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**A novel microduplication in *INPP5A* segregates with Schizophrenia Spectrum Disorder
in the family of a patient with both Childhood Onset Schizophrenia and Autism
Spectrum Disorder**

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Equal contribution

Abstract

Childhood-Onset Schizophrenia (COS) is a very rare and severe psychiatric disorder defined by adult schizophrenia symptoms occurring before the age of 13. We report a microduplication in the 10q26.3 region including part of the *Inositol Polyphosphate-5-Phosphatase A (INPP5A)* gene that segregates with Schizophrenia Spectrum Disorders (SSDs) in the family of a female patient affected by both COS and Autism Spectrum Disorder (ASD). Phenotyping and genotyping (including CGH-array) were performed for mother, healthy sister and affected child according to the GenAuDiss protocol (NCT02565524). The duplication size is 324 kb and is present in a patient with COS and in her mother with SSD, but not in the patient's healthy sister. *INPP5A* encodes a membrane-associated 43kDa type I inositol 1,4,5-trisphosphate (InsP3) 5-phosphatase. This protein is found both in mouse and human brains and we found that its *Drosophila* homologue *5PtaseI* is specifically expressed in the central nervous system. Hydrolyzed products from InsP3 5-phosphatases mobilize intracellular calcium, which is relevant for dendritic spine morphogenesis in neurons, altered in both schizophrenia and ASD. These may constitute arguments in favor of this gene alteration in the pathophysiology of COS.

Keywords: Childhood-Onset Schizophrenia, neurodevelopmental disorder, *INPP5A*, CNV, inositol pathway.

1. Introduction

Schizophrenia spectrum disorders (SSDs) include schizophrenia, other psychotic disorders and schizotypal (personality) disorder [1]. Childhood-Onset Schizophrenia (COS) is a very rare and severe form of schizophrenia defined by Adult-Onset Schizophrenia (AOS) symptoms occurring before the age of 13 according to the Diagnostic and Statistical Manual of mental disorders 5th edition (DSM-5): disorganized speech and behavior, hallucinations and delusions [1-2]. This disorder is highly heterogenic at both clinical and genetic levels. As in other neurodevelopmental disorders, the pathophysiology of COS involves genetic factors as well as environmental factors damaging the brain (*e.g.*, hypoxemia, early childhood trauma or maternal-fetal infections) [3]. The respective responsibility of each of its causes remains unknown [4]. The genetic architecture of COS is complex and involves DNA changes: Copy Number Variations (CNVs) and Single Nucleotide Polymorphisms (SNPs), both inherited and *de novo* [5 - 8]. At a metabolic level, many different pathways have been implicated in the pathogenesis of schizophrenia and alterations in the phosphoinositide signaling pathway leading to changes in Ca²⁺ signaling play a major role [9]. According to the *N*-Methyl-D-Aspartate Receptor (NMDAR) hypo-function hypothesis of schizophrenia pathogenesis, the decline in Ca²⁺ signaling resulting from a decrease in NMDAR activity is responsible for the instability of the GABAergic inhibitory neurons [10]. These neurons express receptors that activate the phosphoinositide signaling pathway acting to increase the Ca²⁺ signal and maintaining an excitatory/inhibitory balance [9].

We present the description of a microduplication in the 10q region including part of the *Inositol Polyphosphate-5-Phosphatase A (INPP5A)*; HGNC: 6076/Entrez Gene ID: 3632/OMIM: 600106/Ensembl: ENSG00000068383) gene that segregates with SSDs in the family of a patient affected by both COS and Autism Spectrum Disorder (ASD). We also show the

expression of the *INPP5A Drosophila* homologue in the central nervous system, supporting its role in the pathogenesis of COS.

2. Materials and Methods

GenAuDiss protocol

GenAuDiss is a translational multicentric study (NCT02565524). Patients with COS or Early-Onset-Schizophrenia (EOS) (with symptoms occurring before the age of 18) were initially recruited through the 2011–2013 Interregional Hospital Clinical Research Program (NCT01512641) whose main goal was to estimate the prevalence of COS and EOS in a population of children and adolescents in child psychiatry care or medical-educational structures [11, 12]. In addition, an enrolment in the present study is offered to inpatients and outpatients of Child and Adolescent Psychiatry (CAP) centers, as well as their first-degree relatives. Participants are included either directly at the study sites or after referral by child or adolescent psychiatrists of the Provence-Alpes-Côte d'Azur (PACA) region. At inclusion (V1), clinical assessments (both psychiatric and neurocognitive) are performed in patients as well as first-degree relatives (parents and siblings). Blood tests are performed in a second visit (V2) within six months.

The study is proposed to children and adolescents presenting COS or EOS with comorbid ASD and to their first-degree relatives. Major inclusion criteria for patients:

- 7–22 years of age;
- Diagnosis of COS (onset before age 13) or EOS (onset before age 18) by the semi-structured interview Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version (K-SADS-PL) psychosis section;

- Diagnosis of ASD by Autism Diagnostic Interview-Revised (ADI-R);
- IQ \geq 40 at Wechsler Intelligence Scale for Children (WISC-V).

Major inclusion criteria for parents and siblings:

- First-degree biological relationship (no adoption) with the index patient.

The main objective of the GenAuDiss protocol is to identify disease-causing genetic mutations in a cohort of patients affected by both COS or EOS and ASD.

Phenotyping

The propositus is an inpatient at the time of the inclusion process. Quantitative and qualitative measures were assessed during hospitalization:

- Medical history (including pregnancy, birth and later development) and biographic parameters, types and dates of significant life events including trauma and environmental exposures (*e. g.*, drugs and substances);
- Clinical parameters from physical examination (*e. g.*, body weight, body mass index and arterial pressure);
- Semistructured interviews to assess main diagnosis at inclusion [K-SADS-PL, ADI-R and Mini International Neuropsychiatric Interview (MINI)][13-16];
- Clinical heteroassessments with specific rating scales [WISC-V, Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Trail Making Test (TMT) A, TMT B, and verbal fluency] [17-20];
- Self-report questionnaires [Cloninger's Temperament and Character Inventory (TCI) 226 and Baron Cohen's Autism Quotient (AQ)] [21-23].

Genotyping

The genetic analysis strategy includes DNA testing for Fragile-X Syndrome by PCR FRAXA [24], high-resolution karyotype or DNA CNV research by CGH array from both parents, siblings and patient. A quantitative PCR (LightCycler® 480 SYBR Green I Master) is made for gene detection and quantification if a putative gene is found to be deleted, duplicated or truncated by a CNV.

In situ hybridization in Drosophila

Drosophila embryos were dechorionated in 50% bleach, fixed in 4% formaldehyde, devitellinized in 100% methanol, and stored in 100% ethanol. The *5PtaseI* anti-sense probe was made from the Drosophila Genomics Resource Center (DGRC) SD05875 cDNA linearized with EcoRI and transcribed with T7 polymerase using the Riboprobe Combination System kit (Promega, Madison, WI) and the DIG RNA Labeling Mix (Roche, Indianapolis, IN). Embryos were stained using the TSA Plus Biotin System (Perkin Elmer, Waltham, MA) according to Tevy *et al.*, 2014 [25].

3. Results

The GenAuDiss protocol [11], a French multicentric study designed to identify disease-causing genetic mutations in a cohort of patients affected by COS or EOS and ASD, allowed us to identify a novel interesting CNV in a COS proband: a ~324 kb duplication including a portion of the *INPP5A* gene. Mitchell *et al.* (1996) used fluorescence *in situ* hybridization to map the gene on chromosome 10 (10q26.3) [26]. The duplication was inherited from the mother diagnosed with psychotic disorder that is included in SSD. The healthy sister of the

patient does not carry this duplication (Figure 1). Unfortunately, the father died at patient's early childhood, is not available for genetic testing and we do not have any psychiatric information about him.

Medical history and developmental features

The proband, a 17-year-old girl, was diagnosed with COS around age 12. She was born at 41 weeks of gestation, by caesarian section. Her birthweight was 3500 g, she measured 51 cm of length and 36 cm of head circumference. Apgar score was normal (10-10). She presents a psychotraumatic family history with the violent father's death murdered at her early childhood (before one year old). Delayed motor milestones were noticed (walking after 24 months) with also communication disorders (first words at three and a half years and stuttering), intellectual disability (IQ = 74) and learning impairments. She was admitted in a medical-social care center since the age of seven years, because of behavioral symptoms including tantrums and poor interactions with other children. At age 12, she presented a delusion of persecution, visual hallucinations and depressive mood and was diagnosed with COS by two independent child psychiatrists. She was treated by a monotherapy of antipsychotic (Risperidone) during five years with a good response on delusion, but mood lability and depressive symptoms remained. At the age of 14, she made a first suicide attempt by drug ingestion. During hospitalization in an adolescent psychiatry unit, a switch to Olanzapine allowed a durable mood stabilization with also a good response for positive symptoms (delusions and hallucinations).

Clinical work-up

At the age of 17, she was hospitalized again for a relapse of suicidal behavior with associated mood-congruent psychotic features. Neurological and general examinations were normal, including EEG, cerebral MRI, standard blood analysis, and metabolic screening.

Somatic features

The patient has been and is presently suffering from moderate asthma (no long-term control medications needed), primary enuresis and primary amenorrhea (first periods at the age of 17) without associated drug-induced hyperprolactinemia.

Clinical Genetics

Fragile-X Syndrome testing by PCR FRAXA was negative. High-resolution karyotype was not carried out because we first performed a molecular karyotype (Array CGH).

Array CGH analysis shows an interstitial 324 kb duplication in the chromosomal region 10q26.3, inherited from the mother (Figure 2A, B) that was confirmed by Quantitative PCR (qPCR). Three genes are contained in this microduplication: *AF086154*, *LINC02870* and *INPP5A*. Only one gene (*INPP5A*) is expressed in the brain, The other two genes have unknown function and no data about the encoded proteins are available (Figure 2C). Only one portion of *INPP5A* is duplicated in this interval (transcript ENST00000368593.7: from exon 1/13 to 12/13 with truncation in intron 12/12; transcript ENST00000368594.8: from exon 1/16 to 12/16 with truncation in intron 12/15; transcript ENST00000342652.6 : from exon 1/13 to 9/13 with truncation in intron 9/12).

Family study

The patient's mother was evaluated with MINI-S and was diagnosed with psychotic disorder, mood/anxiety disorders (suicide ideation without suicide attempt) and Post-Traumatic Stress Disorder (PTSD). The AQ was high (30/50) and revealed autistic traits, near the cut-off

(32/50) for Asperger's syndrome diagnosis. The TCI personality test revealed also a probable personality disorder (cooperation <-2 SD). Finally, IQ was normal around 108. In her medical history, she felt sad very regularly but had never seen a psychiatrist and had never benefited from a psychotropic drug. The patient's sister was diagnosed with tobacco use disorder and past social phobia. Her AQ score was negative for autistic traits (16/50) and no personality disorder was diagnosed. Her medical history was insignificant.

Central nervous system expression in Drosophila

The human *INPP5A* gene has one *Drosophila* homologue called *5PtaseI* [25]. The two proteins present 46% identity and 63% similarity. No *5PtaseI* mutant is currently available and its expression pattern has not been reported. To determine whether the function of *INPP5A* is conserved, we carried out *in situ* hybridization on *Drosophila* embryos. At stages 15 and 16, *5PtaseI* is strongly expressed in the brain and in the ventral nerve cord (Appendix 1). This result reinforces the role of *INPP5A* in nervous system development.

4. Discussion

Our case report is the description of a patient with COS associated with neurodevelopmental disorders (mental retardation, leaning disabilities and ASD) and carrying a 10q26.3 micro-microduplication in the *INPP5A* gene. According to the large Decipher database (<https://decipher.sanger.ac.uk/>), most gain and loss of function CNVs encompassing *INPP5* are predicted to be pathogenic in the general population. In the patient's family, the genetic testing of first degree relatives (Figure 1) revealed a familial segregation of the mutation

where both mother and patient with SSD carry this 10q26.3 CNV microduplication while the 22 year-old sister in good mental health (with typical development) does not carry it.

While the proband has an earlier, very severe and neurodevelopmental form of schizophrenia, her mother's psychotic disorder evolved since adolescence (15 years). We can speculate that a second "hit" is present (*e.g.*, an additional genomic mutation or an epigenetic effect of early childhood trauma). Common variants (SNPs carried by more than 1% of the general population) may also play a role in the pathogenesis of COS when added to rare mutations [5].

INPP5A encodes a membrane-associated 43 kDa type I inositol 1,4,5-trisphosphate (InsP₃) 5-phosphatase that hydrolyzes Ins(1,4,5)P₃ and Ins(1,3,4,5)P₄ to generate Ins(1,4)P₂ and Ins(1,3,4)P₃, respectively [27, 28]. InsP₃ 5-phosphatases hydrolyze Ins(1,4,5)P₃, which mobilizes intracellular calcium and acts as a second messenger mediating cell responses to various stimulation [9]. Primary and modulatory actions of the InsP₃/Ca²⁺ pathway have been implicated in psychiatric disorders (ASD, schizophrenia and bipolar disorder) and in major human diseases affecting the brain (Alzheimer's, Huntington's diseases, amyotrophic lateral sclerosis, epilepsy, and spinocerebellar ataxia) or other tissues (*e.g.*, cardiac diseases) [9]. This protein is found in both mouse [29; <http://mouse.brain-map.org/gene/show/84380>] and human brains [30; <https://www.genecards.org/cgi-bin/carddisp.pl?gene=INPP5A#expression>]. Phosphoinositides are phospholipids participating in membrane remodeling and all the processes linked to it, like cytoskeletal remodeling, cell signaling cascades, ion channel activity, and membrane traffic [31]. At a molecular level, *INPP5A* appears to regulate intracellular Ca²⁺ through modulation of Ins(1,4,5)P₃ levels, which is relevant for dendritic spine morphogenesis in neurons [32-34]. Importantly, dendritic spine morphology and

number are altered in both schizophrenia [35] and ASD [36]. These may constitute arguments in favor of the role of this gene alteration in the pathophysiology of COS.

Furthermore, it would be interesting to explore the levels, in both mother and daughter, of the truncated InsP3 5-phosphatase that we hypothesize is generated by the microduplication. Indeed, the presence of an abnormal InsP3 5-phosphatase would strongly suggest a dominant-negative effect. However, due the inaccessibility of the tissues where InsP3 5-phosphatase is expressed, this important information is lacking.

Lithium, a classic mood stabilizer in clinical practice, reduces the formation of inositol (by inositol monophosphatase inhibition) and seems to be a therapeutic target of this pathway [9]. Reduced brain inositol in rats treated by lithium was first shown more than 50 years ago [37]. Berridge *et al.*, (1989) introduced the inositol depletion hypothesis to explain the clinical effects of lithium, which postulates a reduction in the supply of inositol lipids required for signaling in cells within the CNS (therapeutic action) or in the developing embryo (teratogenic action) [38]. More recently, a growing literature about the neuroprotective action of lithium in various CNS disorders including neurodegenerative disorders is emerging [39]. However, despite a suggested link between the alteration in the inositol pathway (*INPP5A* microduplication) and the diagnosis of our patient, the therapeutic effects of lithium on COS and other forms of schizophrenia remain unknown and should be specifically studied.

In mice, the loss of function of *Inpp5A* (presenting 90,21% similarity with human *INPP5A*) causes ataxia and cerebellar Purkinje cell degeneration [29]. In humans, *INPP5A* has been shown to play a role in the development and progression of cutaneous squamous cell carcinoma and to have a prognostic value in these diseases [40, 41]. Strong proof of the involvement of the brain-expressed *INPP5A* gene in human psychiatric disorders is lacking.

To our knowledge, only two SNVs (rs751524528: p.A80V and rs775793924: p.R168W) were described in human psychiatric disorders. rs751524528 (p.A80V) is a benign non-synonymous mutation (according to Polyphen2) in a 31-year-old female affected by adult-onset schizoaffective disorder (bipolar type) without developmental delays, mental retardation and learning disabilities [42]. rs775793924 (p.R168W) is a rare SNV defined by authors as a «non-synonymous damaging strict and disruptive» variant and was found in a multiplex family with subjects affected by bipolar disorder or SSD with no phenotypic description [43]. Finally, an epigenome-wide significant ($P < 1.7 \times 10^{-8}$) association for phonemic verbal fluency (cg12507869, $P = 2.5 \times 10^{-9}$) was found in an epigenome-wide association study. This CpG site is located in *INPP5A*, but the top SNP (rs113565688) for this site explains only 1.2% of the variance in methylation and rs113565688 was not correlated with alterations in cognitive functions in a recent GWAS. Thus, the environmental influence in *INPP5A* methylation in the cognitive alteration seems predominant over the genetic contribution [44].

In *Drosophila*, all the genes of the phosphoinositol pathway are present except for the I(1,3,4)P₃ 5/6 kinase [45]. The *INPP5A* homolog *5PtaseI* is among the *Drosophila* genes with high probability of having a synaptic function [46] and it is a robust suppressor of Ataxin-3 toxicity in the eye [47]. *5PtaseI* is a modifier of toxicity brought up by expression of expanded PolyQ Ataxin-3 present in Spinocerebellar Ataxia 3 (SCA3) patients [47]. This was found through a deep RNAi screen in the eye and shown to involve protein turnover/quality control, nuclear import/export and mRNA transport/editing/translation. In *Drosophila*, the *INPP5A* homologue is a crucial enzyme in the phosphoinositide pathway. We found that *5PtaseI* is expressed exclusively in the central nervous system of embryos. This original finding suggests that *INPP5A* is a gene involved in central nervous system development.

Furthermore, we can propose that the fly may be an excellent model to study the role of *INPP5A/5PtaseI* in normal and pathological development of the nervous system.

In clinical practice, as suggested by Szego *et al.* for ASD [48], it would seem useful to propose to COS patients systematic whole exome/genome sequencing instead of or in addition to microarrays to improve genetic testing, allow SNV detection and consequently end the “diagnostic Odyssey” [49]. In research, the major challenge of the upcoming years will be the analysis of big data from next generation sequencing (prioritization and interpretation of DNA variations) [50] and the experimental validation of putative mutations in animal models. Sharing patients’ data with other teams around the world will be helpful to unravel the molecular pathophysiology of COS and ASD and their underlying causes, paving the way for an early therapeutic intervention.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figure legends

Figure. 1. Genealogical tree of the patient's family

The propositus is a 17-year-old female with COS (black dot).

Schizophrenia spectrum disorder status: affected (red); unaffected (green); unknown (white)

CNV 10q26.3 status: DUP + = positive; DUP - = negative

Figure. 2. Mapping of a chromosome 10 micro-microduplication «chr10:134,258,887-134,582,804»

(A) Schematic representation of chromosome 10 according to NCBI build 37 (human genome 19).

(B) Known RefSeq Genes in the duplicated chromosomal area.

(C) Summary of coding genes, encoded proteins, corresponding OMIM reference and brain expression (RPKM mean score) included in the microduplication.

OMIM : www.omim.org;

NCBI GENE : www.ncbi.nlm.nih.gov/gene

Appendix 1. *5PtaseI* expression in *Drosophila* embryos. *5PtaseI* expression patterns in embryos detected by *in situ* hybridization with TSA amplification followed by histochemistry.

(A) Ventral view of a stage 15 embryo. Strong expression is observed in the ventral nerve cord. (B) Lateral view of a stage 15 embryo. Strong expression is observed in the brain and in the ventral nerve cord. (C) Lateral view of a stage 16 embryo. Strong expression is observed in the brain and in the ventral nerve cord. In all panels, the anterior end is to the left.