SSBP Syndrome Sheets

SATB2-Associated Syndrome

First description and alternative names

Glass et al. (1989) first described a male with a 2q32.2-q33.1 deletion that included the *special AT-rich sequence-binding protein 2* (*SATB2*) gene, subsequently, the name 'Glass syndrome' (OMIM #612313) was proposed.

Since 1989, varying genetic alternations to the *SATB2* gene have been documented to produce a relatively consistent phenotype, independent of the underlying pathogenic variant. Phenotypic differences are thought to relate to differences in severity rather than the system affected (Zarate & Fish, 2017). *SATB2*-associated syndrome (SAS) was therefore designated as a single clinically recognised syndrome in 2014, in an effort to unify the terms for different alterations affecting the *SATB2* gene (Döcker et al., 2014).

In addition to Glass Syndrome, alternative names include 2q32 Deletion Syndrome, 2q33.1 Microdeletion Syndrome, and Chromosome 2q32-q33 Deletion Syndrome.

Genetics

The SAS phenotype is associated with alterations causing functional haploinsufficiency of the *SATB2* gene (OMIM #608148) located on chromosome 2q33.1 (Cotton et al., 2020; Zarate & Fish, 2017). Alterations can result from a variety of molecular mechanisms, such as missense (31%), nonsense (24%), frameshift (20%), and intragenic deletion (14%) (Zarate et al., 2019).

SAS is an autosomal dominant disorder (an abnormal gene from one parent can cause SATB2). For most individuals, SAS is reported to occur as the result of a de novo genetic alteration; however, instances of mosaicism (where a percentage of cells in the body are affected by the genetic alteration) have been documented (Leoyklang et al., 2007; Zarate et al., 2019).

The *SATB2* gene is a regulator of several gene regulatory networks (GRNs) and has critical roles in multiple developmental processes, including skeletogenesis (skeleton formation), osteogenesis (bone formation) and craniofacial patterning (skull and facial formation) (Britanova et al., 2006; Dobreva et al., 2006; Gong et al., 2014). The *SATB2* gene is also expressed in the developing cortex and other tissues including the kidney and gut (Alcamo et al., 2008; Britanova et al., 2008). The presence of intellectual disability and speech delay/absence in individuals with SAS has been attributed to the essential role of the *SATB2* gene in neuronal connectivity (Döcker et al., 2014).

Incidence/prevalence

The true prevalence of SAS is unknown. However, SAS is estimated to occur in approximately .24-.30% of individuals with an undiagnosed intellectual disability or developmental delay (Bengani et al., 2017; Zarate et al., 2018).

Physical features and natural history

The major features of SAS have been incorporated into a S.A.T.B.2 diagnostic acronym; *S*evere speech anomalies, *A*bnormalities of the palate, *T*eeth anomalies, *B*ehavioural difficulties, with or without bone anomalies and/or brain defects, and age of onset below *2* years of age (Zarate & Fish, 2017).

Minor facial dysmorphisms have been described in individuals with SAS, including a thin upper lip, flat philtrum (grove between the upper lip and nose), prominent chin, micrognathia (small lower jaw), abnormal dentition, deeply set eyes, low-set ears, and a prominent forehead or high anterior hairline (Zarate & Fish, 2017; Zarate et al., 2017; Zarate et al., 2018). Facial change with age is reported, with progressive coarsening of facial features in older individuals (Zarate et al., 2018).

Craniofacial and dental abnormalities are characteristic of individuals SAS. Frequently reported palatal abnormalities include cleft palate and high-arched palate, while bifid uvula (split soft palate at the back of the throat) has been reported in a small number of individuals (Zarate et al., 2019). Dental abnormalities are present in all individuals and become apparent from one year of age (Zarate et al., 2018). Delayed development of the mandibular second premolars (premolars on the lower jaw) or roots of the permanent teeth, dental crowding with malocclusion (misalignment of the upper and lower teeth), abnormal tooth shape, and multiple odontomas (benign tumours linked to tooth development) are reported (Kikuiri et al., 2018; Scott et al., 2018; Zarate et al., 2018). Sialorrhea (drooling or excessive salivation) is often present (Zarate et al., 2018).

Feeding difficulties are common during infancy and into early childhood and have been attributed to the combination of craniofacial abnormalities and hypotonia (low muscle tone). Many infants are of low birth weight and low weight often persists. Tube feeding is often required in infancy, and this process may continue for several years (Zarate et al., 2019; Zarate et al., 2018). Gastrointestinal difficulties are reported, including constipation and/or gastro-oesophageal reflux (Zarate et al., 2021; Zarate et al., 2017).

In some individuals with SAS, skeletal abnormalities have been reported, including scoliosis, tibial bowing (bowing shin bone), pectus excavatum (sunken breastbone), and abnormal bone mineralisation (Mouillé et al., 2022; Zarate et al., 2018). Individuals may experience difficulties with movement and balance (Zarate & Fish, 2017; Zarate et al., 2017). An average age of 25.5 months has been reported for individuals taking their first steps (Zarate et al., 2019).

Clinical seizures are present in some individuals with SAS; however, subclinical seizures with abnormal electroencephalogram (EEG) activity have also been observed (Zarate & Fish, 2017; Zarate et al., 2017). Abnormal EEG activity has included abnormal wakefulness (staring spells, disorientation episodes, and/or laughing fits), slow background, and/or epileptiform discharges (Lewis et al., 2020; Zarate et al., 2018).

Other health problems include otitis media (middle ear infections), visual problems (e.g., strabismus (squint) and refractive errors), genitourinary problems and cardiac defects (Bissell et al., 2022; Zarate & Fish, 2017; Zarate et al., 2021; Zarate et al., 2017).

Behavioural characteristics

Individuals with SAS often display a happy disposition or friendly demeanour, with heightened motivation for social contact (Zarate et al., 2017; Zarate et al., 2018). However, this may be offset by the presence of behaviour that challenges, which are outlined within the S.A.T.B.2 diagnostic acronym (Zarate & Fish, 2017; Zarate et al., 2017). High rates of self-injury (43%), property destruction (49%) and aggression (77%) are reported (Bissell et al., 2022). Rates of self-injury and aggression in SAS are comparable to rates in non-syndromic autism and Angelman syndrome, while rates of property destruction are lower in SAS compared with non-syndromic autism and Angelman syndrome (Bissell et al., 2022).

Self-injurious behaviours, aggressive behaviours, and destruction of property behaviours are present in children, adolescents, and adults with SAS (Bissell et al., 2022). Behavioural changes with age are also indicated from clinical observations suggesting temper outbursts in childhood, with more physical acts of aggression emerging in adolescence and adulthood (Zarate et al., 2017).

An association between SAS and autism characteristics has been consistently reported (Lewis et al., 2020; Zarate & Fish, 2017; Zarate et al., 2021; Zarate et al., 2019). Bissell et al. (2022) report 46% of individuals met cut-off scores suggestive of autism spectrum disorder (ASD) according to the Social Communication Questionnaire (Berument et al., 1999). This concurs with rates of ASD (46%) reported by Zarate et al. (2021). Reported rates of ASD in SAS are comparatively high on screening measures compared to the prevalence of ASD in other syndrome groups associated with autism and intellectual disability (Richards et al., 2015). Fine-grained analyses reveal a distinct profile of autism characteristics and repetitive behaviour in SAS relative to individuals with non-syndromic autism. Key findings include convergent levels of compulsive behaviour and insistence on sameness, and differences in reciprocal social interaction and restrictive, repetitive, and stereotyped behaviour (Bissell et al., 2022). Impulsivity and hyperactivity are also frequently reported as behavioural features of SAS (Bissell et al., 2022; Lewis et al., 2020; Zarate & Fish, 2017; Zarate et al., 2019).

Sleep difficulties are common in children and adults with SAS and are reported to occur in between 50% and 75% of individuals. Difficulties include problems with initiating and maintaining sleep, sleep-wake transitions, early awakening, and sleep-breathing disorders (Cotton et al., 2020; Kumar & Zarate, 2020; Zarate et al., 2021).

Atypical sensory sensitivity has been described in some individuals. This has included reports of hypersensitivity to sound and touch (Balasubramanian et al., 2011; Tomaszewska et al., 2013; Zarate & Fish, 2017) and reports of an atypically high pain-threshold (Rosenfield et al., 2009; Scott et al., 2019; Zarate et al., 2017).

Emotional characteristics

Despite the frequent presence of a jovial disposition in SAS (Zarate et al., 2017; Zarate et al., 2018), individuals may show a propensity towards internalising problems such as anxiety and depression (Balasubramanian et al., 2011; Cotton et al., 2020; De Ravel et al., 2009; Kumar & Zarate, 2020; Van Buggenhout et al., 2005). High rates of anxiety (37%) have been reported by caregivers in a study with adolescents and adults (Zarate et al., 2021). However, lower rates of general anxiety (17%) have been reported in a larger sample including children and adults (Bissell et al., 2022), based on caregiver-report using the Anxiety Depression and Mood Scale (ADAMS; Esbensen et al., 2003). Bissell et al. (2022) further report that 13% of individuals with SAS met cut-off for depressed mood on the ADAMS. Mental health and emotional characteristics are under-researched in SAS; this may be partly attributable to difficulties in the measurement of emotional characteristics in individuals with impaired expressive communication.

Cognitive characteristics

SAS is universally associated with developmental delay and intellectual disability with delayed language acquisition (Zarate et al., 2018). Severe to profound intellectual disability is reported in over 50% of individuals with the syndrome (Zarate & Fish, 2017). Almost all individuals with SAS require assistance with activities of daily living and ongoing care (Zarate et al., 2021).

Communication deficits are observed in both receptive and expressive language (Thomason et al., 2019). Recent papers exploring communication found that fewer than ten words were spoken by 84% of individuals, and 42% of individuals were non-verbal (Zarate et al., 2019). Reported methods of alternative communication include the use of gestures, signs, and/or alternative augmentative communication devices; however, alternative communication skills are limited (Thomason et al., 2019). Marginal strengths in receptive and non-verbal communication are reported compared to spoken language (Zarate et al., 2021; Thomason et al., 2019).

Genotype x phenotype correlations

Limited genotype-phenotype correlations for SATB2 alterations have been established. However, in addition to core features of SAS such as developmental delay, behavioural characteristics, and craniofacial characteristics, individuals with large deletions are reported to evidence some specific characteristics. These include more frequent reports of a history of delayed growth (Zarate et al., 2019; Zarate et al., 2021), genitourinary anomalies (Zarate & Fish 2017), increased risk for cardiac defects (Zarate & Fish, 2017; Zarate et al., 2021), electrodermal changes such as thin skin or reduced subcutaneous fat (Zarate et al., 2021), and variable facial dysmorphism (Zarate & Fish, 2017).

A significantly higher proportion of individuals with disruptive pathogenic variants and missense variants have been reported to have sialorrhea (drooling/excessive salivation) (Zarate et al., 2019).

Zarate et al. (2019) report that individuals with large chromosomal deletions received a diagnosis of SAS at a significantly younger age (mean diagnosis age of 2.5 years) compared to individuals with a disruptive mutation, intragenic deletion, or missense mutation (mean diagnosis age of 8.3 years, 7.6 years, and 7.8 years, respectively).

Life expectancy

Little is known about the life expectancy of individuals with SAS, although current research studies have included participants aged up to 37 years (Bissell et al., 2022; Zarate et al., 2021).

Useful websites/associations for more information

- SATB2 Gene Foundation USA: www.satb2gene.org
- SATB2 Gene Trust UK: www.satb2gene.org.uk
- SATB2 Europe: www.satb2europe.org
- SATB2 Gene Foundation Australia: www.satb2.org.au

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The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation