RHU PsyCARE

WP 1: **Identifying biological markers for guiding therapeutic interventions**

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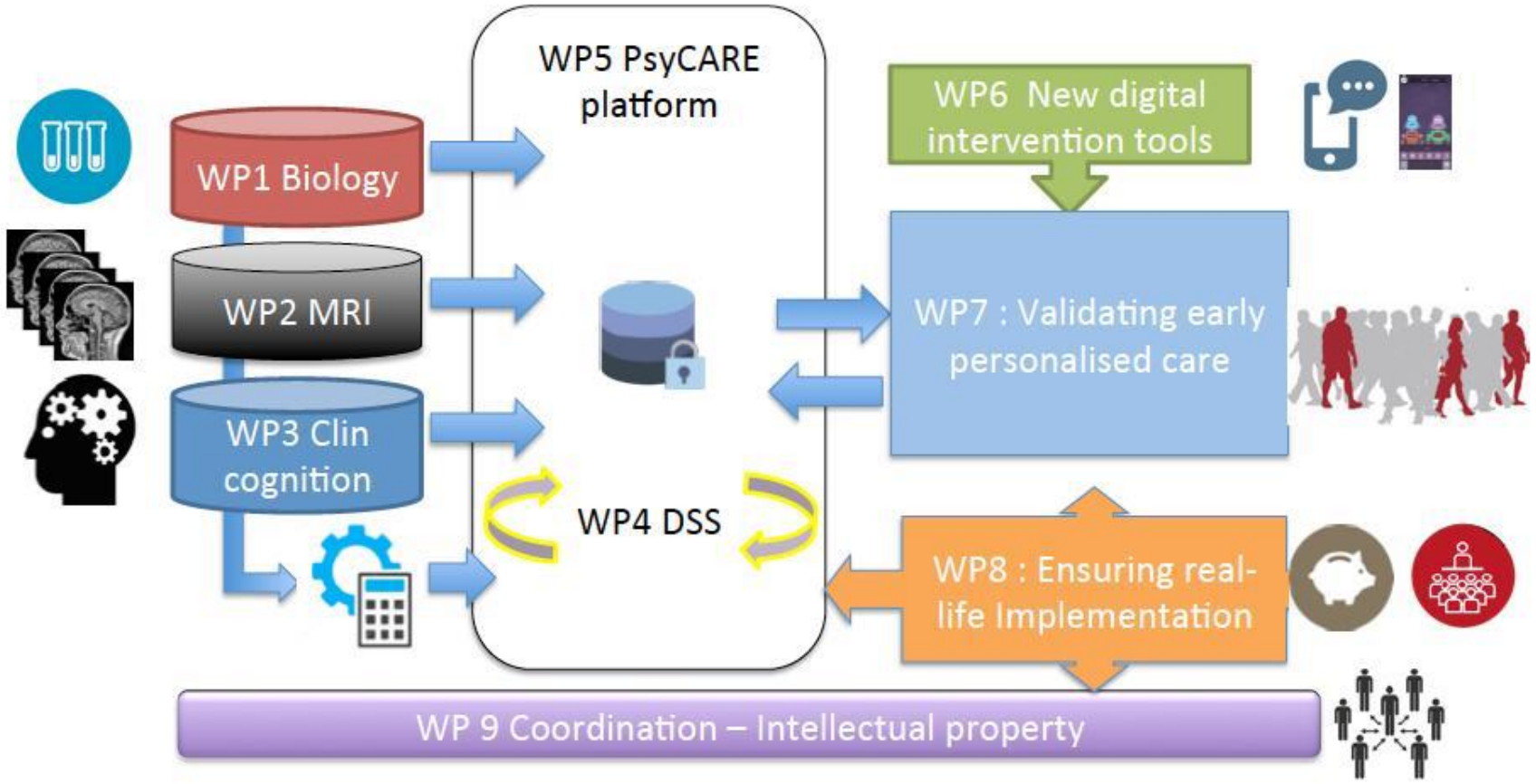
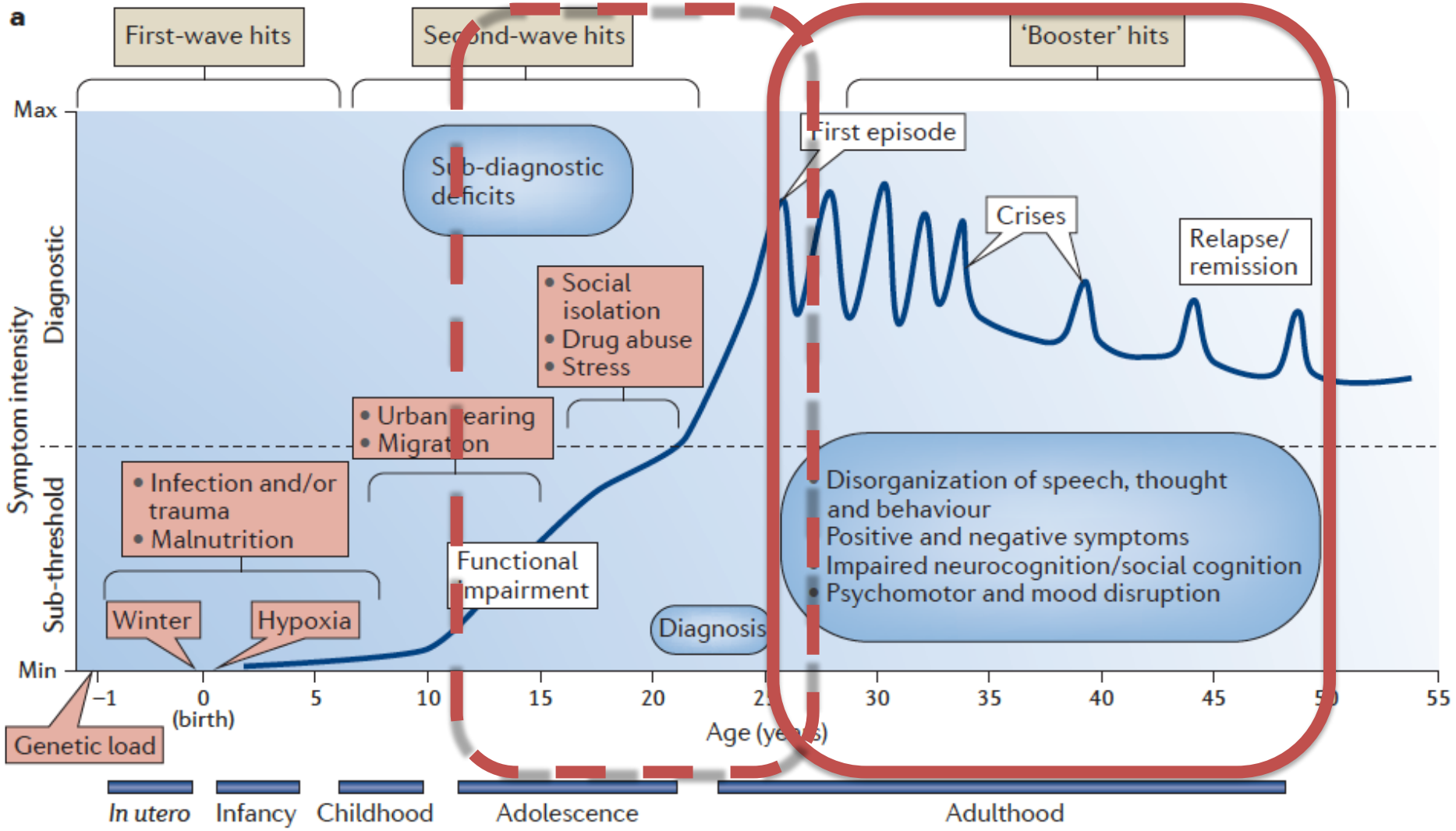

WP1 Biology
WP2 MRI
WP3 Clin cognition
WP5 PsyCARE platform
WP4 DSS
WP6 New digital intervention tools
WP7 : Validating early personalised care
WP8 : Ensuring real-life Implementation
WP 9 Coordination – Intellectual property

Altering the course of schizophrenia: progress and perspectives



Millan et al, 2016

La clinique ne suffit pas

Cohorte populationnelle longitudinale avec PLSI à 12, 18 et 24 ans
PLSI : semistructured Psychosis-Like Symptoms Interview

In our population-based study, which was not sampled on help-seeking behavior, approximately 85% of participants with new-onset psychotic disorder between ages 18 and 24 did not meet criteria for an at-risk mental state at age 18.

→ targeting individuals in non-help-seeking samples based only on more severe symptom cutoff thresholds will likely have little impact on population levels of first-episode psychosis.

A Population-Based Cohort Study Examining the Incidence and Impact of Psychotic Experiences From Childhood to Adulthood, and Prediction of Psychotic Disorder

Sarah A. Sullivan, Ph.D., Daphne Kounali, Ph.D., Mary Cannon, Ph.D., Anthony S. David, M.D., Paul C. Fletcher, Ph.D., Peter Holmans, Ph.D., Hannah Jones, Ph.D., Peter B. Jones, Ph.D., David E.J. Linden, Ph.D., Glyn Lewis, Ph.D., Michael J. Owen, Ph.D., Michael O'Donovan, Ph.D., Alexandros Rammos, Ph.D., Andrew Thompson, M.D., Dieter Wolke, Ph.D., Jon Heron, Ph.D., Stanley Zammit, Ph.D.

Longitudinal omics

Time (1 y)

Controls (help seekers) → controls

UHR → UHR

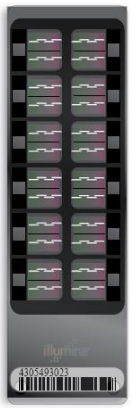
UHR → Converters

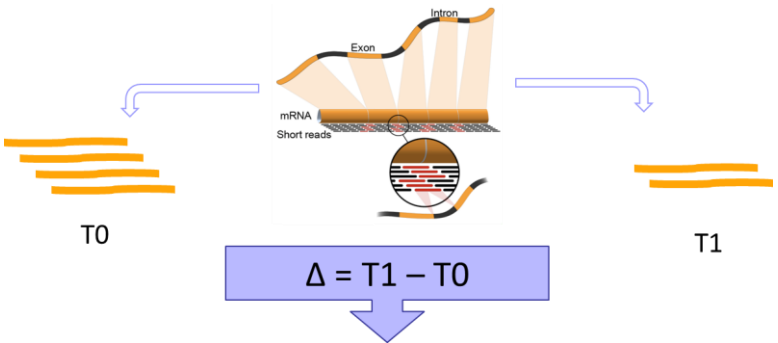
Methylome + Transcriptome @ M0

Methylome + Transcriptome @ 6 months

$\Delta\beta$

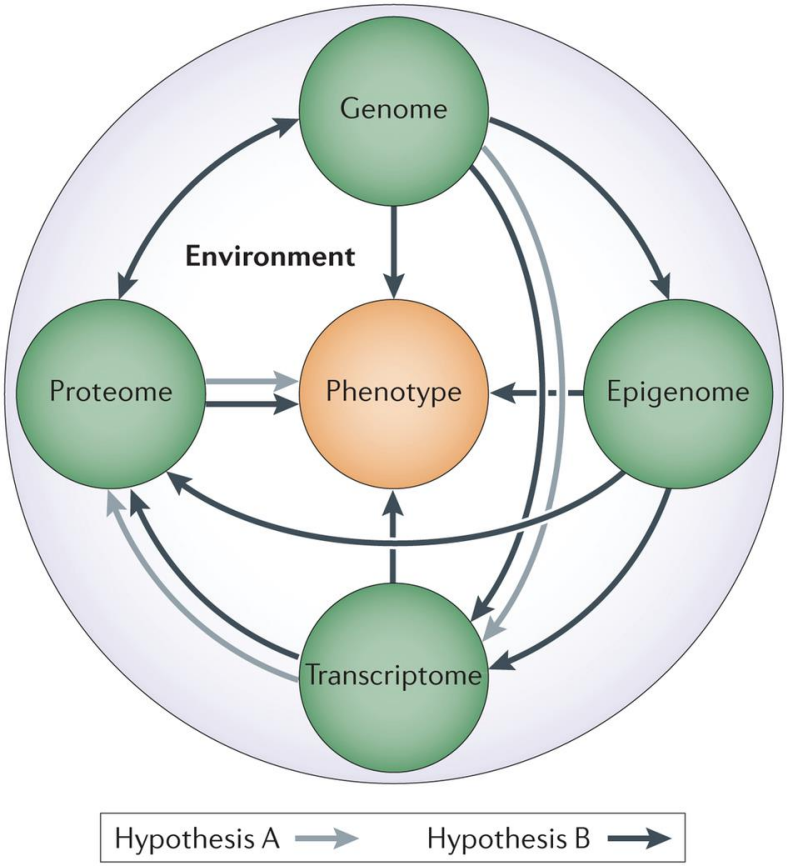
Infinium HumanMethylation450 BeadChip





Intégration multi-omique

(Ritchie et al. 2015)



Candidate markers

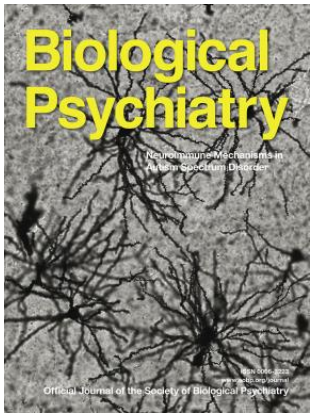
Kebir, Chaumette et al. Mol Psy 2017
Chaumette, Kebir et al. SKZ Bull 2018

CPT1A
No change in methylation
↘expression

GSTM5
↗methylation
↘expression

NRP1
↗methylation
↘expression

Gene name	Role	Previous association with schizophrenia	Hypothetical therapeutic target
Carnitine palmitoyltransferase 1A	long-chain fatty acid oxidation and transport into mitochondria	hypoexpression in blood from first-episode psychosis patients compared to controls	(ω-3) polyunsaturated fatty acid
Glutathione S-transferase Mu 5	synthesis of glutathione and protection against oxidative stress	lower expression has been reported in the prefrontal cortex of patients with schizophrenia	antioxidative drugs
Neuropilin 1	neuronal migration and axon guidance	Close interactor of the class-3 semaphorin	?



The NEURAPRO biomarker analysis: long-chain omega-3 fatty acids improve 6-month and 12-month outcomes in youth at ultra-high risk for psychosis

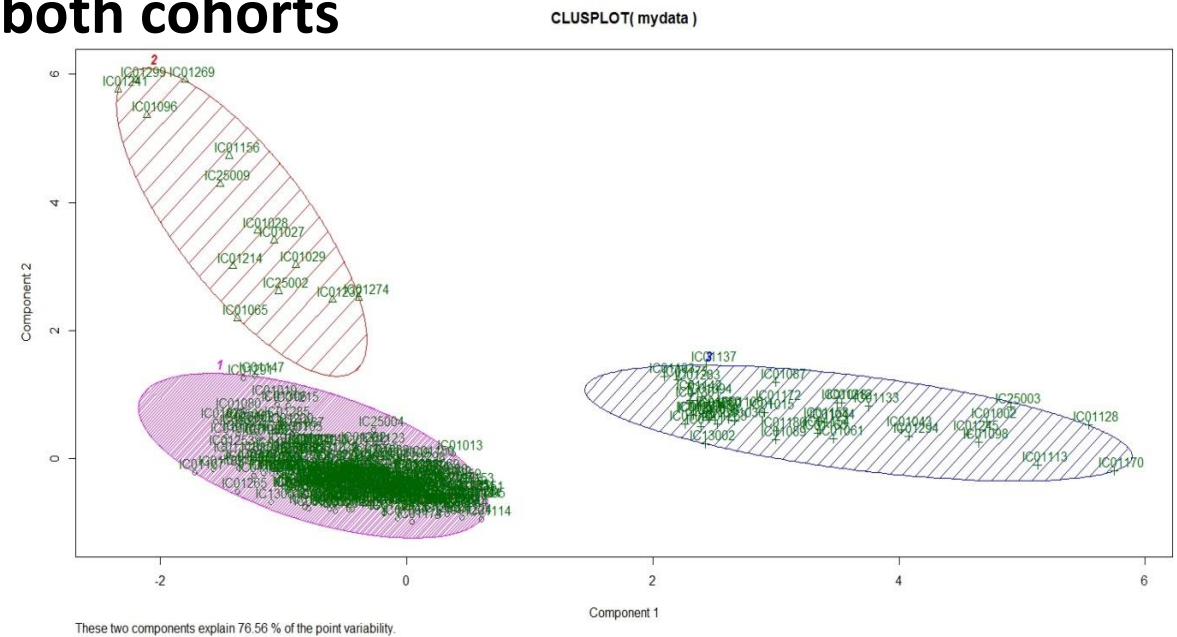
G Paul Amminger, Barnaby Nelson, Connie Markulev, Hok Pan Yuen, Miriam R. Schäfer, Maximus Berger, Nilufar Mossaheb, Monika Schlögelhofer, Stephan Smesny, Ian B. Hickie, Gregor E. Berger, Eric Y.H. Chen, Lieuwe de Haan, Dorien H. Nieman, Merete Nordentoft, Anita Riecher-Rössler, Swapna Verma, Andrew Thompson, Alison Ruth Yung, Patrick D. McGorry

Results: Increases of the n-3 index, EPA and DHA predicted less severe psychopathology and better functioning at both follow-up time points. Higher baseline levels and increases of the n-3 index also predicted overall clinical improvement at month 6 (n-3 index baseline: adjusted odds ratio (95%CI)=1.79 (1.30-2.48); n-3 PUFA increase: adjusted odds ratio (95%CI)=1.43 (1.16-1.76) and at month 12 (n-3 index baseline: adjusted odds ratio (95%CI)=2.60 (1.71-3.97); n-3 PUFA increase: adjusted odds ratio (95%CI)=1.36 (1.06-1.74).

Métabolisme C1

Chaumette, Kebir et al. In preparation

- Cluster 1 :“intermediate 1C metabolism”
- Cluster 2 : “optimal 1C metabolism”
- **Cluster 3 : “at-risk 1C metabolism” (low folate and vitamin B12 levels, elevated homocysteine level).**
- → This 3rd cluster was associated with a **poorer response to usual treatments in both cohorts**



Et la génétique psychiatrique?

- Un modèle polygénique issu des méga-analyses du PGC (21% héritabilité) → score de risque polygénique (PRS)

- Un modèle de variants rares à forte pénétrance (OR très élevés) → présence/absence de ces variants

  - imputabilité démontrée

  - imputabilité très probable

→ prédiction *in silico* et *in vitro*

Analysis of copy number variations at 15 schizophrenia-associated loci

Elliott Rees, James T. R. Walters, Lyudmila Georgieva, Anthony R. Isles, Kimberly D. Chambert, Alexander L. Richards, Gerwyn Mahoney-Davies, Sophie E. Legge, Jennifer L. Moran, Steven A. McCarroll, Michael C. O'Donovan, Michael J. Owen and George Kirov

BJPsych The British Journal of Psychiatry (2014) 204, 108–114. doi: 10.1192/bjp.bp.113.131052

-To determine the contribution of CNVs at 15 schizophrenia associated loci using a large new data-set of patients with schizophrenia (n = 6882) and controls (n = 6316)

- 2.5% of patients with schizophrenia and 0.9% of controls carry a large, detectable CNV at one of these loci.
- Routine CNV screening may be clinically appropriate given the high rate of known deleterious mutations

Table 2 Combined results of previous studies and the current data-set[a]

Locus	*P*-value in previous studies	CNV frequency, % (*n*/*N*)		OR (95% CI)	*P*
		Case group	Control group		
1q21.1 del	1.3×10^{-9}	0.17 (33/19056)	0.021 (17/81 821)	8.35 (4.65–14.99)	4.1×10^{-13}
1q21.1 dup	2.0×10^{-4}	0.13 (21/16247)	0.037 (24/64 046)	3.45 (1.92–6.20)	9.9×10^{-5}
NRXN del	7.9×10^{-9}	0.18 (33/18762)	0.020 (10/51 161)	9.01 (4.44–18.29)	1.3×10^{-11}
3q29 del	2.3×10^{-8}	0.082 (14/17 005)	0.0014 (1/69 965)	57.65 (7.58–438.44)	1.5×10^{-9}
WBS dup	5.5×10^{-5}	0.066 (14/21 269)	0.0058 (2/34 455)	11.35 (2.58–49.93)	6.9×10^{-5}
VIPR2 dup	0.006	0.11 (15/14218)	0.069 (17/24 815)	1.54 (0.77–3.09)	0.27
15q11.2 del	2.2×10^{-7}	0.59 (116/19 547)	0.28 (227/81 802)	2.15 (1.71–2.68)	2.5×10^{-10}
AS/PWS dup	0.014	0.083 (12/14 464)	0.0063 (3/47 686)	13.20 (3.72–46.77)	5.6×10^{-6}
15q13.3 del	2.1×10^{-11}	0.14 (26/18571)	0.019 (15/80 422)	7.52 (3.98–14.19)	4.0×10^{-10}
16p13.11 dup	0.03	0.31 (37/12029)	0.13 (93/69289)	2.30 (1.57–3.36)	5.7×10^{-5}
16p11.2 distal del	0.0014	0.063 (13/20732)	0.018 (5/27045)	3.39 (1.21–9.52)	0.017
16p11.2 dup	3.2×10^{-14}	0.35 (58/16772)	0.030 (19/63068)	11.52 (6.86–19.34)	2.9×10^{-24}
17p12 del	0.0004	0.094 (12/12773)	0.026 (17/65 402)	3.62 (1.73–7.57)	0.0012
17q12 del	0.004	0.036 (5/14024)	0.0054 (4/74 447)	6.64 (1.78–24.72)	0.0072
22q11.2 del	1.0×10^{-30}	0.29 (56/19084)	0.00 (0/77055)	NA (28.27–∞)	4.4×10^{-40}

del, deletion; dup, duplications; NA, not applicable; WBS, Williams–Beuren syndrome; AS/PWS, Angelman/Prader–Willi syndrome.
a. For a more detailed version of this table that includes the CNV frequency, % (*n*/*N*) from previous studies see online Table DS6. *P*-values are based on Fisher exact test, 2-tailed.

Le WP1 : 3 tâches

- Task 1.1: Identification of genetic variants involved in vulnerability to psychosis
- Task 1.2: Screening of the metabolic abnormalities
- Task 1.3: Validation of a panel of peripheral biomarkers to predict clinical outcome

Task 1.1: Identification of genetic variants involved in vulnerability to psychosis (M0-M54)

- 850 patients with psychosis (PsyDev collection)
- 370 individuals with early psychosis (START & ICAAR cohorts)
- CGH and SNP array analysis on 200 samples to validate SNP array as a CNV screener

- PRS → score neurodéveloppement
- CNV → stratification neurodéveloppementale

Task 1.2: Screening of the metabolic abnormalities (M18-M54)

- C1 metabolism : folates, B12, Homocysteine
- Redox metabolism : enzymology
- Lipids markers : Spectrometry

Task 1.3: Validation of a panel of peripheral biomarkers to predict clinical outcome (M18-M54)

- 40 candidate biomarkers
- statistical significance, redundancy, multi-omic level validation, biological plausibility and technical feasibility in a daily routine setting.

- (i) 27 seric analytes with good statistical properties to identify UHR individuals (AUC : 0.90 (0.82-0.98)
- (ii) top epigenetic dynamic markers (convergent genome wide methylomic and transcriptomic longitudinal UHR studies)