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The Role of Genetic Mutations in NSD2 Gene on the Rauch-Steindl syndrome (RAUST)

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Abstract:

Rauch-Steindl syndrome (RAUST) is caused by a heterozygous mutation in the NSD2 gene on chromosome 4p16. Rauch-Steindl syndrome (RAUST) is characterized by poor growth before and after birth, sometimes with short stature and small head circumference, marked dysmorphic facial features, and variable developmental delay with delays in motor and speech learning and intellectual impairment that can be mild. Other features may include hypotonia and behavioral abnormalities. The phenotype reflects a mild form of Wolff-Hirschhorn syndrome (WHS), a contiguous gene deletion syndrome caused by heterozygous deletion of multiple genes on chromosome 4p16. Heterozygous mutations in the NSD2 gene identified in RAUST patients by Lozier et al. (2018), Derar et al. (2019), and Barry et al. (2019) occurred de novo. Most of the heterozygous mutations in the NSD2 gene identified in RAUST patients by Zanoni et al. (2021) occurred de novo.

Key words: rauch-steindl syndrome (RAUST); genetic disorder; NSD2 gene

Introduction:

Overview of Rauch-Steindl syndrome (RAUST)

Rauch-Steindl syndrome (RAUST) is caused by a heterozygous mutation in the NSD2 gene on chromosome 4p16. Rauch-Steindl syndrome (RAUST) is characterized by poor growth before and after birth, sometimes with short stature and small head circumference, marked dysmorphic facial features, and variable developmental delay with delays in motor and speech learning and intellectual impairment that can be mild. Other features may include hypotonia and behavioral abnormalities. The phenotype reflects a mild form of Wolff-Hirschhorn syndrome (WHS), a contiguous gene deletion syndrome caused by heterozygous deletion of multiple genes on chromosome 4p16. The clinical features of RAUST are similar to but milder than WHS, with less severe malformed facial features, less severe overall developmental disabilities, and the absence of seizure disorders. The phenotype and incidence of RAUST are highly variable.[1]

Clinical features of Rauch-Steindl syndrome (RAUST) Lozier et al. (2018) reported a 16-month-old boy with poor physical development, hypotonia, small head circumference, and mild intellectual disability. He had malformed facial features, including a high forehead, hypertelorism, epicanthal folds, a broad nasal bridge, prominent ears with attached earlobes, enamel dystrophy, and clinodactyly. Although the facial features were reminiscent of a mild form of WHS, he did not have seizures.[1]

Boczek et al. (2018) reported a girl with intrauterine growth retardation (IUGR), failure to thrive, short stature, developmental delay, and behavioral abnormalities. She had mild facial dysmorphic features, including hypertelorism, almond-shaped eyes, upward-slanting palpebral fissures, arched eyebrows, flat nasal bridge, prominent ears, and a small chin. She did not have seizures. These features were consistent with a mild form of WHS, and the patient was a carrier of a mutation in the NSD2 gene.[1]

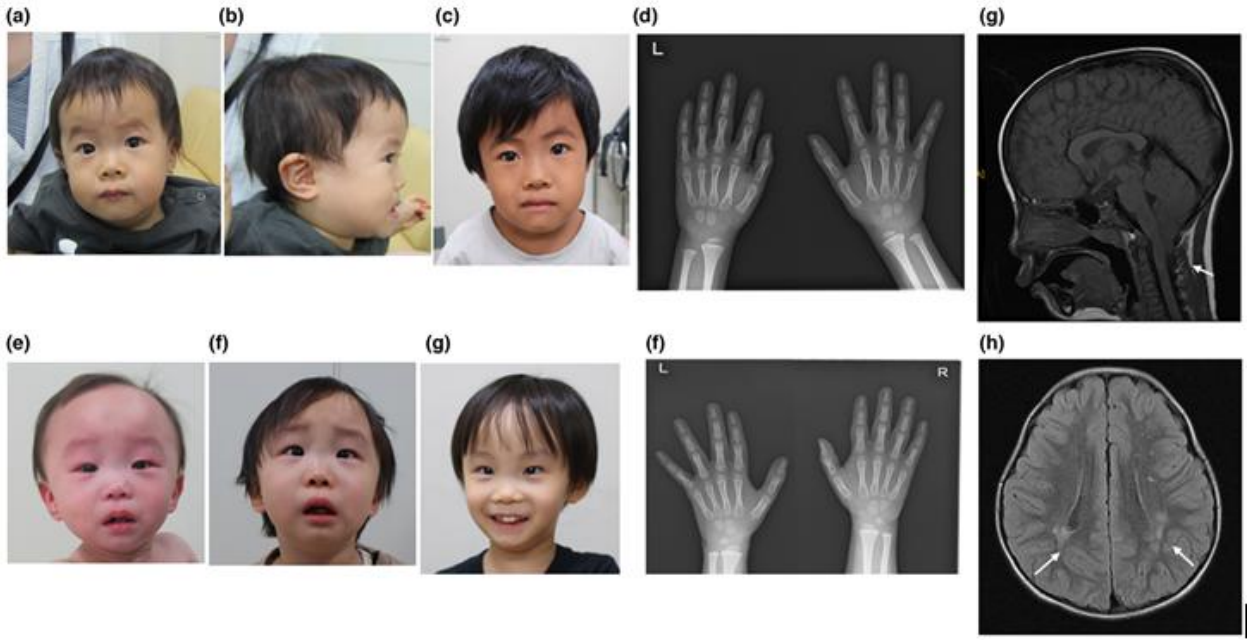

Figure 1: *Photographs of individuals with RAUST. Note that the craniofacial features include relative macrocephaly, a mildly triangular face, a broad forehead, a high anterior hairline, broad, arched eyebrows with low lateral ridges, full cheeks, a thin, high nasal bridge, a short, flat philtrum, a prominent cupid's bow, a thick, upturned lower lip crease, and protruding ears. Neither individual has the "Greek warrior's helmet" facial features of WHS. Photographs of individual 1 (a, b - 1 year and 6 months, c - 5 years and 8 months) and individual 2 (e - 1 year and 2 months, and f - 4 years and 4 months; g - 4 years and 11 months). X-rays of bilateral wrist bones of individual 1 (d - 5 years and 8 months) and individual 2 (f - 5 years). Bone age is delayed by about 2 years in both individuals. Brain MRI findings of subject 2 (g—type 1 Chiari malformation, h—bilateral T2WI high signal in cerebral white matter).1,2*

Darar et al (2019) reported two unrelated Saudi children with IUGR, poor postnatal growth, hypotonia, and developmental delay with speech impairment. They had variable dysmorphic features including small head circumference, craniofacial asymmetry with a broad nasal bridge extending into the forehead, short philtrum, micrognathia, high arched eyebrows with widely spaced eyes, a prominent mouth, and abnormal teeth. One of them had short stature (-3.6 SD). None of the patients had seizures. The authors concluded that the phenotype was consistent with WHS. Each child carried a mutation in the NSD2 gene. [1,2]

Barry et al (2019) reported 3 unrelated children with mutations in the NSD2 gene and variable manifestations of what they termed a subset of WHS, including intrauterine growth restriction (IUGR), short stature, microcephaly, hypotonia, characteristically malformed faces with prominent forehead and broad nasal bridge, and general developmental delay with language impairment. One patient was diagnosed with autism spectrum disorder. They did not have seizures. [1,2]

Jiang et al (2019) reported a 12-year-old Chinese boy with an unusual form of WHS associated with a de novo heterozygous frameshift mutation in the NSD2 gene. He had intrauterine growth restriction, feeding difficulties, poor overall growth, hypotonia, and general developmental delay. There were no seizures. Facial features were similar to those seen in WHS, including a Greek-helmet-like nose, high anterior hairline with prominent glabella, short philtrum, micrognathia, hypertelorism, arched eyebrows, down-turned corners of the mouth, and abnormal teeth. The researchers noted that the phenotype, including intellectual disability, was not as severe as WHS. [1,2]

Hu et al. (2020) reported a Chinese father and daughter with overlapping and unusual features of irritable bowel syndrome (WHS) and a mutation in the NSD2 gene. The subject, a 12-year-old girl, presented at 5 years of age with a history of intrauterine growth restriction (IUGR), poor overall growth with microcephaly (-3 SD), short stature, and mild developmental delay with poor school performance (IQ 75). Her craniofacial features included a low hairline, high arched eyebrows, hypertelorism, epicanthal folds, hypoplastic midface, low-set and retroverted ears, relative micrognathia, and a long neck. Her father had similar distinctive facial features and mild intellectual disability, but no obvious short stature. Growth hormone treatment in the girl resulted in a favorable developmental response. [1,3]

Zanoni et al. (2021) reported 18 patients from 16 unrelated families with a distinct developmental disorder that they termed Rauch-Steindl syndrome (RAUST). Patients, aged 1 to 50 years, were screened through the Gene Matcher program after exome sequencing identified heterozygous, mostly de novo, mutations in the NSD2 gene. The phenotype and severity of the disorder were highly variable. The most common features included pre- and postnatal growth retardation; failure to thrive, sometimes with short stature; small head circumference; hypotonia; delayed gait; weak or absent speech; and variable intellectual development, often with learning difficulties or behavioral abnormalities. Some patients were independent and could dress or feed themselves, and many were able to attend special schools, while a few were dependent for activities of daily living. Happy behavior, hyperactivity, short attention span, anxiety, aggressive behavior, and autistic features were observed in various patients. Only 1 patient had febrile and myoclonic seizures that resolved by the age of 8 years. Common facial dysmorphic features included a triangular face with a broad forehead; high anterior hairline; retrognathia; low, protruding, or backward-rotated ears; hypertelorism; sunken eyes; arched eyebrows; broad or thin nasal bridge; bulbous nasal tip; thick lower lip; and dental anomalies. A few patients had clinodactyly or pas planus of the fifth digit. Other features included gastrointestinal disturbances with poor feeding or constipation and refractive errors of the eye or strabismus. Although most patients were unrelated, there were 2 families that separated

the disorder, including Family 6, which had multiple affected members. The researchers stated that the phenotype was milder than WHS and the facial phenotype was sufficiently distinct from WHS for the disorder to be classified independently. [2,3]

Inheritance Pattern of Rauch-Steindl Syndrome (RAUST):

Heterozygous mutations in the NSD2 gene identified in RAUST patients by Lozier et al. (2018), Derar et al. (2019), and Barry et al. (2019) occurred de novo. Most of the heterozygous mutations in the NSD2 gene identified in RAUST patients by Zanoni et al. (2021) occurred de novo. However, there were 2 families (families 6 and 7) whose transmission pattern was consistent with autosomal dominant inheritance. [2,4]

The transmission pattern of RAUST in a Chinese family reported by Hu et al. (2020) was consistent with autosomal dominant inheritance with incomplete penetrance and variable expression. [2,4]

Cytogenetics of Rauch-Steindl Syndrome (RAUST):

In a 7.5-year-old boy (FN4367) with a partial WHS phenotype, Rock et al. (2001) identified a 191.5-kb heterozygous de novo interstitial deletion on chromosome 4p16.3 that disrupted the WHSC1 (NSD2) gene in intron 5 and encompassed the entire WHSC2 (NELFA) gene. The patient had stunting with normal height and head circumference, dolichocephaly, a malformed face with a prominent glabella and short philtrum, and mild distal skeletal abnormalities. He had generalized developmental delay with learning disabilities and hyperactivity. He did not have seizures. His phenotype was consistent with a mild form of WHS. Rock et al. (2001) suggested that disruption of NSD2, which is ubiquitously expressed early in development, may be responsible for the poor growth, mild neurological deficits, and mild dysmorphic features observed in this disorder. The function of WHSC2 was not clear. [2,5]

Molecular Genetics of Rauch-Steindl Syndrome (RAUST):

In a 16-month-old boy with RAUST, Lozier et al. (2018) identified a de novo heterozygous nonsense mutation in the NSD2 gene (R1138X). This mutation was found by whole-exome sequencing and confirmed by Sanger sequencing. Functional studies of this variant and studies of patient cells were not performed, but it was predicted that this mutation would result in loss of function. [2,6]

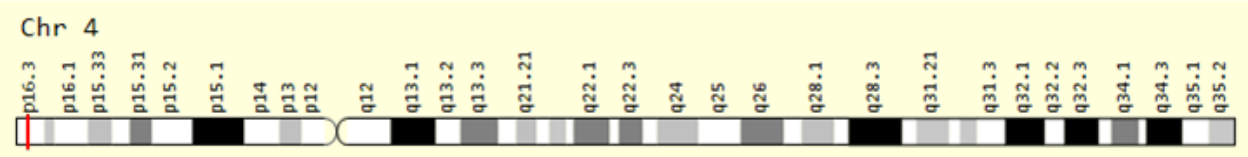

Figure 2: *Schematic of the physical map of chromosome number 4, where the NSD2 gene is located on the short arm of this chromosome as 4p16.3.1,2*

In a 2-year-old girl with RAUST, Bochek et al. (2018) identified a de novo heterozygous frame shift mutation in the NSD2 gene. This mutation was found by whole-exome sequencing and confirmed by Sanger sequencing. Functional studies in this variant and patient cell studies were not performed, but it was predicted to result in loss of function. [2,6]

Derar et al. (2019) identified a novel heterozygous nonsense mutation in the NSD2 gene in a 34-month-old boy (patient 2) with RAUST. Functional studies in this variant and patient cell studies were not performed. [2,6]

Bari et al. (2019) reported 3 unrelated children with RAUST and novel heterozygous nonsense or frame shift mutations in the NSD2 gene. Functional studies were not performed, but it was predicted to result in loss of function. [2,7]

Hu et al. (2020) identified a heterozygous frame shift mutation in the NSD2 gene in a Chinese father and daughter with RAUST. The mutation, identified by exome sequencing and confirmed by Sanger sequencing, occurred de novo in the father, who passed it on to his affected daughter. This variant, which was not present in public databases, was predicted to result in nonsense-mediated mRNA decay and loss of function, although functional studies of this variant and studies of patient cells were not performed. These investigators concluded that loss of NSD2 in WHS is not sufficient to explain all the features of WHS, especially the distinctive facial features. [2,7]

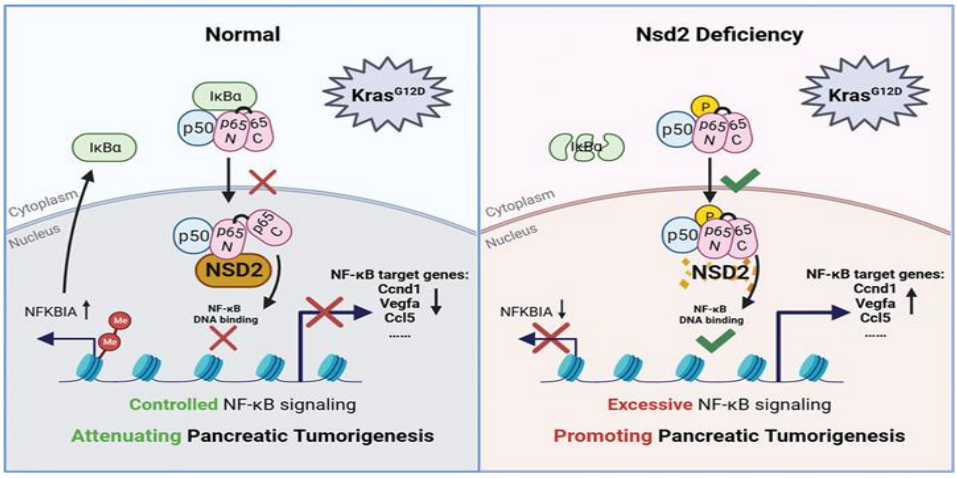

Figure 3: *Schematic of the molecular mechanism of the NSD2 gene in normal and reduced function states.1,2*

Zanoni et al. (2021) identified heterozygous variants in the NSD2 gene in 18 patients from 16 unrelated families with RAUST. These variants were found by exome sequencing. Most mutations were unique and occurred de novo throughout the gene, although 1 was recurrent and 2 were inherited in families. There were 5 missense, 3 nonsense, and 7 frame shift mutations. In vitro functional expression studies showed that some, but not all, of the tested missense variants reduced the level of histone H3 dimethylation at lysine-36 (H3K36me2), impaired NSD2 methylation activity, and were unable to fully restore physiological levels of H3K36me2 in cells lacking NSD2. Notably, C869Y (patient 1) and E1091K (patient 5) gave equivocal results in functional assays, whereas S1137F and K1019R significantly compromised NSD2 function. Nonsense and frame shift mutations were predicted to result in loss of function, although functional studies of these variants were not performed. [2,8]

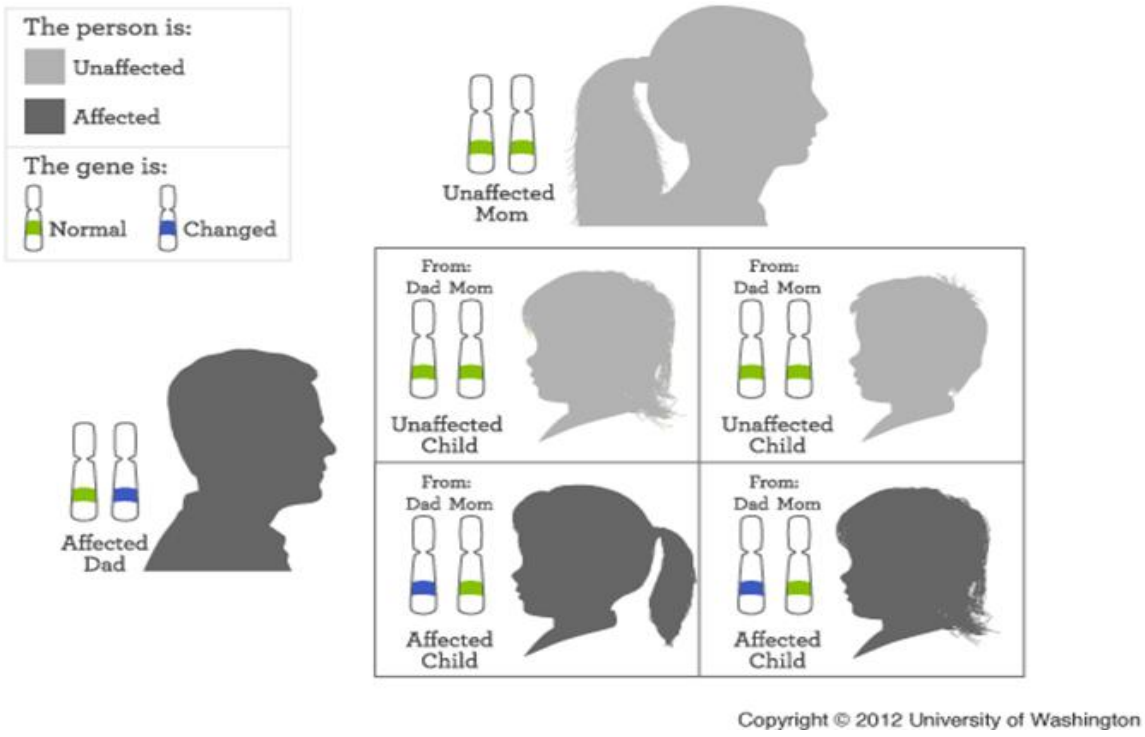

Figure 4: *Schematic of the autosomal dominant inheritance pattern.1,2*

Zanoni et al. (2021) concluded that these mutations result in a reduction or loss of NSD2 methyltransferase activity, leading to a developmental phenotype. While heterozygotes for missense variants were taller than individuals with nonsense or frame shift mutations, overall clinical severity was only weakly correlated with hypothesized or proven alterations in NSD2 enzymatic activity. It is worth noting that several patients had variants of uncertain significance in additional genes that could contribute to the phenotype.2,9

Discussion:

Rauch-Steindl syndrome (RAUST) is caused by a heterozygous mutation in the NSD2 gene on chromosome 4p16. Rauch-Steindl syndrome (RAUST) is characterized by poor growth before and after birth, sometimes with short stature and small head circumference, marked dysmorphic facial features, and variable developmental delay with delays in motor and speech learning and intellectual impairment that can be mild. Other features may include hypotonia and behavioral abnormalities. The phenotype reflects a mild form of Wolff-Hirschhorn syndrome (WHS), a contiguous gene deletion syndrome caused by heterozygous deletion of multiple genes on chromosome 4p16. The clinical features of RAUST are similar to but milder than WHS, with less severe malformed facial features, less severe overall developmental disabilities, and the absence of seizure disorders. The phenotype and incidence of RAUST are highly variable. In a 7.5-year-old boy (FN4367) with a partial WHS phenotype, Rock et al. (2001) identified a 191.5-kb heterozygous de novo interstitial deletion on chromosome 4p16.3 that disrupted the WHSC1 (NSD2) gene in intron 5 and encompassed the entire WHSC2 (NELFA) gene. The patient had stunting with normal height and head circumference, dolichocephaly, a malformed face with a prominent glabella and short philtrum, and mild distal skeletal abnormalities. He had generalized developmental delay with learning disabilities and hyperactivity. In a 16-month-old boy with RAUST, Lozier et al. (2018) identified a de novo heterozygous nonsense mutation in the NSD2 gene (R1138X). This mutation was found by whole-exome sequencing and confirmed by Sanger sequencing. Functional studies of this variant and studies of patient cells were not performed, but it was predicted that this mutation would result in loss of function. Zanoni et al. (2021) concluded that these mutations result in a reduction or loss of NSD2 methyltransferase activity, leading to a developmental phenotype. While heterozygotes for missense variants were taller than individuals with nonsense or frame shift mutations, overall clinical severity was only weakly correlated with hypothesized or proven alterations in NSD2 enzymatic activity. [1-10]

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