

La microduplication récurrente Xq28 int22h-1/int22h-2 : quelle classification?

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CNVs pathogènes portés par l'X

Pénétrance différente entre les M et les F :

- M plus atteints que F et/ou plus sévèrement
- CNV possiblement hérités de F asymptomatiques

→ Difficulté d'interprétation de la pathogénicité des CNV

A horizontal ideogram of Chromosome X, showing its characteristic bands and centromere. The right arm (q arm) is divided into several distinct regions. A red rectangular box highlights the Xq28 region at the very tip of the chromosome.

Xq28

Chromosome X

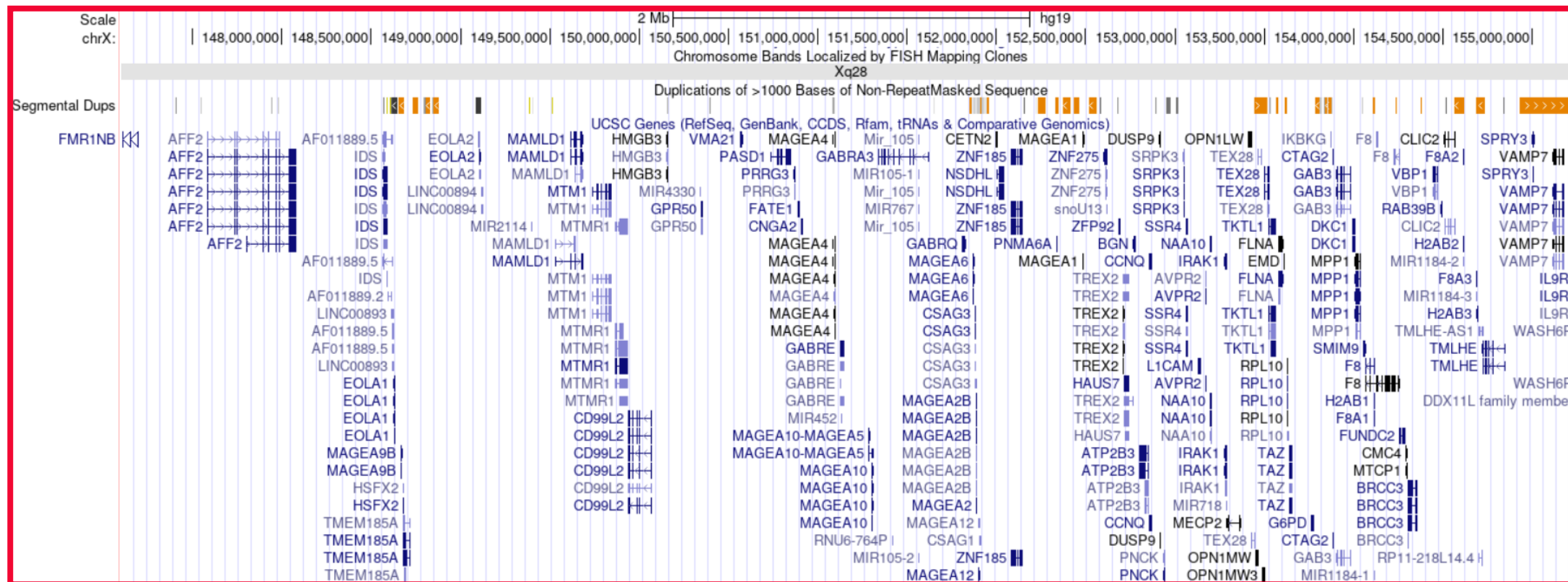
Région Xq28 (chrX:147100001-155270560 GRCh37/hg19)

Chromosome X

Région Xq28 (chrX:147100001-155270560)

→ Haute densité génique

→ Low Copy Repeat (LCR) favorisant réarrangements chromosomiques (CNV) récurrents (NAHR)

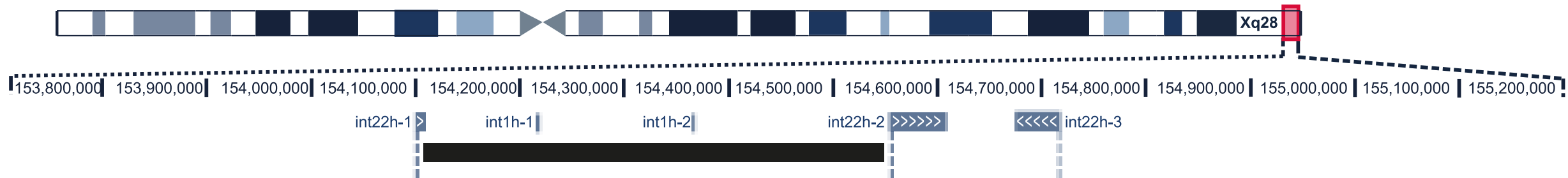


Duplication Xq28 int22h-1/int22h-2 (154.1-154.6 Mb GRCh37/hg19)

Duplication récurrente \approx 0,5 Mb

→ NAHR entre les LCRs int22h-1 et int22h-2

→ Considérée pathogène dans la littérature



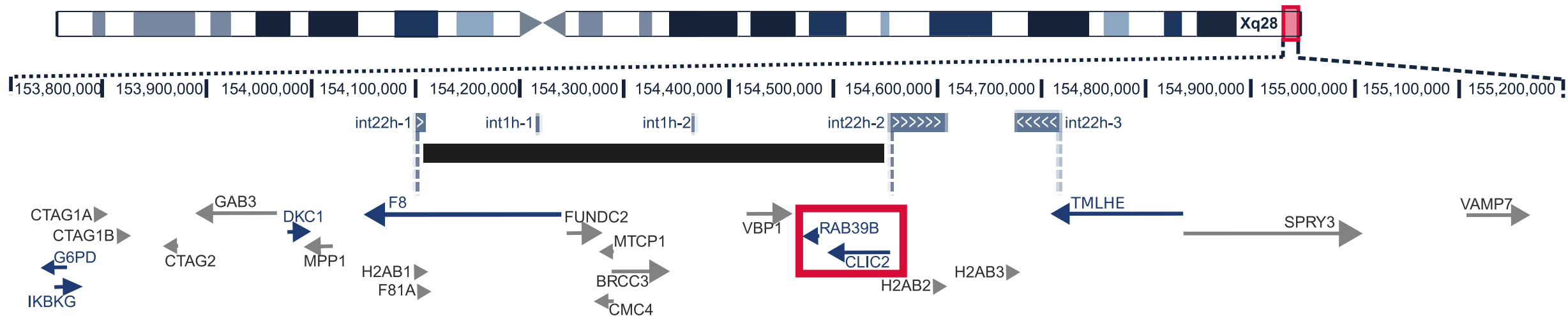
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→ Gène OMIM « morbides » : 2 gènes candidat DI (**CLIC2** et **RAB39B**) ; F8 (hémophilie A)



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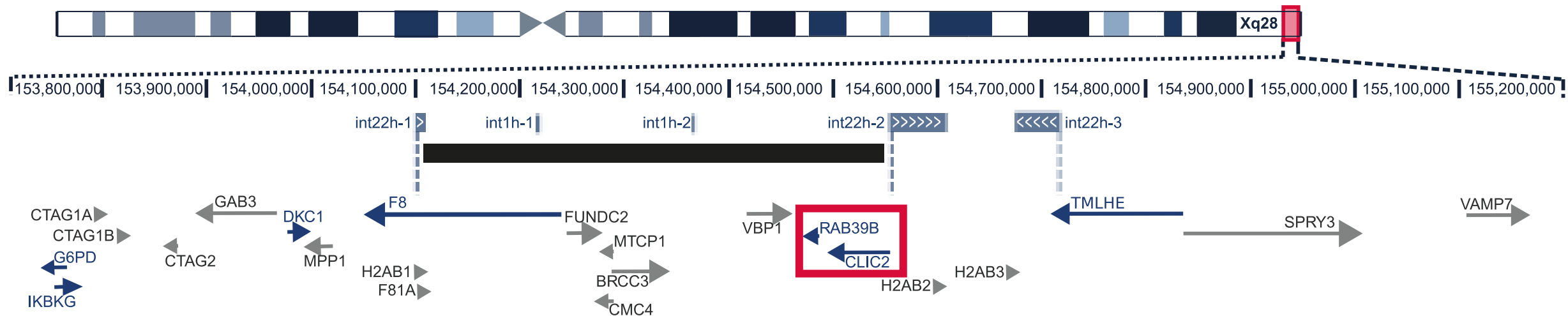
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XLID syndromique :

- particularités comportementales
- dysmorphie faciale aspécifique
- infections à répétition/atopie
- surpoids/obésité



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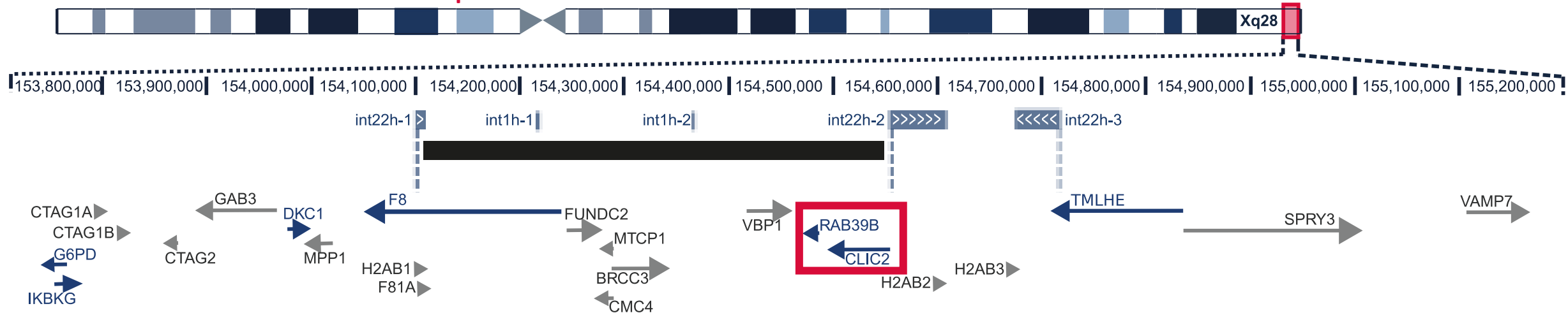
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Avant 2024 → Pénétrance pour DI considérée de **100% chez M** et **≈ 50% chez F**



		Males	Females
Frequent Features		Tall forehead Large ears Sparse scalp and eyebrow hair Thin upper lip Thick lower lip Long eyelashes High-rooted and depressed nasal bridge	
Rare Features		<ul style="list-style-type: none"> - Genitourinary malformations (hydronephrosis, cryptorchidism, hypospadias) - Digital and limb malformations (radial polydactyly, arthrogryposis, clubfoot, 2-3 toe syndactyly) <ul style="list-style-type: none"> - Hearing loss - Strabismus and/or myopia - Cleft lip and/or cleft palate <ul style="list-style-type: none"> - Esophageal atresia with trachea-esophageal fistula - Polyhydramnios - Congenital heart disease (atrial septal defect with concomitant VSD or PDA) <ul style="list-style-type: none"> - Generalized hypotonia - Skeletal malformations (sacral agenesis, missing ribs, vertebral malformations, hip dysplasia) <ul style="list-style-type: none"> - Psychotic disorders - Multiple malignancies 	<ul style="list-style-type: none"> - Recurrent seizures - Café-au-lait macule - Freckling - Hemihypertrophy - Hypothyroidism
		Clinodactyly Motor mannerisms and/or stereotypy Micrognathia kyphoscoliosis	
Distinguishing Features	<i>Intellectual disability</i>	Mild-to-moderate (complete penetrance)	Mild or none (incomplete penetrance)
	<i>Type of insomnia (if and when present)</i>	Difficulty maintaining sleep	Difficulty falling asleep
	<i>Anthropometric abnormalities</i>	Obesity +/- tall stature	Obesity reported in only one female to date
	<i>Immune manifestations</i>	Recurrent sinopulmonary infections + atopy	Neither
	<i>Neurobehavioral and psychiatric manifestations</i>	Aggression and irritability Predominantly hyperactive-type childhood ADHD	- Predominantly inattentive-type childhood ADHD
		Autism spectrum disorder	Mild-to-moderate socialization deficits

VSD: Ventricular septal defect; PDA: patent ductus arteriosus; ADHD: attention-deficit hyperactivity disorder. '-' denotes the lack of the same or comparable feature in heterozygous females, compared to the corresponding feature in affected males.

Review

The *int22h1/int22h2*-Mediated Xq28 Duplication Syndrome: An Intersection between Neurodevelopment, Immunology, and Cancer

Rami A. Ballout ^{1,*} and Ayman W. El-Hattab ^{2,3,*}

[Ballout and El-Hattab, 2020](#)

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Review

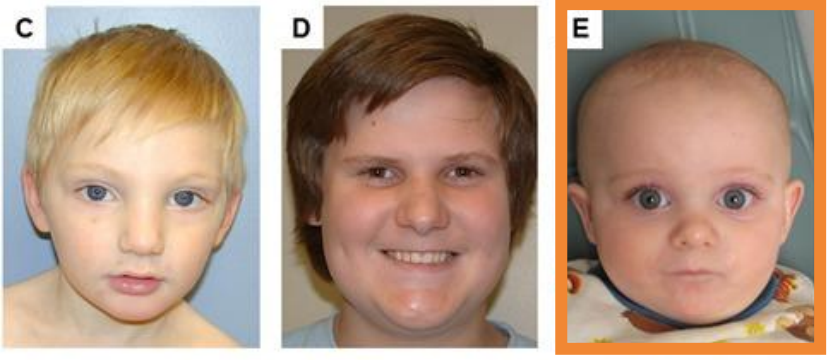
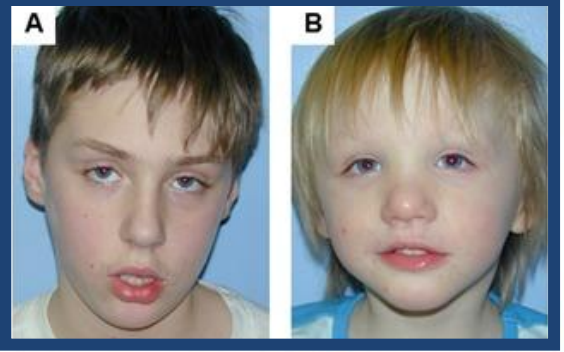
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 Large ears
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 Thin upper lip
 Thick lower lip
 Long eyelashes
 High-rooted and depressed nasal bridge

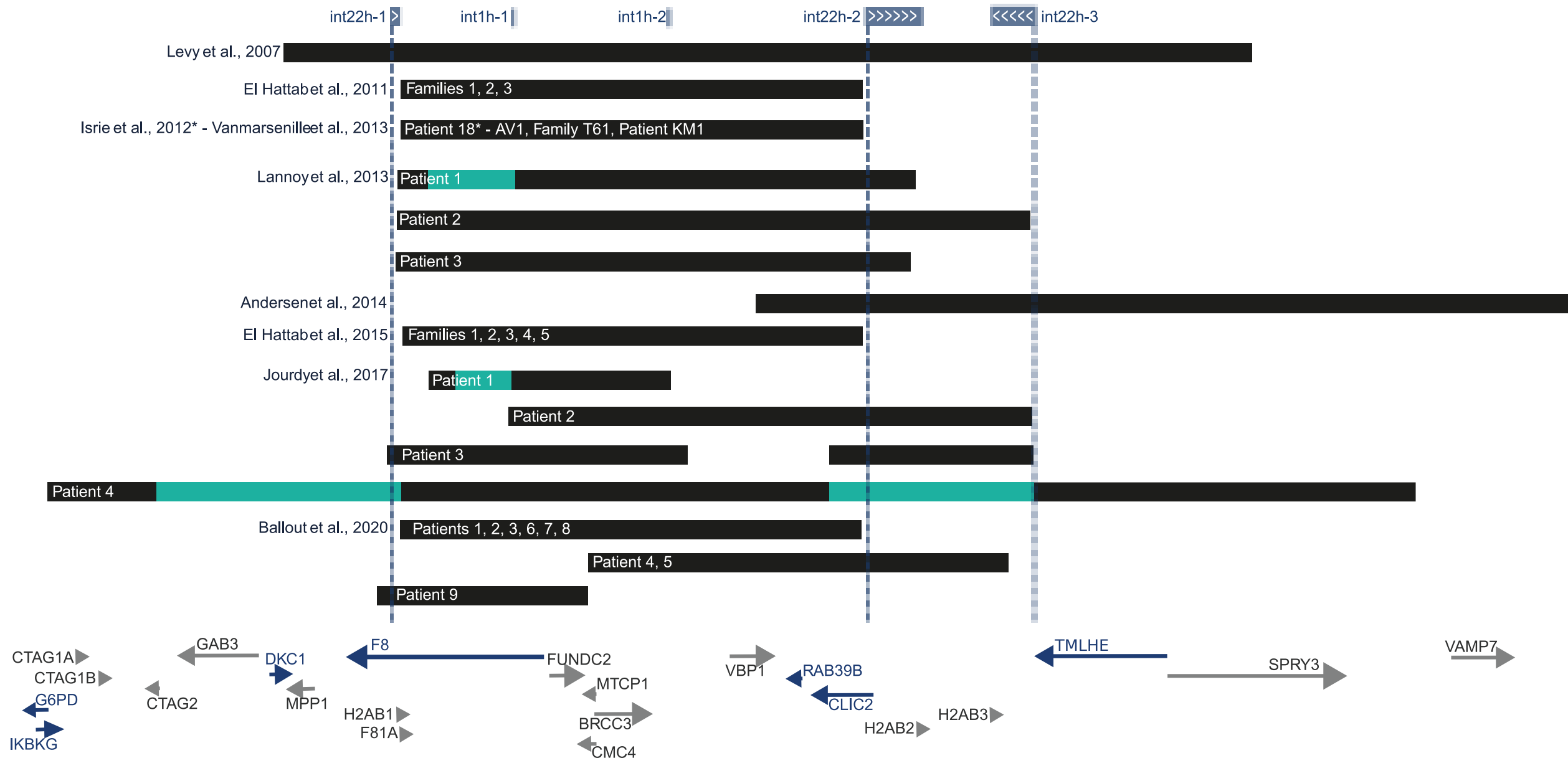


El-Hattab et al., 2011

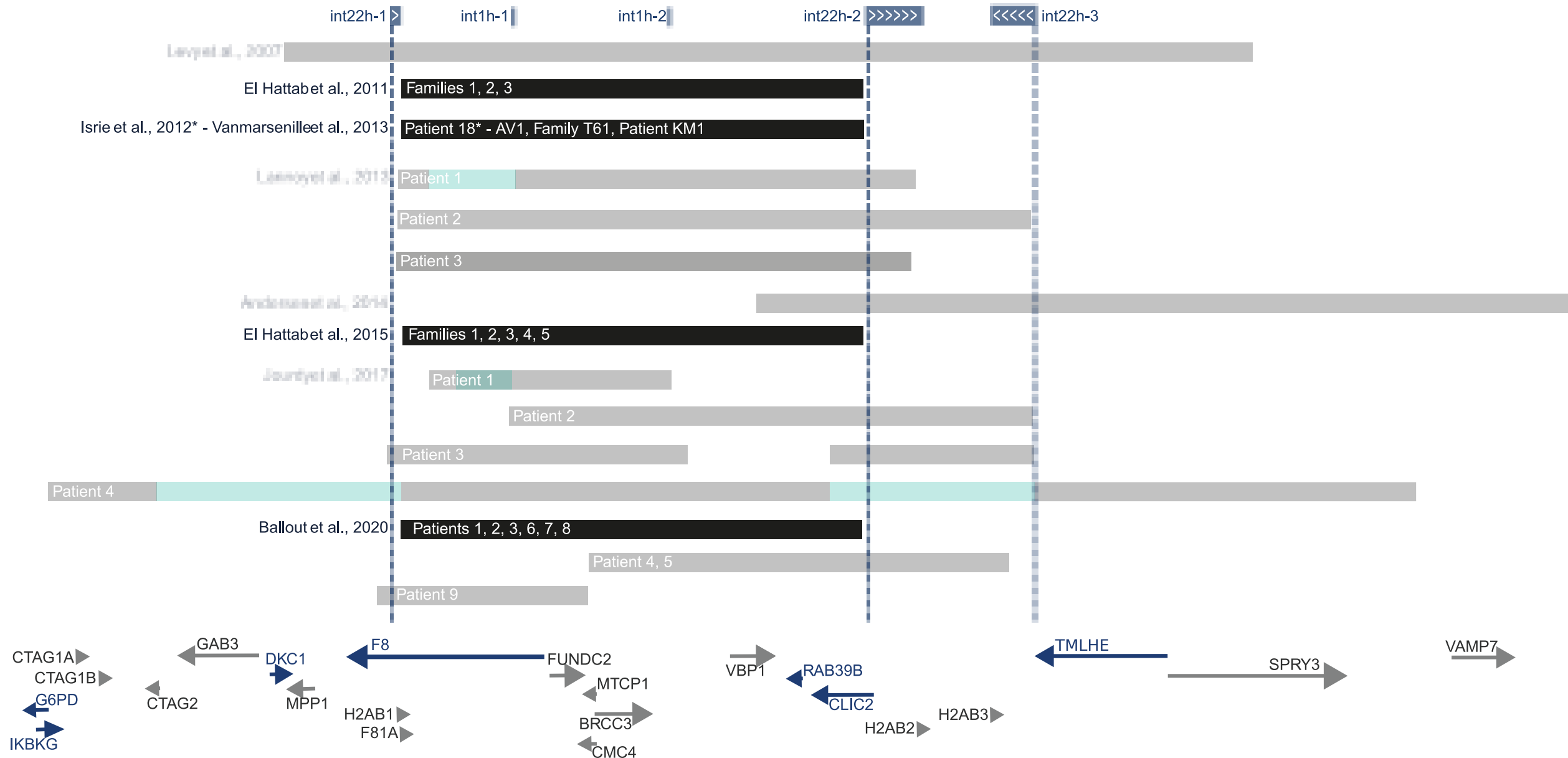


Ballout et al., 2020

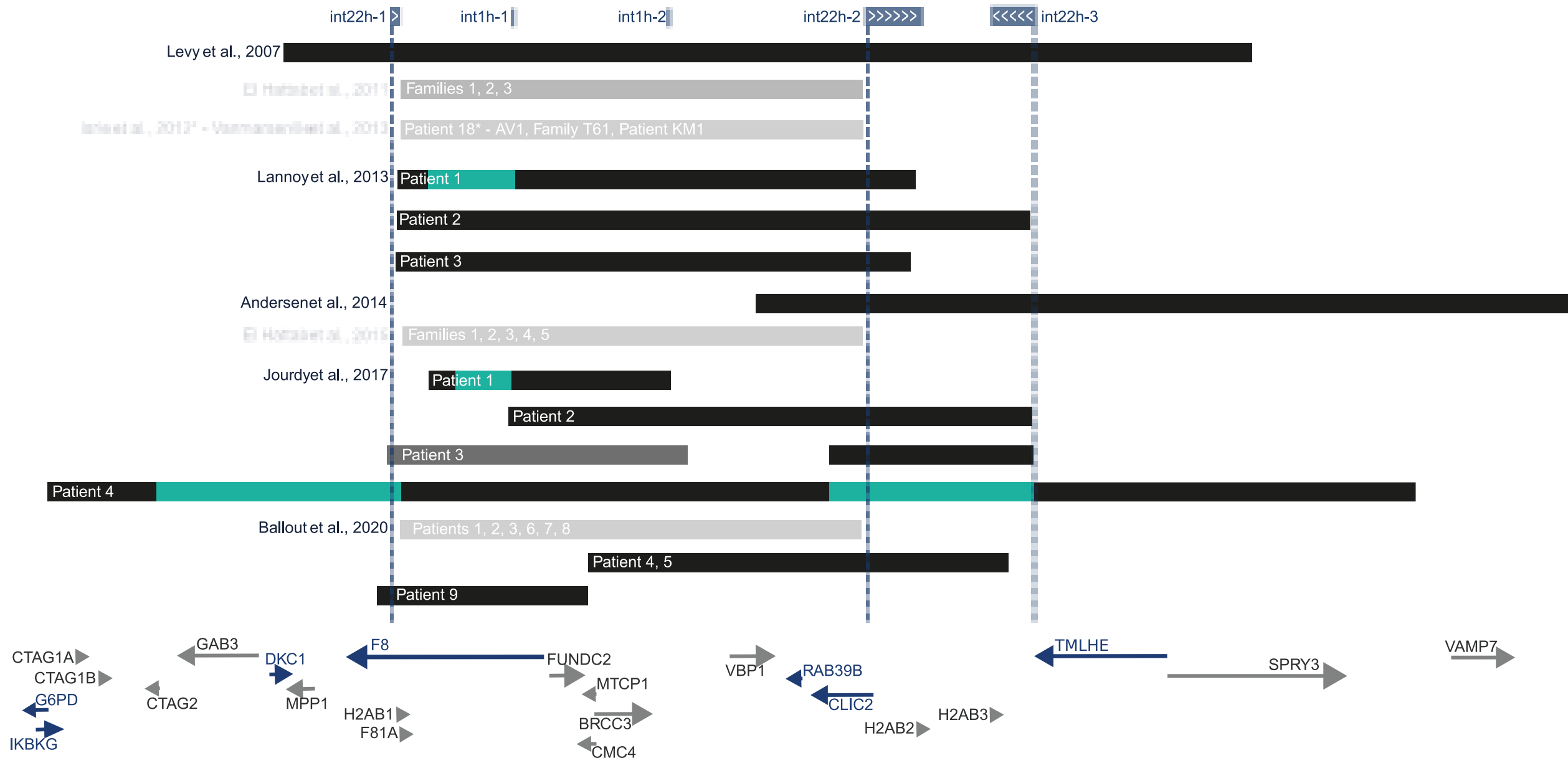
Littérature avant 2024 : duplications typiques et atypiques



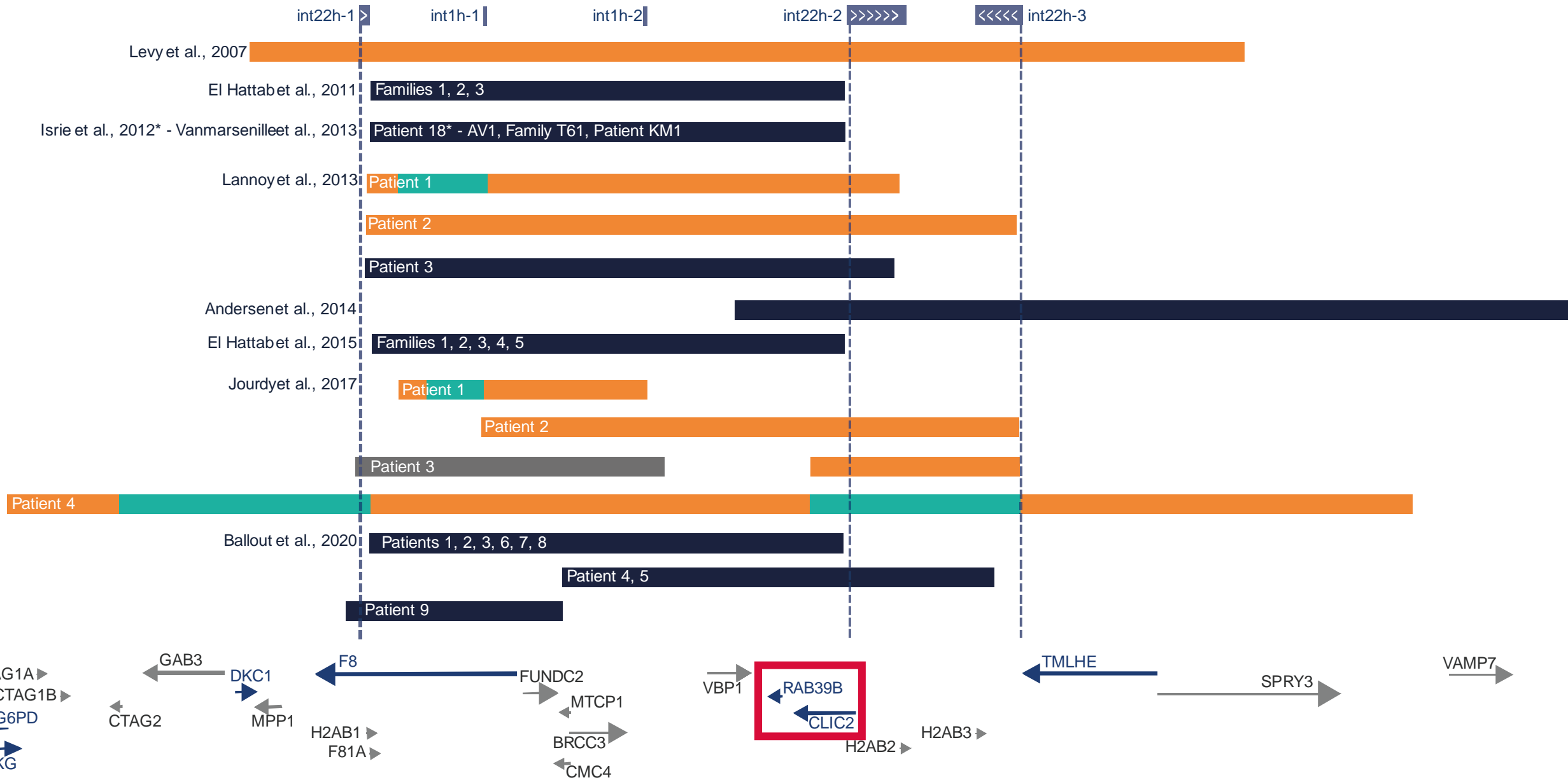
Littérature **avant 2024** : duplications **typiques** (0,5Mb, entre int22h-1 et int22h-2) 35 cas (19 M et 16 F)



Littérature **avant 2024** : duplications **atypiques** : duplications chevauchantes ; +/- **triplifications** et +/- **délétions** associées



Littérature avant 2024 : duplications **typiques et atypiques**, individus de **sexe masculin avec DI** et **sans DI**

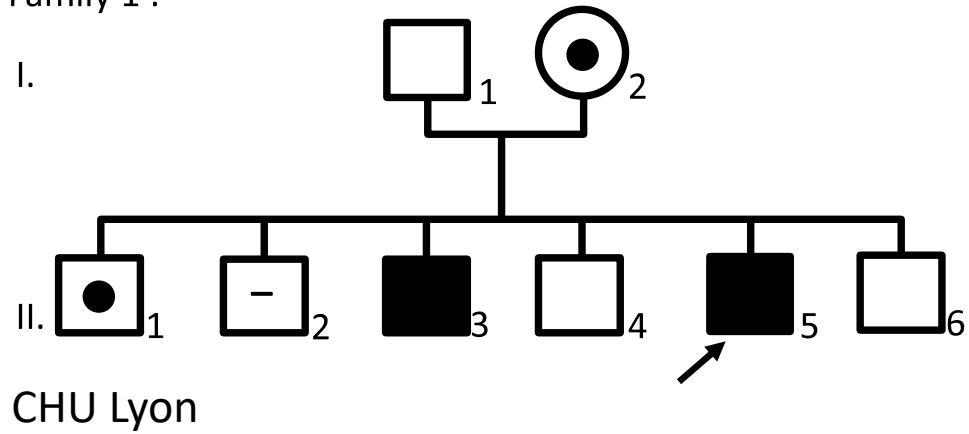


Duplication Xq28 int22h-1/int22h-2 :

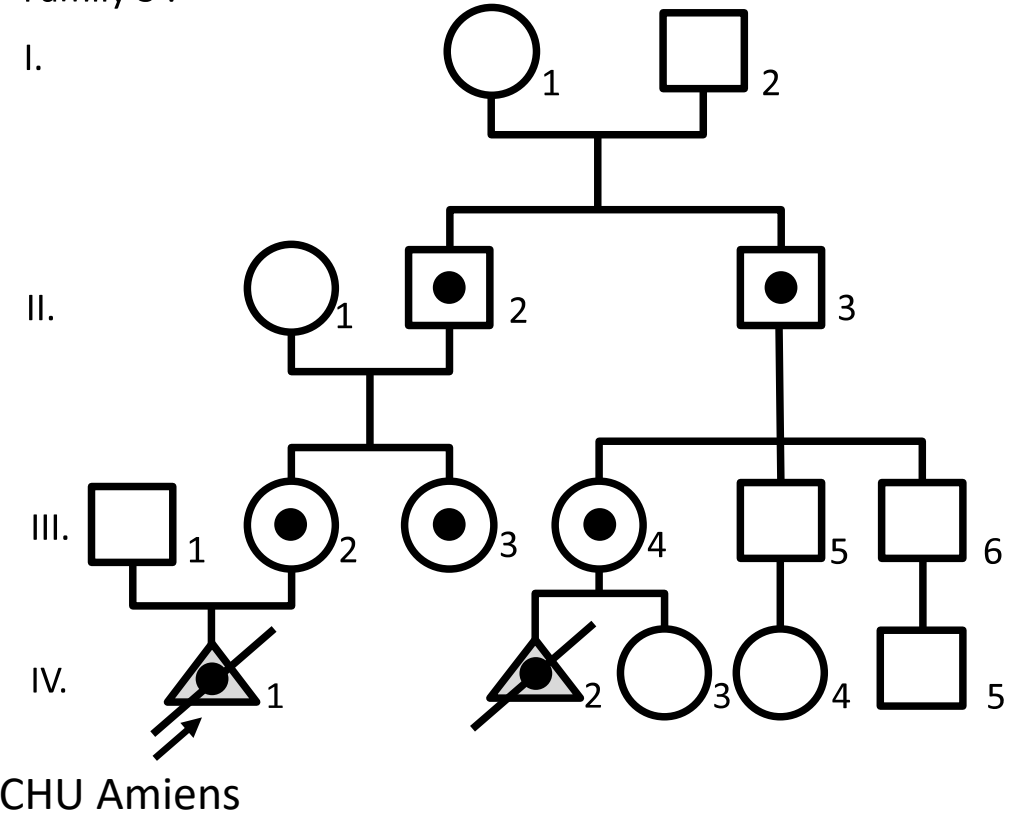
observations contradictoires (dup typiques int22h-1/int22h-2 médiées)

individus de sexe masculin bien-portants







Family 1 :



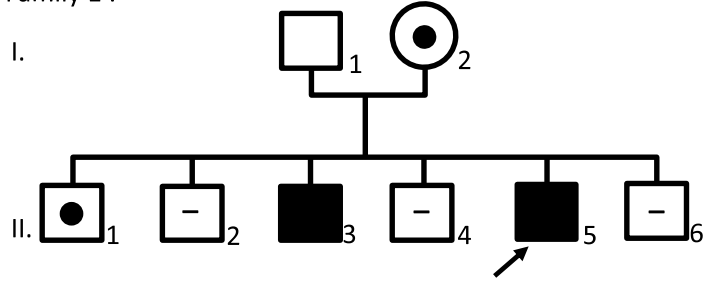
Family 3 :



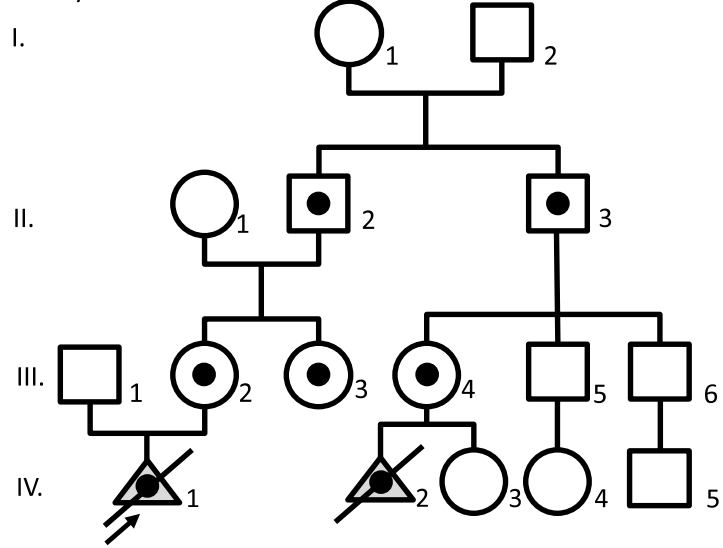
Possible incomplete penetrance of Xq28 int22h-1/int22h-2 duplication

Alexis Billes^{1,2} | Mathilde Pujalte³ | Guillaume Jedraszak^{2,4} | Daniel Amsallem⁵ |
Elise Boudry-Labis⁶ | Odile Boute⁷ | Sonia Bouquillon⁶ |
Elise Brischoux-Boucher⁸  | Patrick Callier^{9,10,11} | Charles Coutton^{12,13}  |
Anne-Laude Avice Denizet⁸ | Klaus Dieterich^{14,15} | Paul Kuentz^{16,17} |
James Lespinasse¹⁸ | Benoît Mazel¹⁹ | Gilles Morin¹ | Florence Amram¹ |
Perrine Pennamen²⁰ | Marlène Rio^{21,22} | Juliette Piard^{8,23}  |
Audrey Putoux^{24,25} | Mélanie Rama⁶ | Virginie Roze-Guillaumey¹⁶ |
Caroline Schluth-Bolard^{3,26,27}  | Marianne Till³ | Chloé Trouvé⁸ |
Gaëlle Vieville²⁸ | Caroline Rooryck^{29,30}  | Damien Sanlaville^{3,26} |
Nicolas Chatron^{3,26} 

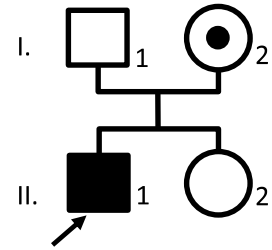
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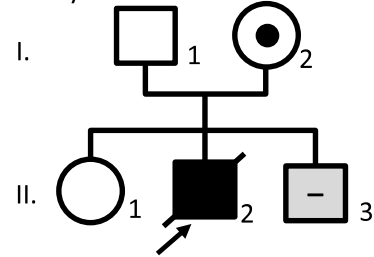
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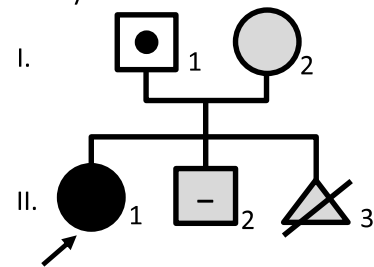
Family 2 :



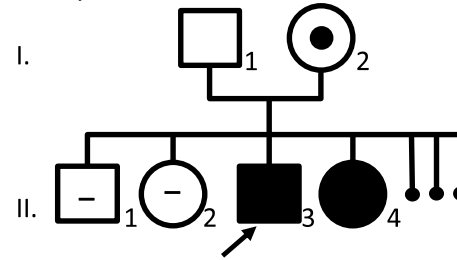
Family 4 :



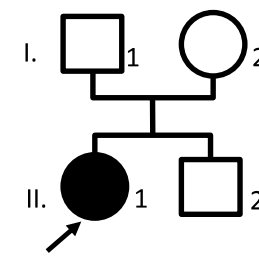
Family 5 :



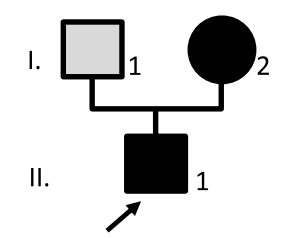
Family 6 :



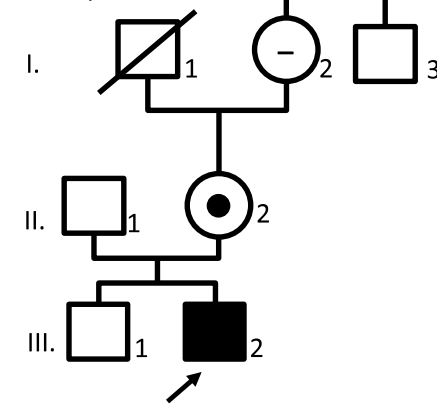
Family 7 :



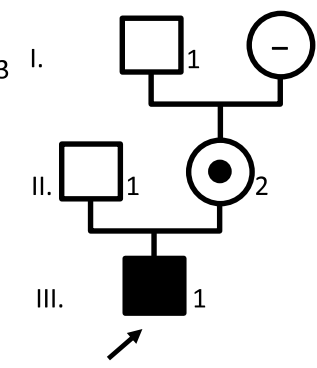
Family 9 :



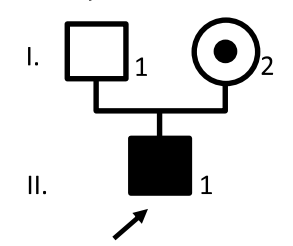
Family 8 :



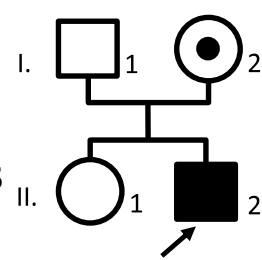
Family 10 :



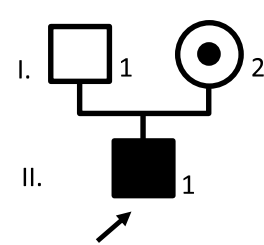
Family 11 :



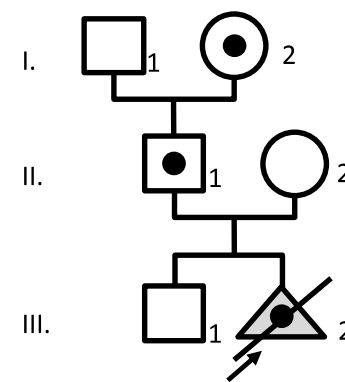
Family 12 :



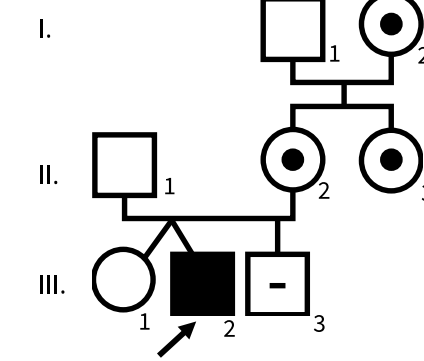
Family 13 :



Family 14 :

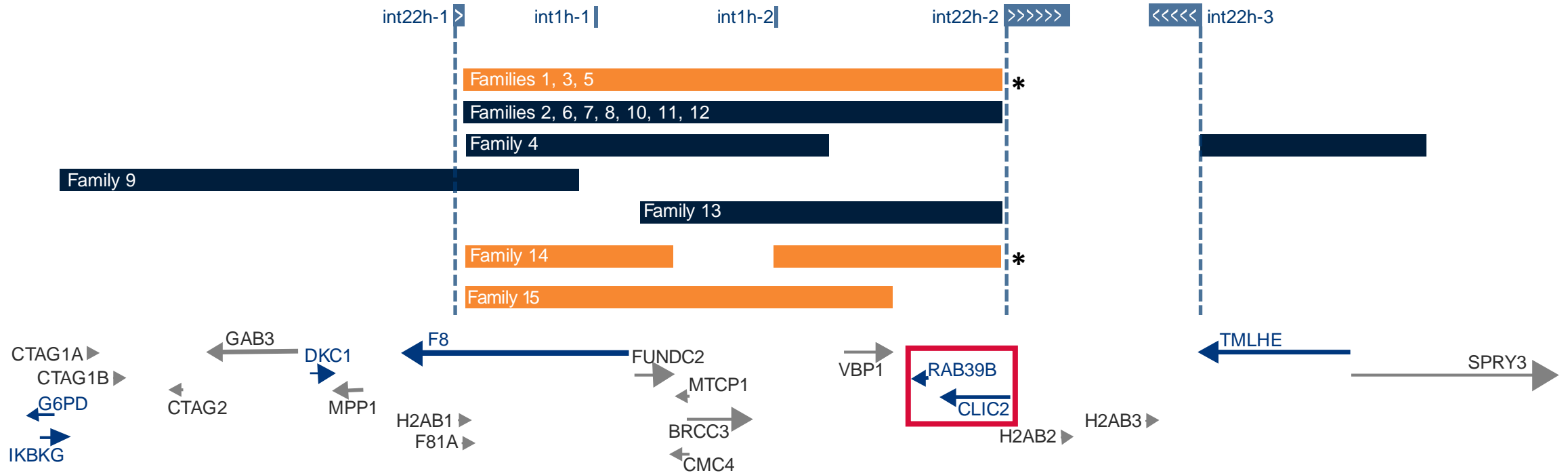


Family 15 :



15 familles non-apparentées
 (40 patient dont 3 fœtus)
 avec des duplications Xq28
 en région int22h-1/int22h-2

Duplications **typiques et atypiques**, individus de **sex masculin avec DI**
 et familles au moins un individu de sexe masculin **sans DI**



15 familles non-apparentées

(40 patient dont 3 foetus*)

Dup typiques : 10 familles (14M et 13F dont 2 foetus M ; 4 M bien-portants).

Dup atypiques : 5 familles (5M et 7F dont 1 foetus F ; 2 M sans DI).

DI peut s'expliquer par d'autres causes chez 2 (voire 4) patient.e.s.

Pas de dysmorphie faciale récurrente.

Surpoids/obésité : 6 (4 dup typique).

Infections récurrentes 1+/-2.



ARTICLE OPEN

Check for updates

Exploring inheritance, and clinical penetrance of distal Xq28 duplication syndrome: insights from 47 new unpublished cases

Michal Levy^{1,2}, Eyal Elron^{1,2}, Mordechai Shohat^{2,3}, Shira Lifshitz³, Sarit Kahana¹, Hagit Shani⁴, Anat Grossman⁴, Shirly Amar⁵, Ginat Narkis⁵, Lena Sagi-Dain⁶, Lina Basel-Salmon^{1,2,7} and Idit Maya^{1,2}

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47 cas (12 postnat ; 35 prenat) 26 familles:

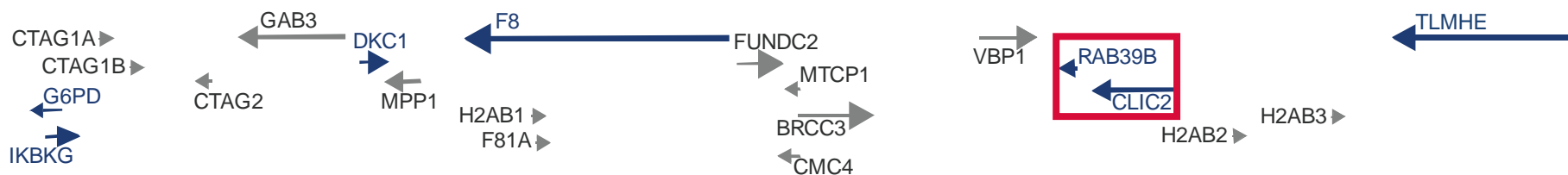
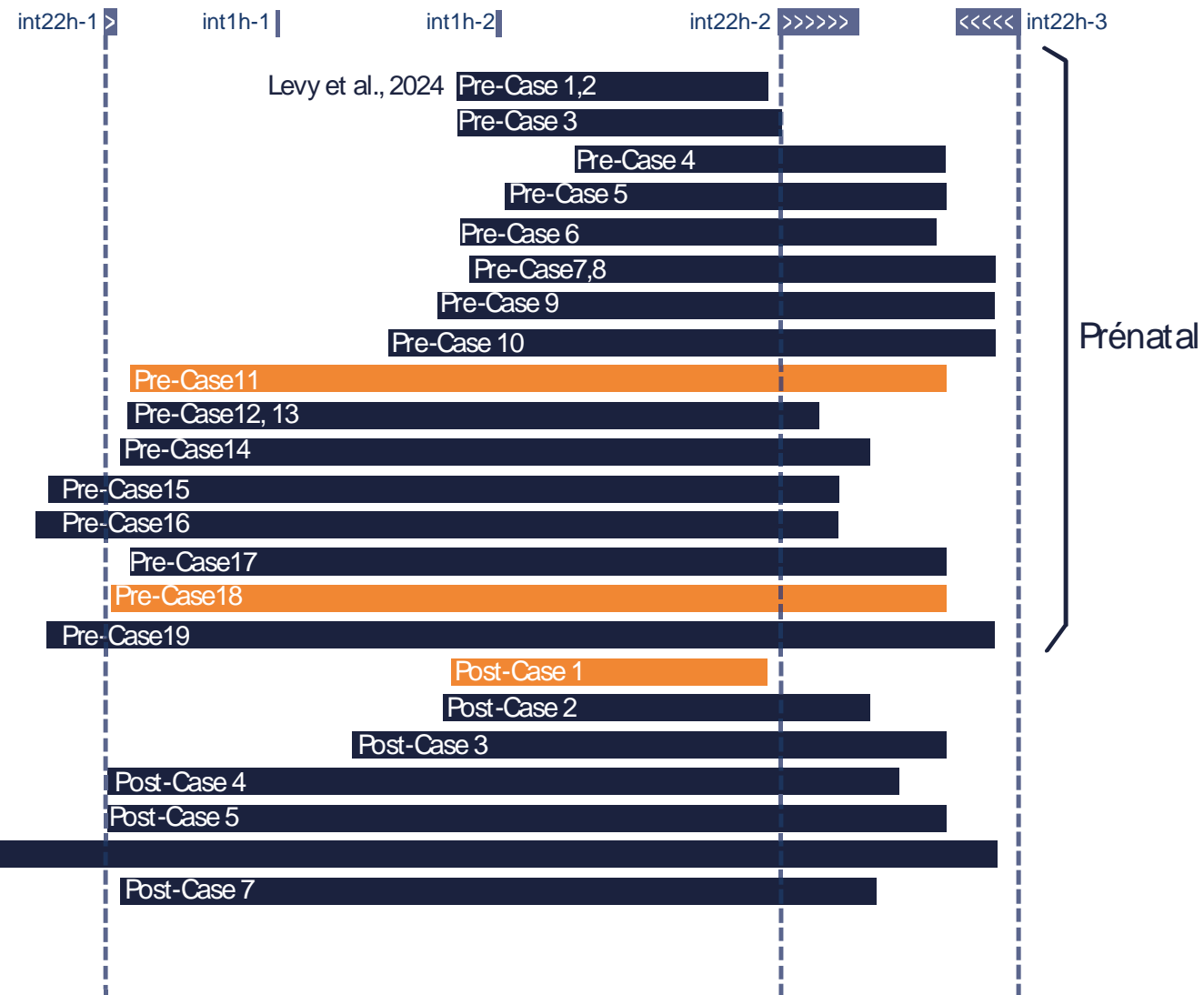
2 M sans DI

1M sans DI avec TDAH

1M DI légère ou troubles des apprentissages

Majorité de découvertes incidentes en prénatal.

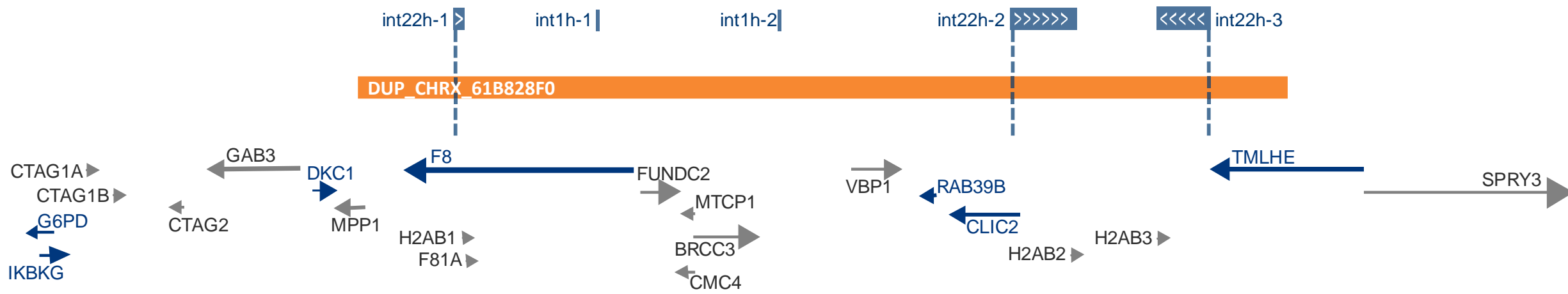
Majorité de mère transmettrices, toutes bien-portantes.



GnomAD

SV v4.0 :

Genetic Ancestry Group		Allele Count	Allele Number	Number of Homozygotes	Number of Hemizygotes	Allele Frequency
▶ Remaining		1	1177	0	0	0.0008496
▶ European (Finnish)		1	4010	0	0	0.0002494
	Overall	10	47049	0	3	0.0002125
▼ European (non-Finnish)	XY	3	12027	0	3	0.0002494
	XX	7	35022	0	0	0.0001999
▶ African/African American		1	25697	0	0	0.00003892
▶ Amish		0	641	0	0	0.000
▶ Admixed American		0	9101	0	0	0.000
▶ Ashkenazi Jewish		0	2451	0	0	0.000
▶ East Asian		0	3002	0	0	0.000
▶ Middle Eastern		0	46	0	0	0.000
▶ South Asian		0	2750	0	0	0.000
XX		10	65798	0	0	0.0001520
XY		3	30126	0	3	0.00009958
Total		13	95924	0	3	0.0001355





Xq28 Duplication Syndrome, Int22h1/Int22h2 Mediated

Synonym: Xq28 Int22h-1/Int22h-2 Duplication Syndrome

Rami A Ballout, MD,¹ Ayman W El-Hattab, MD, FAAP, FACMG,² Christian P Schaaf, MD, PhD,³ and Sau Wai Cheung, PhD, MBA, FACMG⁴

Created: March 10, 2016; Updated: September 4, 2025.

Manifestation	Males (n=34) ¹	Comments
ID or cognitive impairment	~74% ^{2, 3}	Language delay is seen in about 20%.
Sinopulmonary issues	~50%	May include otitis media, pneumonia, URI, asthma, &/or allergic rhinitis
Atopic disease	~40%	
ADHD/ADD	32%	
Overweight or obesity	26%	
Neurobehavioral/psychiatric issues	~20%-25%	May include anxiety, ASD, socialization deficits, mood disorders (mainly depression or bipolar disorder), psychotic disorders (e.g., schizophrenia), aggression/irritability, self-mutilation, or self-harming behaviors
Sleep disturbance	15%	Mainly issues w/sleep maintenance
Tall stature	~12%	
Eye anomalies / refractive error	Rare	Both strabismus & astigmatism have been reported.



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Created: March 10, 2016; Updated: September 4, 2025.

Manifestation ¹	Females (n=39)	Comments
ID or cognitive impairment	11 (28%) ²	Language delay has been reported in 3 (~8%).
ADHD/ADD	4 (10%)	
Neurobehavioral/psychiatric issues	Up to 8%	May include anxiety, ASD, socialization deficits, mood disorders (mainly depression or bipolar disorder), psychotic disorders (e.g., schizophrenia), aggression/irritability, self-mutilation, or self-harming behaviors
Sleep disturbance	3 (~8%)	More commonly issues w/sleep initiation

Pénétrance incomplète, expressivité variable : hypothèses

Biais d'inactivation de l'X chez F? → discordant dans les publications

Modèle double-hit?

Facteurs environnementaux modificateurs?

Dups similaire en profil d'ACPA mais structurellement différentes?

Biais observationnel ?

Quelle classification?

Données épidémiologiques :

- bases population générale → cf. GnomAD DUP_CHRX_61B828F0 ; DGV
- bases patients → chromosome X

Données de ségrégation → ?

Données structurales :

- Taille du CNV → ≈ 500kb
- Contenu génique → densité génique importante ; *RAB39B* et *CLIC2*.
- Nombre de copies → duplication
- Argument bibliographique → discordance entre les phénotypes des cohortes.

Nécessité de données supplémentaires (nouvelles cohortes? Réévaluation des cohortes analyse de génome chez les patients symptomatiques et ségrégation plus poussées? Etudes populationnelles non-biaisées? ; etc.)