# Report of Clinically Significant CNVs in three Iranian patients with Autism and Additional Clinical Features

**Prof. Farkhondeh Behjati**
**Genetics Research Centre,**
**University of Social Welfare & Rehabilitation Sciences, Tehran, Iran**

# Abstract

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder estimated to affect 1 in 68 children. Copy number variations (CNVs) with the overall detection rate of 10-15% are known to be the significant genetic factor in the disease. By the advent of array-based techniques increasing number of pathogenic CNVs have been identified resulting in elevation of the diagnostic yield.

We are reporting three children with autism in which copy number gains have been detected using array CGH technique. All patients had additional clinical features including intellectual disability (ID), craniofacial anomaly and seizure. Patient 1 showed a novel microduplication on chromosome 10q21.2q21.3, candidate for a new syndrome. Patient 2 demonstrated two copy number gains involving the genes *CHRNA7* and *GPRIN2* on chromosome 15q13.3 and 10q11.22, respectively. The CHRNA7 duplication is inherited from a normal father, while GPRIN2 gain is de novo, acting as a probable second hit. Patient 3 had a duplication of 7q36.3 containing the gene VIPR2, providing new evidence for VIPR2 duplication as a candidate gene for Autism.

All copy number gains are considered to be likely pathogenic CNVs, having a role in the etiology of Autism. CNV evaluation in patients with Autism and additional clinical features is warranted.

Key Words: Autism, CNV, Microduplication, 10q21.2q21.3, 15q13.3, 10q11.22, 7q36.3, Iranian

Authors:
Farkhondeh Behjati[1*],Saghar Ghasemi Firouzabadi[1], Roxana Kariminejad[2], Roshanak Vameghi[3],,
Mahboubeh Firouzkouhi Moghaddam[4,5], Hossein Najmabadi[1]

1- Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
2- Kariminejad-Najmabadi Pathology and Genetics Center, Tehran, Iran
3- Pediatric Neurorehabilitation Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
4- Child and Adolescent Psychiatry Department, Zahedan University of Medical Sciences, Zahedan, Iran
5- Research Center for Children and Adolescents Health, Zahedan University of Medical Sciences, Zahedan, Iran
* Corresponding author: Farkhondeh Behjati, Ph.D., Professor of Medical Genetics, Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Koodakyar St., Daneshjoo Blvd., Evin, Tehran 1985713834, Iran, E-mail: f_behjati@uswr.ac.ir; fbehjati@gmail.com

# Autism Spectrum Disorder (ASD)

- **Prevalence**: 1/68 children

- **Etiology**

  - **Genetic Factors**

    Single gene disorders
    Single nucleotide variations
    **Copy number variations (CNVs)**

  - **Epigenetics**

  - **Environmental Factors**

**The etiological diagnosis is possible only in about 20% of affected patients**

# Copy number variations (CNVs)

- **Copy-number variations** (CNVs):
structural variations (**deletions or duplications**)
in the genome with a size of greater than 1 Kb.

- A great number of CNVs have been identified to be involved in autism leading to description of **novel syndromes** and many **candidate genes**:

- Microscopic chromosome abnormality: **~5%**
- CNVs detected by array CGH: **~10%**

The detection rate increases when autism co-occurs with other clinical features, suggesting a syndromic form of autism

# Purpose & Method

▷ CNV analysis on Iranian patients with autism to identify the loci involved in ASD

▷Inclusion criteria :

❖Sporadic patients

❖ Unrelated parents

❖With additional feature:

Intelectual disability (ID), Seizure, ADHD, microcephaly/ macrocephaly, hearing loss, gastrointestinal, liver problem, renal anomaly, obesity, muscle weakness, immune deficiency, sleep disturbance,….

**Method:** Array CGH (8x60 Kit), 50 Kb resolution

# Patient 1

- **Patient Description:** A 16 year-old boy **with autism, ID, macrocephaly, seizure, ADHD and hepatomegaly**

- **aCGH**: arr 10q21.2-21.3 (64269265-65,380,932)x3dn
- **Size**: 1.1 Mb
- **Gene content**: REEP3, JMJD1C (TRIP8), EGR2, ZNF365, ADO genes
- **Point**: not reported in DGV neither in DECIPHER or ClinVar.

▹ 3 genes (REEP3, JMJD1C (TRIP8), EGR2)

are **autism candidates** but only LOF mutations have been reported (SFARI database).

✓2 genes (JMJD1C,REEP3) are involved in liver enzyme regulation (alkalin phosphatase) and **candidate for liver disease**

**We consider this as a novel microduplication/gene contiguous syndrome**

# Patient 2

**Patient description**: A 7-year old boy with autism, ID, microcephaly, seizure, ADHD

- arr 10q11.22 (46,839,243-47,033,415)x3dn
- **Size:** 194 Kb
- statement: could be significant

- **Gene content:** SYT15, **GPRIN2**
- **Function:** GPRIN2 is a regulator of neurite outgrowth.

- **A candidate modifier gene** in Rett syndrome and autism.

- Previous report of **Cooccurrance** of GPRIN2 duplication and SHANK2 mutation.

- arr 15q13.3 (32,065,030-32,509,897)x3pat
- **Size:** 445 Kb

- **Gene content: CHRNA7**
- **Function:** signal transmission at synapses

- There have been some reports of cooccurrance of CHRNA7 duplication and SHANK2 mutations in autism patients

- Variable expression and incomplete penetrance is a common event for CHRNA7

# Patient 3

- **Patient Description**: A 9 year-old boy with **autism, ID and ADHD**

- **aCGH:** arr 7q36.3 (158,815,576-158,941,513)x3
- **Size:** 120 Kb

- **Gene content: VIPR2** A neuropeptide receptor gene (VIP receptor)

- Vacic et al (2011) reported **that autism may be a phenotype associated with VIPR2 dup** (a preliminary evidence, p value: 0.018)

- Ago et al (2015): Overactivation of the VPAC2 receptor in the postnatal mouse results in a reduction in synaptic proteins in the prefrontal cortex (**animal model**)

**Our case is an evidence to support these findings**