreatic damages
Proximal 22q11.2 (DGS/VCFS) (LCR22-A-D ou LCR22-A-B)	<i>LCR22-A-D</i>	<i>TBX1</i>	Dup	Class 3: VOUS
	<i>GRCh37: chr22:18912231-21465672</i> <i>GRCh38: chr22:18924718-21111383</i>		Dup	PIEV (low penetrance)
	<i>LCR22-A-B</i>			
	<i>GRCh37: chr22:18912231-20287208</i> <i>GRCh38: chr22:18924718-20299685</i>			
Central 22q11.21 (LCR22-B/C-D)	<i>GRCh37: chr22:20731986-21465672</i> <i>GRCh38: chr22:20377696-21111383</i>	<i>CRKL, SCARF2, SNAP29</i>	Del	PIEV (low penetrance)
			Dup	Class 3: VOUS
Distal 22q11.21 Type I: LCR22-C/D-E/F Type II: LCR22-E-F Type III: LCR22-D/E/F-H	Type I	<i>BCR, TOP3B, MAPK1</i>	Del type I	PIEV (low penetrance)
	<i>GRCh37: chr22:21090000-23650000</i> <i>GRCh38: chr22:20735712-23307813</i>		Del type II	Class 3: VOUS
	Type II			
Xp22.3	Type III	<i>STS, VCX3</i>	Del type III	PIEV (low penetrance)
	<i>GRCh37: chr22:21917117- 24994433</i> <i>GRCh38: chr22:21562828- 24598466</i>		Dup	Class 3: VOUS
	<i>GRCh37: chrX:6455812-8124954</i> <i>GRCh38: chrX:6537771-8156913</i>		Del	♂: class 3: VOUS ♀: class 2: Likely Benign
			Dup	♂: class 2: Likely Benign ♀: class 1: Benign

Note: Classification - red for pathogenic CNV (class 5), yellow for VUS (class 3), purple for PIEV class, blue for Likely benign (class 2) and green for benign CNV (class 1).

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 Guide du réseau Achro-Puce
pour l'interprétation des CNVs

La question récurrente... le rendu des PIEVs en prénatal ?

Reporting strategies for PIEVs depend on the clinical context. Postnatally, the AchroPuce Network recommends systematic PIEV reporting, allowing the biologist, in consultation with clinicians, to assess whether the PIEV contributes to the patient's phenotype. In prenatal diagnosis, PIEVs are not routinely reported. Reporting decisions must consider the ultrasound findings, the family history, and the specific PIEV involved, with particular attention to those associated with high penetrance [27]. Prenatal PIEV reporting decisions typically require consultation with a multidisciplinary team, including biologists, clinicians, and the local multidisciplinary prenatal diagnosis committee.

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CNV	Variation	Classification
Proximal 1q21.1 (BP2-BP3)	Del	Class 3: VOUS
	Dup	Class 3: VOUS
Distal 1q21.1 (BP3-BP4)	Del	PIEV (high penetrance)
	Dup	PIEV (low penetrance)
2q11.2	Del	Class 3: VOUS
	Dup	Class 3: VOUS
2q13	Del	PIEV (low penetrance)
	Dup	Class 3: VOUS
3q29	Del	PIEV (high penetrance)
	Dup	Class 3: VOUS
10q11.21q11.23 (LCRC-D)	Del	PIEV (low penetrance)
	Dup	Class 3: VOUS
15q11.2 (BP1-BP2)	Del	Class 3: VOUS
	Dup	Class 1: Benign
15q13.3 (BP4-BP5)	Del	PIEV (high penetrance)
	Dup	Class 3: VOUS
15q13.3 (D-CHRNA7 to BP5)	Del	PIEV (high penetrance)
	Dup	Class 1: Benign
16p13.11	Del	PIEV (low penetrance)
	Dup	Class 3: VOUS
16p12.2	Del	PIEV (low penetrance)
	Dup	Class 3: VOUS
Distal 16p11.2 (BP2-BP3)	Del	PIEV (high penetrance) Class 5: Pathogenic in case of obesity
	Dup	Class 3: VOUS
Proximal 16p11.2 (BP4-BP5)	Del	PIEV (high penetrance)
	Dup	PIEV (high penetrance)

Forte ou faible pénétrance ?



Estimations de pénétrance des PIEVs

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**VARIATIONS A
PENETRANCE
"REDUITE"**

Journée Achropuce 27/11/24

Matthieu Egloff (Poitiers)
Céline PEBREL-RICHARD (Clermont-Fd)

Présentation de Céline Pebrel-Richard à la journée Achro-Puce 2024

<https://acpa-achropuce.com/les-journees-achro-puce/>

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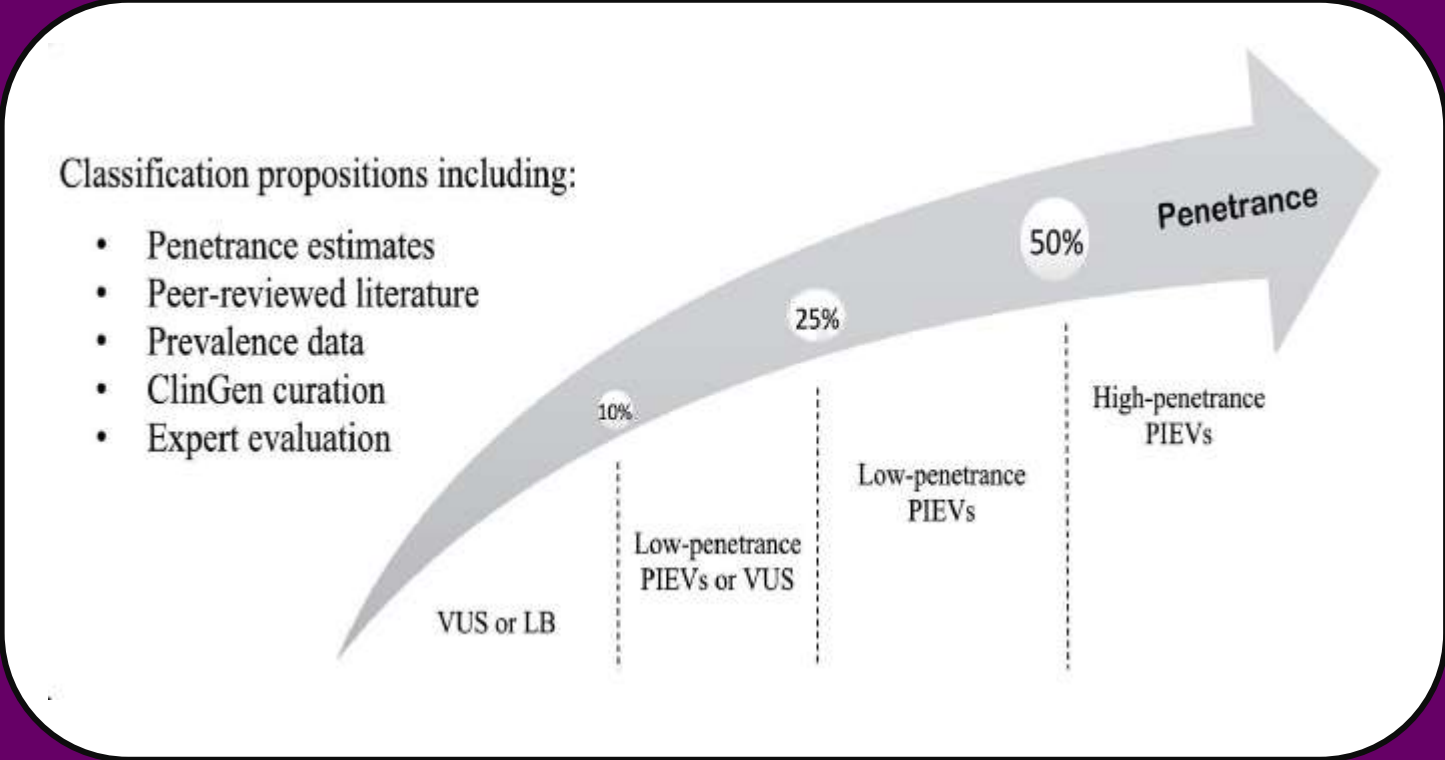
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Estimations de pénétrance des PIEVs

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Attention, ce n'est pas tout à fait ça...

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Guide du réseau Achro-Puce pour l'interprétation des CNVs

Estimations de pénétrance des PIEVs

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Yet, defining strict penetrance thresholds for CNVs classification also remains challenging, due to the limited availability of robust quantitative data, apart from the recent pooled analysis by Goh et al. [27]. In line with the recommendations of the ClinGen Low Penetrance Working Group [17], we chose to provide broad interpretive ranges rather than rigid cutoffs. In brief, CNVs with penetrance exceeding 25% according to Goh et al. [27] have generally been categorized as PIEVs, specifying whether the penetrance appears to be low (typically < 50%) or high (typically > 50%). In contrast, CNVs with less than 10% penetrance have usually been classified as variants of uncertain significance (VUS) or likely benign variants. For CNVs exhibiting interme-

Attention, ce n'est pas tout à fait ça...

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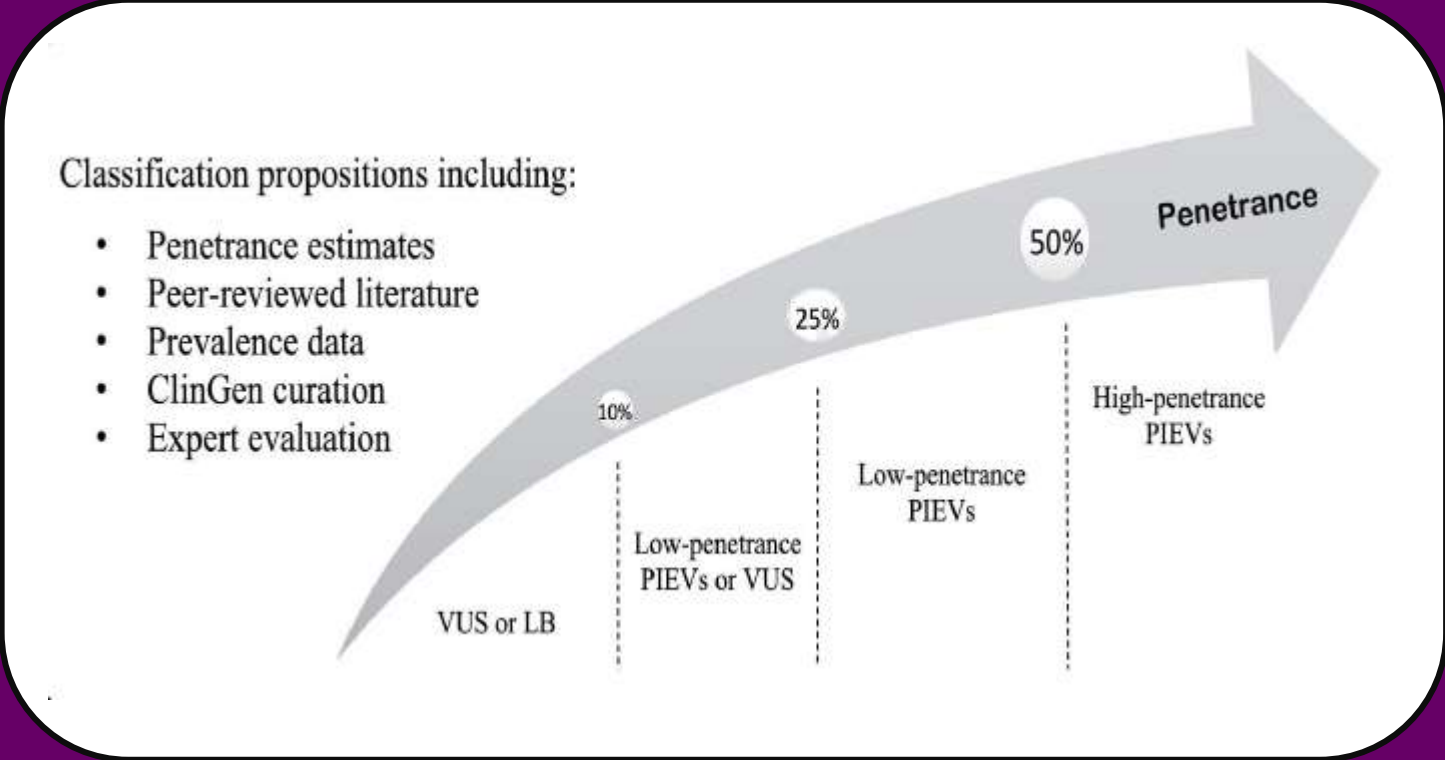
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Estimations de pénétrance des PIEVs

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Attention, ce n'est pas tout à fait ça...

Et d'où viennent ces chiffres ?

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Guide du réseau Achro-Puce pour l'interprétation des CNVs



SYSTEMATIC REVIEW

A systematic review and pooled analysis of penetrance estimates of copy-number variants associated with neurodevelopment



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ABSTRACT

Purpose: Many copy-number variants (CNVs) are reported to cause a variety of neurodevelopmental disabilities including intellectual disability, developmental delay, autism, and other phenotypes with incomplete penetrance. Therefore, not all individuals with a pathogenic CNV are affected. Penetrance estimates vary between studies. A systematic review was conducted to clarify CNV penetrance for 83 recurrent CNVs.

Methods: A systematic review using PRISMA guidelines (PROSPERO #CRD42021253955) was conducted to identify penetrance estimates for CNVs associated with neurodevelopment. Pooled analysis was performed using forest plots. The Ottawa Risk of Bias Assessment facilitated evaluation.

Results: Fifteen studies were reviewed in detail with 9 affected cohorts pooled and compared with the gnomAD v4.0 CNV control cohort of 269,885 individuals. Several CNVs previously associated with nonstatistically significant penetrance estimates now exhibit statistically significant differences, contributing to emerging evidence for their pathogenicity (15q24 duplication [A-D breakpoints], 15q24.2q24.5 deletion and duplication [*FBXO22*], 17q11.2 duplication [*NFI*], 17q21.31 duplication [*KANSL1*] and 22q11.2 distal duplication). Additionally, evidence is presented for the benign nature of some CNVs (15q11.2 duplication [*NIPAI*] and 2q13 proximal duplication [*NPHPI*]).

Conclusion: This is a large-scale systematic review of CNVs associated with neurodevelopment. A synopsis analyzing penetrance and pathogenicity is provided for each of the 83 recurrent CNVs.

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Goh *et al.*
Genet Med 2025

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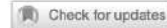
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ARTICLE OPEN



Updated penetrance estimates for recurrent copy number variants – an improved definition and formula

Shuxiang Goh ^{1,2,5}, Tracy Dudding-Byth ^{2,3,4}, Mark Pinese ^{1,5} and Edwin P. Kirk ^{1,2,6,7}

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Many copy number variants (CNVs) are implicated in neurodevelopmental disability, but exhibit incomplete penetrance. The definition of penetrance is often unclear. In published literature, penetrance typically includes the background risk of disease, while clinicians tend to exclude risks unrelated to the genetic variant. We propose a more clinically relevant definition of penetrance and develop a new formula for this. These changes are applied to existing data sources to produce updated penetrance estimates. Our findings indicate that most CNVs studied have significantly lower penetrance than previously published. Eleven CNVs, previously described as low-penetrant, are recalculated as having a penetrance close to 0% for intellectual disability. These include 1q21.1 proximal duplications [*RBM8A*], 2q11.2 deletions [*TMEM127*], 2q13 proximal deletions and duplications [*NPHP1*], 6q16 duplications [*SIM1*], 13q12 deletions [*CRYL1*], 15q11.2 duplications [*NIPA1*, *NIPA2*], 15q13.3 duplications [*CHRNA7*], 16p12.2 duplications [*CDR2*], 16p13.11 duplications [*MYH11*] and Xp22.3 duplications [*SHOX*]. Previous estimates of CNV penetrance, which ranged from 10–40% have been recalculated as 1–10%. In conclusion, many previously published estimates of CNV penetrance are inflated. Re-evaluation of existing data reveals lower and more accurate penetrance estimates for intellectual disability. This has important implications for diagnosis, genetic counselling, and prenatal reporting of recurrent CNVs.

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Genet Med 2025

Sauf que.....

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Eur J Hum Genet 2025

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ARTICLE OPEN

Check for updates

Updated penetrance estimates for recurrent copy number variants – an improved definition and formula

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17 nouvelles publications incluses
Nouvelle formule prenant en compte la prévalence de DI
Exclu tout autre phénotype que la DI

Résultats :

- Pénétrance divisée par 5-10 en moyenne !
- Plus aucun PIEV ne dépasse le seuil de 50%...

Limites :

- Reste un modèle mathématique
- Pas d'analyse des CNVs en « région complexe » (ex: *CHRNA7*) ou avec biais de recrutement majeur (ex: *HNF1B*)
- Les cohortes contrôles sont parfois « douteuses »

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Guide du réseau Achro-Puce
pour l'interprétation des CNVs

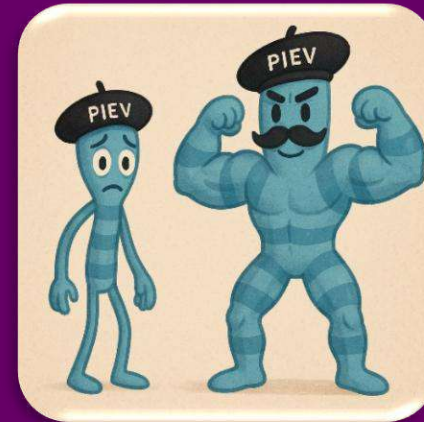
ARTICLE OPEN

Check for updates

Updated penetrance estimates for recurrent copy number variants – an improved definition and formula

Shuxiang Goh^{1,2}, Tracy Dudding-Byth^{2,3,4}, Mark Pinese^{1,5} and Edwin P. Kirk^{1,2,6,7}

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Et pour nos PIEVs ?

- Légitimise encore la classe PIEV \neq patho
- Estimation ne prennent pas en compte les autres TNDs (ex: TSA)
- Des CNVs classés « patho » ou « HFLP » par d'autres sont reclassés dans cette publi « pénétrance 0%, sans lien avec la DI »
-> Ils étaient tous VSI chez nous !

Donc :

Ne remet pas en question les conclusions publiées par le réseau Achro-Puce ni l'estimation « forte » ou « faible » pénétrance pour les TNDs

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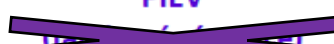

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Guide du réseau Achro-Puce
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Erratum

De **petites erreurs** se sont glissées dans le tableau récapitulatif à la fin de la version 2025 du guide

Distal 16p11.2 (BP2-BP3)	GRCh37: chr16:28822635-29046499 GRCh38: chr16:28811314-29035178	SH2B1	Del	 <p>PIEV Classe 5 : Pathogène en cas d'obésité</p>
			Dup	Class 3: VSI
Proximal 16p11.2 (BP4-BP5)	GRCh37: chr16:29649997-30199852 GRCh38: chr16:29638676-30188531	TBX6, KCTD13, PRRT2	Del	 <p>PIEV</p>
			Dup	 <p>PIEV</p>
Central 22q11.21 (LCR22-B/C-D)	GRCh37: chr22:20731986-21465672 GRCh38: chr22:20377696-21111383	CRKL, SCARF2, SNAP29	Del	 <p>PIEV (low)</p>
			Dup	Classe 3: VSI

Forte pénétrance

Forte pénétrance

Forte pénétrance

Ok faible (mais à traduire)

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Guide du réseau Achro-Puce
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Ce sera corrigé rapidement...



Journée AChro-Puce
26 novembre 2025

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Merci !

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Ainsi qu'à toutes celles et ceux qui participent à l'évaluation des CNVs récurrents :

M Reynaud, G Jedraszak, S Redon, K Uguen, M Massier, G Delplancq, E Pisan, R Mathevet, A Vitrac, F Vialard, C Dupont, M Bouassida, B Herve, N Celton

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